CHELIDONIUM MAJUS L.

Isoquinoline Alkaloids

* Simple Tetrahydroisoquinolines

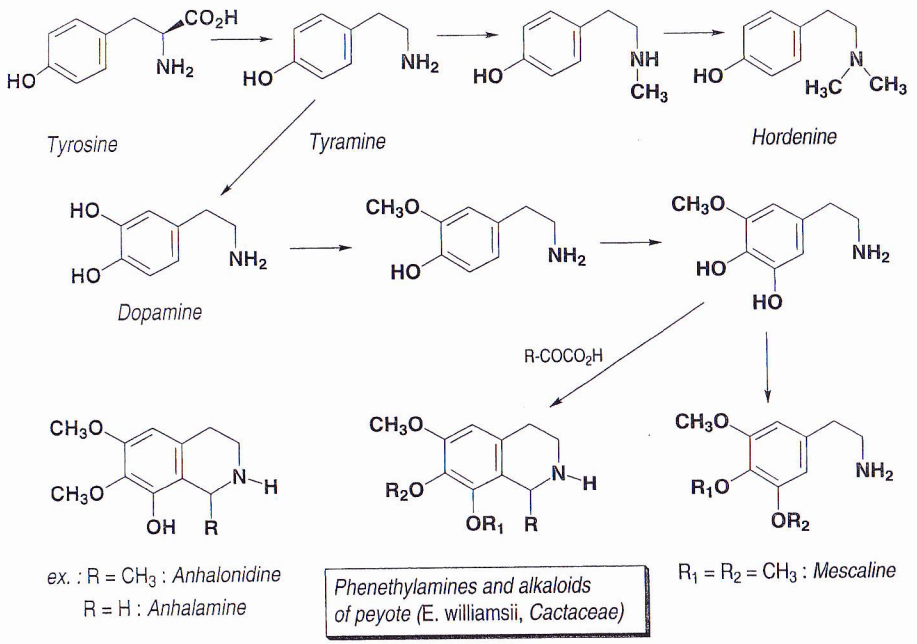
- **PEYOTE,**
  Lophophora williamsii (Salm-Dyck) J. Coulter, Cactaceae

Considered a divine plant by the Aztecs, this cactus is a particularly poten hallucinogen. This is the "plant that makes the eyes amazed", in other words cause visual hallucinations, due to the CNS activity of a phenethylamine alkaloid mescaline.

Peyote is a globular cactus, fleshy, composed of rounded lobes, and spineless reaching a maximum of 20 cm in height and 5-10 cm in diameter. The fleshy stem i divided into 5-14 prominent ribs, themselves further divided into "tubercles". Thes have at their apex an inerm areola from which blossoms, atop a hair cushion, solitary flower which is pink, white, or yellow. Peyote grows from the north c Mexico to Texas, on high limestone plateaus. The drug consists of the aerial par sliced and dried in the sun (mescal buttons). Its harvest was traditionally the occasio for a complex religious ritual.

The drug contains a large amount of mucilage and about fifty nitrogen-containin compounds: phenethylamines and tetrahydroisoquinolines (fresh plant: 0.5-1% mescal buttons: 6%). The phenethylamines include mescaline (= 3,4,5-tri-methoxy phenethylamine) and its derivatives (*N*-formyl, *N*-acetyl, *N*-methyl), hordenine 3-demethyl- and 3,4-demethylmescaline, tyramine and its derivatives methylated o the nitrogen atom, and dopamine. The chief tetrahydroisoquinoline alkaloids ar anhalamine, anhalonidine, anhalidine, pellotine, and lophophorine. They arise fro the condensation of a phenethylamine with an α-ketoacid (glyoxylic acid, pyruvi acid).

The ingestion of peyote essentially causes psychic effects *(p. 888). Mescaline ha clinical effects resembling those of LSD (lysergic acid diethylamide): psychi



cognitive, and physical. Note in particular a distortion of the perception of shapes, an intensification of colors, auditory hallucinations, and a slowing in the perception of time; the intensity and the nature of the effects are highly dependent on the environment and the intellect of the subject (for example, his or her artistic sensitivity). The physical symptoms that accompany these hallucinations are mydriasis, tachycardia, bradypnea, a sensation of change in temperature, nausea, and possibly agitation and anxiety. At high doses, memory loss, hypertensive encephalopathy, and intracranial hemorrhage may be observed.

Not one therapeutic indication is currently recognized for this psychoactive compound which has undergone psychiatric trials and is now listed in France among the substances whose production, marketing, and use are forbidden. In the United States, the use of peyote for sacred Native American purposes is protected by fundamental religious freedom, but disallowed by antidrug laws, a situation which leaves room for some debate and confusion.

BIBLIOGRAPHY

Gennaro, M.C., Gioannini, E., Giacosa, D. and Siccardi, D. (1996). Determination of Mescaline in Hallucinogenic Cactaceae by Ion-interaction HPLC, *Analyt. Letters*, **29**, 2399-2409.

* Identical effects are observed following the consumption of a beverage (*cimora*) prepared from a saguaro-like cactus, the San Pedro cactus or *aguacolla, Echinopsis pachanoi* (Britton & Rose) Friedrich & Rowley (= *Trichocereus pachanoi* Britton & Rose) traditionally used in the Andes (Peru, Bolivia). Many other Cactaceae contain hallucinogenic nitrogen-containing substances (*Carnegiea, Corvphanta, Gymnocactus*, and others).

Isoquinoline Alkaloids

* Benzyltetrahydroisoquinolines

1. Introduction

The alkaloids derived from 1-benzylisoquinoline are surpassed, in structural diversity, only by the monoterpenoid indole alkaloids: the two figures below (pp. 894-895) provide an overview of the chief skeletons encountered and of their biogenetic origin from a common precursor.

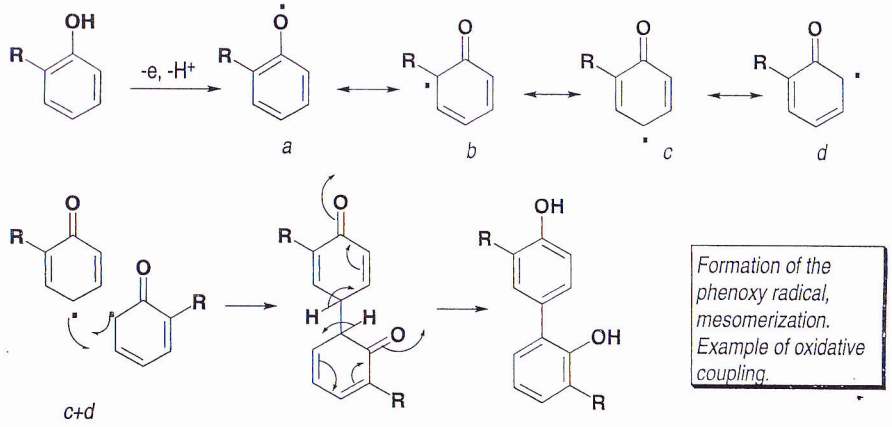
Oxidative Coupling

The above structural diversity results from the broad reactivity of phenolics, particularly their coupling reactions *via* radical intermediates: this is the classic oxidative coupling of phenols. The phenoxy radical, formed upon oxidation of the phenate ion, and stabilized by resonance, is highly reactive: depending on whether the coupling involves the phenoxy radical and its mesomers, or only the latter, the

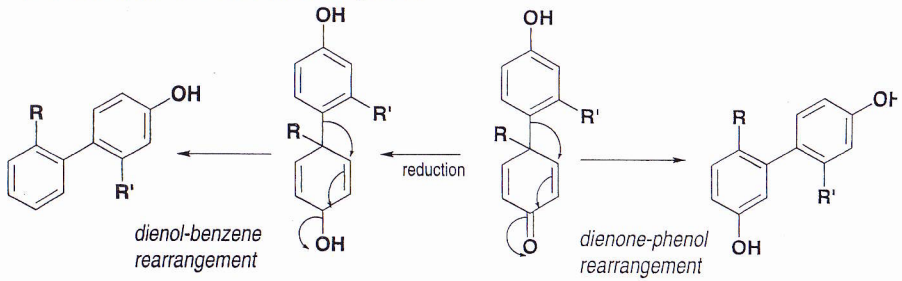
result is either the formation of a biphenylether bond (Ar-O-Ar), or a biphenyl carbon-carbon bond (HO-Ar-Ar-OH).

Although this coupling is generally intramolecular, as in the biosynthesis of morphine, aporphinoids, or cularines, it can also be intermolecular: this explains the formation of the bisbenzyltetrahydroisoquinoline alkaloids and the binary aporphine-benzyltetrahydroisoquinoline alkaloids. These coupling reactions are normally followed by rearomatization (see aporphines). In a few cases, however there is no simple pathway for rearomatization, and rearrangements take place instead, which can lead to new, more or less profound structural variations (see among others, morphinan and erythrinane alkaloids).

Yet other structural variations are explained by oxidative ring openings followed by new ring formation (see benzophenanthridines, rhœadines).



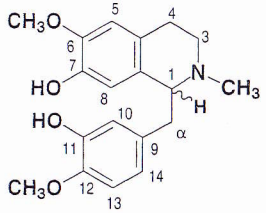
Alkyl substitution at the coupling site leads to a rearrangement, after which rearomatization is possible.



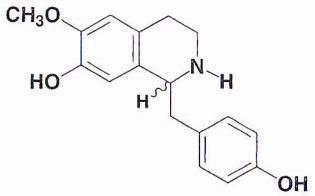
II. Simple benzylisoquinolines

The quasi totality of these simple compounds are 1,2,3,4-tetrahydro derivatives, in other words benzyltetrahydroisoquinolines. In a few exceptional cases, they are aromatic: one example is papaverine. All of these compounds have, for biogenetic reasons, a 6,7-disubstituted isoquinoline nucleus and a mono-, di-, or trisubstituted benzyl moiety: the most common derivatives are of the coclaurine type (12-mono-substituted) and reticuline type (11,12-disubstituted). In that they are the precursors of all other isoquinoline alkaloids, these benzyltetrahydroisoquinolines occur in virtually all of the plants capable of elaborating more complex isoquinoline structures.

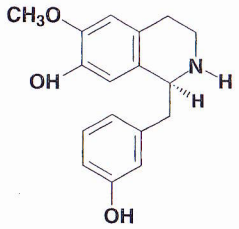
Some of these compounds have an interesting pharmacological potential, for example higenamine from *Annona squamosa* L. and *Aconitum japonicum* Thumb., which is a cardiac stimulant.



(+)- and (–)-Reticulines



(+)- and (–)-Coclaurines

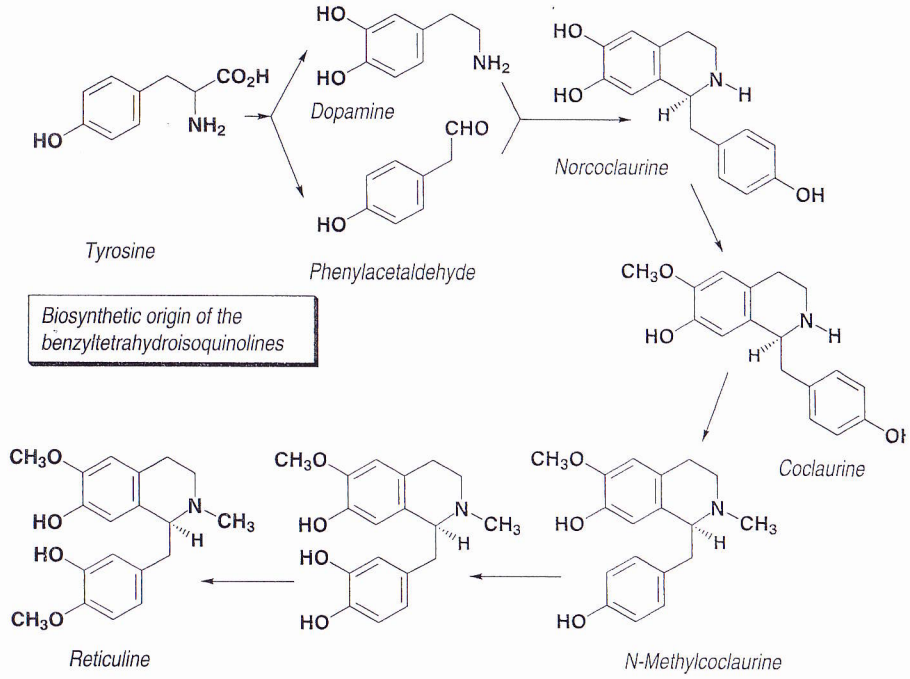


(–)-Norcanelilline

1. BIOSYNTHETIC ORIGIN

Benzyltetrahydroisoquinolines are pivotal intermediates in the metabolism of isoquinoline alkaloids, and are formed by a Mannich-type condensation between two metabolites of phenylalanine: for a long time, it was thought that the condensation of dopamine and 3,4-dihydroxyphenylpyruvic acid led, *via* norlaudanosoline, to reticuline, a central intermediate in the metabolism of isoquinoline alkaloids. In fact, experiments with labeled precursors and cell cultures show that the true precursors are dopamine on the one hand and 4-hydroxyphenylacetaldehyde on the other hand.

The condensation of these two molecules leads to (*S*)-6-demethylcoclaurine, which is subsequently methylated (on the 6-position of the phenol and on the nitrogen atom) before being hydroxylated at C-12 and finally, methylated to (*S*)-reticuline.

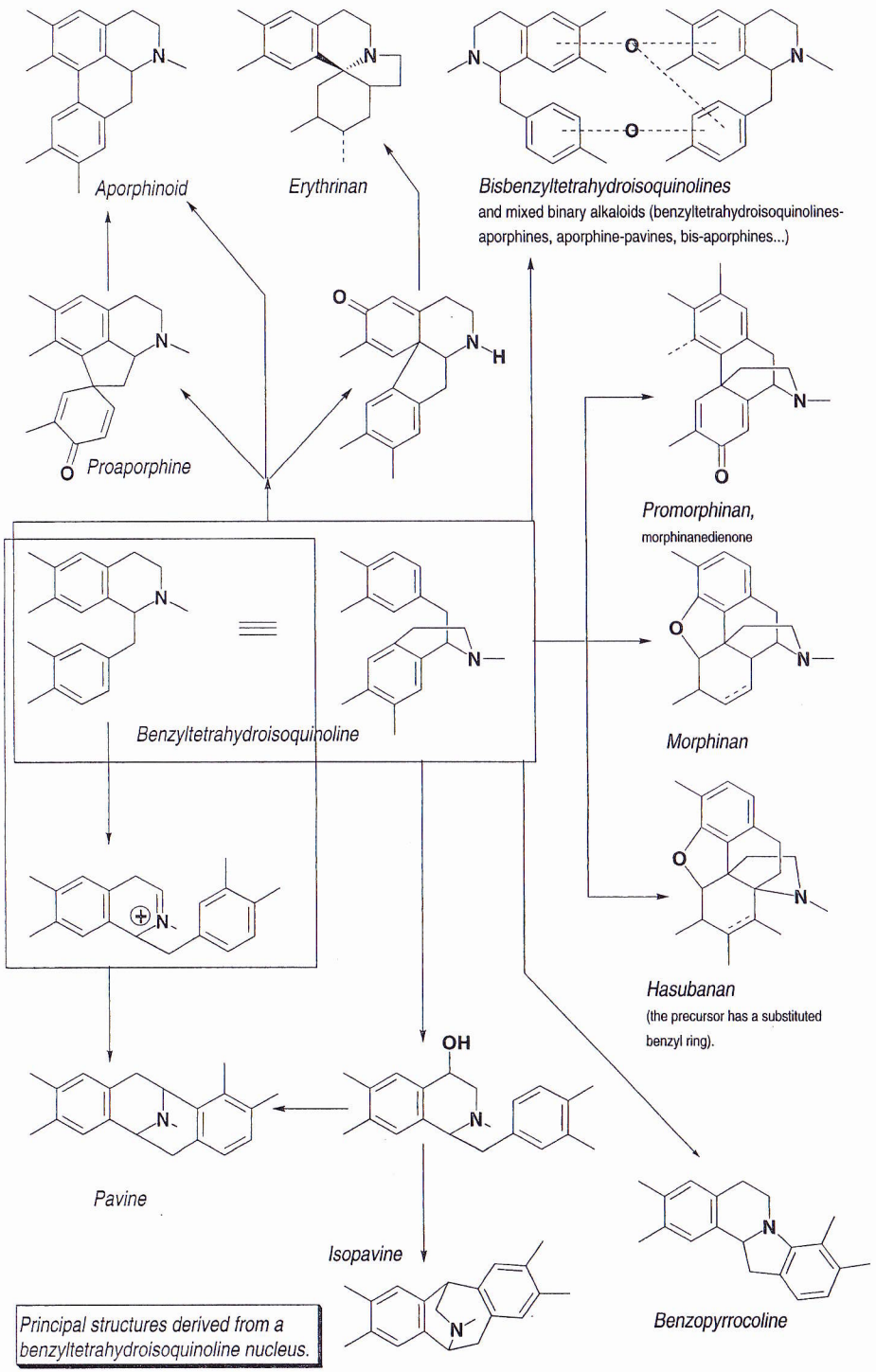


Biosynthetic origin of the benzyltetrahydroisoquinolines

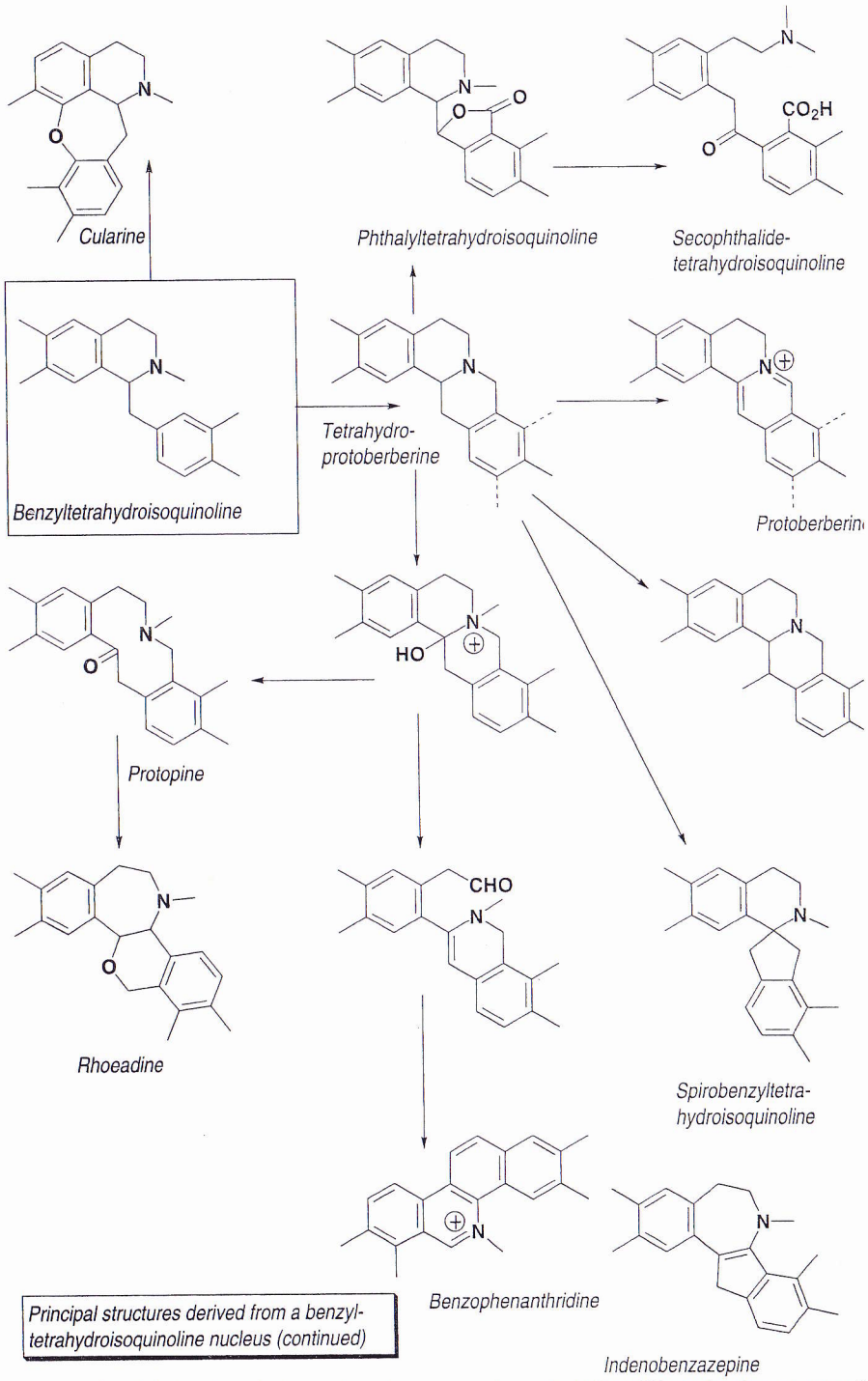
Only one alkaloid in this group is currently used in therapeutics, namely papaverine. Although it is found in opium and in the various parts of the opium poppy, this simple alkaloid is, in practice, obtained by total synthesis.

2. PAPAVERINE

Synthesis. There are many published syntheses for this alkaloid. The simplest of all is based on the condensation of homoveratrylamine and homoveratric acid followed by a Bischler-Napieralski condensation ($POCl_3$) and an aromatization of the cyclization product (Pd/tetralin). Both starting materials are prepared by the chloromethylation of veratrole, followed by the formation of homoveratronitrile which can be converted to either the amine or the acid. A variation of this procedure uses dimethoxystyrene, to which is added one molecule of methanol. After reduction and condensation with the chloride of homoveratric acid, papaverine is obtained directly by cyclization in the presence of phosphoric anhydride. There are also "biomimetic" routes available.



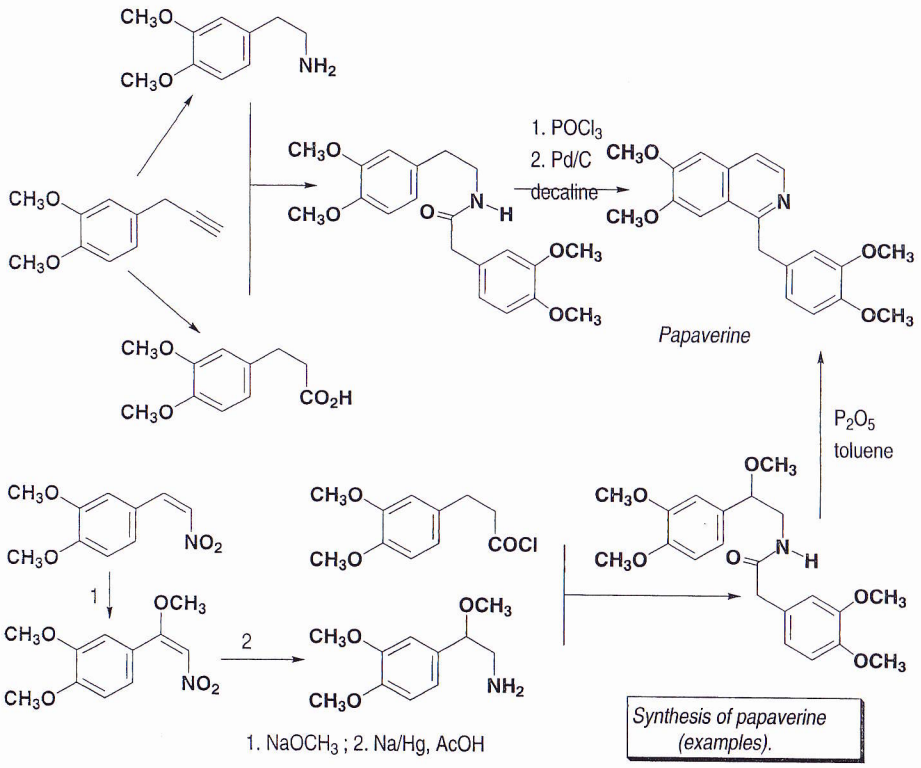
Principal structures derived from a benzyltetrahydroisoquinoline nucleus.



Principal structures derived from a benzyl-tetrahydroisoquinoline nucleus (continued)

For the sake of clarity, the substituents have been purposely omitted (H or CH_3 on the nitrogen atom; C
OCH_3, O-CH_2-O, or H on the aromatic carbon atoms)

Pharmacological Activity. Papaverine is practically devoid of effects on the CNS. It is a musculotropic spasmolytic which relaxes smooth muscle fibers, especially those of cerebral, pulmonary, and systemic peripheral blood vessels, but also those of the bronchia, intestines, ureters, and biliary ducts. The spasmolytic activity is more pronounced in the case of a pre-existing spastic condition. Papaverine has an effect on the heart muscle: it decreases conductibility and excitability, prolongs the refractory period, and increases coronary blood flow. Its activity is linked to its ability to inhibit the phosphodiesterase which hydrolyzes cAMP, and to decrease the intracellular calcium concentration (by inhibiting its entry into the cell or increasing its uptake by the reticulum).



Synthesis of papaverine (examples).

Uses. Despite a lack of consensus regarding its clinical benefits, at least as a "vasodilator and anti-ischemic" in the curative or preventive treatment of cerebral circulatory insufficiency, papaverine is still fairly widely used. In addition to being indicated as a smooth muscle relaxant (injectable solution at 4%) and for the symptomatic treatment of the intermittent claudication due to chronic occlusive arterial disease of the lower limbs, it is proposed: 1. to improve certain symptoms of senility (e.g., loss of attention and memory); 2. for the symptoms of ischemia in the eye. It is also used for vertigo in the elderly and to treat the sequelae of cerebrovascular accidents (see comments, p. 1023). Contraindications include intracranial hypertension, parkinsonism, and intracardiac conductibility alterations, but papaverine is not a hypotensive agent and only rarely has side effects (potenti tachycardia, constipation, altered transaminases, phosphatases, and bilirubinemia For the same indications as above, papaverine is sometimes combined with oth compounds (e.g., butalamine). This alkaloid is also an ingredient of combinatio designed to treat capillary fragility (e.g., combinations with hesperidin meth chalcone, ascorbic acid, and ethoxazorutin, see p. 328). As an antispasmodic, it is component of proprietary drugs designed to relieve the symptoms of function colopathy, particularly flatulence and diarrhea.

III. Bisbenzyltetrahydroisoquinoline

1. GENERALITIES

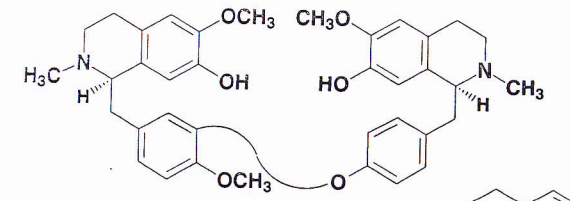
Bisbenzyltetrahydroisoquinolines and aporphine-benzyltetrahydroisoquinoli "dimers" represent over 400 compounds occurring in about ten families, chiefly the Menispermaceae (*Abuta, Albertisia, Cocculus, Stephania, Tiliacora*, for a to of about 25 genera), the Ranunculaceae (*Thalictrum*), the Berberidaceae (*Berber Mahonia*), but also Monimiaceae (*Daphnandra*), the Annonaceae (*Phaeanth Popovia, Pseudoxandra, Uvaria*), or the Lauraceae.

There are approximately thirty classes of compounds, distinguished by following:

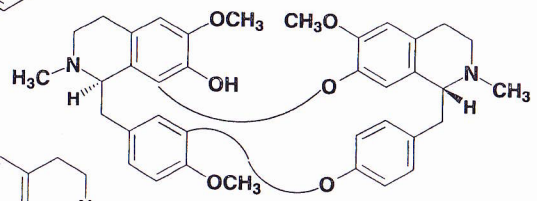
- the "dimer" type, either "head-to-tail" or "tail-to-tail" (i.e., depending whether the bond is established between the benzyl moiety of one half of t molecule and the benzene ring of the tetrahydroisoquinoline nucleus of the ot half, or between the two benzyl moieties);
- the number of bridges (one, two, or three);
- the type of bond between the two parts of the molecule, either biphenyl or et
- the type of substituents.

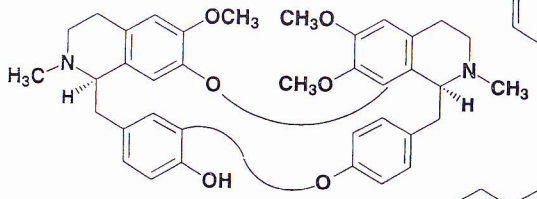
Almost all of the known bisbenzyltetrahydroisoquinolines arise from intermolecular oxidative coupling of two coclaurine (or *N*-methylcoclaurine) un in a few exceptional cases, they are bisreticulines (*Hernandia*).

Pharmacologically, these compounds are of limited interest: although seve have interesting potential, none is currently marketed in Europe. Note the antitu properties of tetrandrine (leukemia), the antituberculosis activity of cepharanthi and the antimalarial properties of pycnamine or nortiliacorinine A. Seve



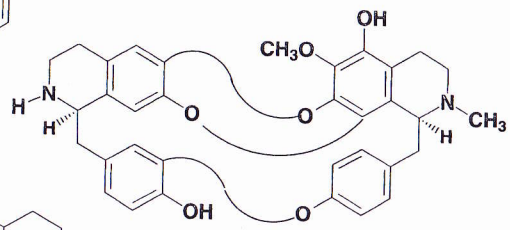
Thaligrisine



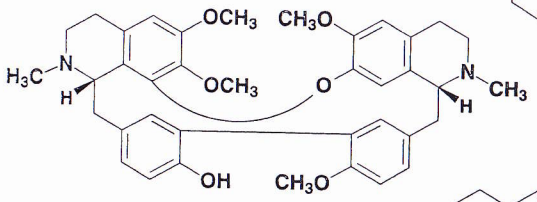


Limacine

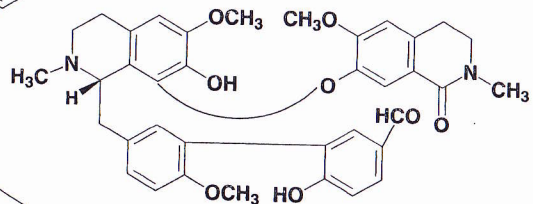
Oxyacanthine



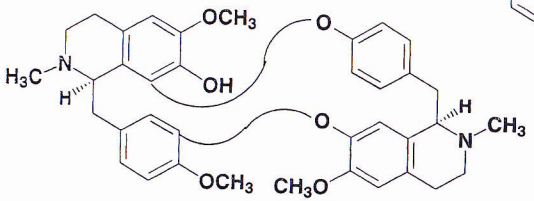
5'-Hydroxyapateline



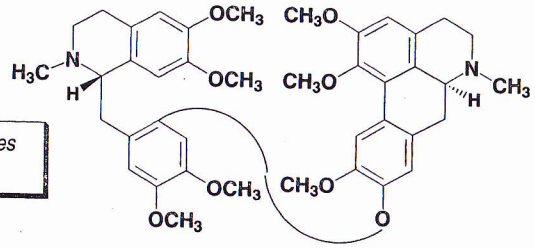
Funiferine



Seco-antioquine



Curine



Thalicarpine

*Bisbenzyltetrahydroisoquinolines *: examples of structures with one, two, or three bridges*

* thalicarpine is an aporphine-benzyltetrahydroisoquinoline "dimer"

compounds in this group are hypotensive (penduline). Some also have a curare-like activity on the motor end-plate, for which they are used, although the actual products currently on the market are semisynthetic or synthetic derivatives.

2. CURARE

The term curare is the phonetic transcription of the Caribbean word *ourari*, originally from Guyana, and is a general term applied to a large number of complex products, of variable geographical and botanical origin, that display identical pharmacological properties. The natives of South America formerly used these preparations to coat the tip of blow darts, or else, but less often, the tip of arrows. For the hunter there are many advantages to these curares:

1. the effect is so immediate that the animal cannot flee;
2. the muscle relaxation induced by the poison prevents parrots, small monkeys, and other game from holding on to branches which are sometimes high in the trees, so that they generally fall to the ground;
3. curare is toxic only by the parenteral route, so that the game caught with it can be consumed safely.

Curares are hunting poisons in forest areas, and are not known to have been used as war poisons: "tight regulations disallow any use against humans" (J. Vellard). The symptoms of curare poisoning (a paralysis that progresses rapidly and, upon reaching the diaphragm, causes death by respiratory arrest, without having altered the consciousness or sensitivity of the victim at any point) are very distinct from those of the war poisons that were commonly used in South America during the period of the *conquistadors*: most often based on latex from Euphorbiaceae*, these caused a particularly painful and slow death (sometimes after several days). This "death that kills slowly" has been linked to curares erroneously for a long time, and one may wonder why, because the effects of war poisons have been correctly described since the beginning of the sixteenth century (i.e., upon arrival of the Spaniards on the American coasts) and because curares, which are specific to the depths of the Amazon forest, were not discovered by explorers and missionaries until much later.

The action of curares on skeletal muscle was studied in detail during the nineteenth century (C. Bernard) even while their botanical origin was still shrouded in mystery. It took a long time to unravel the latter, as well as the structure of the alkaloids, which was elucidated only about fifty years ago.

Classification of Curares. For a long time, and given the lack of data on their botanical origin, curares were classified according to the shape of their storage vessels:

* Examples include the latex of manchineel, *Hippomane mancinella* L., but also from *Sapium, Euphorbia, Colliguaja, Hura*; some Thymelaeaceae are also used as poison in the northwest of

- tube-curare from Brazil and Peru, poured into bamboo tubes, and used as arrow poison;

- pot-curare, poured into clay pots of various shapes, rare and specific to the upper Orinoco and upper Amazon basins;

- calabash-curare, poured into the fruits of various Bignoniaceae, originally from Colombia, Venezuela, and Guyana, and used as arrow poison.

There were some alternative classifications: curares from the foothills of the Andes, Guyanese curare, or curares from the savannas.

Later, curares for pharmaceutical applications were prepared in their countries of origin, from the barks of the fresh plants, by maceration in water. After a lixiviation-type step, the solution was concentrated into a soft extract and poured into one-kilogram tins which were then shipped overseas for the extraction of the active substances. Later still, these substances were extracted directly from the plants. Currently, only one product is marketed in Europe, namely *N,N'*-diallyl-nortoxiferinium dichloride (= alcuronium chloride INN). This dimer can be obtained by conversion from toxiferine or by semisynthesis from monomeric alkaloids of the strychnine type, which can be extracted from various species of *Strychnos* (Loganiaceae) (see below).

Botanical Origin. Tube-curares from the upper Amazon basin (Brazil, Peru) are chiefly composed of extracts of stems of Menispermaceae of the genus *Chondrodendron* (*C. tomentosum* Ruíz & Pavón) and of the very close genus *Curarea* (*C. toxicofera* [Wedd.] Barneby & Krukoff, *C. candicans* [Rich.] Barneby & Krukoff). They are also known to occasionally contain extracts of other Menispermaceae of the genera *Sciadotenia* Miers, *Abuta* Aublet, *Telitoxicum* Mold. and *Cissampelos* L.* Calabash-curares owe their activity to extracts of trunk barks of various shrub or vine species of the genus *Strychnos* (Loganiaceae), including *S. toxifera* R. Schomb., *S. castelnaeana* Wedd., *S. letalis* Barb., and *S. rondetelioides* Spruce ex Benth., among others. Pot-curares almost always contain a mixture of extracts of Menispermaceae and Loganiaceae. In the curares prepared by the natives of the Amazon basin, the plant extracts containing active alkaloids (*Chondrodendron, Strychnos*) were mixed with toxic or supposedly toxic products, for example, snake hooks and livers, as well as thickening plant extracts added to improve the adhesion of the poison onto the arrow tips, or supposedly to increase toxicity (for example, *Capsicum annuum*). There are cases, however, in which the extract was used alone: *Strychnos* of the Nambikwaras of the Mato Grosso, *Curarea* extracts of the Waorani of the eastern part of Ecuador, and so forth.

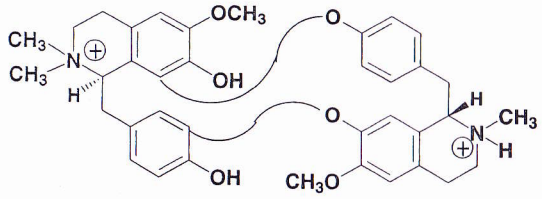
Chemical Composition. The active principles of the curares from Menispermaceae and Loganiaceae are very different: the former are of the isoquinoline type, whereas the latter are of the indole type; both types, however, are

* Although all of the genera are known to elaborate bisbenzyltetrahydroisoquinoline alkaloids, most of the fractions analyzed and described in the literature so far only yielded tertiary bases. Only *C. tomentosum* produces (+)-tubocurarine.

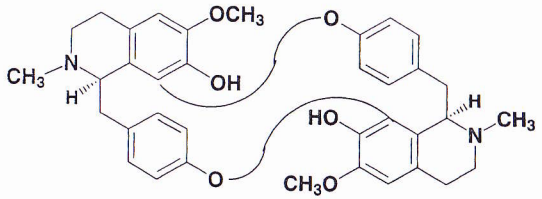
quaternary ammonium salts. Since their pharmacological activities are identical, we shall not dissociate them, even though, biosynthetically, the alkaloids of Loganiaceae are tryptophan derivatives.

Menispermaceous Curares

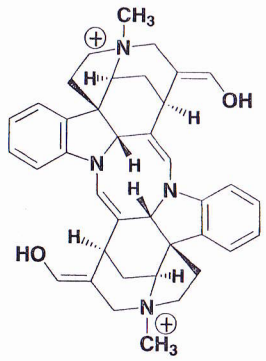
These curares contain from 2 to 10% bisbenzyltetrahydroisoquinoline alkaloids, a very common structure type in this family. The curare molecule is (+)-tubocurarine, which has a "head-to-tail", asymmetrical, quaternary ammonium structure with two ether bridges (8-*O*-12' and 11-*O*-7') linking the two coclaurine units. The other alkaloids are tertiary bases: (–)-curine, (+)-isochondrodendrine, and (+)-chondrocurine. The various species occasionally incorporated into curares (*Curarea, Abuta, Sciadotenia*) contain mostly tertiary bisbenzyltetrahydroisoquinolines with two bridges of the "head-to-tail, tail-to-tail" type (limacine, limacusine), as well as other isoquinoline structures (oxoaporphines, azafluoranthenes).



(+)-Tubocurarine



(+)-Isochondrodendrine



C-Toxiferine

Loganiaceous Curares

In this case, the active constituents are symmetrical bisindoline, bis quaternary ammonium alkaloids, arising from the "doubling" of a strychnane-type unit: C-toxiferine (C stands for calabash), C-curarine, C-alkaloid G and E, C-calebassine, and others (see indole alkaloids). These alkaloids represent 8 to 10% of the weight of the curare; they occur alongside "monomeric" alkaloids of the strychnane type, or of related types.

Pharmacological Activity. Naturally-occurring curares are non-depolarizing (or competitive, or stabilizing) neuromuscular blocking agents. Active only by the parenteral route, they compete with acetylcholine for the cholinergic receptors at the motor end-plate and prevent the formation of the action potential, without modifying nerve conduction elsewhere and without preventing muscular contraction in response to direct stimulation.

The activity of curares manifests itself in several steps: decrease in muscular tone, atony with loss of tone, then progressive paralysis. Curares and other competitive agents have a relaxant activity on skeletal muscle: the paralysis first affects the muscles of the face (eyelids) and neck, then those of the limbs; it then spreads to abdominal and respiratory muscle, and in the end, to the diaphragm. The curarized subject feels extreme fatigue, cannot keep his or her eyes steady, the limbs grow heavy, and gradually, the head and limbs become completely paralyzed, with the diaphragm being last (in 3-5 minutes with the minimal dose chosen for intubation). The effect of curare is temporary, and if respiratory arrest is avoided (artificial respiration), the muscles regain their function in the reverse sequence; the duration of curarization varies depending on the structure of the agent: 25% of muscular strength is recovered in 90 minutes in the case of alcuronium; this takes only a third of the time with synthetic agents such as atracurium (recovery index 25-75%, 10-15 min; 95% recovery time: 35 min) or mivacurium (complete decurarization in 15 min).

Uses. Tubocurarine remains the pharmacological reference product for this class, but its use was discontinued about ten years ago. Currently, a semisynthetic derivative of C-toxiferine is used: *N, N'*-diallylnortoxiferinium dichloride (= alcuronium chloride INN). Alcuronium chloride is used (IV) as an adjunct in anesthesia (0.05-0.15 mg/kg, inject more every 15-25 minutes), particularly to achieve muscle relaxation during surgical procedures (especially if they take a long time). It is also used in preparation for tracheal intubation.

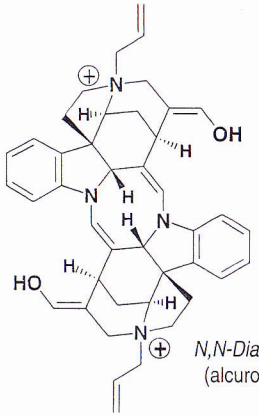
Other non-depolarizing neuromuscular blocking agents are currently preferred. They are synthetic compounds, but they are analogous to the naturally-occurring curares: quaternary nitrogen atoms separated by a long carbon chain or steroidal moiety, voluminous molecules, and bulky substituents on the nitrogen atoms, which facilitates a non-depolarizing mechanism. The compounds currently available are the following:

- synthetic compounds composed of two benzyltetrahydroisoquinolines linked by an aliphatic chain and quaternized, such as atracurium besilate and mivacurium chloride, the latter with a duration of action half as long as the former. The latest product of this type to be marketed in France is cisatracurium besilate, in other words one of the isomers of atracurium (1*R-cis*, 1'*R-cis*), obtained by condensation of (*R*)-tetrahydropapaverine and 1,5-pentanediol diacrylate, followed by chromatographic purification. The product is more potent than atracurium and has fewer side effects.

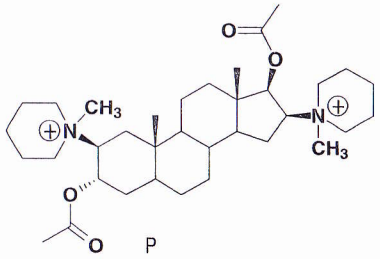
- steroids substituted by nitrogen-containing heterocycles, which are mono- or bis-quaternary ammonium salts: vecuronium bromide, pancuronium bromide, or rocuronium bromide, which was introduced more recently, and has a rapid onset of action and an intermediate duration of action

The current indications of non-depolarizing neuromuscular blocking agents are generally as follows: as adjuncts for general anesthesia during surgical procedures, to facilitate tracheal intubation, to achieve muscle relaxation, and to facilitate assisted ventilation.

As a general rule, non-depolarizing neuromuscular blocking agents are contra-indicated in case of known hypersensitivity to the product (anaphylactic reactions



N,N-Diallylnortoxiferine (alcuronium, DCI).



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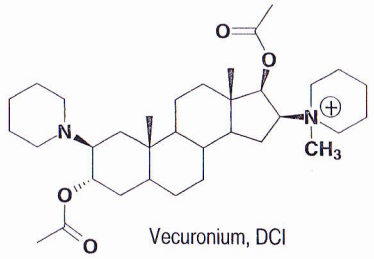
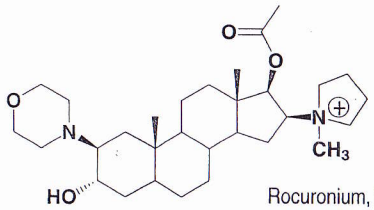
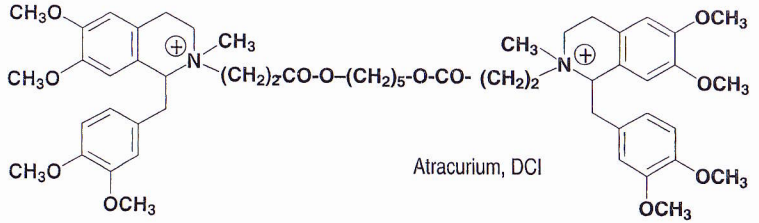


Vecuronium, DCI

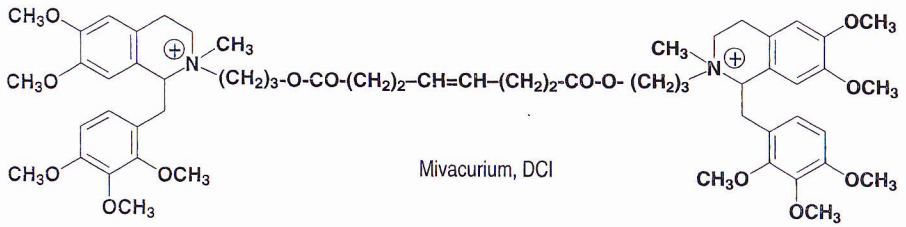


Rocuronium, DCI

Principal competitive neuromuscular blocking agents



Atracurium, DCI



Mivacurium, DCI

have been described for muscle relaxants in general); they must be used with caution in case of myasthenia and other neuromuscular disorders, electrolyte disorders (e.g., hypokalemia, hypocalcemia), or renal insufficiency.

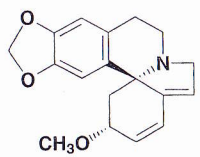
They must be used only by trained hospital personnel (assisted ventilation must be at hand). They have few side effects (although the release of histamine is possible, and the corresponding risk varies depending on the product), but they give rise to many drug interactions and are subject to chemical incompatibilities which vary with the product. In case of overdose, assisted ventilation with oxygen therapy is required; when decurarization is sufficient, an anticholinesterase must be administered (IV, neostigmine, pyridostigmine, edrophonium), and its side effects prevented by the concomitant administration of atropine.

C. OTHER NATURALLY-OCCURRING SUBSTANCES WITH CURARE-LIKE ACTIVITY

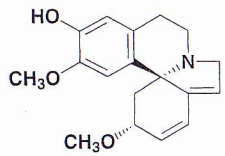
Erythrina Alkaloids

These alkaloids have a structure which is very different from that of the curares in the strict sense of the term. We describe them at this point only because they fit from a pharmacological point of view. In a sense, they are 1-benzyltetrahydro-isoquinolines having undergone a particular intramolecular oxidative coupling!

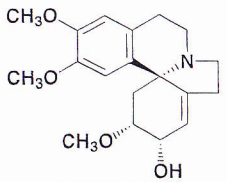
Erythrina are tropical Fabaceae, often arborescent, which grow in South America, Africa, and the tropical regions of Asia, and are sometimes appreciated for their decorative value. As the genus name reminds us, their flowers are most often scarlet red. Most of the species in this genus contain tetracyclic isoquinoline alkaloids which are structurally very similar: dienes (e.g., erysotrine, erythraline), alkenes (e.g., erythratine), and lactones arising from the oxidation of the benzene ring (e.g., erythroidines). Pharmacologically, these alkaloids are curares *per os* and very toxic.



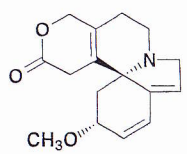
Erythraline



Erysodine

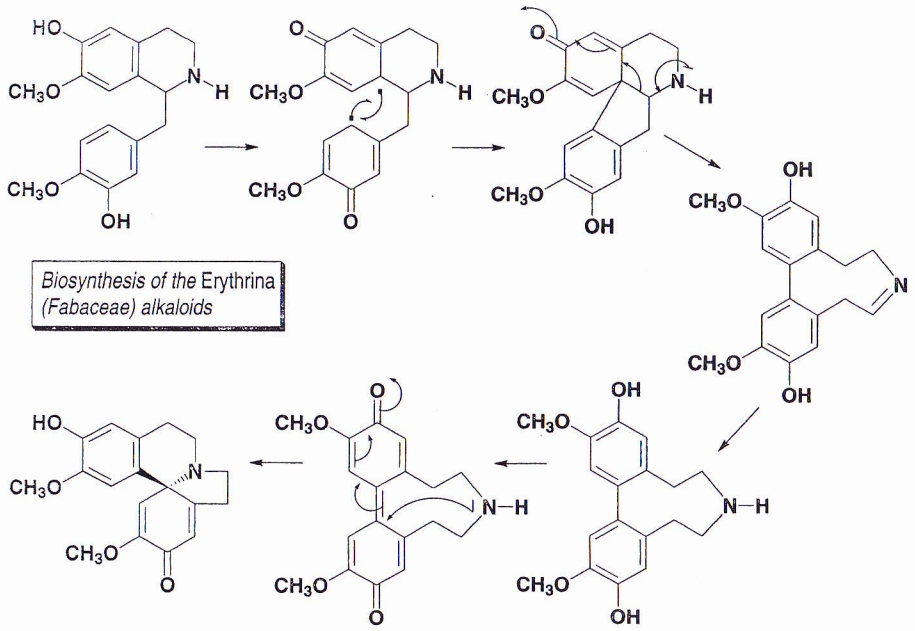


Erythratidine



β-Erythroidine

Alkaloids of related structure (cocculine, cocculidine, coccoline, coccolinine, coccuvinine) have been isolated from various *Cocculus* (for example *C. laurifolius* DC., Menispermaceae); experiments in animals show that they are ganglioplegics and hypotensive agents.



Biosynthesis of the Erythrina *(Fabaceae) alkaloids*

Biosynthetically, these alkaloids are tetracyclic spiroamines arising, like all of the isoquinoline alkaloids, from the metabolism of phenylalanine. Labeling experiments show that norprotosinomenine is incorporated, and that the biosynthesis probably proceeds *via* a symmetrical dibenzazonic intermediate (the isolation of such structures and of erysodienone confirm this hypothesis).

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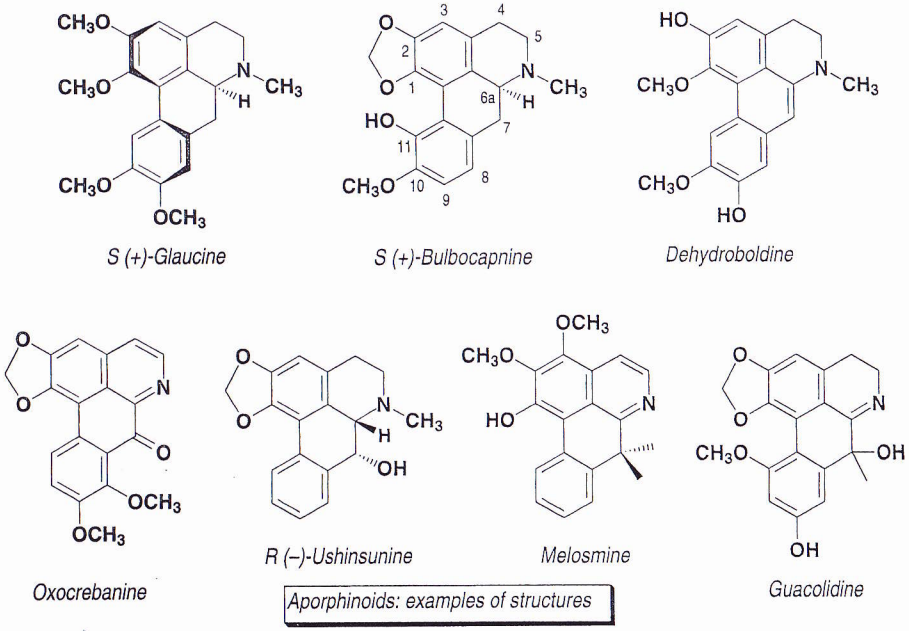
IV. Aporphinoids

A very large group of more than 500 alkaloids (proaporphines, aporphines, and derivatives), aporphinoids occur frequently mostly in certain archaic families, including the Annonaceae, Lauraceae, Magnoliaceae, Monimiaceae, Menispermaceae, Hernandiaceae, and Ranunculaceae.

Aporphines (*N*-methylated) and noraporphines are virtually always substituted at C-1 and C-2 by hydroxyl groups, methoxy groups, or a methylenedioxy group; they are often substituted at C-9, and C-10, or C-11, or both, and less often at C-8 and C-3. Aporphines are sometimes oxidized at C-7 (7-hydroxy- and 7-oxo-aporphines), and less often at C-4. Also known are 7-alkylaporphines and various degradation products of these molecules (e.g., phenanthrenes).



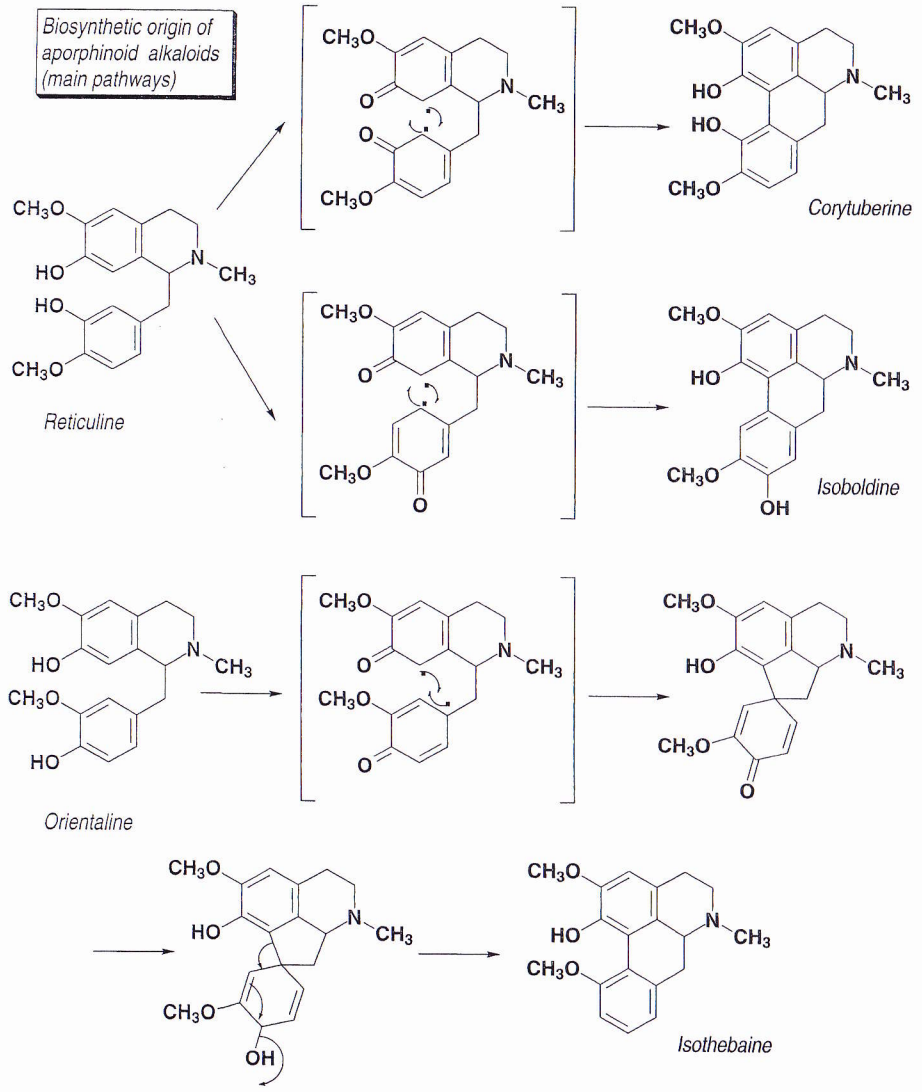
S (+)-Glaucine — *S (+)-Bulbocapnine* — *Dehydroboldine*

Oxocrebanine — *R (–)-Ushinsunine* — *Melosmine* — *Guacolidine*

Aporphinoids: examples of structures

1. BIOSYNTHETIC ORIGIN

Several pathways lead to these aporphinoid structures. The simplest one is a direct oxidative coupling (*ortho-ortho* or *ortho-para*, see figure on p. 908). The same



molecules can also arise from a rearrangement (dienol-benzene, dienone-phenol) of a proaporphine (in other words from the spirodienone arising from the oxidative coupling involving the C-9 of a benzyltetrahydroisoquinoline).

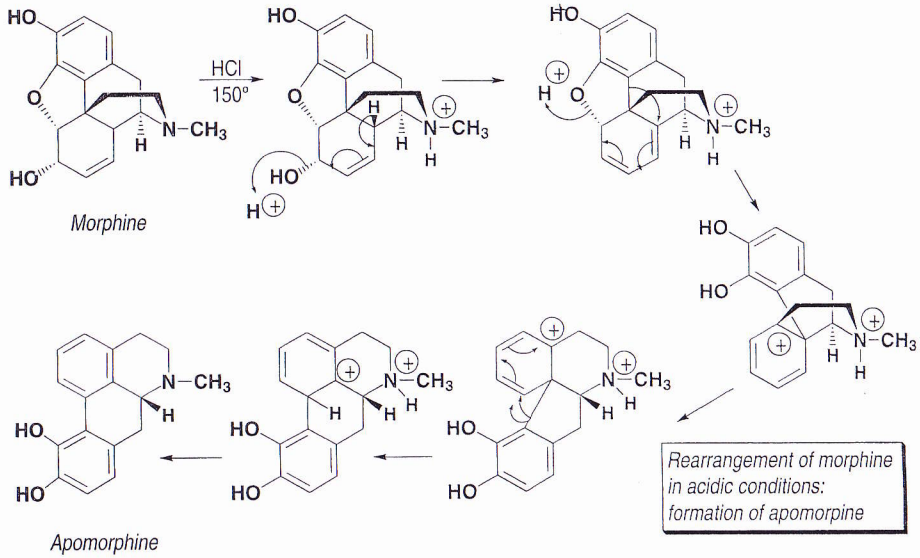
In animal experiments, some of the aporphines display a broad pharmacological potential: CNS depressant (corydine), dopaminergic antagonist (bulbocapnine), antitussive (glaucine), or antifungal (certain oxoaporphines), to name only a few.

Only two aporphines are ingredients of pharmaceuticals marketed in France today: one is boldine, extracted from the leaves and bark of the South American tree, namely boldo; the other is apomorphine, a semi-synthetic product which does

not occur naturally, but results from the treatment, under acidic conditions and at high temperature, of morphine.

2. APOMORPHINE

The figure below summarizes the mechanism of the rearrangement which leads from morphine to apomorphine. Like most aporphines, this molecule can also be synthesized.



Apomorphine is a dopaminergic D2 agonist. Its action on the substantia nigra and corpus striatum makes it a potential treatment for parkinsonism: its administration objectively improves tremor and rigidity, although only for a time (see bromocriptine, pp. 992 and 996); it acts in synergy with levodopa, improving mostly akinesia. In addition, it is an emetic, which acts by direct stimulation of the trigger zone, a central entity which in turn activates the vomiting center.

Apomorphine hydrochloride (a controlled substance on French *liste I*, i.e., a prescription drug that may not be renewed) is used in subcutaneous injection (injectable solution or premeasured doses in cartridge-needle units) to abolish akinesia paradoxica in parkinsonism patients undergoing long-term treatment with levodopa "as adjunctive treatment of the severe fluctuations in the efficacy of the therapy of parkinsonism by levodopa (on-off phenomena)" (i.e., bradykinetic episodes). Contraindicated in case of psychotic symptoms, mental confusion, hepatic insufficiency, and in debilitated individuals, apomorphine can induce gastrointestinal distress (nausea, vomiting), itching at the injection point, and psychic alterations which can limit its use; in fact, prevention of the emetic side effect is required by

administering, before and during treatment, a peripheral dopaminergic antagonist (domperidone).

The injectable solution at 5% is also used for its emetic properties to treat intoxications, when vomiting is not contraindicated (as it is in cases of poisoning by caustic solutions, when the patient is in a coma, after opiate ingestion, or in case of respiratory depression, cardiac insufficiency, or hypertension); vomiting is induced by injecting 5-10 mg of the alkaloid subcutaneously. Experts find this indication questionable, considering that there are no clinical studies that unambiguously demonstrate the efficacy of apomorphine. The compound must be injected within minutes after toxin ingestion to remove an appreciable quantity. Apomorphine is toxic and apparently seldom used in France (in human medicine) at this time.

Apomorphine has also been used *per os* in alcoholism recovery programs.

3. BOLDO, *Peumus boldus* Mol., Monimiaceae

The dried leaf of boldo is the subject of a monograph in the 10th edition of the French Pharmacopoeia. It is used to obtain galenicals said to have cholagogue and choleretic properties. The bark is used for the extraction of boldine.

The Plant, the Drug. Boldo is a small tree with indeciduous leaves which grows only in the part of Chile that enjoys a Mediterranean climate. It is a dioecious species: male flowers with pale yellow perianth, female flowers with a unique ovule which turns into to a translucent blue-green drupe.

The leaf is easy to identify: the blade is oval, grayish green, hard, and brittle, and its edges are slightly curled downward; the upper side is covered with bumps which give it a granular aspect and make it rough to the touch. Under the microscope, the features of the upper side appear covered with unicellular covering trichomes which are simple, fairly brittle, have a narrow lumen, and occur in bundles.

Chemical Composition. The dried drug contains 10 to 30 mL/kg essential oil composed of monoterpenoids (including hydrocarbons [limonene, β-pinene, *p*-cymene], linalol, cineole, camphor, ascaridole). Note also the presence of common flavonol glycosides (rhamnetin, isorhamnetin, and kaempferol derivatives).

The alkaloids (0.2-0.5%) are aporphinoids, and include boldine (chief constituent), isoboldine, isocorydine, norisocorydine, laurotetanine, and laurolitsine.

Tests. The TLC analysis of the total alkaloids shows the presence of boldine and of the chief alkaloids in the drug. The French Pharmacopoeia requires two quantitations. The first is that of the essential oil (not less than 20 mL/kg), and the second is that of the total alkaloids: extraction with ethyl acetate under alkaline conditions, purification through the formation of sulfates, return to the bases, and quantitation of the latter by indirect acidimetry: the boldo leaf must contain [illegible]

than 0.2% total alkaloids, expressed as boldine, and calculated relative to the dried material.

Pharmacological Activity. Although research carried out in 1977 established that high doses of boldine, of total alkaloids, or of purified ethanol extract of boldo transiently increased biliary secretion in anesthetized rats, more recent experiments in the same animal showed no detectable choleretic activity. On the other hand, the recent work showed that high doses of the hydroalcoholic extract inhibit lipid peroxidation (in rat hepatocyte cultures) and protect hepatocytes against damage by different xenobiotics. Boldine is responsible for these activities and its ability to protect *in vitro* biological systems against the peroxidizing action of free radicals was confirmed by other authors in rat brain homogenates. In addition, boldine exerts, *in vitro*, a relaxant effect on smooth muscle (rat ileum), by interfering directly with the cholinergic mechanism involved in the contraction.

Uses. Boldo extracts, and the boldine extracted from the tree bark are ingredients of proprietary drugs used for the adjunct treatment of dyspepsia and heart burn. In this type of medicine, boldo is generally combined with other drugs with a reputation as cholagogues, such as artichoke or combretum. Other combinations (with senna, buckthorn, cascara, aloe) are indicated for the symptomatic treatment of constipation.

In France, phytomedicines based on boldo leaves may claim two indications (orally): traditionally used to enhance renal and digestive elimination functions; traditionally used as a choleretic and cholagogue [French Expl. Note, 1998]. Manufacturers are required to propose a limit for the concentration of the active constituent in this type of product.

The German Commission E monograph only lists uses of boldo based on activities as a "spasmolytic, choleretic, and stimulant of gastric secretions": gastrointestinal problems such as cramps and dyspepsia. The monograph specifies that 1. boldo is contraindicated in case of obstruction of the biliary tract or serious liver disease; 2. in case of lithiasis, the drug must be used only after seeking medical advice; 3. that neither boldo oil nor boldo distillates must be used (ascaridole is toxic).

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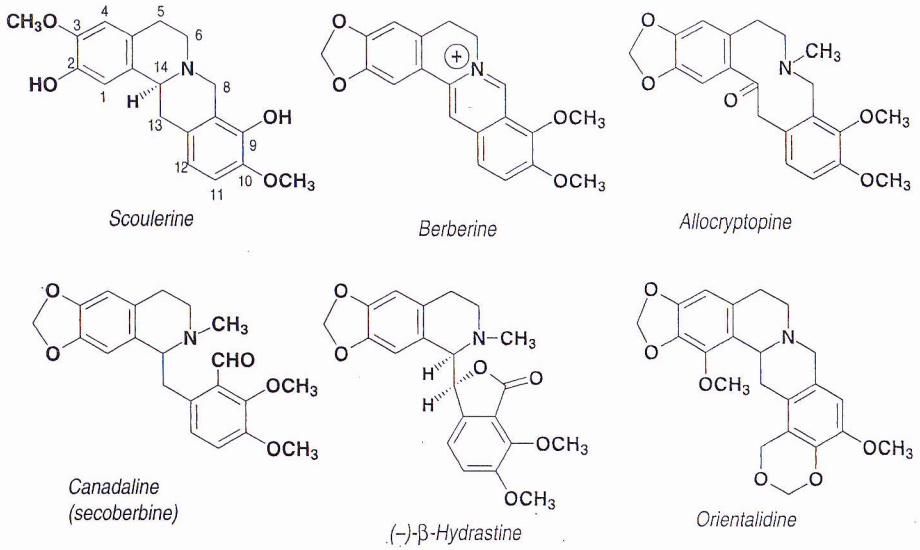
HYDRASTIS CANADENSIS L.

V. Protoberberines and Derivatives

1. GENERALITIES

Protoberberines are fairly widespread quaternary or tertiary tetracyclic alkaloids (in the latter case they are referred to as tetrahydroprotoberberines), found in the Berberidaceae, Menispermaceae, Ranunculaceae, and also in the Annonaceae or Papaveraceae. Their biogenetic potential is substantial, particularly through the protopines, which arise from the cleavage of the bond between C-14 and the nitrogen atom.

Like the other isoquinoline alkaloids, the protoberberines are formed from a benzyltetrahydroisoquinoline: the C-8 carbon atom comes from the oxidative cyclization of the *N*-methyl group of a molecule of this type. This cyclization, catalyzed by a *berberine bridge enzyme* (= BBE) is thought to involve the iminium ion (corresponding to the oxidation of the *N*-methyl group) which, by reacting with the *ortho* position relative to C-9 (i.e., *ortho* or *para* relative to the free phenol group on ring C) leads to a 2,3,9,10-tetrasubstituted tetrahydroprotoberberine or to its *pseudo* homolog (2,3,10,11-tetrasubstituted).



Among the many derivatives arising from the oxidation and the rearrangement of tetrahydroprotoberberines, some display interesting pharmacological properties. For example, the phthalidetetrahydroisoquinolines have antitussive properties (narcotine = noscapine, see p. 938 and 944), or are antagonists of gamma-aminobutyric acid (bicuculline). Another example is the quaternary benzophenanthridines: antitumor properties of nitidine and fagaronine, inhibition of viral reverse transcriptase by the same compounds which bind with specific base pairs. They react with biopolymers through their iminium bond, by intercalation, and by virtue of their cationic character.

Although many compounds in the various series derived from protoberberines have interesting pharmacological properties, to date, therapeutics has found use for only a few of them. Nevertheless, a certain number of species that contain them are currently used either as galenicals (goldenseal, fumitory), or, either directly or after a simple transformation, as phytopharmaceuticals which represent a renewal of folk medicine: in both cases, the relationship between the activity which tradition attributes to these drugs and the alkaloids that they contain is far from having been demonstrated (so are the clinical benefits of some of them).

2. DRUGS CONTAINING PROTOBERBERINES AND RELATED ALKALOIDS

• GOLDENSEAL, *Hydrastis canadensis* L., Ranunculaceae

Goldenseal is listed in the 10th edition of the French Pharmacopoeia which specifies that the part to be used "consists of the dried rhizome and roots [and that] they must contain not less than 2.5% hydrastine, calculated relative to the dried drug".

The Plant, the Drug. Goldenseal is a perennial herbaceous plant with a short horizontal rhizome bearing multiple slender roots. The stem is erect, and bears two or three palmatilobate leaves and a unique terminal, greenish-white flower. The plant grows wild in the eastern part of North America where it was formerly used by the Cherokee peoples.

The rhizome has an unpleasant odor and a bitter taste. It is gnarly, wrinkled in all possible directions, covered with scars where the aerial stems have fallen off, and bears tangled roots, which are generally all on the same side of the main axis. The center part of the cut is bright yellow to greenish-yellow, and it looks waxy. All of the parenchymas are full of starch grains, which are clearly visible in the powder.

Composition and Tests. The chief components of the drug are isoquinolines: hydrastine (a phthalyltetrahydroisoquinoline) and berberine, a bright yellow quaternary ammonium protoberberine.

Part of the assay is a TLC characterization of the alkaloids extracted by simple contact with 60% ethanol. The plate is examined in the daylight (berberine), under UV (fluorescence), then visualized by potassium iodobismuthate. The quantitation of hydrastine begins with an alkaline extraction of the alkaloids with petroleum ether, a solvent that does not dissolve berberine. Next the solvent is evaporated, the residue redissolved in dilute hydrochloric acid, and the concentration of hydrastine estimated by dual absorbance measurements (at 295 and 313 nm) relative to a reference standard solution.

Pharmacological Activity and Uses. Berberine is a bacteriostatic at low doses and a bactericide at higher doses. *In vitro*, it is active against many germs (staphylococcus, streptococcus, but also salmonella, proteus, vibrio, and more). It is also a fungicide, and is toxic for various protozoa (leishmania, *Plasmodium*). It decreases intestinal peristalsis.

Hydrastinine chloride (the iminium ion which results from the cleavage with HNO_3 of the C-1–C-α– bond) is combined with synephrine and chlorhexidine in eye drops used to treat conjunctival hyperthermia of allergic or seasonal origin, and eye strain due to environmental irritations.

In the absence of clinical data, vasoconstricting and hemostatic properties are traditionally attributed to goldenseal. Its galenicals (tincture, extracts) are still used in some proprietary drugs in combination with other plants thought to be vascular protective agents (witch hazel, cypress, black haw). These pharmaceuticals are used in the symptomatic treatment of venous and lymphatic vessel insufficiency. In North America, goldenseal root infusions enjoy a solid reputation for (undemonstrated) efficacy in the treatment of disorders of the mouth, including ulcerations (analgesic and healing mouthwashes).

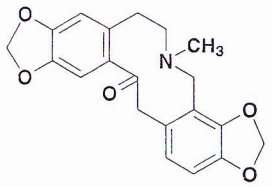
• FUMITORY, *Fumaria officinalis* L., Fumariaceae *

Known to the physicians of antiquity, fumitory is, according to folk medicine, a biliary stimulant, known as the "jaundice herb".

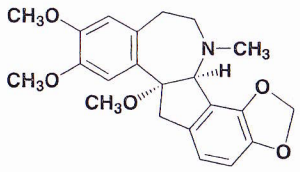
The Plant, the Drug. Official fumitory and the closely related species, are perennial herbaceous plants with bi- or tripinnatisect bluish-green leaves. The irregular flowers have an upper petal prolonged by a spur. The fruit is an indehiscent silicle. The latest mention of this drug in the French Pharmacopoeia (revised drug table in the 10th Ed.) indicates that the drug consists of the flowering plant: *F. officinalis* and closely related species. The identification of these species which tend to invade cultivated ground is difficult; the species *officinalis* is in fact divided into two subspecies distinguishable by the number of flowers in the inflorescence and the size of the sepals (ssp. *officinalis* Sell and ssp. *wirtgenii* [Koch] Arcangeli).

* Or is it Papaveraceae? Opinions differ. De Candolle, and, more recently, Hutchinson, Cronquist, and Takhtajan refer to a Fumariaceae; Emberger, Fedde, and Tutin *et al.* (i.e. Flora Europaea) consider that the Fumarioideae are a subfamily of the Papaveraceae.

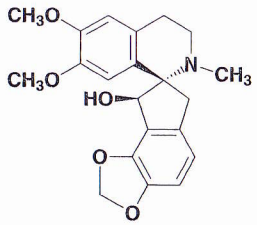
Chemical Composition. Fumitory is mostly known for its alkaloids (0.3%): about one hundred compounds have been described in the various species in the genus that have been studied. The principal alkaloid of *F. officinalis* is protopine together with spiro-benzyltetrahydroisoquinolines (fumaricine, fumariline) and protoberberines and indenobenzazepines such as fumaritrine or fumarofine. Malates of hydroxycinnamic acids (caffeic acid, ferulic acid) are also found, with the caffeic derivative in appreciable quantity (1.2%) only if the drug has been carefully dried or lyophilized.



Protopine



Fumaritrine



Fumaricine

Pharmacological Activity. Several workers have attempted to verify the reputation of fumitory: apparently the nebulisate is an "amphocholeretic", in other words it normalizes the biliary flow. It is also a spasmolytic, active, for example, on Oddi's sphincter.

The pharmacology of protopine is better known: it is a spasmolytic, an anticholinergic, an antiarrhythmic and an antibacterial, and it increases the binding of gamma-aminobutyric acid to its central receptors. Do the malic esters contribute to the activity attributed to fumitory?

Uses. In the absence of valid clinical trials (besides, how would one evaluate the improvement of gastrointestinal symptoms that are not well defined and often of psychosomatic origin?), fumitory-based phytomedicines are traditionally used in France to enhance urinary and digestive elimination functions, and as a choleretic and cholagogue (orally [French Expl. Note, 1998]). The German Commission E monograph states that the moderate spasmolytic effect of the drug on the upper digestive tract is sufficiently well established; therefore the drug (DAB 10) is used for constipation and spastic biliary pain (package insert indications).

• (GREATER) CELANDINE, *Chelidonium majus* L., Papaveraceae

A perennial herb growing wild on old walls, in piles of rubble, and in ditches, celandine is characterized by a thick stump, limp leaves which are bluish-green on the lower side and deeply divided, by flowers with four yellow petals, and by glabrous and bumpy siliques. When damaged, the plant tissues produce an orange colored caustic latex.

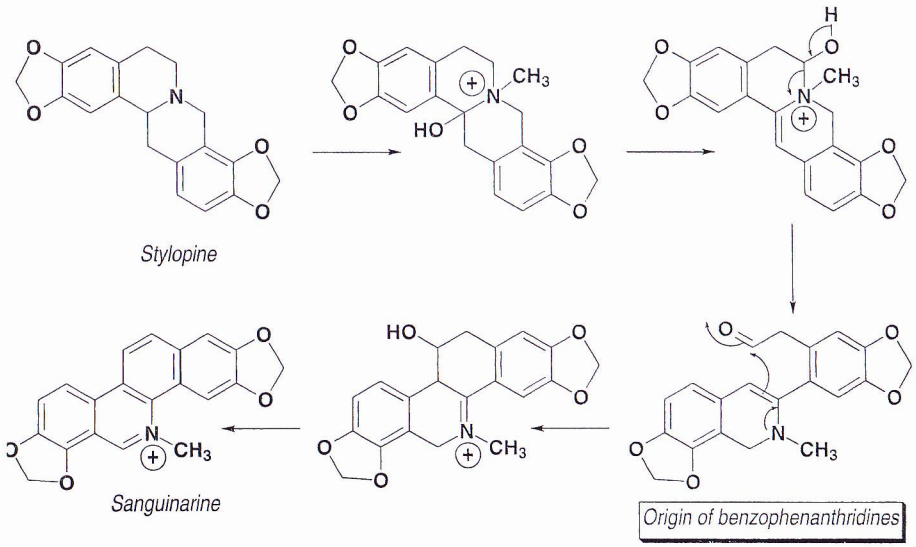
The whole plant contains about thirty alkaloids (mostly concentrated in the subterranean parts: up to 2%). The chief alkaloids are benzophenanthridines (chelidonine, chelerythrine, sanguinarine). These occur alongside protopines, protoberberines (berberine, coptisine, stylopine), and magnoflorine (five of these seven alkaloids are quaternary ammonium salts and extracts contain mostly coptisine). The other alkaloids are found only in small quantities. Like fumitory, the drug contains esters of hydroxycinnamic and other hydroxyacids (malic, threonic, and glyceric acids).

In folk medicine, celandine latex is a remedy for warts. The extract is an antibacterial and antiviral agent. The benzophenanthridines are cytotoxic. The drug—which some think is toxic—is apparently no longer used in allopathy, except for one cholagogue and choleretic solution in which are combined about ten plant tinctures.

Celandine is not listed in Annex I of the 1998 French Explanatory Note. In Germany, it is official (DAB 10) and it is the subject of a Commission E monograph. In it, celandine is described as a mild spasmolytic for the upper digestive tract, with an effect similar to that of papaverine. The plant is used for cramp-type gastrointestinal and biliary disorders.

• BLOODROOT, *Sanguinaria canadensis* L., Papaveraceae

Bloodroot is a perennial herb producing a red latex, common in North America, from Florida to Quebec and to the Mississippi. The alkaloids, which occur in all of



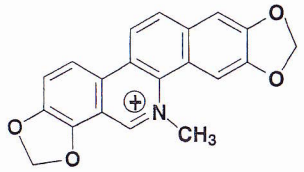
Stylopine

Sanguinarine

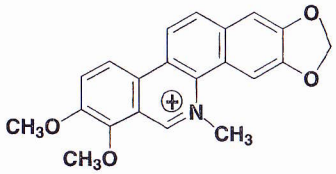
Origin of benzophenanthridines

* Celandine is thought to be hepatotoxic. See: Greving, I., Meister, V., Monnerjahn, C., Müller, K.M. and May, B. (1998). *Chelidonium majus*: a Rare Reason for Severe Hepatotoxic Reaction, *Pharmacoepidemiol. Drug Safety*, **7**, S66-S69. See also: Strahl *et al.*, 1998, *Dtsch. Med. Wschr.*. **123**. 1410-1414.

the parts of the plant, are mostly concentrated in the rhizome (4-7%). The chief constituent (50%) is a benzophenanthridine, namely sanguinarine which occurs alongside other derivatives of the same type: chelerythrine (25%), sanguilutine,



Sanguinarine



Chelerythrine

sanguirubine, chelirubine, chelilutine, and other isoquinoline alkaloids.

Sanguinarine has antimicrobial, antifungal, and anti-inflammatory (edema of the rat's foot) properties. It inhibits the Na/K-dependent ATPase, has a positive inotropic action, and interacts with nucleic acids. Sanguinarine chloride is used in mouthwashes and toothpastes, especially in the United States: by binding selectively to dental plaque, it inhibits 98% of bacteria at concentrations ranging from 1 to 16 ug/mL (an activity comparable to that of chlorhexidine).

Toxicity of Sanguinarine. Several studies attribute epidemics of chronic wide angle glaucoma associated with dropsy, which were recorded in India in the past, to the contamination of edible oils by the oil of *Argemone*, a Papaveraceae rich in sanguinarine. Subsequently, however, other authors questioned these conclusions. In addition, it was shown that the LD50 of sanguinarine chloride in rats was 1.66 g/kg (*per os*); a daily dose of 0.6 mg/kg of sanguinarine for 30 days does not seem to affect rats. The intravenous toxicity is far greater (29 mg/kg).

• California Poppy, *Eschscholtzia californica* Cham., Papaveraceae

The dried flowering aerial parts of the plant constitute the drug (Fr. Ph., 10th Ed.).

The Plant. California poppy, a small plant which brightens many a European garden with its orange corollas, originated in California where it colonizes vast expanses, from coastal dunes to plains to arid valleys. This is an annual plant, characterized by bluish-green leaves deeply divided into linear segments and by flowers with four deciduous petals which close up at dusk. Numerous stamens surround a unilocular ovary which turns into a linear capsule, which opens by two valves.

Chemical Composition. The composition of the drug is fairly well known, at least as far as the alkaloids are concerned. Besides the pavines, which predominate and are characteristic of the genus (eschscholtzine, californidine), protopine and

(sanguinarines, chelerythrine) occur only in traces in the leaves and stems, but they are, with allocryptopine and protopine, the chief alkaloids in the roots (in which the concentration of total alkaloids is far greater than in the stems [>2.5%]). The drug is identified by TLC analysis of its total alkaloids, by its macroscopic characteristics, and by the microscopic examination of its powder. It must contain not less than 0.5% total alkaloids (expressed as californidine): the alkaloids are extracted in methanol, isolated as iodomercurates in the presence of hydrochloric acid, and titrated by acidimetry in a non-aqueous solvent after decomposition of the complex on ion exchange silica gel.

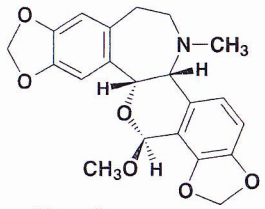
Pharmacological Activity. There have been few studies of the pharmacology of the drug: the tincture prolongs the duration of induced sleep in mice and reduces their motor activity (IP). *In vitro*, it is a spasmolytic. More recent studies confirm the sedative activity and emphasize the anxiolytic effect of the aqueous extract (sleep induction, relief in conflict situations). To what extent are these properties due to the alkaloids? The properties of compounds such as protopine are partially known (see fumitory), but nothing is known of the properties of pavine and... alkaloids are not the only compounds in the drug! In the absence of clinical trials, a review of the literature provides consistent observations in humans: preparations based on *Eschscholtzia* (e.g., nebulisate) accelerate the onset of sleep and improve sleep quality.

Uses. The phytopharmaceuticals containing California poppy may claim the following indication: traditionally used in the symptomatic treatment of neurotonic disorders in adults and children, especially for minor sleeplessness [French Expl. Note, 1998]. Manufacturers are required to propose a concentration limit for the active constituent. Phytotherapists frequently use this drug in combinations (with passion flower, olive tree, valerian).

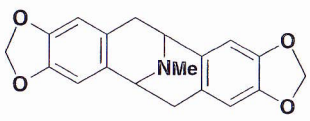
• Corn Poppy, *Papaver rhœas* L., Papaveraceae

The petals of this small herbaceous plant common along country roads and on neglected lands all over Europe enjoy a reputation as mild sedative and antitussive. They are known to contain anthocyanins and a small amount of alkaloids (0.07%) of the same type as those occurring in the remainder of the plant: the chief alkaloid is a tetrahydrobenzazepine, namely rhœadine. The pharmacology of this alkaloid has not been studied, but closely related derivatives are dopaminergic antagonists and neuroleptics. Officially, corn poppy petals may be "traditionally" used in: 1. the treatment of cardiac rhythm abnormalities in adults (normal heart); 2. the symptomatic treatment of neurotonic disorders in adults and children, especially for minor sleeplessness; 3. the symptomatic treatment of cough [French Expl. Note, 1998]. They are an ingredient of cough teas (and of compound ipecac syrup). The

efficacy has not been demonstrated, its therapeutic use is not recommended (it is an acceptable additive to herbal teas).



Rhoeadine



Eschscholtzine

3. OTHER DRUGS CONTAINING ISOQUINOLINE ALKALOIDS

• CALUMBA ROOT, *Jateorhiza palmata* Miers, Menispermaceae

The roots of this climbing herbaceous plant from the eastern coast of Africa were formerly the subject of a monograph in the French Pharmacopoeia. The drug contains 2-3% total alkaloids, chiefly protoberberines (palmatine, jatrorrhizine, columbamine), as well as furanoditerpenoid lactones which impart to it a very bitter taste (columbin, isocolumbin, palmarin, chasmanthin, jateorin, and more). The drug was formerly used as a bitter tonic.

• CHINESE PHARMACOPOEIAL DRUGS *

Several drugs in the traditional Chinese Pharmacopoeia are believed to have properties attributable to isoquinoline alkaloids. This is the case in particular for drugs containing protoberberines:

Coptis sinensis Franchet and other *Coptis* species (Ranunculaceae). Also known as *huanglian*, the drug consists of the rhizome, which contains 5-8% berberine occurring alongside coptisine, palmatine, columbamine, and jatrorrhizine. The drug is used crude and as a source of berberine. According to some workers, the antibacterial properties of berberine justify the use of the drug in the treatment of bacillary dysentery and of various bacterial infections. However, controlled clinical

* The interested reader can find a complete study of the species mentioned here in: Chang, H.-M. and But, P.P.-H. (editors) (1986). Pharmacology and Applications of Chinese Materia Medica, vol. **1** and **2**, World Scientific, Singapore (in English, but with most references from reviews in Chinese). See also a very comprehensive and recent publication on the chemistry and pharmacology of the major drugs of the Chinese pharmacopoeia: Tang, W. and Eisenbrand, G. (1992). Chinese Drugs of Plant Origin - Chemistry, Pharmacology, and Use in Traditional and Modern Medicine, Springer-Verlag, Berlin.

trials have failed to confirm the usefulness of berberine salts in the treatment o diarrhea of various etiologies.

Berberis soulieana Schneider, *B. wilsonae* Hemsley and other species. The root of these Berberidaceae (*sankezhen, cihuanglian*) have marked antibacterial an antifungal properties which, according to some authors, have been confirmed i humans (dysentery, gynecological infections). The principal species of interes contain chiefly berberine (0.5 to 6%) and other protoberberines (palmatine jatrorrhizine), as well as bisbenzyltetrahydroisoquinolines (berbamine oxyacanthine, isotetrandrine). Palmatine is a potent antifungal. The drug als possesses hypotensive properties due to the different alkaloids, particularl berbamine.

Corydalis turtschaninovii Bess., f. *yanhusuo* Y.H. Chou and C.C. Hsü. Thi Fumariaceae and other species in the genus are used in the treatment of pain c various origins (neuralgia, dysmenorrhea, headaches). The analgesic activity of th tubercle (*yanhusuo*) is chiefly linked to a tetrahydroprotoberberine, namel tetrahydropalmatine. This alkaloid is a sedative, hypnotic, and tranquilizer. Lik several other representatives from the group of tetrahydrogenated protoberberines it is thought to act by blocking post-synaptic dopaminergic receptors. It can b extracted from other, more accessible sources, particularly various species Stephania (e.g., *S. sinica* Diels, Menispermaceae).

Menispermum dauricum DC., (Menispermaceae). The drug (*beiduogen*), well as the total alkaloids that can be extracted from it (*beiduogen pian*), a considered analgesics and antipyretics. The drug contains bisbenzyltetrahydr isoquinolines: dauricine (chief constituent), daurisoline, and dauricinoline, as w as aporphines and isoaporphines. The effects of dauricine are close to those tetrandrine (hypotensive, antiarrhythmic).

Stephania tetrandra S. Moore (*hanfangji, fangji*, Menispermaceae). Traditi nally used as an antirheumatic, analgesic, and anti-inflammatory, as well as to tr hypertension, this drug, which consists of the dried root, is known to contain seve bisbenzyltetrahydroisoquinoline alkaloids, including tetrandrine (0.7-1.3% fangchinoline, oxofangchirine, cyclanoline, and demethyltetrandrine. Tetrandrine a calcium antagonist: it decreases the contractility of the myocardium, rela

* These properties have been described and studied by several authors. They can be correla with the use, in Vietnam, of the roots of *Stephania rotunda* Lour. as a sedative. Note tha Vietnam, various *Coptis, Berberis*, and *Thalictrum* are used to treat dysentery and ot intestinal infections; they all contain berberine. See Khuong-Huu, Q. (1986). The Importa of Medicinal Plants in Vietnam, *in* "Advances in Medicinal Phytochemistry", (Barton, D. Ollis, W.D., editors), John Libbey Ltd., London. See also: Dung, N.-X. and Loi, D.-T. (19 Selection of Traditional Medicines for Study, *J. Ethnopharmacol.*, **32**, 57-70 which mentions, for the same indications, a berberine-containing *Fibraurea* (Menispermaceae).

arterial muscle fibers, and counteracts their contraction. It is a hypotensive agent and a coronary vasodilator. Its quaternary derivatives are used in anesthesiology: dimethyltetrandrine iodide is a non-depolarizing neuromuscular blocking agent, and is used as a muscle relaxant in combination with different techniques in anesthesia (including acupuncture).

S. tetrandra was distributed in France and Belgium in the late 1980s. It was an ingredient of weight loss preparations. The use of these products resulted in several dozen case reports of impaired renal function due to tubulo-interstitial nephropathy. Some of the female patients had to undergo a kidney transplant and recently, hyperplasia was observed, which subsequently became disseminated and evolved toward urothelial malignancy. The origin of this serious intoxication seems to be an adulterant of *fangji* (i.e., *S. tetrandra*), namely the root of another species used in China (*Aristolochia fangchi* Y.C.Wu & L.D. Chou ex S.M. Wang), known to contain aristolochic acids. These phenanthrenic acids are nephrotoxic and carcinogenic in rodents, therefore they are highly likely to have caused the reported intoxications (their DNA adducts were detected in the kidney tissue of five patients). However, the large difference in frequency of cases of renal insufficiency observed in Belgium and France has led the authors of a large epidemiologic study published in 1998 to propose the hypothesis of a third, unknown factor. Sales of *S. tetrandra* and *A. fangchi* are permanently prohibited in France (decree 98-397 of May 20, 1998).

Stephania cepharantha Hayata. The tubercles of this species contain aporphines and dimeric alkaloids: isotetrandrine, berbamine, and cepharanthine. The latter is an inhibitor of platelet aggregation; it decreases the leukopenia due to the use of antitumor agents and counteracts the development of experimental silicosis.

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Stephania - Aristolochia

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FUMARIA OFFICINALIS L.

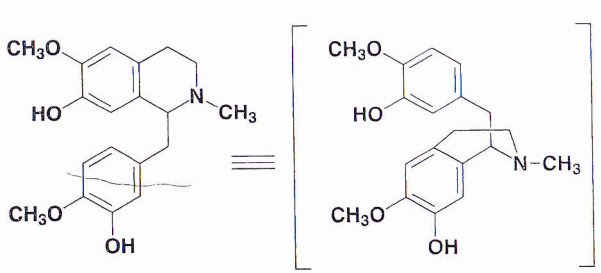
VI. Morphinanes

1. INTRODUCTION: BIOSYNTHETIC ORIGIN

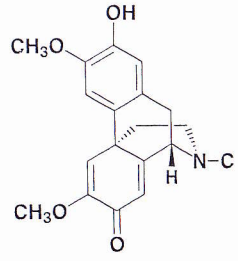
In contrast to isoquinoline alkaloids, which occur particularly frequently in th Papaveraceae (*Argemone, Bocconia, Chelidonium, Eschscholtzia, Glaucium Meconopsis, Papaver, Roemeria*, and more), morphinan alkaloids are specific t *Papaver*: we must emphasize, however, that out of more than one hundred speci in this genus of complex taxonomy, only about ten biosynthesize thebain (*P. bracteatum* Lindl., *P. orientale* L., and others), and that morphine is on elaborated by *P. somniferum* and *P. setigerum* DC. (or ssp. *setigerum*!); see below.

Structurally, we can distinguish true morphinan alkaloids, which are alkaloi specific to *Papaver*, and morphinandienones, which are a little more common and a distributed less specifically, although not widely (Papaveraceae, Menispermacea Lauraceae, Euphorbiaceae).

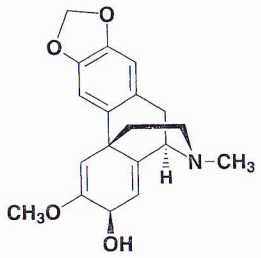
Scrutinizing the structure of these compounds shows that they are indeed benzy tetrahydroisoquinolines: in the figure p. 927, we can see that their biogenetic precurs



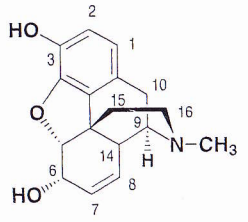
Reticuline



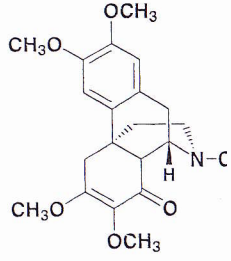
(–)-Pallidine



Nudaurine



Morphine



Erromangine

Human interest in the opium poppy dates back more than 4,500 years. There is proof that the capsules were exploited in Europe (Switzerland, Germany, Jura mountains between France and Switzerland, south of Spain) during the recent neolithic era: they were probably used for the dietary value of the seeds that they contain. A little later, the opium poppy surfaced in the eastern part of the Mediterranean area (Crete) where it was used (from 1,600 to 1,400 B.C.) for different purposes, probably religious, and perhaps medicinal, as suggested by a statuette from the ancient Mycenaean era in which incised poppy capsules appear. The opium poppy continued to spread eastward, among other reasons because it was transported * in capsule-shaped vases to Cyprus and Egypt. Jewelry, pins, and other objects, as well as the decoration of tombs and various monuments might be a testimony ** of its use in Egypt beginning during the eighteenth dynasty (from 1,500 B.C. on). Objects of the same type and dating from the same period have also been found in Anatolia. Opium (lion's grease) and the opium poppy (the plant of joy) are thought to have been known to the Assyrians as well. Closer to us, Greek physicians used it for pain relief, and Dioscorides distinguished opium, the latex from the capsule, from the meconium, obtained by infusion of the cut plant. An ingredient of Galen's theriaca, which was to remain in use for centuries, it became, during the seventeenth century, the active principle of Sydenham's laudanum (opium tincture with saffron) which was the most commonly used anesthetic, until the use of morphine hydrochloride became generalized. Introduced early on in the Orient by the Arabs, opium was known and used for several centuries for its medicinal virtues, and the smoking habit did not appear until the end of the seventeenth century: we know how the incredibly rapid development of trafficking, organized by the British, led to the first "opium war" (1839-1842), the first of a series of events which coerced China to open up to western nations. On the other hand, the western world remained untouched by opium addiction until the end of the eighteenth century: at that time, opium was eaten or smoked, until restrictive regulations were put in place (France: 1908; first international convention: The Hague, 1912). Morphine addiction was a fad at the end of the nineteenth century and has since then been replaced by a practice which is often fatal, and is still expanding in France and Europe, namely heroin addiction.

The licit production of opium *, restricted to seven countries since the 1950s, is now strictly limited to India, and the worldwide needs of the pharmaceutical industry for alkaloids are fulfilled to a larger and larger extent by direct extraction from opium poppy straw. The major part of the morphine produced industrially is converted, mostly into codeine. Morphine consumption remains low, although it is slightly on the rise as the use of oral forms is becoming more generalized.

* As opium? This hypothesis dates from the beginning of the twentieth century. Its weakness is that the results of some of the analyses leave a doubt (no alkaloid analysis). On the other hand, different authors reported the presence of morphine in Egyptian alabaster vases found in a tomb of the eighteenth dynasty. Actually, it is unlikely that *P. somniferum* was known at that time in Egypt. Finally, a thorough study using the most modern methods (GC, GC-MS, *radioimmunoassay* = RIA, TLC) and published by N.G. Bisset in early 1994 failed to characterize morphine in this type of vase, and again raised serious doubts about the original hypothesis. Although a negative analysis does not prove that these vases never did contain opium, Bisset and co-workers did shed some light on the history of the opium poppy in the eastern part of the Mediterranean area. See: Bisset, N.G., Bruhn, J.G., Curto, S., Holmstedt, B., Nyman, U. and Zenk, M.H. (1994). Was Opium Known in 18th Dynasty Ancient Egypt? An Examination of Materials from the Tomb of the Chief Royal Architect Kha, *J. Ethnopharmacol.*, **41**, 99-114.

** The publication by Bisset *et al.* points out that "stylization makes the identification questionable in some cases [...] and that [...] many pictures in tombs bear some similarity to *P. rhœas* and are accepted as representing that species."

• Opium Poppy, *Papaver somniferum* L., Papaveraceae

A. The Plant

The opium poppy is an annual plant with an erect stem, about 1 to 1.5 m in height, with alternate, amplexicaul, glabrous leaves most often bluish-green, pinnatisect at the base and dentate near the apex. The flower is solitary and actinomorphic: its calyx comprises two sepals that fall when the four petals of the corolla open. The flower is white, red, or purplish depending on the cultivar, includes numerous stamens with black anthers, and a superior unilocular ovary resulting from the fusion of the 8-12 carpels. This ovary, divided by incomplete placentas and surmounted by a flattened disc formed by the stigmas, turns into an ovoid or spherical capsule, sometimes indehiscent, containing a multitude of tiny seeds. After incision, all of the parts of the plant exude a white latex.

The taxonomy of the genus is complex, since approximately one hundred species fall into 9 or 12 sections, according to different workers. Initially classified in the section *Mecones* Bernh., *P. somniferum* L. and *P. setigerum* DC. are now isolated in a section *Papaver* characterized by the occurrence of alkaloids related to the morphinan skeleton. Are these two different species? Expert opinions differ: considering the large number of publications about the genus *Papaver*, it appears that while many authors refer to two species, others consider *P. setigerum* a subspecies of *P. somniferum*: *P. somniferum* ssp. *setigerum* (DC.) Corb. In the opinion of some

* The illicit poppy cultures that supply the worldwide heroin market are chiefly located in the "golden crescent" (Pakistan, Afghanistan, Iran) and in the "golden triangle", at the edge of Thailand, Burma, and Laos. In 1994, Afghanistan is believed to have produced 3,200 to 3,300 t of opium. The Burmese production was estimated at 2,575 t in 1993. Pakistan, the second world producer of heroin, exports from 30 to 40 t per year of this alkaloid. Furthermore, some think that part of the Indian production finds its way to the black market. Apparently, countries such as Colombia, which is deeply involved in the production of cocaine, now cultivate opium poppy on a large scale (20,000 hectares) with low yield (120-160 t of opium). Figures and data from: Observatoire géopolitique des drogues (1995). Géopolitique des drogues 1995, La Découverte, Paris.

authors—and according to the Flora Europæa—there are three subspecies of *P. somniferum*: two cultivated (ssp. *somniferum* and ssp. *songaricum* Basil) and one wild: ssp. *setigerum* (DC.) Corb. with a smaller capsule. Without going into further detail, we shall emphasize that experts are also divided on the origin of *P. somniferum*, with most of them agreeing to consider ssp. (or species!) *setigerum* the ancestral form.

Are varieties the correct concept? Because humans have cultivated poppy since ancient times, the morphological variability is substantial (color of the flowers and seeds, dehiscence). Several classification systems have been proposed and the proliferation of cultivars arising from the optimization attempts of the last thirty years do not make the task any easier.

In the 3rd edition of the European Pharmacopoeia, all references to the concept of variety have been deleted * (this was not the case in the previous edition).

For the sake of example, we shall list here the distinctions found in classic pharmacognosy texts **:

- the poppy with white flowers and seeds is cultivated in India. The capsules are ovoid and devoid of pores. This variety is traditionally referred to as *album*;
- the black poppy is traditionally cultivated in Europe for the seeds. The flowers are purplish, and the "maw seeds" are slate gray. The capsule is more globular than that of the white poppy, and its dehiscence involves pores that are under the stigmas. This variety is known as *nigrum*;
- the Asia Minor poppy has purple flowers, and a wide (10-12 cm) globular capsule. The seeds are purplish-black. This variety is known as *glabrum*.

B. Production

Cultivation of the Opium Poppy. The classic distinction is between cultivation for the production of opium in India, and cultivation for the production of the straw for extraction, chiefly in temperate climates.

Opium Production. In northern India (Rajasthan, Madhya Pradesh, Uttar Pradesh), poppy seeds are sown at the end of the fall. After sprouting, the plants are thinned. The floration occurs in April-May and the capsules, six to eight per plant, appear in May-June. Upon ripening they change color: they are bluish-green at first, then turn yellow. At this stage, before the capsules dry, latex collection takes place. The capsules are incised with great caution, one by one: the unique incision

* Things are far from simple: a fairly old study on 1,600 specimens revealed a wide range of variability of the morphological characteristics and led the author to distinguish seven subspecies and 36 varieties; according to other botanists, "convarieties" must be distinguished and subdivided into varieties. Yet other authors feel that "from a botanical point of view, it is impossible to distinguish actual varieties".

** Paris, R.-R. and Moyse, H. (1976). Précis de Matière Médicale, **2**, (2nd Ed.), p. 186, Masson, Paris; Evans, W.C. (1996). Trease and Evans' Pharmacognosy, 14th Ed., p. 367, Saunders, London

or the multiple incisions must be deep enough to cut into the laticiferous ducts, without cutting into the endocarp, otherwise the latex flows inside the capsule and is lost. White latex flows out and rapidly turns brown. The morning after the incision, the latex exudate is collected by scraping, agglomerated, and air dried. After several days of drying, the residual water is on the order of 10%; finally the product is shaped into cakes of about 5 kg. According to the French *Observatoire géopolitique des drogues*, the (illicit) Afghan cultures yield 40 kg/ha of wet opium (30 kg dried) on the best lands, and reach 65 kg/ha (wet) in areas where the land is irrigated.

Straw Production. Poppy has been cultivated since ancient times in Europe, primarily for the purpose of producing seeds as a source of unsaturated oil. The advent of procedures for the direct extraction of alkaloids from the capsules with an acceptable yield, the development of varieties optimized for alkaloid production, and the improvement of cultivation practices have allowed the notion of producing the alkaloids without going through the opium step.

There are two options for the harvest: either at complete maturity, when the leaves are dry and the seeds rich in oil, in which case "straw" is obtained, or before maturity, about three weeks before the floration, in which case "green poppy" is obtained, rich in alkaloids, but needing to be dehydrated rapidly.

In the specific case of the French production, the optimization of poppies designed to produce straw for extraction has multiplied their alkaloid concentration by a factor of four in thirty years. Initially, the capsules were harvested at a stage of maturity that required drying in alfalfa dryers, which consume a lot of energy. Today, for more than half of the total production, the capsules are harvested ripe or almost ripe, when they can be dried by simple ventilation. In 1995, 4,866 ha were exploited and 41.1 t of morphine equivalent were produced [Source: OICS].

Quantitative Data. The licit world production of opiates has increased for the past ten years or so, and should reach the equivalent of 330 t of morphine in 1997. The prediction is that it will increase for a few more years to meet the demand and fulfill the need to have a sufficient stock (in 1996, consumption was about 240 t and was expected to exceed production by 14.5 t) [Source: OICS, 1996 report]. Indian opium exports are decreasing regularly (49 t of morphine equivalent in 1995) whereas the world exports of poppy straw concentrate are increasing: 118 t of morphine equivalent in 1995, with 57% of these exports coming from Turkey, where 60,000 ha are devoted to poppy. In the same year, France exported 9.5 t of concentrate, far behind Australian exports (29 t).

C. Characteristics of the Drugs

• **Opium** is a paste of pungent and bitter taste, characteristic odor, and variable consistency. The microscopic examination of a dried sample, pulverized and suspended in a potassium hydroxide solution, shows latex granules agglomerated into irregular masses and elongated filaments. There are also fragments of epicarp, pieces of vessels, refringent crystals, and some starch grains.

• The **capsules** vary in shape and dimensions: spherical or ovoid, taller than wide or wider than tall, dehiscent or not, they are yellowish and odorless. Under the microscope, note the presence, in the phloem, of valvar lignified phloem bundles and multiple laticiferous ducts anastomosed into bundles.

• The **seeds** are tiny (their weight does not exceed 2 x 10-4 g) and their reticulated tegument varies in color from yellowish white to purplish black*.

D. Opium

Chemical Composition. Opium can contain between 10 and 15% water; sugars are abundant (20%) as well as organic acids: lactic, fumaric, and oxaloacetic acid, and most of all meconic acid (over 5%). The latter, a dicarboxylic pyrone, only occurs in a limited number of poppies and can be used as an identification marker. The active principles are represented by 10 to 20% alkaloids.

Morphinan Alkaloids

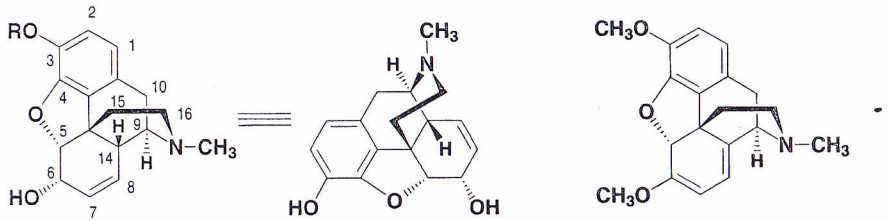
Morphine, the major alkaloid of the morphinan group, is also the most abundant alkaloid in opium (10-12%). It is a pentacyclic molecule with five asymmetric centers: only the naturally occurring enantiomer (levorotatory, 5*R*,6*S*,9*R*,13*S*,14*R*) is active. The presence of a phenolic hydroxyl group (at C-3) imparts to this alkaloid specific solubilities: solubility in alkali metal hydroxide or alkaline-earth metal hydroxide solutions due to the formation of morphinates, and classic solubility of alkaloids (although morphine as a free base is sparingly soluble in ether). The phenol function is responsible for the reducing properties of the molecule, which can be characterized in the presence of ferric salts.

The phenol group at C-3 and the hydroxyl group at C-6 can be etherified or esterified: besides the naturally-occurring derivatives like codeine or thebaine,

* Poppy seeds, whole or crushed, are used in central Europe and in the United States, in breads and cakes. Poppy seeds contain variable (but low) quantities of alkaloids: morphine (4-250 mg/kg) and codeine (0.4-60 mg/kg), in large part from contamination by the latex. Experience shows that seed ingestion, under normal conditions—rare cases of abuse are known—does not cause any of the symptoms that characterize the administration of opiates. On the other hand, urine tests for opiates can be positive and can be misinterpreted. Conversely, in American drug testing programs, individuals with a urine test positive for opiates sometimes use the "poppy seed defense", i.e., they claim to have consumed poppy seeds and not abused opiates. In fact, measuring levels and characterizing metabolites make it possible to resolve most cases unambiguously. See, among other, Meneely, K.D. (1992). Poppy Seed Ingestion: the Oregon Perspective, *J. Forensic Sci.*, **37**, 1158-1162 ; Pelders, M.G. and Ros, J.J.W. (1996). Poppy Seeds: Differences in Morphine and Codeine Content and Variation in Inter- and Intra-Individual Excretion, *J. Forensic. Sci.*, **41**, 209-212.

The oil concentration in the seeds can reach 40%, with linoleic acid as the chief constituent (70%). The ethyl esters of the fatty acids of poppy seed oil are used as a radiopaque material (lymphography, fistulography, sialography).

semisynthetic derivatives can be prepared (see below); note, however, that the esterification or etherification of the hydroxyl group at C-3 decreases the analgesic activity. In terms of structure-activity relationships, note that the inversion of configuration at C-9 and C-13 makes the activity disappear, but that neither the alcohol function at C-6 nor the 7(8) unsaturation are strictly required. Substituents on the nitrogen atom are crucial: the replacement of the methyl group by small alkyl radicals (allyl, cyclopropylmethyl, cyclobutylmethyl) transforms the compound into a complete or partial opioid antagonist. One means of increasing the analgesic activity is to introduce a hydroxyl group at C-14.



R = H : *Morphine*
R = CH_3 : *Codeine*

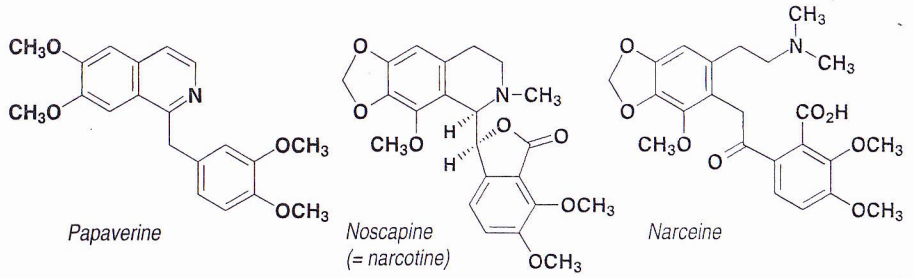
Thebaine

The other morphinan alkaloids occur in opium in variable quantities, and include codeine (2.5-5%), the 3-methyl ether of morphine, thebaine (less than 1%), the methyl enol ether of codeinone, neopine, codeinone, and oripavine. Thebaine is of interest for synthesis: the two 6(7) and 8(14) unsaturations allow the formation of Diels-Alder adducts, which are complex and rigid structures with potent activities, either as agonists (etorphine) or antagonists (buprenorphine). It is also a starting material for the obtention of codeine and a possible starting material for the preparation of 14-hydroxymorphinan alkaloids.

Other Alkaloids

Another opium alkaloid which is important by weight is (–)-noscapine (= narcotine): its level ranges from 2 to 10%. This compound is a very weak base, its salts are sparingly soluble, and because of the lactone in its structure, it is vulnerable to alkaline pHs. Other derivatives in the same group, which are phthalyltetrahydroisoquinolines, occur in smaller quantities (narcotoline); they occur alongside secophthalylisoquinolines: narceine, nornarceine, and narceinimide.

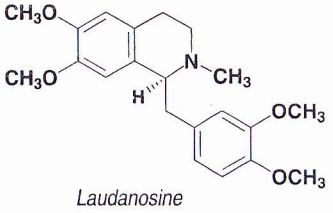
Also found in opium are benzyltetrahydroisoquinolines (laudanine, laudanosine, laudanidine, codamine, reticulines) and an isoquinoline derivative, namely papaverine (average concentration: 0.5-1.5%). *P. somniferum* also elaborates compounds with other structural types: aporphines (isoboldine, corytuberine), tetrahydroprotoberberines and protoberberines (coreximine, canadine, berberine, coptisine), benzophenanthridines (sanguinarine), protopines (protopine, cryptopine, allocryptopine), and morphinandienones [(–)-salutaridine].



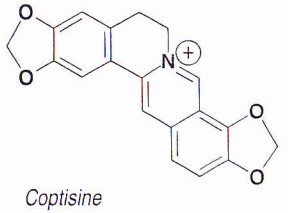
Papaverine

Noscapine (= narcotine)

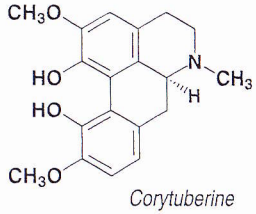
Narceine



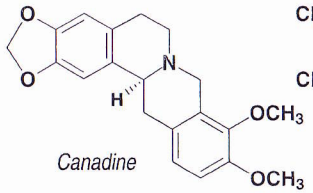
Laudanosine



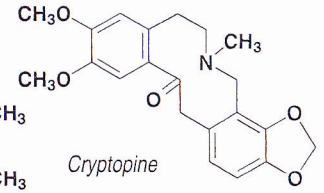
Coptisine



Corytuberine



Canadine



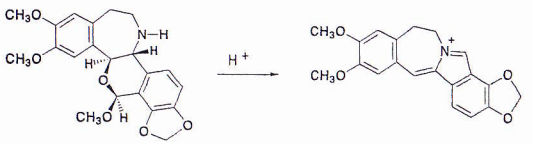
Cryptopine

Opium : occurence of other alkaloids

Tests. The identity of opium can be verified by directly adding ferric chloride to the aqueous extract: a red color develops (characteristic of meconic acid *). TLC analysis characterizes the principal alkaloids contained in a 70% ethanol extract (visualization with iodobismuthate).

The assay includes loss on drying (<15%) and total ash (<6%), as well as a quantitation by HPLC, which has replaced the acidimetry described in the older editions of the French Pharmacopoeia * (p. 936), which still appears with slight

* The older editions of the French Pharmacopoeia used to describe two characterization reactions: the first one, to be carried out after ether extraction of an acidified aqueous macerate, showed the presence of meconic acid; the second one, to be carried out after extracting the alkaloid in alkaline conditions, acidifying, and heating, showed the presence of porphyroxine: this alkaloid, now known as papaverrubine D, is converted in acidic conditions to a bright red quaternary isoindolebenzazepine (this is applicable to TLC)



variations in other pharmacopoeias. The solution to be examined is prepared as follows: alkaloid extraction by maceration in 50% ethanol and purification of the resulting extract by column chromatography on kieselguhr. The eluate, evaporated to dryness, is redissolved in the mobile phase, and an appropriate volume is injected on a column packed with functionalized silica gel. Thus, the concentrations of morphine and codeine are determined. Quantitating thebaine is also required (<3%).

Other methods. There are many other methods, and they are often complex. It is possible to titrate, in a non-aqueous solvent, the precipitate obtained by treating an aqueous morphine solution with 2,4-dinitrochlorobenzene. First the aqueous alkaloid solution must be purified (filtration on alumina, selective extraction of the non-phenolic alkaloids; see Helv. VII).

E. Pharmacological Activity

Morphine. Morphine exerts its effects by binding stereospecifically, reversibly, and with a very high affinity, to the specific receptors found mainly at various levels of the CNS. These effects are classically considered to include central and peripheral activities.

(1) CNS Activity

• ***Analgesic Effect***. Morphine induces a selective analgesia: it markedly depresses nociceptive perception, and raises the threshold of pain perception. The mind-altering activity of the alkaloid also contributes to the analgesic activity: it induces, in the patient, a certain indifference toward the pain.

The psychomotor activities of morphine vary depending on the animal species, and in humans, they depend on pre-existing pain. Thus, in a subject in pain,

* First, morphine is dissolved by treating the opium powder with limewash to displace the alkaloids from their salts and precipitate meconic acid. Morphine, which is a phenol, is solubilized as calcium morphinate. A small fraction of the other alkaloids is also dissolved.
The second step is the purification of the extracted morphine. To this end, ammonium chloride is added to one part of the calcium morphinate solution: the reaction between these two salts leads to the formation of calcium and ammonium chloride, which makes morphine precipitate. The morphine precipitate is recovered, washed with water saturated with both morphine free base and diethyl ether, and dried.
In a final step, morphine is dissolved in boiling methanol, and after dilution, titrated with hydrochloric acid in the presence of methyl red. Reference: supplement to the 9th edition of the French Pharmacopoeia published in 1977 (official publication of the French government or *J. O. Rép. fr.*, July 28, 1977) and erratum (supplement n° 21) of November 13, 1978.

This method closely resembles the one recommended by the British Pharmacopoeia (BP 1988), in which the quantitation is achieved by dissolving morphine in an excess of titrated sulfuric acid, and measuring the acid in excess by titration with a sodium hydroxide solution of known concentration.

sedation, indifference to physical or psychic sensations, and sometimes, a state of euphoria linked to a decrease in the affective reaction to pain are observed, whereas in a normal subject, the administration of morphine frequently causes more or less intense agitation, delirium, anxiety, and nausea, among others.

Morphine is a pure agonist which acts by mimicking the activity of endorphins on the presynaptic receptors of the myelinated fibers of small diameter that transmit nociceptive information: the result is an inhibition of the release of substance P, which is a pain neurotransmitter.

This mechanism of action also explains the dependence: morphine inhibits the production of enkephalins and the number of receptors increases as a result, hence the tolerance. During withdrawal, the receptors cannot be saturated by their natural ligands, and the withdrawal syndrome results as the clinical manifestation of the physical dependence.

• ***Respiratory Effects***. Morphine depresses the respiratory centers in the brain stem: the decrease in sensitivity of these centers to carbon dioxide and to hypoxia is proportional to the administered dose; with higher doses, substantial bradypnea and an irregular rhythm appear. The speed of onset of this depression is a function of the route of administration: very fast (5-7 minutes) by IV injection, most gradual by intrathecal injection (12-24 hours).

• ***Other Central Effects***. Morphine depresses the cough center. It causes myosis, at least in humans and in animal species that respond to narcotization. This myosis of central origin is an important sign of chronic intoxication *. A complex action on the vomit center most often results in vomiting. Note, finally, that morphine acts on the pituitary to decrease the secretion of FSH, LH, and ACTH.

• ***Dependence***. The psychoactive effects of morphine are substantial. The euphoria and the transient sensation of well-being or sleepiness explain the development of the psychic dependence (impulse to take the product in order to experience again this particular psychic climate) soon followed by tolerance (the requirement for increasing the doses and the frequency of administration in order to obtain the same effect). The abrupt discontinuation of administration causes, in the chronic user, a withdrawal (or abstinence) syndrome: rhinorrhea, sweating, lacrimation, then agitation, mydriasis, pain in the joints and in the muscles, together with anxiety and insomnia; later, tachycardia, polypnea, nausea, and diarrhea appear. This withdrawal syndrome justifies medical intervention and is most often compensated by seeking further alkaloid administration: this is physical dependence, which characterizes opiate intoxication (i.e., a state of adaptation characterized by the appearance of physical symptoms when the administration is discontinued abruptly [the dependent subject consumes more to avoid the discomfort of withdrawal]).

* Chronic intoxication is also characterized by psychic disturbances, constipation which is often long-term, frequent itching (compulsive scratching), and in intoxicated women, by amenorrhea.

(2) Peripheral Activity

Of note are the digestive effects: vomiting (not in all cases) and activity on smooth muscle fibers. This activity, in part of enkephalinergic origin, results from a decrease in tone of the longitudinal fibers and an increase in tone of the tissue and sphincter fibers. The result is lasting constipation, an effect for which little tolerance develops.

Note also that morphine induces urinary retention (again as a result of its action on smooth fibers and sphincters). It is antidiuretic, and also, at high doses, bradycardic, vasodilating, and hypotensive.

Codeine. Codeine has an antitussive activity, demonstrated in healthy subjects by using cough-inducing aerosols (minimum dose 15 to 20 mg/single dose). This activity is accompanied by a slight depression of the respiratory centers, a slight bronchoconstriction due to a direct effect on smooth muscles, a decrease in secretions, and a release of histamine.

Codeine is also a potent analgesic, acting like morphine on the enkephalinergic receptors, but with a much less intense action. An efficacious analgesic *per os*, its effect is cumulative with those of pain killers such as acetylsalicylic acid or paracetamol.

Noscapine. Noscapine is not derived from morphinan and is devoid of addicting effects. It is not an analgesic, nor does it induce respiratory depression. It is a specific antitussive through its central and peripheral activities.

Papaverine. See simple benzylisoquinolines.

F. Extraction of the Alkaloids

The major part of opium is directed toward alkaloid extraction. There are several extraction methods. The traditional procedure begins with an aqueous maceration of opium, which dissolves all of the alkaloids except for noscapine. To the solution of the salts (meconates, lactates, and so forth) is added calcium chloride: the organic acids precipitate as calcium salts and the alkaloids, converted to hydrochlorides, remain in solution. Upon concentrating the aqueous solution, crystals appear, which are a mixture of morphine and codeine hydrochloride (known in France as Gregory's salt). The other alkaloids remain in solution. Gregory's salt is redissolved in water, and morphine is precipitated selectively. A variation on this procedure consists of precipitating all of the alkaloids contained in the aqueous phase at pH 9, then selectively redissolving the crude morphine by controlled acidification. In other procedures, also ancient, opium is treated with hot water, the total alkaloids are precipitated by the addition of sodium carbonate, and finally they are extracted with benzene; next, morphine is isolated selectively as a tartrate, while the other alkaloids remain in solution in benzene.

Like the industrial methods for the preparation of alkaloids from straw *via* a "straw concentrate" obtained by solid-liquid extraction, the current procedures make use of ion-exchange resins and selective precipitations.

G. Uses

Opium. Opium and straw are used for the extraction of the alkaloids. Opium is also still used for the preparation of the following galenicals.

• **Opium Powder**. Opium powder is available in France, titrated to contain 10% morphine (10.0±0.2, Fr. Ph., 8th Ed., maximum dose = 0.2 g/single dose, 0.5 g/day). From the powder is prepared the opium tincture with saffron (Sydenham's laudanum, Fr. Ph., 9th Ed.). The powder is still used in France today to prepare paregoric, an opium tincture with the following ingredients: opium powder (5 g), benzoic acid (5 g), anise oil (5 g), camphor (2 g), and 60% alcohol (985 g). For a long time, paregoric (a controlled substance on French *liste II*, i.e., a prescription drug) was exempt from the requirement for a prescription as long as the total amount was not more than 25 g and as long as it was diluted 1:1 with sucrose syrup. Since this precaution, designed to prevent distillation, did not prevent abuse, paregoric was converted to a controlled substance on French *liste I*, i.e., prescription drug which may not be renewed, and the exempt dosages were deleted (official publication of the French government or *J. O. Rép. fr.*, February 18, 1989). Paregoric is used for the symptomatic treatment of diarrhea, and must be used only for a short time. A formulation of the same type is now available in France in tablets containing 5 mg of opium powder (by prescription only).

• **Opium Extract.** Opium extract is titrated to contain 20% morphine (20.0±0.4, Fr. Ph., 8th Ed., maximal dose: 0.1 g/single dose, 0.25 g/day). This extract is the starting material from which products seldom used today were formerly prepared, for example opium tincture (1% morphine) and the opiate-containing syrups listed in the French National Formulary: dilute opium syrup (0.01% morphine), concentrated opium syrup (0.05% morphine), and antitussive herb syrup. Opium powder and extract are also ingredients of a small number of French antalgic proprietary drugs.

Opium tincture, presented as a syrup (concentration lower than 2%) is exempt as long as the unit dose is less than 0.25 g, the maximum quantity for dispensation less than 2.5 g, and the formulation such that the tincture cannot be extracted (official journal of the French Republic or *J. O. Rép. Fr.*, August 1, 1991).

Morphine. Only a small quantity of extracted morphine is currently used as an analgesic, and the major part of the production is converted to various other compounds (codeine, ethylmorphine, pholcodine, oxycodone, nalorphine, naloxone): in 1994, the consumption of morphine was increasing steadily in Germany, France, the United Kingdom, Japan, and the United States, and reached 14 t worldwide. Also

in 1994, the world consumption of codeine was around 170 t, and that of dihydrocodeine was 30 t.

Indications. Morphine is a nonspecific antalgic used for the management of severe acute persistent pain (chronic nociceptive pain), particularly cancer pain. It is used when other antalgics become ineffective in relieving pain (pain level 3 according to the WHO *). The current preferrence is for the oral route and for the prevention of pain, rather than its treatment after onset (administration on a regular schedule). The posology must be individualized and can be increased as needed, with the optimal dose being that which provides relief to the patient. Morphine (SC, IM, intrathecal) is also indicated for post-traumatic pain, post-operative pain, kidney and gall stone pain (acute pain and/or pain unresponsive to peripheral antalgics).

Once methadone and buprenorphine became commercially available, morphine sulfate could no longer be used to treat heroin addiction, except in rare cases where no other therapy is effective.

(1) Morphine by the Oral Route

• **Morphine Hydrochloride.** Marketed in France for several years now, oral preparations are used more and more. Initially, "elixirs" were used, in which morphine hydrochloride was combined with cocaine hydrochloride **. Gradually, these were replaced by "potions" containing only 5 to 100 mg of morphine hydrochloride in 10 mL of a 95:5 (v/v) water and chloroform mixture, or in purified or distilled water. A solution for oral administration became available not long ago: it is free of flavor and sweetener, and packaged in 10-mL ampules containing 10 and 20 mg of morphine hydrochloride.

The low bioavailability, the intense hepatic metabolism, and the goal of pain prevention make administration every four hours necessary. The doses must be low at first (e.g., 6 x 10 mg/24 h; 6 x 5 mg in the elderly), and can be increased regularly by the physician without limitation as long as the side effects are under control.

• **Morphine Sulfate.** Morphine sulfate is available in France in slow-release, 10-, 30-, 60-, and 100-mg tablets, which make oral administration twice a day possible. To avoid overdose, these must never be chewed or crushed. Capsules are also available to physicians; they can be opened and the microgranules mixed with fluid food (for patients with dysphagia) or administered through a stomach catheter. The formulation most recently marketed in France makes it possible to administer

* The WHO defines three levels of intervention: level 1, non-opioid antalgics (paracetamol, acetylsalicylic acid, and other NSAID); level 2, minor opiates (codeine, dihydrocodeine, possibly buprenorphine, tramadol); level 3, morphine *per os*.

** Saint Christopher potion (Brompton's elixir): morphine hydrochloride (5 to 100 mg); cocaine hydrochloride (10 mg); 60% ethanol (1.25 mL); aromatized syrup (2.5 mL); 95:5 (v/v) water and chloroform mixture to make 10 mL.

the drug once a day (capsules containing up to 200 mg). If these formulations are taken after morphine hydrochloride solutions, the total daily dose remains in effect. In the United States, morphine sulfate (a controlled substance in category II) is available in tablets or capsules (10-30 mg), sustained release tablets (15-200 mg), and oral solution (10-100 mg).

Comments: ***Posology and French Guidelines for Prescription***. Addendum number 38 (*additif n° 38*) to the French Pharmacopoeia (decree or *arrêté* of August 25, 1997; see also *arrêté* of February 6, 1998) sets the usual doses for immediate-release forms (hydrochloride or sulfate), per single dose and per 24 hours. Usual doses: adults, 10 mg/single dose, 60 mg/24 h; children: 1 mg/kg, only if over 6 months of age, to be distributed over 24 h.

The same French regulatory text (article 5) specifies that 1) the recommended doses correspond to the initial dose [...] which must be adjusted for each patient; 2) the doses must be increased until the antalgic effect has been achieved; 3) there is no maximum posology as long as the adverse effects are under control. The treatment of acute pain must follow specific protocols.

The French Pharmacopoeial posology tables do not include recommendations for sustained-release forms.

Magistral preparations and pharmaceuticals based on morphine salts for oral administration can be prescribed for 14 days (instead of 7 days for most narcotics). In 1995, the duration for which the prescription of sustained-release forms based on morphine sulfate is authorized was extended to 28 days. The duration of prescription for injectable forms remains limited to 7 days, except in the case of controlled-infusion devices (28 days). In all cases, prescription and dispensation must comply with the rules that are in effect for narcotics.

(2) Morphine by the Parenteral Route

The "traditional" form of utilization of morphine in France is the hydrochloride (solution at 1% for SC or possibly IV injection, French National Formulary, controlled narcotic). Ampules containing 10 mg and 5-mL ampules containing 50 and 100 mg are available at the pharmacy and at the hospital, and higher dosage forms may become available in the near future.

Usual doses for the SC route (half the doses of the oral route): adults, 5 mg/single dose - 30 mg/24 h; children: 0.5 mg/kg to be distributed over 24 h, only if over 6 months of age. For the IV route, the usual doses are divided by three compared to the oral doses (3.33 mg/single dose and 20 mg/24 h for adults; 0.3 mg/kg in children over the age of 6 months, to be distributed over 24 h).

The parenteral route is not optimal for the treatment of chronic pain, unless oral administration lacks efficacy or is not an option, due to dysphagia, inability to swallow, intestinal occlusion, or uncontrollable vomiting. In such cases, continuous SC administration (syringe systems, pumps, infusion), or continuous IV infusion are used. Patient-controlled administration is possible by the latter routes.

In the United States, morphine sulfate (a controlled substance in category II) is available in solution at 0.5-50 mg/mL for IV injection [as well as epidural and intrathecal injection, see (3) below].

(3) Morphine by the Epidural and Subarachnoid Routes

This route is justified by the presence of opiate receptors in the posterior horns of the spinal cord, and it creates a lasting spinal analgesia. The longest-lasting analgesia is obtained by intrathecal injection: direct injection into the cerebrospinal fluid accelerates the onset of activity and the very low resorption into the blood leads to an analgesia which often exceeds 24 hours. The risk of respiratory depression is low, but it exists, with a delay after administration. It is mostly linked to the technique of administration, and caused by errors in posology, repeated administrations too close in time, error in the route of administration, combination with morphine by IV injection, or poor injection technique. There are other side effects, including vomiting, itching, and urinary retention, in addition to the risk inherent to the administration technique. Even by this route tolerance can develop, however, withdrawal symptoms are not normally observed when the treatment is discontinued.

The indications for this route of administration are post-operative analgesia and cancer pain. These techniques allow cancer patients to go home after the insertion of a permanent catheter, possibly attached to an implanted pump, and to continue to receive long-term treatment.

Contraindications. Morphine has many contraindications: respiratory insufficiency, acute abdominal symptoms of unknown origin, serious hepatocellular insufficiency, trauma of the head and intracranial hypertension, alcohol intoxication, treatment with MAO inhibitors, and it must not be used in infants. In patients with renal or hepatic insufficiency, in the elderly, and in pregnant women, the greatest caution is in order. The oral route is contraindicated in children under the age of 6 months, in nursing women, as well as in case of uncontrolled respiratory insufficiency and impaired liver function.

The most common side effects are the following:

- constipation, almost inevitable, and requiring proper management (e.g., increased fluid intake, laxatives);
- nausea and vomiting, which generally subside after 4-5 days of treatment;
- possible neurological and psychic disturbances, which might reflect overdose.

Following oral administration of morphine, there is a moderate risk of respiratory depression—at therapeutic doses. Although tolerance can develop and can make it necessary to increase the doses to obtain the same antalgic effect, the results of all clinical studies converge and show that dependence is practically never observed, even in patients with a history of drug abuse.

Codeine

• As an antalgic. Codeine (a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed) and its combinations are indicated for the symptomatic treatment of pain in adults, including cancer pain (WHO pain level 2). The minimum dose is 30 mg every 4 h (and 180 mg/24 h); it can be increased to 60 mg every 4 h (ANDEM). The French Pharmacopoeia sets the maximum doses of codeine base at 100 mg per single dose up to 300 mg per 24 h (adults); for codeine phosphate, the maximum single and 24-h doses are 150 and 400 mg, respectively. In France, there are no medicines containing codeine alone (for adults *), only combinations, for example with paracetamol (but magistral preparations are always a possibility). Such combinations are logical, but various authors think that, given the dose of paracetamol that they contain, these products do not allow to prescribe codeine doses larger than the minimum doses, which are efficacious only as adjunctive treatment (up to 120 mg every 4 h according to the WHO). The same authors emphasize, with good reason, that allowing medicines with low doses to be exempt (*vide infra*) contributes to making their use commonplace; yet these products have nonnegligible risks, particularly their potential for abuse.

• As an antitussive. Codeine (most often as a salt) is an ingredient of dozens of proprietary drugs indicated or recommended for the symptomatic treatment of difficult, non-productive coughs. The drugs are often syrups combining codeine with plant-based preparations (aconite tincture, eucalyptus syrup, extract, or essential oil; eucalyptol; *Grindelia* or *Erysimum* extracts), or with synthetic compounds (bromoform, promethazine, phenyltoloxamine, sodium camphosulfonate, sulfoguaiacol, ethylmorphine), or both.

• Codeine *per os* is used in place of heroin by some addicts (on a case by case basis or on a long term basis, most often by self-medication). Non-prescription (= over-the-counter) medicines are abused, especially certain syrups designed for the symptomatic treatment of cough. (Products are exempt when the quantity of codeine obtained at one time does not exceed 300 mg with a maximum of 20 mg per single dose or a concentration equal to or lower than 0.1% for forms that are not predivided into doses.)

Codeine is contraindicated in case of respiratory insufficiency and for asthmatic coughs; to be cautious, its administration to nursing mothers and to pregnant women during the first trimester must be avoided.

There are many side effects, especially at the higher doses: nausea, dizziness, light headedness, constipation, allergic skin reactions; they can appear even after low doses in sensitive subjects. The consumption of alcohol must be avoided during the treatment. The risk of overdose exists, especially in young children, who are very sensitive to this alkaloid: respiratory depression and alterations, myosis, signs of

* A pediatric syrup was marketed in France in 1998. Titrated to contain 0.62 mg of codeine base/mL, it is designed for pain management in children over the age of 1 (recommended

histamine release, urticaria, puffy face, collapse (toxic threshold at 2 mg/kg). The risk of dependence is low in the absence of pre-existing physical dependence.

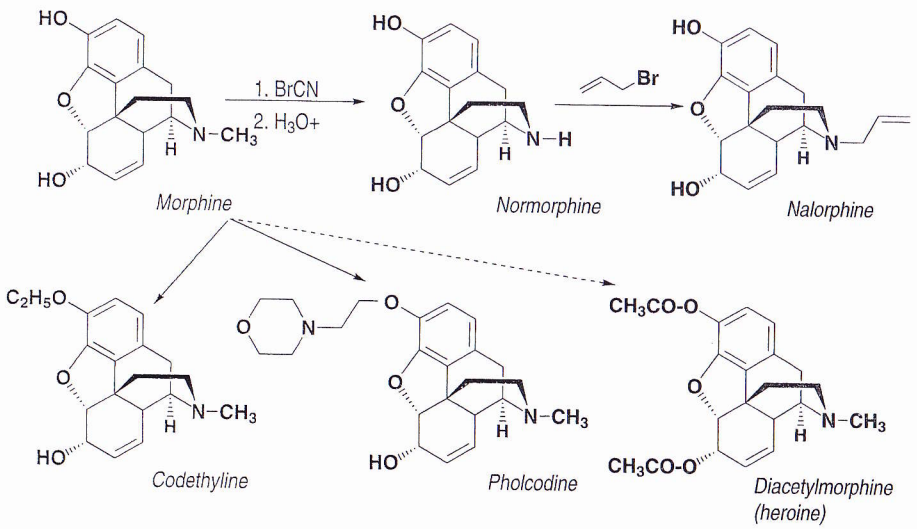
Noscapine. Noscapine is indicated in the treatment of non-productive coughs (30-90 mg in adults, 1 mg/kg in children). The hydrochloride, camphosulfonate, or the form bound to a carboxylic resin are often combined with another active principle (antalgic, antihistamine, eucalyptol). It is contraindicated in case of asthmatic cough and respiratory insufficiency.

Papaverine. See the previous chapter (benzylisoquinolines, p. 893).

H. Semisynthetic and Synthetic Alkaloids.

Here, we shall cover, succinctly, only the derivatives that still have the morphinan skeleton: the other central analgesics (phenylpiperidines, 3,3-diphenylpropylamines, 4-anilino-piperidines) are further developed in classical therapeutic chemistry and pharmacology textbooks.

Ethylmorphine. Ethylmorphine is the 3-ethyl ether of morphine. It is an antitussive rarely used alone (20-50 mg/day in adults; 0.6 mg/kg/day in children from 8 to 15 years of age). The available combinations (syrups, suppositories) are similar to those containing codeine, over which it does not seem to have any advantages. The contraindications, side effects, and precautions are the same as for codeine.



Pholcodine. Pholcodine is a semisynthetic alkaloid, specifically 3-morpholinyl-ethylmorphine. Like codeine and ethylmorphine, it is an antitussive. More specific than codeine, it is not a strong analgesic, has a more prolonged action, and does not

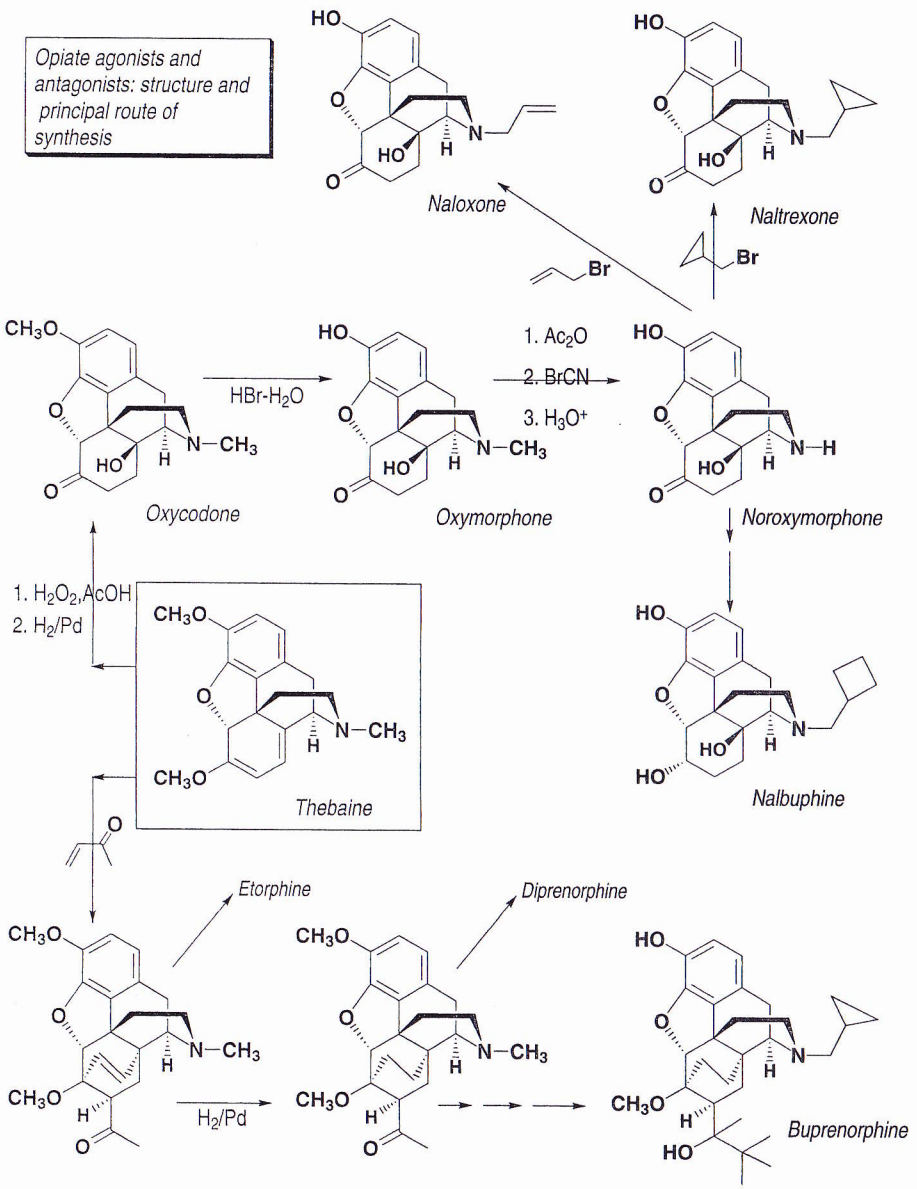
induce dependence. A substitute for codeine in several pediatric preparations, it is an ingredient (mostly in France) of a large number of proprietary products, syrups and suppositories, in which it is combined with many other extracts or compounds (ephedrine, aconite tincture, promethazine, tenoic acid, paracetamol, quinine, eucalyptol, to name only a few). Normal doses (*per os*): 0.5 mg/kg/day in young children (>30 months old), 1 mg/kg/day in children from 8 to 15 years of age, and 60-120 mg/day in adults.

Dihydrocodeine. Dihydrocodeine (a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed) was recently marketed in France as a tartrate and as a slow-release form, indicated in the symptomatic treatment of pain of moderate intensity. A mild opiate already in use for a long time in other countries, it has many side effects (nausea, vomiting, drowsiness, constipation).

***N*-Allylnormorphine.** *N*-Allylnormorphine (= nalorphine, INN, a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed) is an opioid antagonist and partial agonist. It interrupts the effects of morphine by displacing it from the receptors to which it is bound; for example, it interrupts the deep respiratory depression due to high doses or repeated doses of morphine. It is used as a hydrochloride to treat the respiratory insufficiency due to opiates. It is contraindicated in drug addicted patients (risk of withdrawal syndrome) and in case of hepatic insufficiency.

***N*-Cyclopropylmethyl-14-hydroxynordihydromorphinone** (= naltrexone, a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed). This is a pure agonist. Its affinity is sufficient to prevent its displacement from the receptors by opiates administered subsequently (rendering the latter inactive). Therefore, naltrexone is indicated for the treatment of opiate addiction, after detoxification (otherwise, the first administration would precipitate withdrawal symptoms). The indication is the long-term treatment of opiate addiction, to help prevent relapse, and support rehabilitation. The treatment must be applied by trained drug rehabilitation personnel; it requires understanding and collaboration on the part of the patient.

***N*-Allyl-14-hydroxynordihydromorphinone** (= naloxone, INN, a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed; a prescription drug in the United States). This is a pure antagonist: 1 mg blocks the effects of 25 mg of heroin completely. It is indicated in the treatment of the respiratory depression due to the opiates used during therapeutical or diagnostic surgical procedures, in the treatment of opiate intoxications, and for the differential diagnostic of toxic comas (but it has a fairly short duration of action). Another (sometimes controversial) indication is the "naloxone test", to confirm the absence of opiate dependence in the drug user who has been rehabilitated for a long enough time, and as a prerequisite to treatment with a morphine antagonist with a long duration of action. Naloxone is added to analgesic (United States Pharmacopeia) tablets of



pentazocine at a dose too small to have any pharmacological activity *per os*, but sufficient to prevent the effect of pentazocine if the product is misused by injection.

Levorphanol (in the USA , a controlled substance in category II) is an analgesic.

Hydrocodone (in the United States, a controlled substance in category III) is an analgesic and an antitussive.

Hydromorphone (in the United States, a controlled substance in category II) is an analgesic and an antitussive.

The following two partial agonists are marketed in France and in the United States, and prescribed as analgesics.

***N*-Cyclobutylmethyl-14-hydroxynordihydromorphine** (nalbuphine, INN, a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed; a prescription drug in the United States). The analgesic activity is equivalent to that of morphine, and the respiratory depression is moderate. It can be used in young children (> 18 months).

Buprenorphine (INN). This is an *N*-cyclopropylmethyl hexacyclic derivative (in other words, it results from a cycloaddition onto a thebaine-type molecule). When it was marketed in France, it was initially considered a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed. In view of the reports of abuse, even tighter accounting and record keeping have become required as of September, 1992 *. An agonist-antagonist and a potent long-acting antalgic, buprenorphine binds to *mu* receptors in the brain in a slowly reversible fashion, which minimizes the addict's craving for drugs for a long time. Because of its partial agonist activity, buprenorphine has a good safety margin.

Indication. Buprenorphine (hydrochloride, sublingual tablets) is used as an opiate substitute in the treatment of addiction, and it must be administered as part of a comprehensive program that must include medical, social, and psychological components. The hydrochloride solution for injections (0.3 mg/mL) is indicated in circumstances that require rapid and efficacious sedation of intense pain, particularly post-operative and cancer pain. In the United States, it is a controlled substance in category V.

O,O-Diacetylmorphine = heroin. This is a very special case, since this compound has no use in therapeutics, but has great abuse potential. The production, marketing, and use of heroin are prohibited in France (article R. 5179 of the Public Health Code or CSP, and rule of September 10, 1992).

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* This is to implement the modifications in the narcotics regulations: French rule of September 10, 1992, official publication of the French government or *J. O. Rép. fr.*, September 10, 1992, p. 13 039.

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Isoquinoline Alkaloids

✲ Phenethylisoquinolines

● Autumn Crocus, *Colchicum autumnale* L., Liliaceae

An industrial source of colchicine, used to specifically cure the acute attack of gout, the seeds of the autumn crocus or meadow saffron, namely colchicum seeds were the subject of a monograph in the French Pharmacopoeia until 1965 (8th edition).

The autumn crocus, known to the Greeks for its toxicity, was used in the Byzantine empire since the fifth century to treat gout. Rejected by "the Faculty" at the beginning of the sixteenth century, it reappeared at the end of the eighteenth century in the form of a tincture: "two ounces of roots in four ounces of rectified wine". Another century went by before chemists succeeded in crystallizing colchicine (Laborde and Houdé, 1884), 70 more years before the formula was established (Dewar, 1945), and another 20 years before the first synthesis was published (Woodward, 1963). The synthesis of (–)-(a*S*,7*S*)-colchicine continues to stimulate the imagination and endeavors of chemists: this is because naturally-occurring colchicine displays an asymmetry which is due to the lack of planarity of the benzene and tropolone rings. The two rings are at a torsion angle of about 53° and the helicity is counterclockwise. The torsion of the molecule is required for a bond to be established with tubulin: the (a*R*) enantiomer cannot form this bond. This bond prevents the formation of the microtubules and is required for the antimitotic activity of the alkaloid.

COLCHICUM AUTUMNALE L.

The Plant. A herbaceous plant of the damp meadows of Europe, the autumn crocus is thought to have originated on the eastern banks of the Black Sea (from Colchide, which is part of Georgia today). Also known as meadow saffron, it is characterized by a peculiar vegetative cycle. In October, the corm grows a group of two to six trimerous flowers with a purplish-pink perianth, which blossoms into six lobes spread out at the apex of a very long and narrow tube (10-15 cm), with the ovary remaining at the level of the corm, underground; following the winter resting season, oblong and linear leaves appear, and, at the same time, the fertilized ovary or fruit emerges from the ground and completes its maturation: it is a small septicidal three-lobed, three-celled capsule vaguely reminiscent of a walnut (hence the risk of intoxication of young children), The species is perennial: each year, a replacement corm develops at the expense of the parent.

The Drug. Colchicum seeds are small: their diameter does not exceed 3 mm. They are globulous and particularly hard. The seed tegument is reddish-brown and finely punctuated, and develops abnormally on one side of the seed to form a strophiole which contains starch.

Sources of Colchicine. The drug supply essentially comes from harvesting wild plants (in central and eastern Europe). According to the French *Office National Interprofessionnel des Plantes Aromatiques et Médicinales* (= ONIPPAM), the French needs for colchicum seed are nearly 50 metric tons. Attempts at optimization and *in vitro* propagation have yet to result in profitable cultivation. For the purpose of extraction, the corm harvested at the beginning of the summer, after the leaves wilt, can also be used.

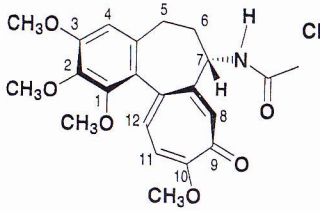
Colchicine can also be extracted (this is done by several European industrial companies) from an Indian Liliaceae, *Gloriosa superba* L., which is reported to contain, on average, 0.9% colchicine.

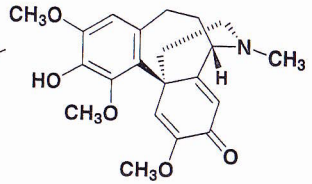
Chemical Composition. The concentration of total alkaloids is very variable, from 0.3 to 1.2%. About 20 alkaloid-type compounds have been isolated from the drug. Most of them occur only in small quantities. Almost all of them are amides that are weakly or not basic, and do not readily form salts. Some occur as glycosides (colchicoside: 0.4%). Structurally they have in common a tropolone nucleus, in other words a tricyclic structure comprising two heptagonal rings; their nitrogen atom is exocyclic.

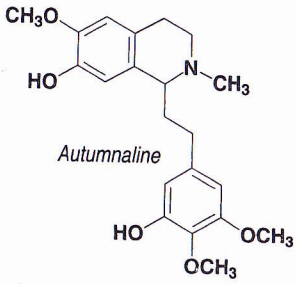
The chief constituent is colchicine (0.6% on average). It is sensitive to light and photoisomerized to lumicolchicines (pharmacologically inactive) upon exposure to UV radiation.

Colchicine can be extracted in water. For example, consider the (historical) method of Houdé: colchicine is extracted by a hydroalcoholic solution; back-extraction with chloroform after removal of the alcohol separates colchicoside (which remains in the aqueous phase) and the alkaloids (dissolved in chloroform). Colchicine can be crystallized from the chloroform solution after washing with an alkaline solution

The other alkaloids have a very closely related structure, and include cornigerine, demecolcine, colchicilline, and colchifoline and its demethylated derivatives.

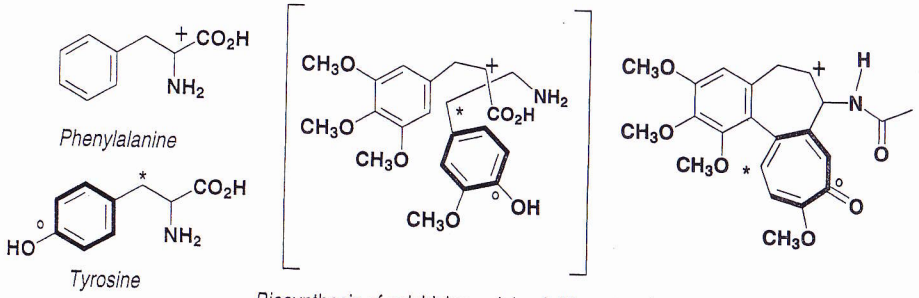

Colchicine


Androcymbine


Autumnaline

Biosynthetic Origin. The biosynthesis of these alkaloids is not obvious. Of course, phenylalanine is incorporated: it is the origin (*via* a cinnamic acid) of ring A and of C-5, -6, and -7, but tyrosine is also incorporated, and labeling experiments prove that it is the precursor of the tropolone nucleus. If in fact the C-3 and C-4' of tyrosine become the C-12 and C-9 of colchicine, respectively, (see figure), then it implies that there has been an enlargement of the cycle with incorporation of the benzylic carbon atom of tyrosine in the heptagonal ring being formed.

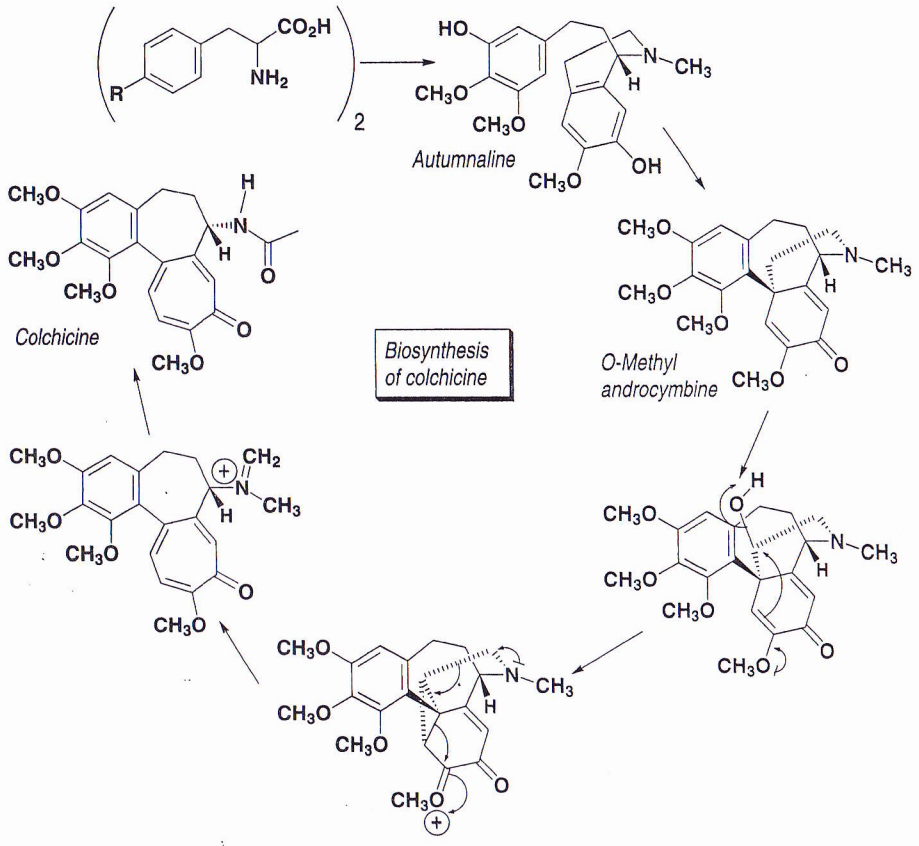
It is the isolation of a seven-membered cyclic dienone, androcymbine, from a plant botanically close to the autumn crocus (*Androcymbium melanthioides*) which has permitted the reconstruction of the likely biosynthetic pathway. That the process really takes place is supported by the incorporation of labeled androcymbine. Note also that the hypothetical precursor of androcymbine, namely autumnaline, has been isolated from a *Colchicum, C. cornigerum* Schweinf. The loss of C-2 from tyrosine during the rearrangement fits in the postulated fragmentation (which probably follows a hydroxylation).


Phenylalanine

Tyrosine

Biosynthesis of colchicine: origin of different carbon atoms

Pharmacological Activity. The autumn crocus is very toxic: "ingested, it [the corm] kills by suffocation, like the mushrooms", Dioscorides noted already during the first century. The ingestion of all or part of the plant causes swallowing



difficulties, sialorrhea, abdominal pains with diarrhea, muscle cramps, hypotension, and respiratory difficulties. In case of serious intoxication, death occurs by respiratory arrest or cardiovascular collapse, several days after the intoxication.

- **Antimitotic Properties**. Colchicine blocks mitosis at the metaphase stage by preventing the formation of the mitotic spindle. This activity is linked to the ability of the alkaloid to bind to tubulin and therefore to inhibit the formation of the microtubules, which are required for the formation of the spindle. In vegetable cells, it inhibits the separation of the two batches of daughter chromosomes, which remain attached by their common centromeres, and tetraploids form as a result: agricultural research sometimes uses colchicine to create polyploid strains. The cellular toxicity of colchicine is too great, so it cannot be used as an antitumor agent.

- **Anti-inflammatory Properties**. Colchicine is an anti-inflammatory specific to the microcrystalline arthritis caused by sodium urate crystals: it is particularly efficacious in the treatment of the acute attack of gout. This activity seems to be linked mainly to the activity on the polynuclear neutrophils, whose responsibility in the acute attack of gout has been well established*: decrease in motility, chemo-

tactism, and adhesivity, decrease in phagocytosis and in the lysosomal degranulation responsible for the release of highly phlogogenic contents which maintain the inflammation. Colchicine has no effect on the metabolism of uric acid: the basic treatment of hyperuricemia must use uricosurics (benzbromarone, sulfinpyrazone), inhibitors of the synthesis of uric acid (allopurinol), or urate oxidase.

• **Colchicine Toxicity**. The toxic dose in humans is around 10 mg; the ingestion of doses greater than 40 mg is always fatal within three days of the ingestion of the alkaloid. The intoxication, most often deliberate **, is always extremely serious (15 to 30% mortality according to different authors ***). After a latency of three to five hours, the intoxicated patient experiences abdominal pains, gastroenteritis with hemorrhage, abundant diarrhea leading to dehydration, hypokalemia, and metabolic acidosis. The hematological alterations due to bone marrow damage and the state of shock occur later; septicemia and renal insufficiency complete the picture. Death generally occurs after one week. In the absence of an antidote, the treatment can only be symptomatic, and its goal is to restore the electrolyte balance and relieve the abdominal pain.

Uses. Colchicum seeds and corm are used for the extraction of colchicine. This compound (a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed) is generally used alone. It can also be combined with active principles capable of limiting the onset and extent of the diarrhea caused by the alkaloid (opium powder, tiemonium iodide and phenobarbital).

Colchicine is prescribed orally and indicated in the treatment of gout: it is efficacious in over 95% of cases if it is taken as soon as the first symptoms are experienced. The guidelines for prescription are as follows: 3 mg on the first day (in three single doses), 2 mg in two doses on the second and third day, 1 mg on the following days, up to a maximum dose of 10 mg. Other indications of colchicine are: to prevent the acute attack of gout in chronic patients, particularly when hypouricemic therapy is initiated; other types of acute crystal-induced attacks (chondrocalcinosis and hydroxyapatite-induced rheumatism); recurrent attacks; Behçet's disease (1 md/day for these other indications). Trials are in progess to evaluate the benefits of colchicine in the treatment of mucosiscidosis. In the United States, colchicine is a prescription drug; it is available as an injectable solution and also in tablets, in combination with a uricosuric agent (probenecid).

* Precipitation of urate in the joints attracting polynuclears and triggering inflammation.

** Cases of suicide using *Gloriosa superba* have been reported in Sri Lanka and India. (Fernando, R. and Fernando, D.N. (1990). Poisoning with Plants and Mushrooms in Sri Lanka: a Retrospective Hospital Based Study, *Vet. Hum. Toxicol.*, **32**, 579-581).

*** In an experiment conducted in France in 1991, a patient intoxicated with 60 mg of colchicine was saved by the administration of fragments of goat antibodies to colchicine (Scherrmann, J.-M., U26 INSERM [= *Institut National pour la Santé Et la Recherche Médicale*]).

Contraindicated in case of renal insufficiency, severe hepatic insufficiency, and pregnancy, colchicine has side effects, particularly gastrointestinal problems: nausea, vomiting, and especially diarrhea. The latter is the first sign of overdose and it leads to decreasing the dose or even discontinuing treatment. Hematologic disturbances are observed only in exceptinal cases, but during prolonged treatments, regular blood tests are recommended.

Derivative related to colchicine: thiocolchicoside. This compound, prepared by semisynthesis, is the sulfur-containing analog of the naturally-occurring glycosidic alkaloid, namely colchicoside. Pharmacologically, this compound is said to be a muscle relaxant. It is not a curare and it acts through a central effect on the spastic hypertony of the skeletal muscle. It is a gamma-aminobutyric acid receptor agonist. Thiocolchicoside, a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed, is indicated (*per os*) for the adjunctive treatment of muscle spasm pain in rheumatology. An injectable form is also available; it is indicated for the adjunctive treatment of (muscle) spasm pain in acute back pain.

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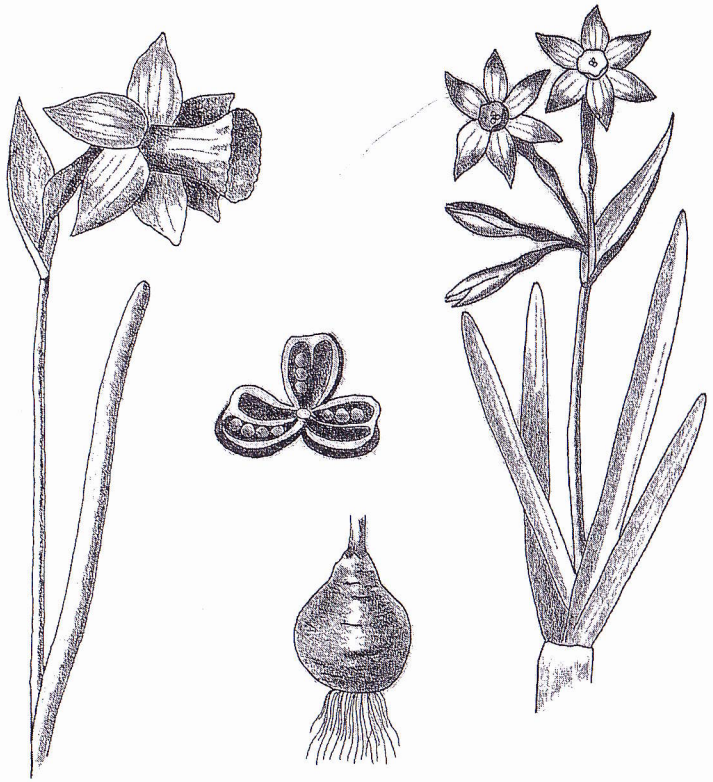


NARCISSUS Sp.

Isoquinoline Alkaloids

✲ Alkaloids of the Amaryllidaceae

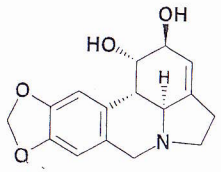
These alkaloids are not used in therapeutics, nor are the different species that contain them. We must, however, describe them here, because they impart a non-trivial toxicity to these plants, which are often grown for their ornamental qualities in parks and gardens, where they bloom early, and also as house plants.

Over one hundred alkaloids have been isolated from this family: the principal structural variations are illustrated below (next page).

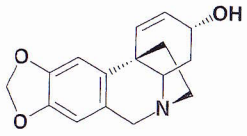
Biosynthetic Origin

The biosynthesis of these alkaloids is rather complex, although in simple terms, it results from an intramolecular oxidative coupling within a precursor of the C_6C_2-N-C_1C_6 type. Whether the coupling occurs between the *para-ortho'*, *ortho-para'*, or *para-para'* positions determines whether the structural type is galanthamine, lycorine, or else haemanthamine or crinine, respectively. Secondary rearrangements are possible (e.g., tazettine).

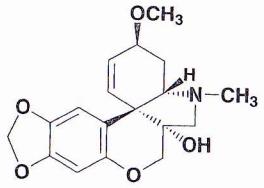
The C_6C_2 unit arises directly from a molecule of tyrosine, whereas the C_6C_1 unit originates from a molecule of phenylalanine. The latter is converted to cinnamic acid then hydroxylated (caffeic acid); after elimination of two carbon atoms, the resulting 3,4-dihydroxybenzaldehyde reacts with tyramine to form norbelladine, then methylnorbelladine, which undergoes the oxidative couplings described above.



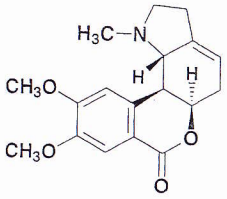
Lycorine



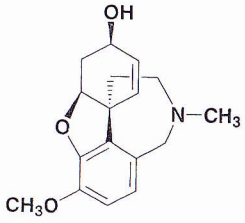
Crinine



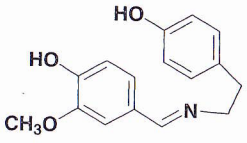
Tazettine



Homolycorine



Galanthamine

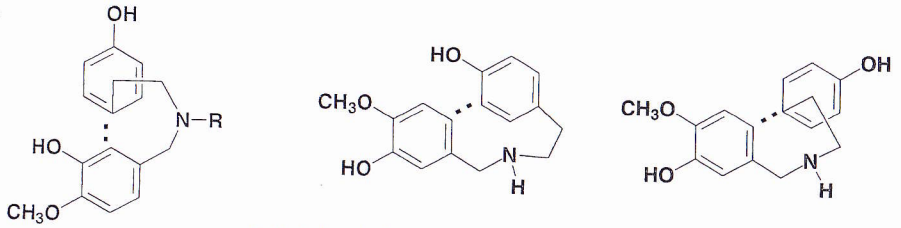


Isocraugsodine

In all of the indicated species (e.g., *Amaryllis*, snowdrop [*Galanthus*], daffodil, narcissus [*Narcissus*]), the alkaloids are mostly concentrated in the bulbs.

Serious intoxications are rare, and are almost always due to a confusion between the bulbs of edible Liliaceae (onions, shallots) and those of the garden Amaryllidaceae (e.g., *Narcissus pseudonarcissus* L. and other species). The ingestion of these bulbs, like that of the leaves, which can be mistaken for leek, rapidly induces nausea and vomiting, followed by profuse diarrhea. The symptoms normally subside rapidly. Narcissus also cause cutaneous reactions (dermatitis).

The most common toxic principle is lycorine, a cholinesterase inhibitor which, at low doses, causes salivation, vomiting, diarrhea, and at higher doses, paralysis and collapse. Lycorine, narciclasine, and other compounds are cytotoxic.



O-Methyl-norbelladine and derivatives: different coupling possibilities

The therapeutic potential of these alkaloids includes the cytotoxic properties of lycorine, haemanthamine, pretazettine, and narciclasine. In some cases, their weak *in vitro* activity can be enhanced by quaternarization: lycobetain acetate (produced by oxidation of lycorine) has undergone preliminary clinical studies in China, with significant results, especially for ovarian cancer.

• GALANTHAMINE

Isolated from various snowdrops (*Galanthus*) in the early 1950s and found in several genera of the same family (*Narcissus, Lycoris*), this alkaloid can be extracted from *Leucojum aestivum*, in which it represents up to 2% of the dry weight. It can also be prepared by synthesis.

Galanthamine is an acetylcholinesterase inhibitor. Injected into animals (or humans) previously curarized by alcuronium or gallamine, it ends the neuromuscular block. It is less active than neostigmine or pyridostigmine and it induces a few muscarine-type side effects (hypersalivation, nausea, bradycardia). It crosses the blood-brain barrier and exerts central effects, and in animals, it improves the results of behavior and memory tests. It is thought that galanthamine could, by inhibiting acetylcholinesterase in cortical synapses, promote central cholinergic transmission, which is impaired in Alzheimer's disease. Several trials conducted in humans (open and placebo-controlled) tend to show that galanthamine induces a significant improvement of cognitive performance (or slows its deterioration) in subjects probably affected by a mild form of this disease. These trials show that the compound is well tolerated and is not hepatotoxic.

Galanthamine hydrobromide has been used extensively in anesthesiology in eastern European countries. It can be used to treat intoxications by central anticholinergics and it is marketed for this indication in Italy. Austria recently approved its use for the treatment of mild to moderate forms of Alzheimer's disease.

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CEPHAELIS SP.

Isoquinoline Alkaloids

✲ Monoterpenoid Isoquinolines

• IPACACUANHA, *Cephaelis* sp., Rubiaceae

The latest edition of the European Pharmacopoeia provides the following definition for this drug: "Ipecacuanha consists of the fragmented and dried underground organs of *Cephaelis ipecacuanha* (Brot.) A. Rich., Matto Grosso ipecacuanha, or of *Cephaelis acuminata* Karsten, known as Costa Rica ipecacuanha, or of a mixture of both species" *.

The term ipecac is of Native American origin. It is applied to official *Cephaelis* but also, improperly, to various emetic roots of the family Rubiaceae (*Psychotria emetica* L. *f.*, *Richardia scabra* L. or false ipecac) or other families, such as Asclepiadaceae (*Asclepias curassavica* L. or milkweed bloodflower), Araceae (*Cryptocoryne spiralis* [Retz.] Wydler or Indian ipecacuanha), Rosaceae (*Gillenia stipulata* [Willd.] Baillon or American ipecac), Violaceae (*Hybanthus calceolaria* [L.] Oken or white ipecacuanha), Meliaceae (*Naregamia*), etc. These various drugs were formerly used to adulterate the official drug.

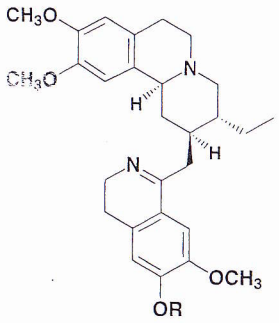
The drug, used by Native Americans for its emetic and antidysenteric properties, was introduced in Europe at the end of the sixteenth century. It has been listed in the French Pharmacopoeia since the first edition in 1818.

* For consistency's sake, the Pharmacopoeial denominations are used here. According to D. J. Mabberley, ipecacuanha is *Psychotria ipecacuanha* (Brot.) Stokes (= *Cephaelis ipecacuanha* [Brot.] Tussac) (*in* The Plant Book - A Portable Dictionary of the Vascular

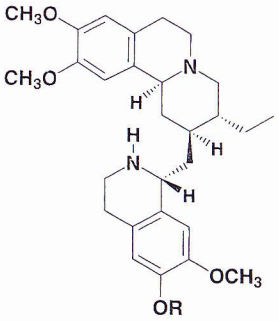
The Plants. Ipecacuanhas are small perennial subshrubs (20-40 cm) bearing opposite decussate leaves with laciniate stipules between the petioles, and with white flowers gathered into compact cymes (etymologically: *Cephaelis* = grouped at the head). Rio or Brazilian Ipecac (from Matto Grosso) grows wild in the damp forests of southern Brazil and of Bolivia: after uprooting the plant, the majority of the roots are collected, and the plant is replaced in the ground where it can produce further crops *. The roots are dried (sun, fire) and cut before exportation. Cultivation has been attempted in Brazil and other tropical areas (Malaysia, Burma, India), but only with limited success (strict pedological conditions, 3-4-year delay before harvest). Cartagena, Nicaragua, or Panama Ipecac, as its names indicate, essentially comes from Central America (Costa Rica).

The Drugs. *C. ipecacuanha* roots consist of twisted fragments that rarely exceed 15 cm, and are reddish-brown, no thicker than 6 mm, and annulated, with rounded ridges close to one another and encircling the root completely. *C. acuminata* roots are much thicker (often up to 9 mm) and they are covered with transverse constrictions that are 1 to 3 mm apart and only encircle about half of the root.

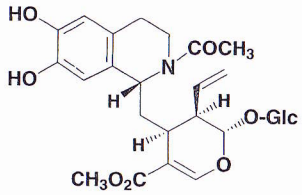
The microscopical examination shows, in the phelloderm and the medullary rays, simple or compound parenchymatous cells filled with simple starch grains reaching 15 µm (*C. ipecacuanha*) or 22 µm (*C. acuminata*); note also the crystals, which consist of bundles of raphides of calcium oxalate of 30 to 80 µm in length. Starch and raphides characterize ipecac powder, which also contains fragments of tracheidal as well as areolate and pitted vessels.



R = H : *Psychotrine*
R = CH_3 : *O-Methylpsychotrine*



R = CH_3 : *Emetine*
R = H : *Cepheline*



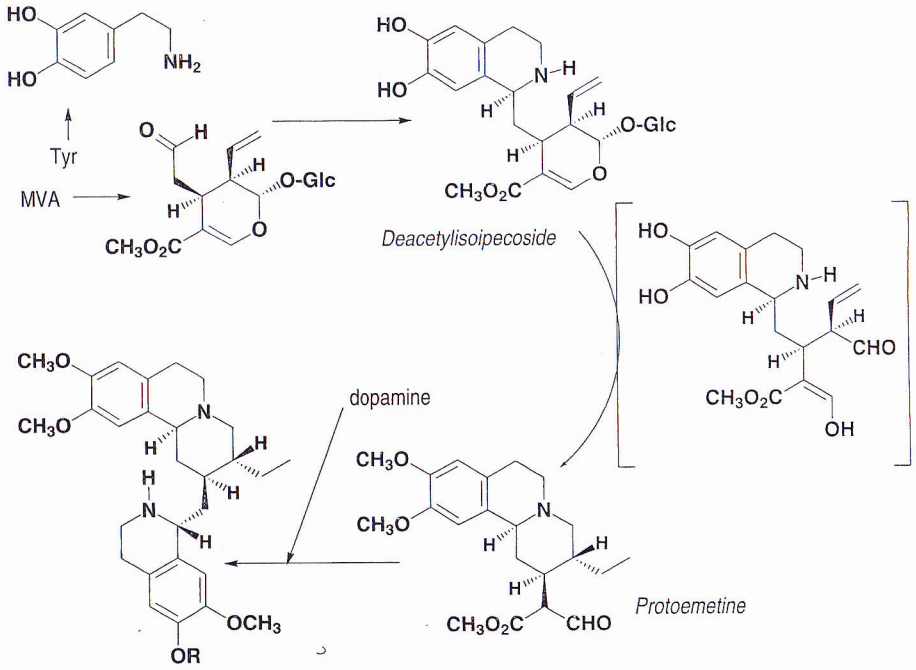
Ipecoside

Chemical Composition. The active principles, localized in the cortex of the root and rhizome, are isoquinoline alkaloids at a concentration ranging from 2 to 2.5% for Rio Ipecac, or from 2 to 3.5% for Cartagena Ipecac. Emetine is by far the major constituent of Rio Ipecac (60-75% of the total alkaloids), but it represents only 30 to

* According to Evans, W. C. (1996). Trease and Evans' Pharmacognosy, 14th Ed., p. 376, Saunders, London.

50% of the total alkaloids of Cartagena Ipecac. The other alkaloids have similar structures: cepheline (monophenolic), psychotrine and *O*-methylpsychotrine, both 1',2'-unsaturated. The drug also contain a large amount of starch (30-40%), an allergenic glycoprotein, and monoterpenoid isoquinoline glycosides such as ipecoside: the structure of this compound suggests the biosynthetic origin of the alkaloids.

Biosynthetic Origin of the Ipecac Alkaloids. These monoterpenoid isoquinoline alkaloids are rare: they are found in *Cephaelis* and in other Rubiaceae (e.g. *Pogonopus*), and also in the Alangiaceae and Icacinaceae. Their pathway of formation resembles that of the monoterpenoid indole alkaloids characteristic of the Apocynaceae, Loganiaceae, and also of many Rubiaceae (*Corynanthe*, *Pausinystalia*). The first step in the process is the condensation of one molecule of dopamine with a seco-iridoid, secologanin, to form desacetylisoipecoside. The 3β isomer is acetylated (ipecoside). The hydrolysis of the 3α isomer (desacetyl-isoipecoside) leads to an unstable aglycone: the dihydropyran ring opens and the aldehyde reacts with the secondary amine to form ring C. Subsequently, the molecule loses a carboxymethyl group and undergoes a condensation with a second molecule of dopamine.



Tests. The assay includes a TLC analysis of a chloroform extract prepared in the presence of aqueous ammonia. The chromatogram is examined under UV light after spraying with an iodine solution in chloroform and heating at 60°C: the intensity of the light blue fluorescent band due to cepheline allows the distinction between the two *Cephaelis* species.

The quantitation is achieved by classic methods: alkaloid extraction (diethyl ether) after alkalinization (NH_4OH), solvent evaporation, redissolution in ethanol, heating to 100°C, evaporation, redissolution of the residue in excess hydrochloric acid of known concentration, and titration of the excess acid with a sodium hydroxide solution of known concentration. The drug must contain not less than 2% alkaloids expressed as emetine.

In addition, emetine can be characterized by a color reaction: in the presence of potassium chlorate or hydrogen peroxide, a red hexacyclic iminium species is formed.

Pharmacological Activity. Ipecac preparations, when administered orally at low doses, are emetics. The emetic activity is due at first to a direct peripheral stimulation (excitation of the sensory fibers of the glossopharyngeal and vagus nerve), and secondarily, to the stimulation exerted on the brain stem centers that control vomiting. Cephaeline is the main alkaloid responsible for the emetic activity, whereas emetine is mostly an expectorant.

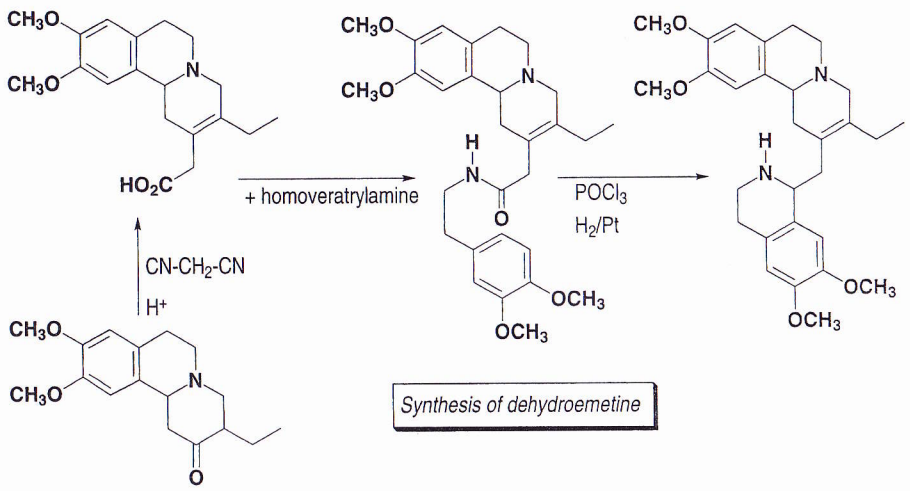
Emetine is an amebicide which destroys the motile forms of the ameba, *Entamœba histolytica*, the species responsible for amebic dysentery; its activity on the cysts only appears at concentrations that are toxic for humans. Emetine inhibits protein synthesis in animal and vegetable cells, and in protozoa. It perturbs, and can even inhibit the synthesis of DNA. It kills viruses, but is not an antibacterial.

Emetine is toxic for humans: cardiac toxicity (arrhythmias), hypotension, muscular weakness, and gastrointestinal distress are common side effects. It is excreted in urine at a particularly slow rate (60 days).

Uses. Emetine is no longer used in therapeutics. It was formerly obtained by extraction, and the yield used to be increased by methylating cephaeline. It has been replaced by a synthetic derivative, dehydroemetine, whose subacute and chronic toxicity are decreased by lower accumulation. This synthetic alkaloid remains on the market in spite of the predominant use of metronidazole, secnidazole, and related compounds. Dehydroemetine (dihydrochloride, a controlled substance on French *liste II*, i.e. a prescription drug) is indicated in case of acute intestinal amebiasis, serious colic amebiasis, hepatic amebiasis, hepatobiliary distomatosis, and bilharziosis in case of contraindication or lack of response to other schistosomicides. The normal posology is 1 mg/kg/day for 10 days, by SC injection. Treatment cycles must be 10 days apart. The main side effects are gastrointestinal distress (nausea, diarrhea), cardiovascular symptoms (hypotension, tachycardia, ECG alterations), and neuromuscular problems.

The drug is still used to prepare ipecac powder (French Pharmacopoeia, titrated to contain 2.0±0.1% total alkaloids, a controlled substance on French *liste II*, i.e. a prescription drug) and mostly syrups: ipecac syrup, balsam syrup, compound ipecac *

* Ipecac roots (30 g), senna folioles (100 g), wild thyme (30 g), corn poppy flowers (125 g), magnesium sulfate (100 g), white wine (750 g), orange flower water (750 g), potable water (3,000 g), sucrose to make syrup; a controlled substance on French *liste II*, i.e. a prescription drug, but exempt in amounts lower than 650



Synthesis of dehydroemetine

syrup, better known as Desessartz syrup. The latter is the chief ingredient of another syrup still used in France: compound bromoform syrup *. These syrups are often, like Tolu balsam syrup, incorporated into other compound (proprietary) syrups.

Ipecac syrup (a controlled substance on French *liste II*, i.e., a prescription drug, but which is exempt up to 40 g) is used as an emetic in the treatment of intoxications (except if the patient is unconscious or comatose, or if the intoxication is due to acids, bases, convulsants, or volatile hydrocarbons). The syrup must be used as soon as the intoxication is diagnosed (induced vomiting is only justified within the hour that follows ingestion). Doses are 15 mL in adults with tepid water, with the option of a second dose after 15 minutes, and 15 mL in children from 1 to 12 years of age. In general ipecac syrup is well tolerated, but it can have side effects. The administration of apomorphine by SC injection is often preferred: its effect is quasi instantaneous.

A late 1990s critical review of published results has led European and North American toxicologists to recommend against the routine use of ipecac syrup: there is no clinical evidence of a beneficial effect on the outcome of the intoxication. Ipecac administration can delay (or diminish the efficacy of) the oral administration of activated charcoal or antidotes.

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* Official bromoform solution (1 g), codeine (0.05 g), 90% alcohol (3.45 g), aconite root tincture (0.5 g), cherry-laurel water (5 g), Tolu balsam syrup (30 g), compound ipecac syrup (60 g); a controlled substance on French *liste II*, i.e. a prescription drug, but exempt in