Plant Alkaloids

Secondary article

Jack G Woolley, *De Montfort University, Leicester, UK*

Article Contents

Alkaloids are basic (alkali-like), nitrogen-containing organic constituents found in some plants. They give positive responses with Dragendorff, Mayer, Hager and Wagner reagents.

Introduction

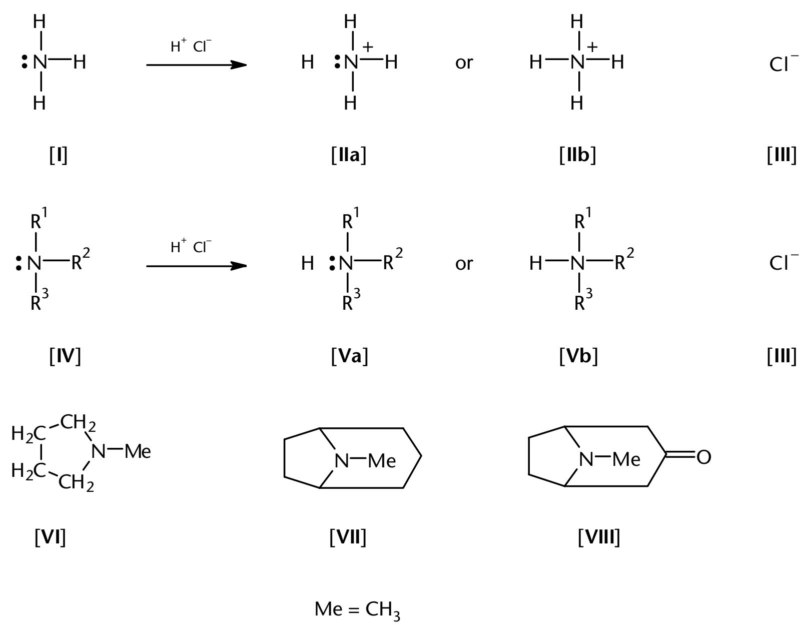
Alkaloids are organic bases. Many alkaloids are poisonous, others are addictive (e.g. cocaine), and some are used clinically (e.g. morphine [**XXXI**]). More than 10 000 alkaloids are now known, the first discovered being narcotine [**XXVII**], isolated from opium by Derosne in 1803. Alkaloids exist as salts (**Scheme 1**) in the cell sap. They may be extracted from the cell with acidified water or alcohol, or alternatively they are soluble in organic solvents (e.g. chloroform) when the plant is rendered alkaline. Alkaloids are normally classified according to the heterocyclic ring system they possess, but some authors prefer a classification based on their biosynthetic origins from amino acids, e.g. phenylalanine [**XVII**], tyrosine [**XVIII**] or tryptophan [**XIX**] (**Scheme 2**).

Occurrence in the Plant Kingdom

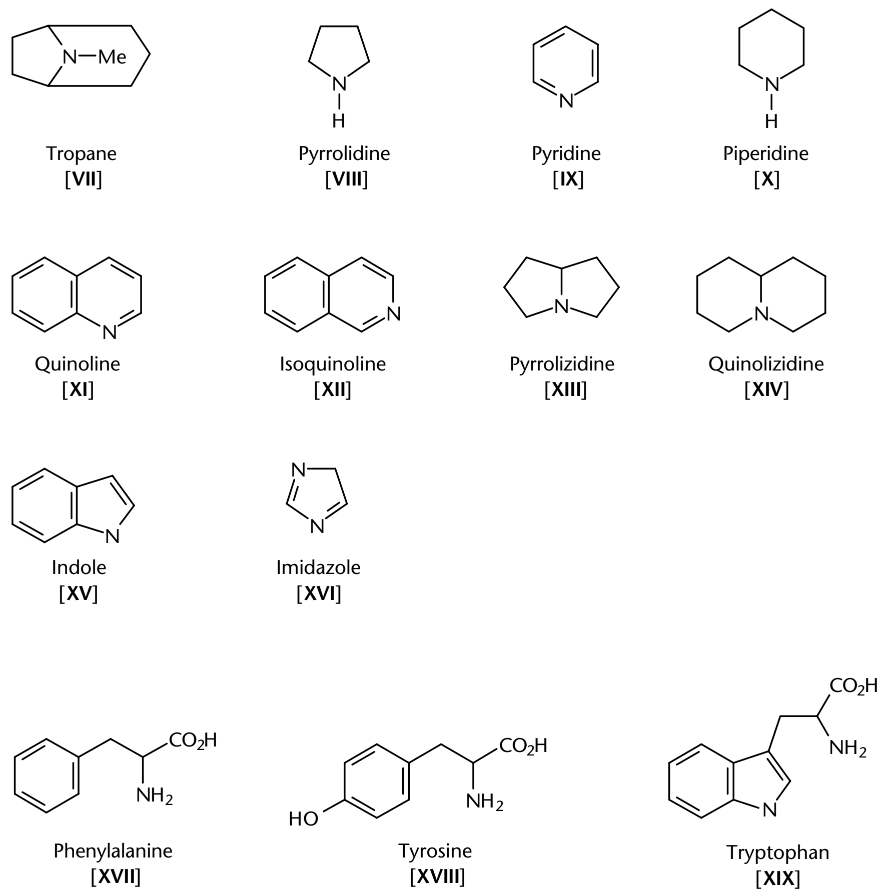
Alkaloids are common in the Angiosperms (Mono- and Dicotyledons), but rare in lower plants, although there are exceptions, for example pacletaxel from yew (a Gymnosperm), lycopodine [**XXXII**] from *Lycopodium* and palustrine [**XXXIII**] from *Equisetum* (both Pteridophytes), and even fungi, e.g. ergometrine (*Claviceps*). These structures are shown in **Figure 1**. The distribution of alkaloids in the plant kingdom is listed in **Table 1**.

Occurrence in the Animal Kingdom

Many authors consider alkaloids to be exclusively plant products, but similar compounds are found elsewhere. Of particular interest are the extremely toxic skin secretions from 'poison dart' frogs of South America (e.g. batrachotoxin from *Dendrobates* and *Phyllobates*). Simply wiping the dart across the back of the frog is said to be sufficient to produce a poison dart. *Epipedobates tricolor* (Ecuadoran



Scheme 1 General structure and basicity of alkaloids.



Scheme 2 Classification of alkaloids.

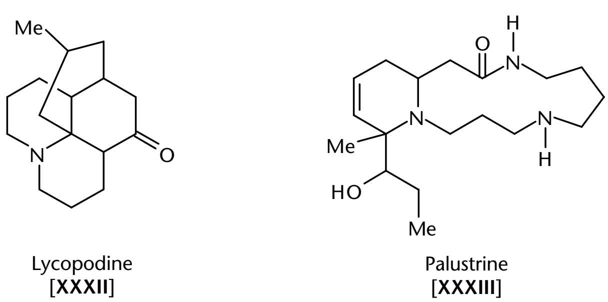


Figure 1 Alkaloids from primitive plants.

tree frog) is of much interest since epibatidine [**XXXIV**] is *c.* 200 times more potent than morphine [**XXXI**] as an analgesic. Even the humble ladybird secretes the alkaloid coccinelline [**XXXV**] for defence (**Figure 2**).

Biosynthetic Pathways

Alkaloids are produced by secondary metabolism of primary metabolites, usually amino acids. These pathways are long, intricate, stereochemically precise and energy consuming, and are assumed to be of evolutionary benefit. Normally these routes are explored using isotopically labelled precursors that are introduced into the plant, as shown in **Schemes 3** and **4**.

In many instances enzymes mediating single steps in the pathways have been isolated and characterized and in a growing number of cases the gene encoding the enzyme has been isolated and cloned. Good examples are the *PMT* (putrescine methyltransferase) and *H6H* (hyoscyamine 6-hydroxylase) genes involved in the biosynthesis of hyoscine [**XLI**] (scopolamine) in *Atropa* and *Hyoscyamus*. The H6H enzyme is unusual in that it catalyses two steps, as illustrated in **Scheme 5**.

Table 1 Distribution of alkaloids in the plant kingdom

Family	Alkaloid	Plant genus[a]	Biological activity[b]
Agaricaceae	Bufotenine	*Amanita* (m)	Hallucinogen
	Muscarine	*Amanita* (m)	Acetylcholine-like
	Psilocybine [**XXII**]	*Psilocybe* (m)	Hallucinogen
Amaryllidaceae	Lycorine	*Amaryllis* (b)	
	Galanthamine	*Galanthus* (b)	Alzheimer disease
		Narcissus (b)	
Apocynaceae	Alstonine	*Alstonia* (bk)	Antimalarial
	Aspidospermine	*Aspidosperma* (bk)	Respiratory stimulant
	Yohimbine [**XXI**]	*Yohimbe* (bk)	Aphrodisiac
	Conessine	*Holarrhena* (bk)	Antidysenteric
	Ellipticine	*Ochrosia* (bk)	Anticancer
	Akuammigine	*Picralima* (s)	Antimalarial
	Reserpine [**XX**]	*Rauwolfia* (rh)	Tranquillizer
	Serpentine [**XXIV**]		
	Vinblastine [**XXV**]	*Catharanthus* (l)	Anticancer
	Vincristine		
Aristolochiaceae	Aristolochic acid	*Aristolochia* (rh)	Tumour-inducing
Berberidaceae	Berberine [**XXIX**]	*Berberis* (bk)	Antibacterial
		Mahonia (bk)	Antimalarial
Boraginaceae	Indicine *N*-oxide	*Heliotropium* (l)	Anticancer
Cactaceae	Mescaline [**XXX**]	*Lophophora* (l)	Hallucinogen
Campanulaceae	Cathine	*Catha* (l)	CNS stimulant
	Ephedrine		
Celastraceae	Maytansine	*Maytenus*	Anticancer
Chenopodiaceae	Anabasine	*Anabasis* (l)	Insecticidal
Clavicepitaceae	Ergometrine	*Claviceps* (fb)	Postpartum haemorrhage
	Ergotamine		Migraine
Convolvulaceae	Calystegines [**XLII**]	*Calystegia* (r)	Antiviral
	Agroclavine	*Ipomoea* (l)	Hallucinogen
Ephedraceae	Ephedrine	*Ephedra* (hb)	CNS stimulant
Equisitaceae	Palustrine [**XXXIII**]	*Equisetum* (l)	
Erythroxylaceae	Cocaine	*Coca* (l)	Local anaesthetic
Graminae	Loliine	*Lolium* (l)	
Leguminosae	Castanospermine	*Castanosperma* (s)	Antiviral, 'locoism' (stock)
	Cytisine	*Cytisus* (hb)	Very toxic
		Anagyris (hb)	Teratogenic
	Sparteine		Diuretic
	Swainsonine	*Swainsona*	Glysosidase inhibitor 'locoism' (stock)
	Monocrotaline	*Crotalaria* (l)	Hepatotoxic, tumour-inducing
	Physostigmine	*Physostigma* (s)	Ophthalmology
			Cholinesterase inhibitor
Liliaceae	Colchicine	*Colchicum* (c)	Induces polyploidy
	Cevadine	*Schoenocaulon* (s)	Insecticidal
	Rubijervine	*Veratrum* (r)	Antihypertension

continued

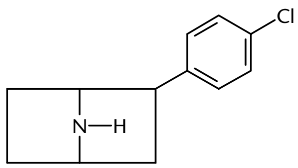
Table 1 – *continued*

Family	Alkaloid	Plant genus[a]	Biological activity[b]
Loganiaceae	Strychnine	*Strychnos* (s)	Very poisonous
Lycopodiaceae	Lycopodine [**XXXII**]	*Lycopodium* (l)	
Menispermaceae	Tubocurarine	*Chondrodendron* (bk)	Neuromuscular blocking agent, muscle relaxant
Moraceae	Calystegines	*Morus* (l)	Antiviral, oral hyperglycaemic agent
Orchidaceae	Dendrobine	*Dendrobium* (hb)	
Palmae	Arecoline	*Areca* (s)	Anthelmintic
Papaveraceae	Chelerythrine	*Dicentra*	Diuretic
	Codeine	*Papaver* (lt)	Analgesic
	Morphine [**XXXI**]		Analgesic, narcotic
	Narcotine [**XXVII**]		Cough suppressant
	Papaverine [**XXVI**]		Anti-impotence vasodilator
	Thebaine		
Ranunculaceae	Aconitine	*Aconitum* (hb)	Diaphoretic, rheumatism, neuralgia (topical)
	Ajaconine	*Delphinium* (hb)	
Rubiaceae	Emetine [**XXVII**]	*Cephaelis* (rh)	Amoebic dysentery
		Psychotria (r)	
	Quinine	*Cinchona* (bk)	Antimalarial
	Quinidine		Antiarrhythmia (heart)
Rutaceae	Harmaline	*Peganum* (sd)	Anthelmintic
	Pilocarpine	*Pilocarpus* (l)	Glaucoma, ophthalmology
	Canthin-6-one	*Pentacerus*	Antibacterial
Solanaceae	Capsaicin	*Capsicum* (fr)	Hot taste
	Hyoscine [**XLI**]	*Atropa* (hb)	Travel sickness, amnesia
	Hyoscyamine [**XXXIX**]	*Datura* (hb)	Antagonist of acetylcholine
		Hyoscyamus (hb)	
		Duboisia (hb)	Preoperative treatment
		Mandragora (r)	
	Tigloidine	*Duboisia* (hb)	Parkinson disease
	Solanidine	*Solanum* (tb)	Toxic
	Nicotine	*Nicotiana* (1)	Insecticidal, smoking
Taxaceae	Pacletaxel	*Taxus* (1)	Anticancer drugs
	Baccatin		Anticancer drugs

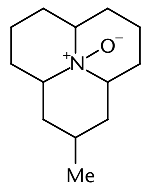
[a]Part of plant used: (l), leaves; (s), seeds; (hb), herbs; (bk), bark; (rh), rhizome; (tb), tuber (green); (fr), fruits; (lt), latex; (r), roots; (c), corm; (fb), fruiting body; (b), bulb; (m), mushroom.
[b]Biological activity relates to the plant and not necessarily the alkaloids that are listed as representative examples of the families.

Sequestration by Insects from Plants

Moths of the Arctiidae and Ctenuchidae are well known to sequester pyrrolizidine alkaloids, but many insects of the Coleoptera, Homoptera, Lepidoptera and Orthoptera do the same as a means of protection against predators. Aphids ingest pyrrolizidines from the sap of plants and ladybirds feeding on the aphids are thereby able to accumulate these alkaloids. Eggs acquire the bases, usually from the male during copulation, the eggs subsequently being laid on a suitable (protective) plant. On hatching the larvae sequester pyrrolizidines from eating the leaves of the host. There is often a specific relationship between insect and host. The cinnabar moth (*Tyria jacobaea*) feeds on ragwort (*Senecio jacobaea*) and accumulates senecionine [**XLVI**] and other bases. The death's-head hawk moth (*Acherontia atropus*) sequesters calystegines [**XLII**] from potato plant leaves. Some insects of the Arctiidae feeding



Epibatidine
[**XXXIV**]



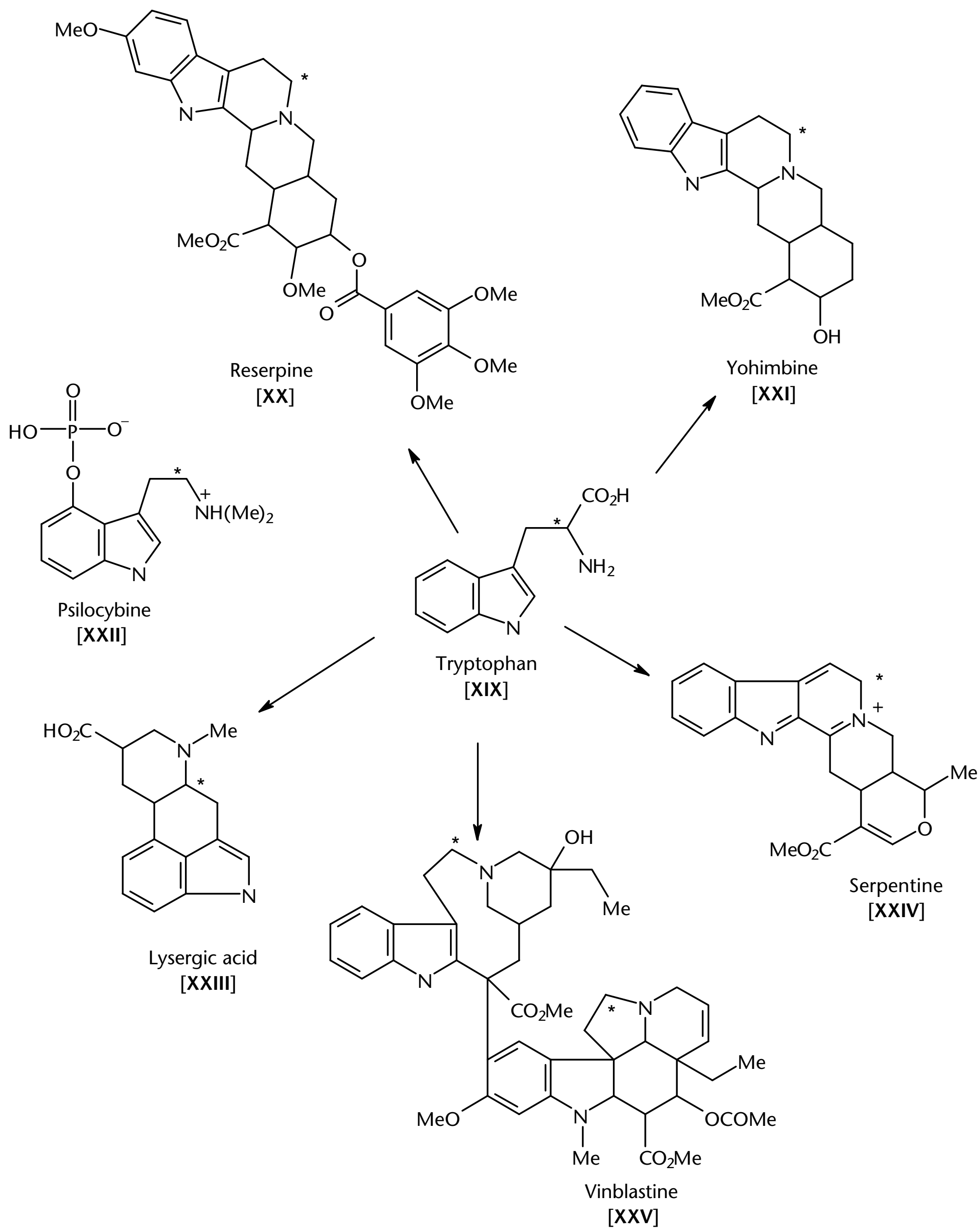
Coccinelline
[**XXXV**]

Figure 2 An alkaloid from a frog [**XXXIV**] and from an insect [**XXXV**].

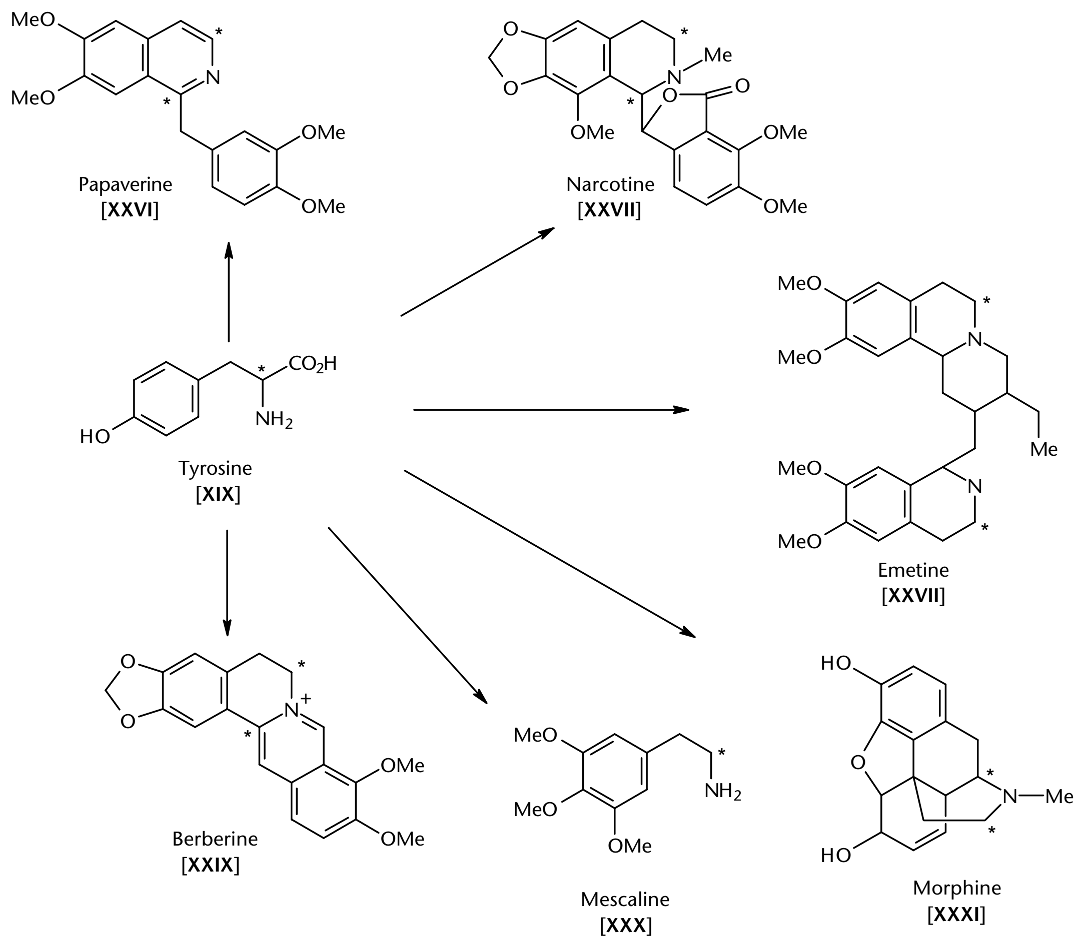
on Boraginaceous plants convert sequestered pyrrolizidine alkaloids, e.g. [**XLIII**] into the male courtship pheromone hydroxydanaidal [**XLIV**]. (**Figure 3**).

Physiological Properties

The poisonous and therapeutic effects of plants have been known since time immemorial, but the active constituents have been studied for only about 200 years.



Scheme 3 Some alkaloids are derived from the labelled (*) amino acid tryptophan.



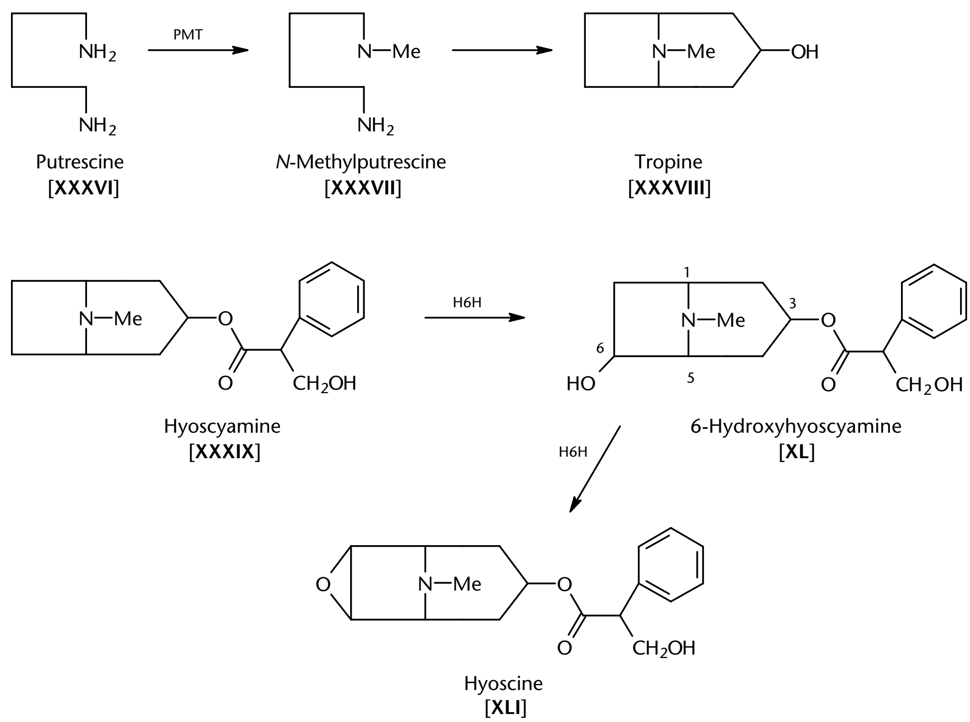
Scheme 4 The biosynthetic origins of some alkaloids. The precursor tyrosine is labelled with isotopic carbon (*) and during biosynthesis the alkaloidal metabolites are specifically labelled at the sites shown (*).

After the discovery of the first alkaloid, narcotine, other alkaloids were rapidly discovered: morphine (opium), strychnine (*Strychnos nux-vomica* seeds), emetine (ipecacuanha root), quinine (*Cinchona* bark) and coniine (hemlock).

Alkaloids are used medicinally in their own right e.g. hyoscyamine [**XXXIX**] and vinblastine [**XXV**] and they have often provided lead compounds for the development of synthetic drugs. For example, cocaine was the first local anaesthetic, quinine the first antimalarial and tubocurarine the first neuromuscular blocking agent. Recent discoveries include pacletaxel from the Pacific Yew and epibatidine [**XXXIV**]. Alkaloids frequently have powerful physiological effects; some of these are listed in **Table 2**.

Site of Synthesis in Plants

Establishing the site of synthesis is difficult since the site of storage is not necessarily the site of synthesis. Grafting experiments (within the same plant family) where the scion of a non-alkaloid-producing plant (e.g. *Cyphomandra*) was bound to the stock of an alkaloid-producing plant (e.g. *Datura*) showed that the scion contained tropane alkaloids. The reciprocal graft gave a *Datura* scion devoid of alkaloids. Root cultures of Solanaceous plants (*Datura*, *Atropa*, *Hyoscyamus*, *Duboisia*, *Nicotiana*, etc.) all produce alkaloids in the absence of the aerial parts. In contrast, the shoot is the site of synthesis in *Ephedra* (ephedrine), hemlock (coniine) and lupin (lupanine). At the subcellular level, alkaloids frequently accumulate as salts within the vacuole, which has a slightly acid pH. It is now possible to show where individual genes are activated within tissues. The *H6H* gene is not switched on unless its adjacent 5′



Scheme 5 Biosynthesis of hyoscine (scopolamine); this involves the enzymes putrescine methyltransferase (PMT) and hyoscyamine 6-hydroxylase (H6H).

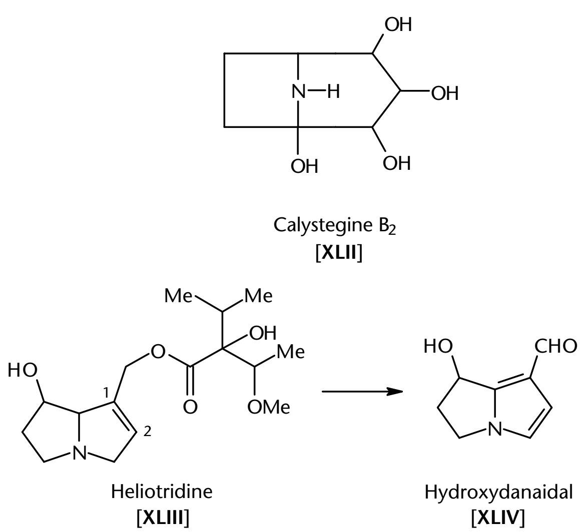


Figure 3 Some alkaloids sequestered and metabolized by insects.

promoter region of the DNA is activated. Replacing the *H6H* gene with a 'reporter' gene (*GUS*, a β-glucuronidase-encoding gene) behind the promoter ensures that the new gene is expressed when the promoter is activated. The new construct was transferred to *Atropa* and *Hyoscyamus*. Sections of the plant were then incubated with a substrate that becomes blue by the action of the GUS enzyme. The *GUS* was expressed solely in the pericycle region of the root and therefore the *H6H* gene is as well.

Production in Cell Culture

Many useful plants grow in inaccessible parts of the world or where access is limited by political uncertainties. Some are in short supply and do not lend themselves to farming, or are perhaps slow growing (e.g. the Pacific Yew, *Taxus brevifolia*, the source of pacletaxel). Sometimes the desired alkaloid is present only in trace quantities (e.g. vinblastine [**XXV**] from *Catharanthus roseus*). For these and other reasons, there has been an enormous effort to grow medicinal plants in flasks (or fermenters) where alkaloid production may be optimized, carried out without seasonal variations and when required. Plants are differentiated into roots, shoots, etc. and within the tissues into xylem, phloem, etc. Under the influence of plant hormones (IAA, indoleacetic acid, or the synthetic weedkiller 2,4-D), plants dedifferentiate into identical single-cell clumps (callus). Callus can be broken down into a suspension culture when

Table 2 Some biological actions of alkaloids

Pharmacological biological action	Alkaloid
Acts directly on blood vessels (dilate)	Papaverine [**XXVI**]
Acts on adrenergic receptors	Ergotamine, ergometrine, yohimbine [**XXI**]
Acts on ganglia	Nicotine, lobeline
Amoebiasis	Emetine [**XXVII**], conessine
Analgesics	Morphine [**XXXI**], codeine
Antibacterial	Berberine
Anticancer	Camptothecine, demecolcine (desacetylmethylcolchicine), ellipticine, indicine *N*-oxide, maytansine, pacletaxel, vincristine, vinblastine [**XXV**]
Anticholinesterase activity	Physostigmine
Antiemetic	Hyoscine, (scopolamine) [**XLI**], hyoscyamine [**XXXIX**]
Antihypertensive	Cevadine, veratrine, reserpine [**XX**], serpentine [**XXIV**], rubijervine
Antimalarial	Quinine, alstonine
Cardiac arrhythmias (control of)	Quinidine, quinine
Cholinergic receptors (bind to)	Arecoline, hyoscyamine [**XXXIX**], muscarine, pilocarpine
Central nervous system (CNS) depressant	Reserpine [**XX**], serpentine [**XXIV**]
CNS stimulants	Caffeine,[a] cathine, cocaine, ephedrine, lobeline, strychnine
Cough depressant	Codeine, narcotine [**XXVII**]
Expectorants	Emetine [**XXVII**] (emetic)
Hallucinogens	Bufotenine, harmine, mescaline, psilocybine [**XXII**]
Helminthiasis (treatment of)	Arecoline, pelletierine
5-Hydroxytryptamine (5-HT) antagonists	Harmine, yohimbine [**XXI**]
Local anaesthetic	Cocaine
Monoamine oxidase (MAO) inhibitors	Cocaine, ephedrine, harmine
Neuromuscular blocker	Tubocurarine
Oral hyperglycaemic agents	Calystegines (as [**XLII**])
Rheumatism, gout	Colchicine, aconitine (topical)

[a] Caffeine is sometimes regarded as an alkaloid, even though it fails to give the normal alkaloid precipitation tests. It is related to the nucleic acids.

the culture fluid is agitated and this kind of homogeneous culture is ideal for large-scale production. Unfortunately, despite much effort, cultures cannot yet be persuaded to produce anything like the quantity of alkaloid found in the parent plant.

Hairy root cultures are much used in research into the biosynthesis of alkaloids. They are produced by exposing sterilized plant parts to strains of the soil microorganism *Agrobacterium rhizogenes*, which is able to transfer part of its own DNA (T-DNA) from a plasmid (a circular loop of double-stranded DNA) to the plant's nuclear genome. The T-DNA carries genes encoding the biosynthesis of plant hormones and for the production of opines, unusual nutritional amino acids required by the microorganism. As a consequence the invaded tissue, when rid of *Agrobacteria* using antibiotics, continues to produce opines and it generates hairy (fluffy) roots (even from leaf tissue). By inserting desirable genes into their plasmids, *Agrobacteria* are used to transfer new genes to plants. Some plants that have been grown in culture are listed in **Table 3**.

Alkaloids and Stock Poisoning

Alkaloids of the pyrrolizidine [**XIII**] and indolizidine [**XLVII**] types cause serious toxicity (and death) in livestock, mainly horses, cattle and sheep that graze on plants containing them (**Table 4**). Pyrrolizidines, especially those bases with a C1–C2 double bond, e.g. heliotridine [**XLIII**], cause chronic liver damage and malignant tumours, but monocrotaline [**XLV**] damages the lungs as

Table 3 Alkaloids from plants that have been grown in tissue culture conditions

Alkaloid	Plant	Culture type[a]			
		r	hr	c	sc
Ajmalicine	*Catharanthus roseus*	++	++		
Serpentine [**XXIV**]				++	++
Catharanthine				++	++
Berberine	*Coptis japonica*			++	++
	Berberis wilsoniae				++
	Thalictrum minus				++
	Argemone mexicana				++
Camptothecine	*Camptotheca acuminata*			t	t
Ellipticine	*Ochrosia elliptica*			t	t
Emetine [**XXVII**]	*Cephaelis ipecacuanha*	+++		t	t
Hyoscine [**XLI**] and	*Atropa belladonna*	+++	+++	t	t
Hyoscyamine [**XXXIX**]	*Atropa caucasica*	+++	+++	t	t
	Brugmansia sanguinea	+++	+++	t	t
	Datura innoxia	+++		t	t
	Datura metel	+++		t	t
	Datura wrightii (meteloides)	+++		t	t
	Datura stramonium	+++	+++	t	t
	Datura tatula	+++		t	t
	Duboisia leichhardtii	+++		t	
	Duboisia myoporoides	+++	+++	t	t
	Hyoscyamus muticus	+++	+++	t	t
	Scopolia japonica	+++	+++	t	t
	Scopolia carniolica	+++	+++	t	t
Morphine [**XXXI**] and codeine	*Papaver* sp.			t	t
Nicotine	*Nicotiana africana*	+++			
	Nicotiana alata	+++			
	Nicotiana cavicola		+++		
	Nicotiana glauca	+++			
	Nicotiana hesperis		+++		
‘	*Nicotiana rustica*	+++	+++	t	t
	Nicotiana tabacum	+++	+++	t	t
	Nicotiana umbricata	+++			
	Nicotiana velutina		+++		
Pacletaxel	*Taxus baccata*			+	
Quinine and quinidine	*Cinchona ledgeriana*		+	+	
	Cinchona robusta			t	t
	Cinchona succirubra		t	t	
Reserpine [**XX**]	*Rauwolfia serpentina*		t		
Ajmaline	*Rauwolfia serpentina*			t	
Vincamine	*Vinca minor*				++

[a] r, root; hr, hairy root; c, callus; sc, suspension cultures. Relative quantities of alkaloids, +; t, trace. (A very approximate series of estimations.)

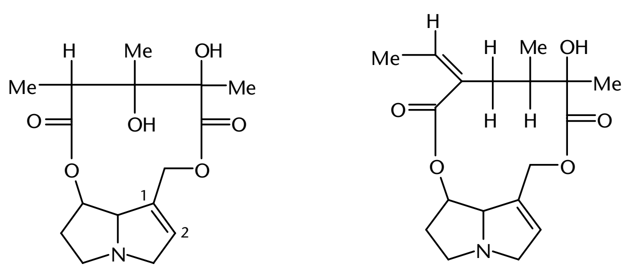
well. Ironically the pyrrolizidine alkaloid indicine *N*-oxide is used in the treatment of cancer. Indolizidines, swainsonine [**XLVIII**] and castanospermine [**XLIX**], are powerful glycosidase inhibitors that cause ‘locoism’, leading to histologically visible neurological damage to neurons in the brain and ultimately death. (**Figure 4**).

Less well known are the more-recently described calystegines (*nor*tropanes), e.g. calystegine B_2 [**XLII**],

Table 4 Toxic plants

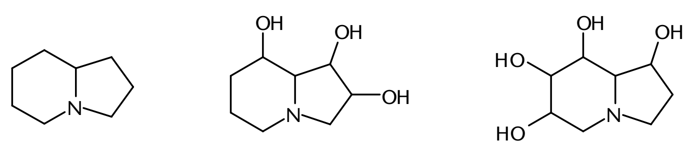
Genus[a]	Species	Typical alkaloid[b]	Toxicity[c]	Location
Amsinkia (B)	*intermedia*	Lycopsamine (P)	Hepatotoxic	NW USA
Echium (B)	*lycopsis*	Echimidine (P)	Hepatotoxic	SE Australia
Heliotropium (B)	*lasiocarpum*	Heliotrine (P)	Hepatotoxic	C Asia
	europaeum		Hepatotoxic (s)	Australia
Trichodesma (B)	*incanum*	Trichodesmine (P)	Hepatotoxic (h)	C Asia
Senecio (C)	*jacobaea*	Senecionine [**XLVI**]	Pictou disease (c,h,p)	Canada
		Seneciphylline (P)	Winton disease (c,h,p)	N Zealand
	latifolius	Seneciphylline (P)	Molteno horse disease	S Africa
	burchelli			
Alexa (L)	*leiopetala*	Alexine (P)	Hepatotoxicity (c)	
Astragalus (L)	*lentiginosa*	Swainsonine [**XLVIII**]	Locoism (c,h)	USA
Castanosperma (L)	*australe*	Australine (P)	Hepatotoxicity	Australia
		Castanospermine [**XLIX**]	Pompe disease	Australia
Crotalaria (L)	*sagitalis*	Monocrotaline [**XLV**]	Missouri bottom disease (h)	USA
Crotalaria (L)	*spectabilis*	Monocrotaline [**XLV**]		
Crotalaria (L)	*dura*	Dicrotaline (P)	Hepatotoxic	S Africa
Crotalaria (L)	*retusa*		Walkabout disease (c)	N Australia
Oxytropis (L)	sp.	Swainsonine [**XLVIII**]	Locoism (c)	USA
Oxytropis	*kansuensis*	Swainsonine [**XLVIII**]	Locoism	China
Solanum (S)	*dimidiatum*	Calystegines [**XLII**]	Crazy cow syndrome	USA
Solanum (S)	*kwebense*	Calystegines (as [**XLII**])	Maldonksiekte	S Africa
Swainsona (L)	*canescens*	Swainsonine [**XLVIII**]	Locoism (c)	Australia
Ipomoea (C)	sp.	Swainsonine [**XLVIII**]	Weir vine disease (c, h, s)	Australia

[a] (B), Boraginaceae; (C), Compositae; (L), Leguminosae; (C), Convolvulaceae, (S) Solanaceae.
[b] (P), Pyrrolizidine.
[c] (c), cows; (h), horses; (p), pigs; (s), sheep.



Monocrotaline
[**XLV**]

Senecionine
[**XLVI**]



Indolizidine
[**XLVII**]

Swaisonine
[**XLVIII**]

Castanospermine
[**XLIX**]

Figure 4 Some alkaloids that cause poisoning of livestock.

which are, like the indolizidines, sugar-mimic glycosidase inhibitors. Since these are widely distributed in the Solanaceae and occur in potato, aubergine, etc., some concern has been expressed as to their possible toxicity to humans.

Further Reading

Bull LB, Culvenor CCJ and Dick AT (1968) *The Pyrrolizidine Alkaloids*. Amsterdam: North-Holland.

Cordell GA (1981) *Introduction to Alkaloids*. New York: Wiley.

Cordell GA (1998) *The Alkaloids*, vol. 52, New York: Academic Press. [a continuing series of expert reviews].

Evans WC (1996) *Pharmacognosy*. London: WB Saunders.

Manske RFH and Holmes HL (1950) *The Alkaloids*, vol. 1. New York: Academic Press.

Pelletier SW (1983) *Alkaloids: Chemical and Biological Perspectives*, vol. 1. Oxford: Pergamon Press.

Pelletier SW (1998) *Alkaloids: Chemical and Biological Perspectives*, vol. 12, Oxford: Pergamon Press [a continuing series of expert reviews].