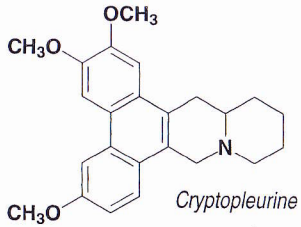
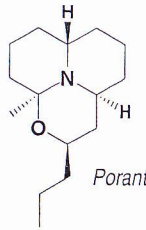
Quinolizidine Alkaloids

Quinolizidine is a bicyclic nitrogen-containing heterocycle which is particularly common in alkaloid structures. One must distinguish, however, the compounds that comprise this moiety as one element in a complex edifice (e.g., protoberberines, most of the indole alkaloids, or solanidanes), from those known as "simple quinolizidines", which arise from the metabolism of lysine: this biogenetic restriction allows us to not cover here the furanoquinolizidines of *Nuphar*, which are nitrogen-containing sesquiterpenes.

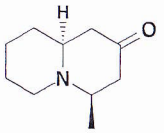
Other structures will also not be covered here: pharmacologically they are of little interest, or most often, of unknown interest. Examples include myrtine (from



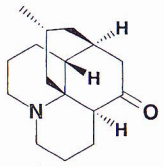
Cryptopleurine



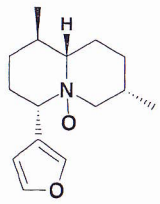
Porantheridine



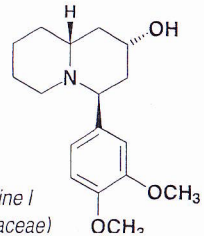
Epimyrtine



Lycopodine



Nupharidine



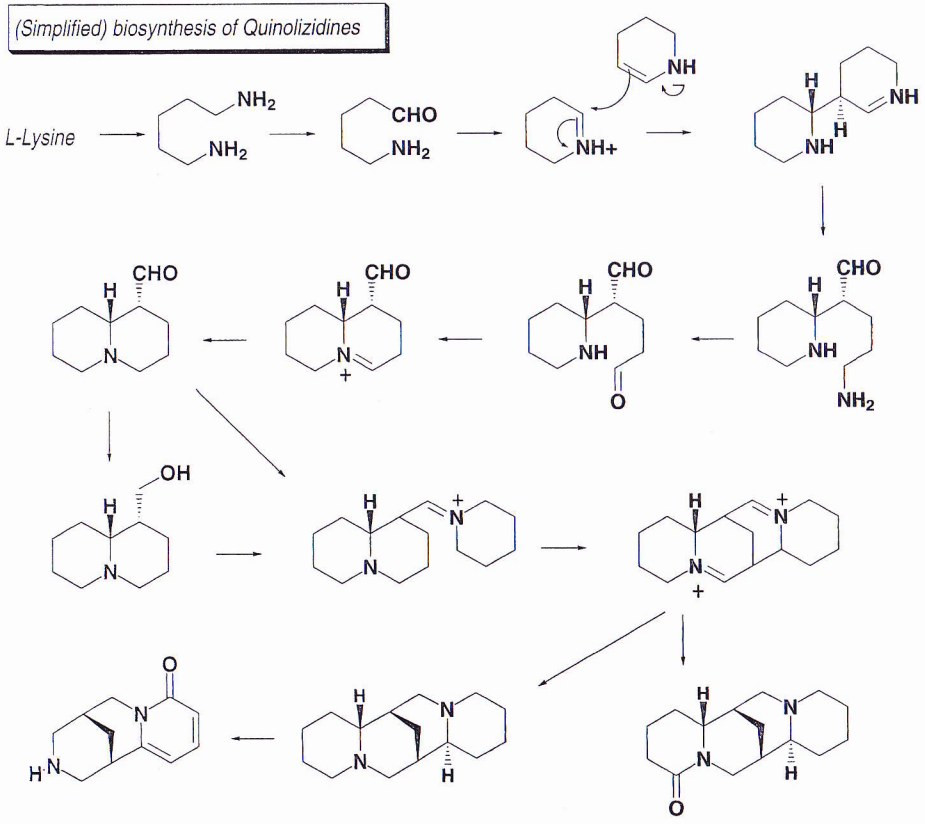
Lasubine I (Lythraceae)

Vaccinium myrtillus, Ericaceae), porantherine and its analogs, isolated from *Poranthera corymbosa* A. Brongn. (Euphorbiaceae), most of the alkaloids of the Lythraceae, and finally the phenanthroquinolizidines, even though one representative, cryptopleurine, has known antimicrobial properties.

Therefore, the only quinolizidines remaining to be mentioned here are the bi-, tri-, or tetracyclic derivatives which characterize the family Fabaceae, and which, in a certain number of cases, are responsible for their toxicity. Nearly 200 quinolizidines are known; they are distributed in seven structural groups depending on the number and arrangement of the rings.

Biosynthesis. Biogenetically, the (obvious) hypothesis that cadaverine plays a role of precursor is clearly demonstrated by labeling experiments. Thus, the incorporation of [1,2-$^{13}C_2$]-cadaverine by *Lupinus luteus* leads to (–)-lupinine and (–)-sparteine labeled in the expected positions, as shown by ^{13}C NMR spectroscopy. The key intermediate appears to be Δ^1-piperideine, which occurs as two tautomers (enamine and iminium) that undergo condensation with one another.

(Simplified) biosynthesis of Quinolizidines



• Scotch Broom, *Cytisus scoparius* (L.) Link., Fabaceae

Broom has been used since Antiquity to prepare diuretic infusions. Its branches are a source of sparteine, a quinolizidine alkaloid which is a ganglioplegic and a cardiac analeptic. Sparteine sulfate is listed in the 10th edition of the French Pharmacopoeia, as is the dried flower.

The Plant. This plant, also known as *Sarothamnus scoparius* (L.) Wimmer ex Koch, is a bushy shrub (50-150 cm) fond of siliceous soils and very common in all of Europe. It is characterized by erect, angular, and glabrous branches, at the apex of which are inserted simple and sessile leaves, whereas at their base the leaves are petiolate and trifoliolate. The flower's zygomorphous corolla with vexillar prefloration is typical of the Fabaceae. It has a short, bilabiate, and scarious calyx, and a coiled style. The fruit is a hairy and flattened pod which turns black when ripe. Scotch broom is often confused with rush-leaved broom, *Spartium junceum* L., a species commonly found around the Mediterranean, which is widely used for ornamental purposes and known for the toxicity of its seeds (they contain cytisine and other closely related quinolizidines). Rush-leaved broom differs from Scotch broom by its greater height, its cylindrical branches, and its flowers with a monolabiate calyx and straight style. The flowers are used to prepare an absolute of complex composition which is used in perfumery.

The industrial needs for branches are low, and are fulfilled by harvesting wild plants during the dormant season (the concentration of alkaloids reaches a maximum in the winter).

Chemical Composition. The plant is rich in active substances belonging to different chemical classes.

- Amines are concentrated especially in the flowers (up to 2% of the dry weight): tyramine, dopamine and its *N*-methyl derivative, epinine.
- Flavonoids occur in all of the parts, and consist of isoflavones and of flavone *C*-glycosides. The chief constituent is scoparoside, which is 5,7,4'-trihydroxy-3'-methoxyflavone 8-*C*-glucoside.
- Alkaloids are represented by a major constituent (0.5-1%), by far the chief constituent in the branches (60%), namely (–)-sparteine, a tetracyclic alkaloid without oxygen atoms and with two *trans*-fused *cis*-quinolizidine nuclei (6*R*,7*S*,9*S*,11*S* isomer). The other alkaloids are lupanine and its hydroxylated derivatives, ammodendrine and closely related compounds (lupanine and related compounds accumulate in the seeds, pods, and roots).

Pharmacological Activity. Sparteine is a mild ganglioplegic, which blocks conduction and prevents the depolarization of the post-synaptic membrane. In the heart, after a transient phase of ganglionic excitation, it shields the myocardium from central neurovegetative regulation, and decreases excitability, conductibility, and the frequency and amplitude of the contractions. This alkaloid is also oxytocic: it causes a moderate increase in the tone and strength of the contractions of the uterus.

Tests. The quality control of the flowers is mostly qualitative: TLC analysis of the phenethylamines (visualization with ninhydrin) and alkaloids; the other tests are water (<12%), total ashes (<5%), and foreign elements (<5%).

Uses. The potency of sparteine (particularly on the heart) is the reason why broom stems are not used—in France—to prepare infusions, but only to extract sparteine: after extracting with acidified water, the aqueous phase is alkalinized and undergoes steam distillation; sparteine separates within the condensate, based on the difference in density. The crude product is purified and converted to the sulfate.

Uses of Sparteine. Sparteine sulfate (on French *liste II*, i.e., a prescription product that may be renewed), are indicated for sinusal tachycardia of neurotonic origin and cardiac erethism (50-100 mg/day, IM or SC), as well as in obstetrics, as an oxytocic during labor (100-150 mg, SC or IM, repeated after one hour).

Uses of Scotch broom. In France, phytomedicines based on broom flowers may be (traditionally) used to enhance urinary and digestive elimination functions and to enhance the renal excretion of water [French Expl. Note, 1998].

The German Commission E monograph states that hydroalcoholic extracts of broom stems are used for cardiac and circulatory functional disorders. Package inserts must bear a warning not to use broom preparations during pregnancy and in case of hypertension. The occurrence of tyramine in broom creates a risk of drug interaction with MAO inhibitors.

• Golden Chain Tree,
Laburnum anagyroides Medic.
(= *Cytisus laburnum* L.), Fabaceae

The golden chain tree is a shrub growing on limestone hills, and numerous varieties are cultivated for their beauty. Trifoliolate leaves, goldenrod flowers in dangling racemes, and black pods, which are hairy when immature, are all characteristic of this species. Alkaloids occur in all of the parts of the plant, and are especially concentrated in the seeds. Cytisine and related compounds are responsible for the toxicity.

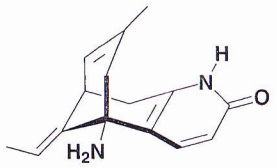
The fruits of the golden chain tree and those of bean and peas look somewhat similar, and this may explain why young children are the most frequent victims of intoxications by this species. Although poisoning by *Laburnum* is one of the leading

causes of calls to European poison control centers, fortunately there are not very many serious intoxications. Most often the symptoms are limited to hypersalivation, burns in the mouth and throat, and early and persistent vomiting, which prevents a massive absorption of the alkaloids. After ingestion of massive doses, the effects of central stimulation by cytisine are observed: excitation, convulsion, and respiratory arrest.

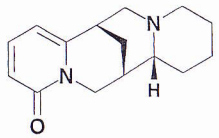
• Lupines,
Lupinus spp., Fabaceae

Lupines are herbaceous plants with compound palmate leaves, and with tight inflorescences of flowers of variable color. They can achieve the fixation of nitrogen out of the air and could be an interesting green fertilizer. Their seeds are rich in proteins, but several varieties are bitter, because they are rich in alkaloids (lupanine, lupinine), which limits the use of lupines as animal feed to the "sweet" cultivars.

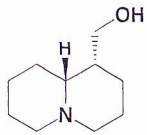
Several species of lupines, especially in North America, owe their toxicity to anagyrine, which is responsible for a teratogenic activity in bovines. There are only anecdotal intoxications in humans: the contamination of milk is possible, but it is normally limited by the industrial practice of mixing the milk from several cows, and the reported cases of poisoning are limited to families producing their own dairy products or to insufficient debittering of alkaloid-containing lupines.



Huperzine A



Anagyrine



Lupinine

Special Case: Alkaloids of the Lycopodiaceae

• *Huperzia serrata* (Thunb.) Trevis.
= *Lycopodium serratum* Thunb.

Traditionally the spores of the *Lycopodium* are used as an absorbent powder.

H. serrata is a traditional Chinese remedy (*Qian Ceng Ta*) said to have been used to treat fever and inflammation. It contains $C_{16}N_2$ alkaloids (flabellidanes), including huperzines A and B, lycodine, lycodoline, and serratinidine.

Pharmacologically, huperzine A is a reversible inhibitor of acetylcholinesterase, like physostigmine. Huperzine A binds specifically and strongly to acetylcholinesterase. It crosses the blood-brain barrier. It has a long half-life in that the complex formed with the enzyme dissociates slowly. In tests conducted on cultured

Animal experiments show that huperzine A has an interesting potential for the treatment of poisoning by soman and other chemical weapons, and that it counteracts the memory loss caused by scopolamine.

According to clinical trials conducted in China, huperzine A is not very toxic and it is thought to have some potential for the treatment of memory loss; it has also been tested in the treatment of myasthenia.

The action of huperzine A is more prolonged than that of physostigmine and it is devoid of the side effects of tacrine (currently used, like donepezil and rivastigmine, to treat Alzheimer's disease). More clinical trials are in the planning stages. Although it has no immediate clinical applications, huperzine is an interesting structural model for the design of molecules with a high affinity for acetylcholinesterase. Synthetic analogs have also been tested and research is in progress in animals, mainly in the context of learning and memorization.

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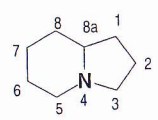
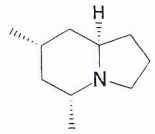
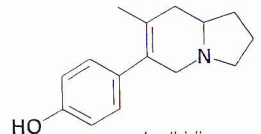
Indolizidine Alkaloids

Indolizidine alkaloids are toxic principles occurring in the skin of certain Amphibia (e.g., pumiliotoxins) and are rather rare in plants: alkylindolizidines and bisindolizidines of *Dendrobium* (Orchidaceae), arylindolizidines of certain *Ipomœa* (Convolvulaceae). Although no plant producing alkaloids derived from this bicyclic heterocycle is currently used in therapeutics, compounds such as swainsonine and castanospermine are undoubtedly interesting because of their ability to inhibit glycosidases. We shall not cover here the phenanthroindolizidines of *Tylophora* and of some of the Moraceae (arising from the mixed metabolism of tyrosine and ornithine), the alkaloids of the Elaeocarpaceae, or the alkaloids of *Securinega* (Euphorbiaceae).

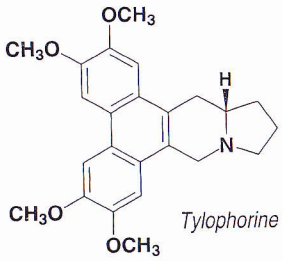




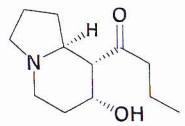
Dendroprimine



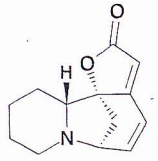
Ipalbidine



Tylophorine



Elaeokanine C



Securinine