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Plant poisons: their occurrence, biochemistry and physiological properties

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ABSTRACT

Plants produce poisons as a defence against predators. Many of these substances are biosynthesised from non-protein amino acids by biosynthetic pathways which have been deduced from the results of isotopic tracer analysis. These secondary metabolites have been used by humans over thousands of years, both as drugs and as agents to kill animals and commit homicide.

Keywords: *plant poisons, drugs, biosynthetic pathways*

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Introduction

The myths surrounding the poisonous effects of plants are many and it was not always easy to separate fact from legend. The study of phytochemistry, however, clarified this ambiguity considerably. Isolation of the chemicals present and the testing of their physiological effects established with certainty whether or not a plant is poisonous and the effects the poison has on animals, including man.

Plate 1 *Ragwort (Senecio Jacobaea) en.wikipedia.org/wiki/Jacobeae_vulgaris*

Studies of biosynthetic pathways have shown that the majority of plant poisons are the result of secondary metabolism.

Historically, plant metabolism was separated into primary and secondary. Primary metabolism produces the building blocks of life: carbohydrates, proteins and fats, while a large number of secondary metabolites are synthesised to protect the plant from attack by animals, fungi, bacteria and viruses. Although it is now accepted that the processes of primary and secondary metabolism are interrelated and that such a sharp division is no longer valid, it is helpful when considering the biosynthetic pathways producing the wealth of compounds found in plants.

Plant poisons are products of secondary metabolism, generally being biosynthesised from quite simple compounds, such as amino acids or sugars through pathways involving catalysis by enzymes. Their main aim is to protect the plant from animal and insect attack. Compounds, such as the alkaloids and cyanogenic glycosides have a bitter taste, warning the animal of their toxicity. Should the animal continue to eat, however, it is likely that it will be killed and toxic plants are of great economic importance to farmers, especially in the developing countries. Herbaceous plants that grow where animals graze are the most dangerous and many losses occur from the pyrrolizidine alkaloids in ragwort (*Senecio* species, Compositae, Plate 1).

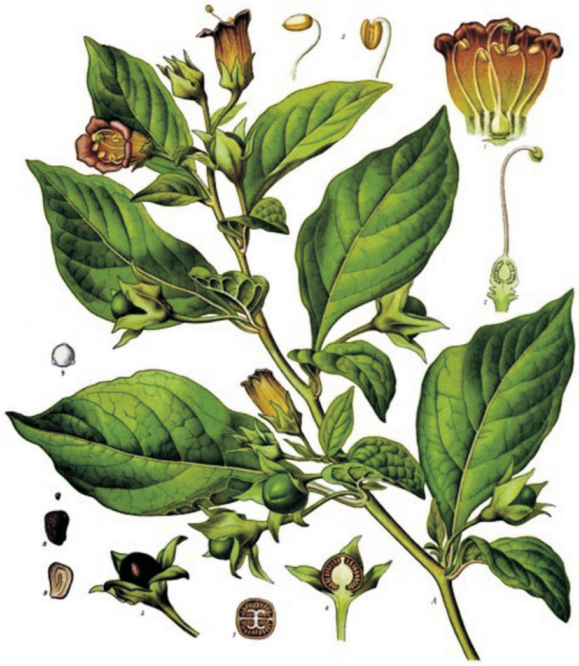


Plate 2 *Deadly nightshade (Atropa belladonna); en.wikipedia.org/wiki/Atropa_belladonna*

Stock losses would be much greater however, if animals were not able to recognise and avoid poisonous plants within an area well known to them. Animals moved to a strange environment will not have this ability and are not always deterred by a bitter taste. Cattle can become addicted to buttercups (*Ranunculus* species, Ranunculacea) and will continue to eat the plants even after recovering from a serious bout of poisoning. The compounds most useful to the plant itself though, the insecticides, are generally non-toxic to animals, at least in the concentrations found in plants.

Poisonous plants are also dangerous to man as they can be eaten by children or mistaken for edible plants by adults. Particularly dangerous to children are plants with attractive fruits, such as deadly nightshade (*Atropa belladonna*, Solanacea, Plate 2), while hemlock (*Conium maculatum*, Umbelliferae) is easily mistaken for parsley (*Petroselium crispum*) or other edible umbelliferous herbs. In the past, human epidemics due to plant toxins have occurred, such as milk sickness resulting from *Eupatorium rugosum* (Compositae) ingested by cows.

For thousands of years plants have been used as medicines and many plant drugs are still prescribed today, especially in alternative medicine. Plant poisons have also been used by man to kill animals, commit murder or in warfare. The use of arrow poisons to kill animals is probably almost as old as the arrow head itself. These poisons were generally prepared from plants containing cardiac glycosides or alkaloids, while alkaloid-containing plants such as deadly nightshade, mandrake (*Mandragora officinalis*, Solanacae) and hemlock have been used for centuries to commit homicide.

Compounds derived from amino acids

The amino acids are the precursors of the toxic compounds in plants which contain nitrogen, either in a heterocyclic ring system or in a side chain. The amino acids themselves are derived from glutamate (**1**) or glutamine (**2**), primary products of ammonia assimilation by pathways which involve the enzymes glutamine synthase and glutamate synthase. All other amino acids are formed by transamination catalysed by aminotransferases (transaminases). A simplified pathway is shown in Figure 1.

Several hundred amino acids have been isolated from plants of which only 22 normally occur in plant proteins.. The majority of the non-protein amino acids result from deviations in the biosynthetic pathways of the protein amino acids. Many non-protein amino acids are analogues of protein acids and act as metabolic inhibitors and are thus toxic to microorganisms and insects, and sometimes to animals, including man. They mimic protein amino acids in forming protein-like molecules which poison enzymes and cause cells to die. Plants protect themselves by storing these compounds in vacuoles

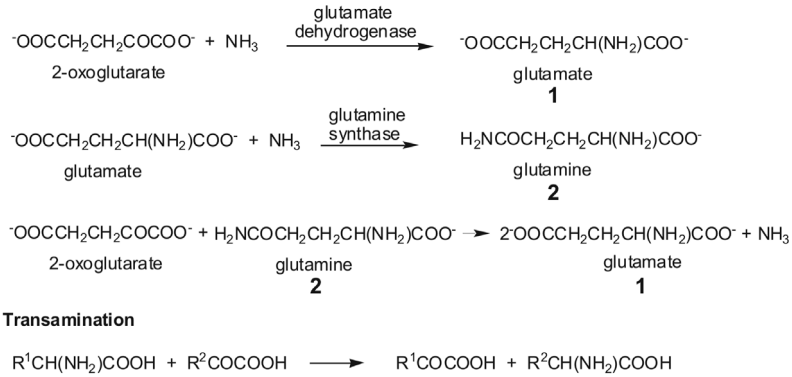
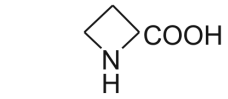


Fig. 1. *Biosynthesis of aminoacids in plants.*

away from active sites of metabolism. Plants of the Liliaceae family have evolved enzymes which are not susceptible to the non-protein amino acid azetidine-2-carboxylic acid (**3**), which they produce for defence from predators.



azetidine-2-carboxylic acid

3

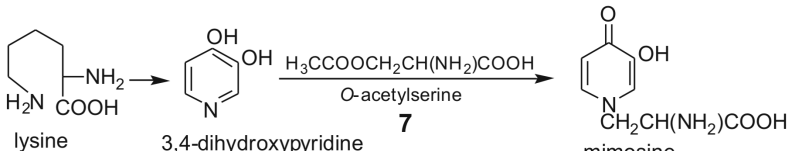
Some non-protein amino acid derivatives

Mimosine

Mimosine (**4**) occurs in *Mimosa* and *Leucaena* species (Leguminosae) and is found in the seeds and leaves. *Mimosa* species are small trees native to Australia, which have delicate, pinnate leaves and 'fluffy' yellow flowers. *Leucaena* species are similar, *L. glauca* is often grown as a hedge and has small balls of white flowers.

Mimosine causes hair loss in horses, donkeys, mules, pigs and sheep. It does not have this effect in cattle as it is degraded in the stomachs of these animals. Other symptoms of mimosine poisoning include loss of hoof, eye cataract, loss of fertility and haemorrhagic enteristis. Mimosine acts in three ways: chelating with with metals, especially iron, inhibiting pyridoxyl phosphate and competing with tyrosine. Poisoning can thus be combated by supplying animals with excess iron, pyridoxyl phosphate and tyrosine.

Mimosine is biosynthesised from lysine (**5**) through 3,4-dihydroxypyridine (**6**) and *O*-acetylserine (**7**) as shown in Figure 2.



lysine **5**

3,4-dihydroxypyridine **6**

O-acetylserine **7**

mimosine **4**

Fig. 2. *Biosynthesis of minosine.*

N^3-oxalyldiaminopropionic acid

N^3-oxalyldiaminopropionic acid (**8**) found in the Indian pea (*Lathyrus sativus*, Leguminosae) is responsible for neurolathyrism, a disease that was prevalent amongst the poor of India in times of famine, when pea meal was the only food available. Neurolathyrism causes muscular rigidity, paralysis of the legs, convulsions and in extreme cases, death. *L. sativus* is a typical member of the pea subfamily, Papilionacea, so called because the flowers are reminiscent of butterflies. Lathyrus species are characterised by their angular or winged stems. Some other members of the Leguminosae also contain this non-protein amino acid including several *Lathyrus* and *Crotalaria* species.

Strains of *L. sativus* with reduced neurotoxin content have been bred as a result of repeated selection.

N^3-oxalyldiaminopropionic acid (**8**) is biosynthesised from diaminopropionic acid (**9**) and oxalic acid (**10**) through oxalyl CoA (**11**) as shown in Figure 3.

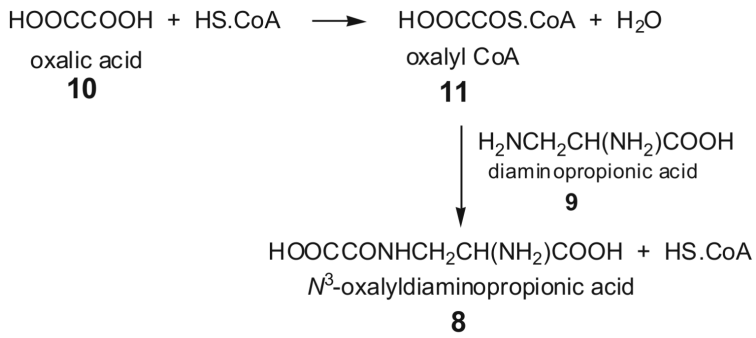


Fig. 3. *Biosynthesis of* N^3*-oxalyldiaminopropionic acid.*

Selenoamino acids

Some plants are natural selenium accumulators while others absorb the element if grown on seleniferous soils. Of the 500 species of *Astragalus* (Leguminosae) found in North America at least 25 accumulate the element. Other selenium-accumulating plants include *Haplopappus fremontii* (Compositae) and *Stanleya pinnata* (Cruciferae). In such plants selenium replaces sulphur and the major non-protein amino acid is *Se*-methylselenocysteine (**12**), whereas in the Australian *Neptunia amplexicaulis* (Leguminisae) and *Morinda reticulata* (Rubiaceae) it is selenocystathionine (**13**). The latter is also found in *Lecythis ollaria* (Lecythidaceae) in sufficient concentration in the nuts to be toxic to man.

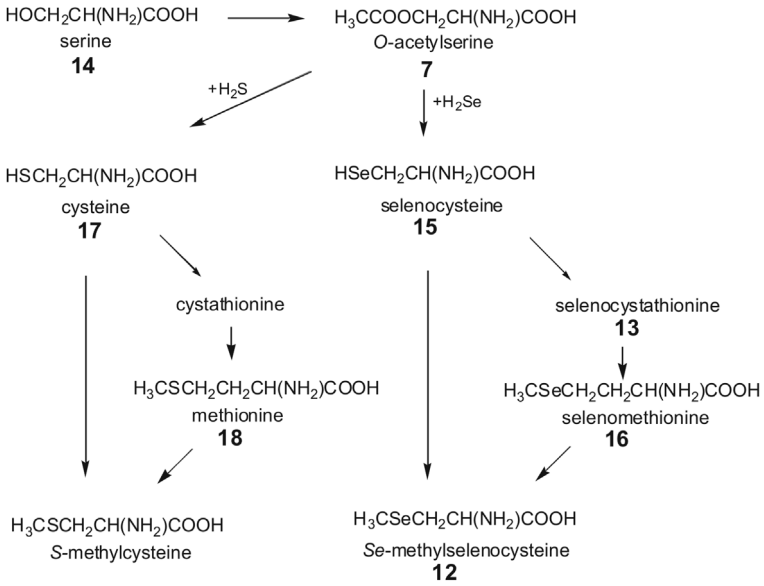


Fig. 4. *Biosynthesis of cysteine, selenocysteine,* S-*methylcysteine and* Se-*methylcysteine.*

Forage plants, which accumulate selenium if grown on seleniferous soils, include the clovers (*Trifolium repens* and *T. pratense* (Leguminosae) and the Gramineae members, rye grass (*Lolium perenne*) and wheat (*Aestivum sativum*). These plants are able to accumulate the element in concentrations which are harmful to animals even if the soil contains only a few parts per million, causing alkali disease and blind staggers.

Se-methylselenocysteine (**12**) is biosynthesised from the amino acid serine (**14**) through *O*-acetylserine (**7**) and selenocysteine (**15**), with selenomethionine (**16**) donating the methyl group (Figure 4). Selenomethionine is biosynthesised from the amino acid selenocysteine in a pathway analogous to that of the conversion of cysteine (**17**) to methionine (**18**).

The unpleasant odours of many selenium-accumulating plants are due to volatile selenium compounds, *e.g.* dimethylselenide (**19**) and dimethyldiselenide (**20**) which are formed by enzymatic cleavage of selenium-containing amino acids.

Colchicine

Because of its pharmacological properties colchicine (**21**) is often included with the alkaloids, but it is not a true alkaloid as it does not contain a heterocyclic ring system and is not basic. Colchicine was first isolated from the autumn crocus (*Colchicum autumnale*) but has since been found in many members of the Liliaceae family. The molecule is derived from phenylalanine (**22**) and tyrosine (**23**) with acetate and methionine providing the acetyl and methyl groups respectively. *O*-Methylandrocymbine (**24**) and demecolcine (**25**) are the intermediates in the biosynthesis of colchicine in the autumn crocus (Figure 5).

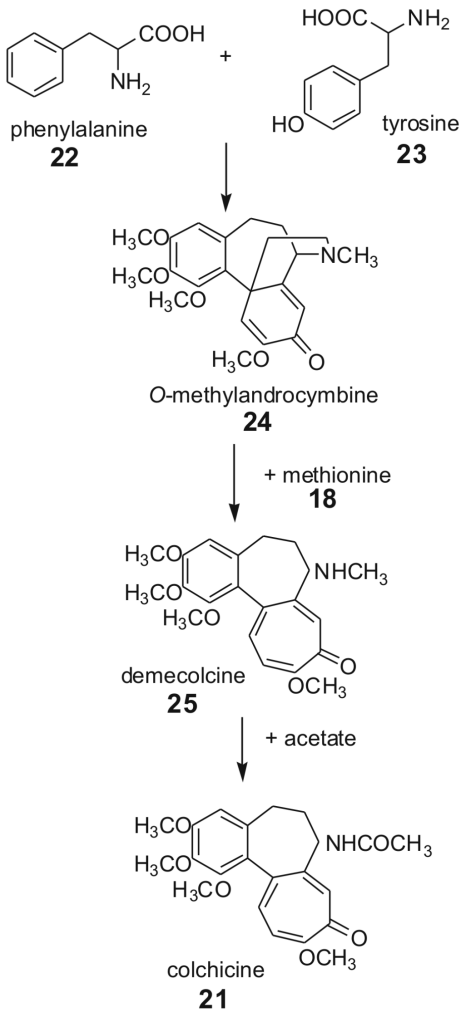


Fig. 5. *Biosynthesis of colchine.*

In the nineteenth century colchicine was prescribed for the relief of pain due to gout, and poisoning due to overdosage was frequent, 3–5 mg being sufficient to cause death. Typical symptoms of colchicines poisoning are vomiting, diarrhoea, pain in bowels, lowering of body temperature, circulatory collapse and death due to asphyxia. Colchicine has also caused human poisoning through its use as an abortifacient and accidently through mistaking the leaves for those of the onions.

Cyanogenic glycosides

Many plants contain cyanogenic glycosides which can be degraded to hydrogen cyanide (**26**) by enzyme-catalysed hydrolysis. In the living, undamaged plant these glycosides are metabolised to amino acids, but when the plant is damaged free hydrogen cyanide is produced (Figure 6). Thus cyanogenic glycosides protect the plant from predation, the bitter taste of cyanide acting as a warning . The production of these compounds is particularly characteristic of the Rosaceae, Passifloraceae, Leguminosae, Sapindaceae and Graminae families. Some common cyanogenic glycosides are shown in Table 1, and are exemplified by Linamarin, produced in flax (Linum usitatissimum,

Plate 3 *Flax (Linum usitatiissimum); en.wikipedia.org/wiki/flax*

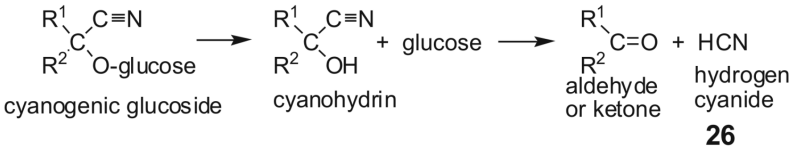
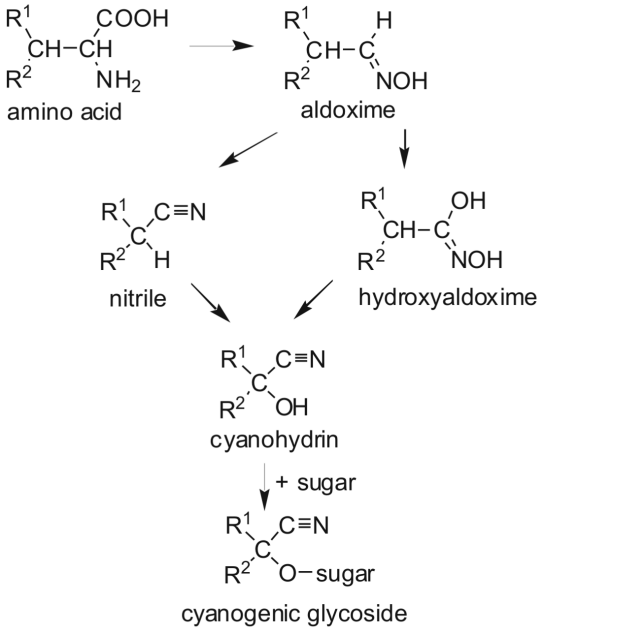


Fig. 6. *Degradation of cyanogenic glycosides.*

Linaceae, Plate 3). In all cases they are biosynthesised from amino acids through the intermediate formation of the aldoxime to form cyanohydrins which link to sugars as shown in the pathway (Figure 7). Generally, but not always, this sugar is glucose.

Cyanide poisoning often causes death with no previous symptoms, although rapid breathing, vomiting and convulsions may occur. In animals, listlessness, cessation of feeding and convulsions are characteristic of mild poisoning, with sheep being amongst the



$R^1 = CH_3, R^2 = CH_3$, sugar = glucose: linamarin **27a**

$R^1 = CH_3, R^2 = CH_3CH_2$, sugar = glucose: lotaustralin **27b**

Sugar = glucose: prunasin, prulaurasin
Sugar = gentiobiose: amygdalin
Sugar = vicianose: vicianin

Fig. 7. *The biosynthesis of cyanogenic glycosides.*

Table 1 *Common cyanogenic glycosides*

Glycoside	Sugar	Amino acid precursor	Occurrence
Linamarin	Glucose	Valine	*Linum usitatissimum* (Flax) *Phaseolus lunatus* (Lima bean) *Manihot esculenta* (Cassava)
Lotaustralin	Glucose	Isoleucine	*Trifolium repens* (Clover)
Prunasin	Glucose	Phenylalanine	Rosaceae
Sambunigrin	Glucose	Phenylalanine	*Sambucus* sp.
Amygdalin	Gentiobiose	Phenyalanine	Rosaceae
Vicianin	Vicianose	Phenylalanine	*Vicia* sp.
Dhurrin	Glucose	Tyrosine	*Sorghum* sp.
Taxiphyllin	Glucose	Tyrosine	*Taxus* sp.

most susceptible, only 2.4 mg HCN/kg body weight being sufficient to kill these animals. The cyanide ion exerts its effect by combining with metal atoms particularly iron in metal-containing enzymes. This inactivates the enzyme, one of the most important being cytochrome oxidase, the respiratory enzyme, whose inactivation leads to death by asphyxia. In ruminants the continuous ingestion of sub-lethal quantities of cyanide eventually leads to iodine deficiency and goitrous conditions, this being due to conversion of cyanide to thiocyanate in the rumen.

Glucosinolates

As with the cyanogenic glycosides the glucosinolates, commonly known as mustard oils, are produced by plants, particularly those belonging to the Cruciferae family, to protect them from predators. These compounds are biosynthesised from amino acids by the pathway shown in Figure 8. As with the cyanogenic glycosides, the amino acid is first converted to an aldoxime. Some glucosinolates found in members of the Cruciferae are listed in Table 2. When the plant is damaged, glucosinolates are catalytically hydrolysed to isothiocyanates (Figure 9) which have distasteful, pungent odours and tastes, although they are unlikely to be lethal to animals. Symptoms of isothiocyanate poisoning include vomiting and diarrhoea and irritation of the digestive tract. Isothiocyanates act as excellent insecticides, although a few insects have adapted to not only tolerate these compounds but to use them in their own defence. This is particularly true of the cabbage white butterflies (*Pieris brassicae* and *P. rapae*) whose caterpillars feed on many members of the Cruciferae family. Mustard oils are released if the caterpillar is damaged and thus make them distasteful to birds and other predators.

Table 2 *Common glucosinolates*

Glucosinolate	Amino acid precursor	Occurrence
Glucocapparin	Alanine	Capparidaceae
Gluconapin	Serine	Cruciferae
Sinigrin	Serine	Cruciferae
Glucotropaeolin	Phenylalanine	Several familes
Sinalbin	Tyrosine	Cruciferae
Gluconasturtiin	Phenylalanine	Cruciferae
Glucobrassicin	Tryptophan	*Brassica* sp.

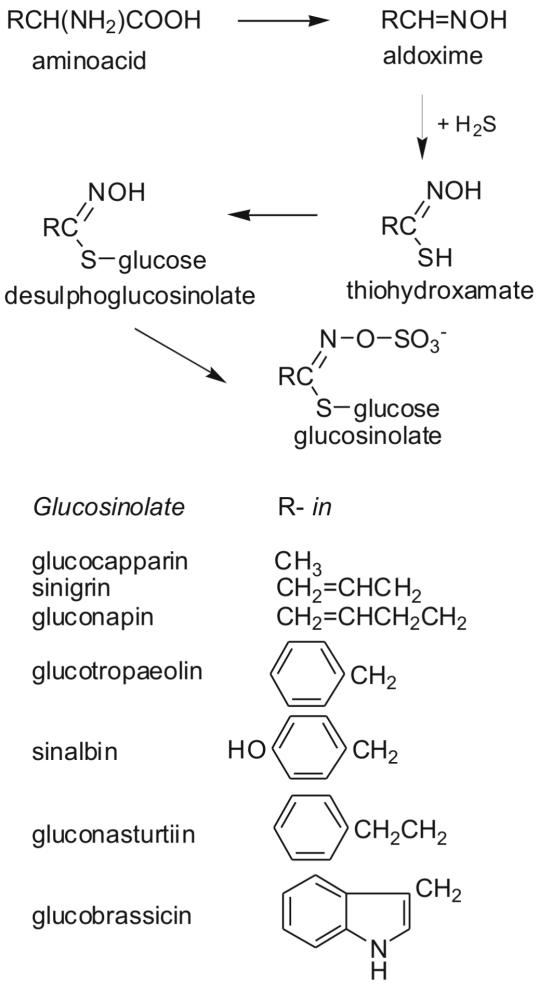


Fig. 8. *The biosynthesis of glucosinolates.*

Alkaloids

The alkaloids are among the best known of the plant toxins. Plants synthesising these compounds are worldwide and occur in many families ranging from the primitive mosses to the highly

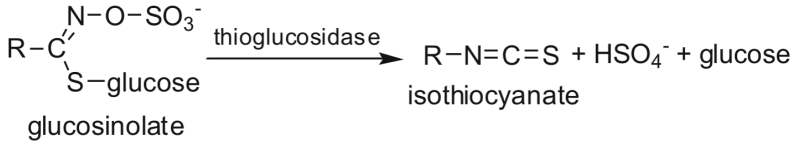


Fig. 9. *The degradation of glucosinolates.*

complex Graminae. Because of the proven medicinal value of a number of alkaloids and their ease of extraction, many plants have been screened for these compounds. The alkaloids are a diverse collection of compounds, their only similarity being the presence of nitrogen. The true alkaloids, as opposed to the protoalkaloids and pseudoalkaloids, contain nitrogen as part of a heterocylic ring system and are biosynthesised from amino acids. Many plants synthesise alkaloids during metabolic processes but the compounds only occur in trace amounts and the plants are generally non-toxic. Only plants storing alkaloids in quantities that are poisonous to animals will be considered here.

The amino acids most often encountered in alkaloid biosynthesis are the aliphatic ornithine (**28**) and lysine (**5**), and the aromatic nicotinic acid (**29**), phenylalanine (**22**), tyrosine (**23**) and tryptophan (**57**). All these compounds originate from glucose, a product of primary metabolism.

All alkaloids have some physiological action, generally on the central nervous system. This has been used to benefit man in the alkaloid drugs but many of these compounds are too toxic to be used in medicine and all are toxic in sufficient concentration A few naturally occurring alkaloids cause addiction, the most potent being morphine and cocaine. Some alkaloids have teretogenic properties, causing defects in the foetus when plants containing them are eaten by the mother. Compounds belonging to the pyrrolizidine, quinolizidine and nicotine groups are the most potent. Skeletal damage is the defect most often encountered.

Alkaloid-containing plants probably cause more stock damage throughout the world than any other types of poisonous plants. However, the bitter taste of these plants does act as a feeding deterrent. The specific actions of an alkaloid can vary with the animal species. Morphine for example causes sleep in man and dogs but acts as a stimulant in horses and cats. Even if they do not die, farm animals poisoned by alkaloid-containing plants often never completely recover and are thus an economic loss.

Poisoning of animals is usually accidental although poisoned arrow tips are still used in Africa and South America especially by poachers. Human poisoning can also be accidental but many alkaloids have been used to commit murder or suicide. These days it is the pure drugs which are used, particularly nicotine, morphine, strychnine and atropine. Accidental poisoning occurs most often in children or in mistaking a poisonous plant for an edible one.

Alkaloids biosynthesised from ornithine

The amino acid ornithine (**28**) is the precursor of the nitrogen-containing five-membered heterocylic rings found in the pyrrolidine, tropane and pryrrolizidine alkaloids.

The pyrrolidine and tropane alkaloids

Both pyrrolidine and tropane alkaloids are abundant in the Solanaceae, the potato family and in coca plants (*Erythroxylum* spp. Erythroxalaceae). These alkaloids contain the tropane ring system and isotropic tracer analysis has shown that the immediate precursors of the tropane alkaloids are the pyrrolidine derivatives hygrine (**30**) and ecgonine (**31**) which are biosynthesised from ornithine, the pathway involving acetoacetyl Coenzyme A (Figure 10).

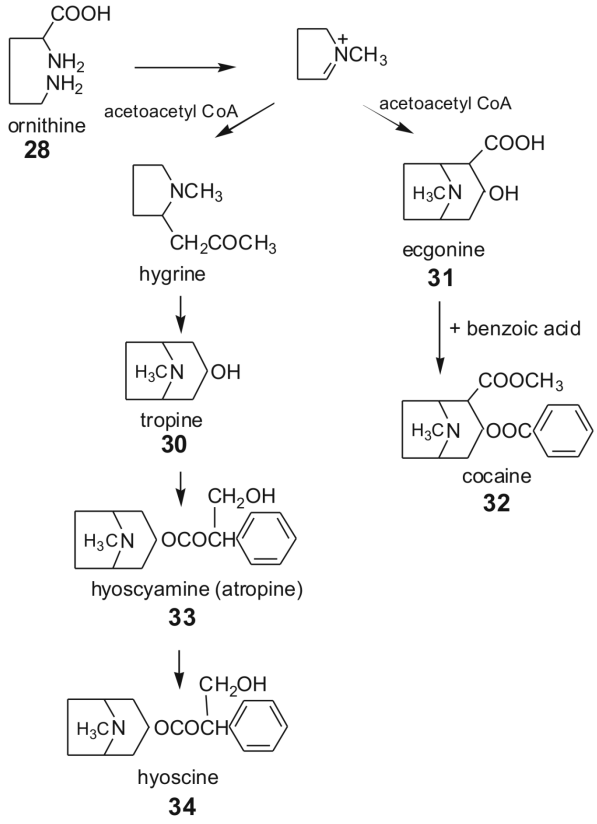


Fig. 10. *Biosynthesis of hygrine and the tropane alkaloids.*

Cocaine

Cocaine (**32**) is found in the coca plant (*E. coca*), a shrub which grows in the humid tropics particularly on the mountain forest slopes of the Andean highlands of South America. It seems that the plant produces the alkaloid to protect it from insect predation. The alkaloid is a stimulant and hunger depressant and coca leaves have been chewed in South America since before the times of the Incas to give sustained energy and the will to work under excessively hard conditions. However, cocaine is an addictive drug and causes life dependency. Cocaine was a popular drug in Europe in the nineteenth century and probably came to the notice of the general public through Sir Arthur Conan Doyle's books in which the detective, Sherlock Holmes took the drug as an aid to solving crimes. Until the early twentieth century Coca-Cola, the drink popular in America and Europe, contained cocaine, but this was banned in 1904. Cocaine acts on the mucous membranes to reduce swelling and was included in popular catarrh medicines. The availability to an unsuspecting public of such seemingly innocent sources of cocaine must have led to many addictions.

Cocaine is also a powerful local anaesthetic and was used in dentistry and eye surgery before less harmful drugs, such as procaine were synthesised.

The effects of arousal of the central nervous system and stimulation of the sympathetic nervous system produced by cocaine are similar to those of the amphetamines, but are far less durable so that a continuous source is required to maintain a ''high''. Although an addict does not suffer the dramatic physical effects on withdrawal associated with morphine, mental effects, including depression are so severe that the addict will return to the drug for relief.

As shown in Figure 10 the alkaloid is biosynthesised in the plant from ornithine (**28**). Catalysis by acetyl co-enzyme A leads to the precursor ecgonine (**31**) which reacts with benzoic acid to form cocaine (**32**).

Atropine (hyoscyamine)

Ornithine (**28**) is also the precursor of the drug atropine (hyoscyamine) (**33**) found in deadly nightshade (*Atropa belladonna*, Solanaceae). Deadly nightshade is a tall herb with a thick root and stout stems. It grows wild in Europe and Asia Minor and is

cultivated in North America. Its black glossy berries are very attractive to children who mistake them for cherries with fatal consequences. The plant contains many alkaloids but it is (–)hyoscyamine which is the most toxic. The drug produces flushed skin, dilated pupils of the eyes, dry mouth, delirium, convulsions, coma and death from respiratory failure. It has been widely used as a homicidal poison and in small doses as an hallucinogen. It was one of the drugs connected with witchcraft in Roman times and the Middle Ages. A witch would concoct a paste containing an extract from deadly nightshade which when applied to the skin would produce hallucinations of flying.

Other poisonous plants of the Solanaceae family containing atropine include the jessamines (Cestrum spp.) mostly native to tropical America and cultivated in the southern United States. These plants are known to have caused poisoning of children and animals.

Atropine is an anticholinergic drug, depressing the central nervous system. It has been used as an antispasmodic, particularly in preparations to treat diarrhoea and in ophthalmia. When applied topically to the eye it paralyses the muscle and dilates the pupil, allowing unimpeded inspection of the eye. It is used particularly as a diagnostic tool in the treatment of glaucoma. Atropine given before an anaesthetic dries up secretions and quickens the heart beat.

Atropine is biosynthesed in the plant by a pathway similar to that of cocaine (Figure 10).

Hyoscine (scopolamine)

Hyoscine (**34**) another solanaceous alkaloid found in deadly nightshade is more characteristic of *Datura* species (Solanaceae), especially *D. Stramonium*, known locally as jimson weed or thorn apple. Jimson weed (Plate 4) is a tall annual with large, white, pink or purple, highly scented flowers which are trumpet shaped. It is a common weed of waste areas throughout North America. The fruits are covered with sharp spines and so are not as attractive to children as deadly nightshade but all parts of the plant are poisonous. It is also widely cultivated for its beautiful flowers.

The symptoms of poisoning are similar to those of atropine, and hyoscine has similar uses as an antispasmodic drug and in eye treatment. It is a sedative and has been used as a constituent of some travel sickness pills, and given, combined with morphine, before operations. It was once used to produce loss of memory (twilight sleep) during painful processes such as childbirth. The

Plate 4 *Jimson weed (Datura stramonium); en.wikipedia.org/wiki/Datura stramonium*

combined effects of hyoscyamine and hyoscine in plants cause inebriation and delirium followed by drowsiness. In toxic amounts this is followed by convulsions, coma and death.

Hyoscine is biosynthesised from hyoscyamine (Figure 10).

The pyrrolizidine alkaloids

The pyrrolizidine alkaloids are widely distributed in the plant world but are particularly characteristic of *Senecio* species (Compositae), *Crotlaria* species (Leguminosae) and some genera belonging to the Boraginaceae family. These alkaloids contain the pyrrrolizidine ring system and isotopic tracer analysis has shown that biosynthesis from ornithine involves the precursors retronecine (**35**) and its stereoisomer heliotridine (Figure 11).

The toxicity of the pyrrolizidine alkaloids varies considerably and depends on the presence of the C-1═C-2 double bond in the ring. Those alkaloids such as senecionine (**36**) and monocrotaline (**37**), which contain two ester groups, are the most toxic. In the liver these alkaloids are oxidised by liver oxidases to pyrroles which interfere with a number of enzyme systems. Some insects have evolved to make use of these alkaloids. For example, the *Danais* butterflies convert the alkaloids to an insect pheromone which promotes mating while the caterpillars of the Cinnabar

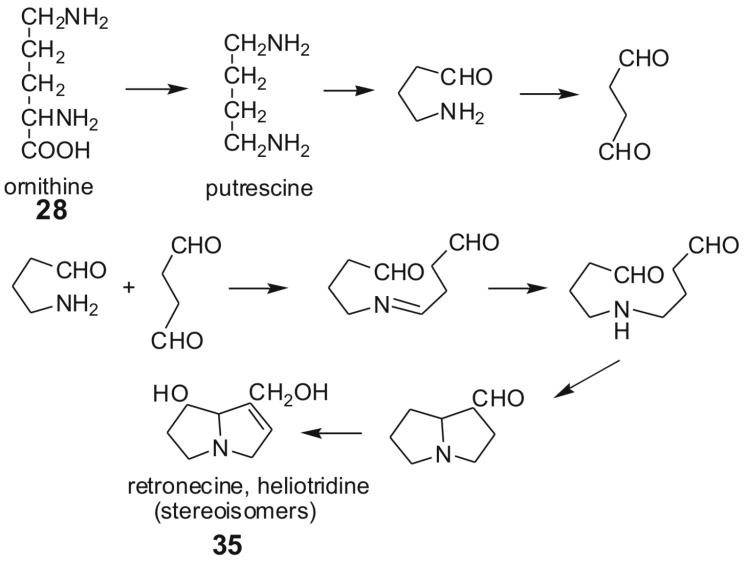
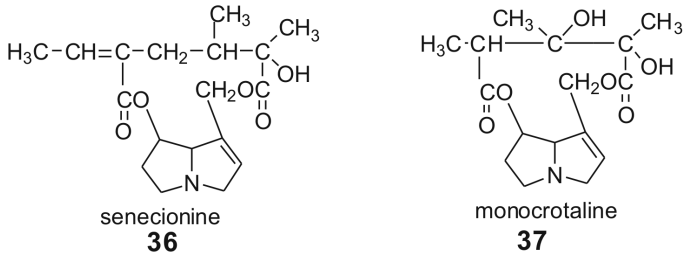


Fig. 11. *Biosynthesis of the pyrrolizidine alkaloids.*

moth (*Tyria jacobaeae*) feed on common ragwort (*Senecio jacobaea*), their orange and black striped bodies warning predators that they are poisonous.

Senecionine and monocrotaline

Senecionine (**36**) and monocrotaline (**37**) are hepatoxic and occur in *Senecio* species, the groundsels and ragworts, *Crotalaria* species (rattle-box), and *Armsinckia*, *Cynolglossum*, *Heliotropium* and *Trichodesma* species, all members of the Boraginaceae family. Groundsels and ragworts are ubiquitous herbs with yellow flowers. They occur as weeds on cultivated ground. Common ragwort occurs throughout Europe and has been responsible for many stock losses.



In Africa, Australia and the United States, *Crotalaria* species are similarly responsible for much loss of stock, especially rattlebox *C. spectabilis* and *C. assamica*. *Crotalaria* species are typical members of the pea family, being generally shrubby herbs with digitate leaves and yellow or blue flowers. The seeds rattle within the pod when ripe, hence the common name.

When eaten over a period of time, all these plants cause seneciosis, a condition in man and animals which damages the liver and may result in eventual death. Large doses cause convulsions and death. In man, poisoning can result from eating flour contaminated with ragwort, a condition known as 'bread poisoning' in South Africa. In the West Indies poisoning has resulted from drinking bush teas made from *Crotalaria* species. Horses are particularly susceptible to senecionine poisoning through eating ragwort. The typical symptoms of 'horse staggers' are nervousness, yawning, drowsiness and a staggering gait.

Senecionine (**36**) and monocrotaline (**37**) are biosynthesised in the plants from retronecine (**35**) by esterfication of the hydroxyl groups with senecic acid and monocrotalic acid respectively.

Alkaloids biosynthesised from lysine

Lysine (**5**) is the precursor of the nitrogen-containing six-membered heterocyclic ring systems found in the piperidine derivatives and the lupin alkaloids. The piperidine alkaloids occur in a number of unrelated plant families including Moraceae, Chenopodiaceae, Piperaceae, Crassulaceae, Caricaceae, Punicaceae, Solanaceae and Lobeliaceae.

The lupin alkaloids

The lupin alkaloids were first isolated from *Lupinus* species (Leguminosae) but also occur in several unrelated families including Chenopodiaceae, Berberidaceae and Solanaceae. They are, however, characteristic of the Papilionoideae subfamily, sparteine (**38**) or lupanine (**39**) occurring in the majority of the genera belonging to these tribes.

Lupins are indigenous to North America and the Mediterranean region but are cultivated widely in gardens and as fodder crops. They are perennial herbs with brightly coloured, pea-like flowers ranging from blue through pink to yellow. The popular Russell garden lupins are varieties produced by crossing *L. arboreus* with *L. polyphyllus*, natives of western North America.

The lupin alkaloids are toxic causing nausea, vomiting, convulsions and death due to respiratory failure. Poisoning of man can occur when the seeds are used as a food unless special precautions are taken in their preparation. Lupins are a popular fodder crop for animals, especially sheep, the yellow and blue lupins (*L. luteus* and *L. angustifolius*) being the species usually used for this purpose in Europe. Poisoning of animals, known as lupinosis can occur from a fungus which infests the plant and whose effects are cumulative. Lupinosis causes extensive liver damage and has resulted in the loss of many sheep in Australia, Europe and the United States.

Poisoning of animals due to the alkaloid content of the plants can also occur, particularly from *L. sericeus*, *L. leucophyllus*, *L. perennis*, *L. argenteus* and *L.caudatus*. The plants are most dangerous when in seed, and drying for hay has no effect on toxicity. However, such poisoning is not cumulative and is due to animals eating large quantities of the plant at one time. Varieties known as sweet lupins have been bred with very low alkaloid content and are cultivated for fodder.

Sparteine is also found in *Cytisus scoparius* and has been used as a substitute for quinidine to treat atrial fibrillation. It is also a diuretic.

Sparteine (**38**) and lupanine (**39**) are biosynthesised in the plant from lysine (**5**) through the intermediate cadaverine (**40**) which loses one nitrogen atom on conversion to the aldehyde, the second being incorporated into the heterocyclic ring (Figure 12).

Alkaloids biosynthesised from nicotinic acid

The tobacco alkaloids

Nicotine (**41**) has been found in trace amounts in plants belonging to many different families but only in *Nicotiana* (Solanaceae), particularly the tobacco plant (*N. tabacum*) is this alkaloid accumulated to any extent. Anabasine was first isolated from *Anabasis* and was subsequently found in other genera belonging to the Chenopodiacaea family. It also occurs in the Araliaceae, Lauraceae and Compositae.

The tobacco plant originated in tropical America and has been cultivated by the American Indians for at least 1,000 years. It has formed an important part of religious and other ceremonies for these people. Columbus was the first European to discover the properties of tobacco and the Spanish explorers introduced smoking of the plant to Europe at the beginning of the sixteenth century. By the

Table 3 *Some alkaloids*

Alkaloid	Amino acid precursor	Occurrence	Main physiological action
Atropine (hyoscyamine)	Ornithine	*Atropa belladonna* (deadly nightshade)	Respiratory failure
Cocaine	Ornithine	*Erythroxylum coca* (cocaine plant)	Stimulant, addictive
Senecionine	Ornithine	*Senecio* spp (ragworts)	Hepatoxic
Monocrotaline		*Crotalaria* spp (rattle-box)	
Lupinine Lupanine Sparteine	Lysine	*Lupinus* spp (lupins)	Respiratory failure
Nicotine	Nicotinic acid	*Nicotiana tabacum* (tobacco plant)	Cardiac failure, addictive
Morphine	Tyrosine	*Papaver somiferum* (opium poppy)	Respiratory failure, narcotic, addictive
Galanthamine	Phenylalanine Tyrosine	*Galanthus* sp. (snowdrop)	Paralysis of general nervous system
Physostigmine	Tryptophan	*Physostigma venenosum* (Calabar bean)	Respiratory and heart failure
Vincaleucoblastine Leurocristine	Tryptophan	*Catharanthus rosea* (Madagascar periwinkle)	Antileukaemic
Strychnine	Tryptophan	*Strychnos nux vomica*	Convulsions, respiratory failure
Quinine	Tryptophan	*Cinchona* sp	Antimalarial

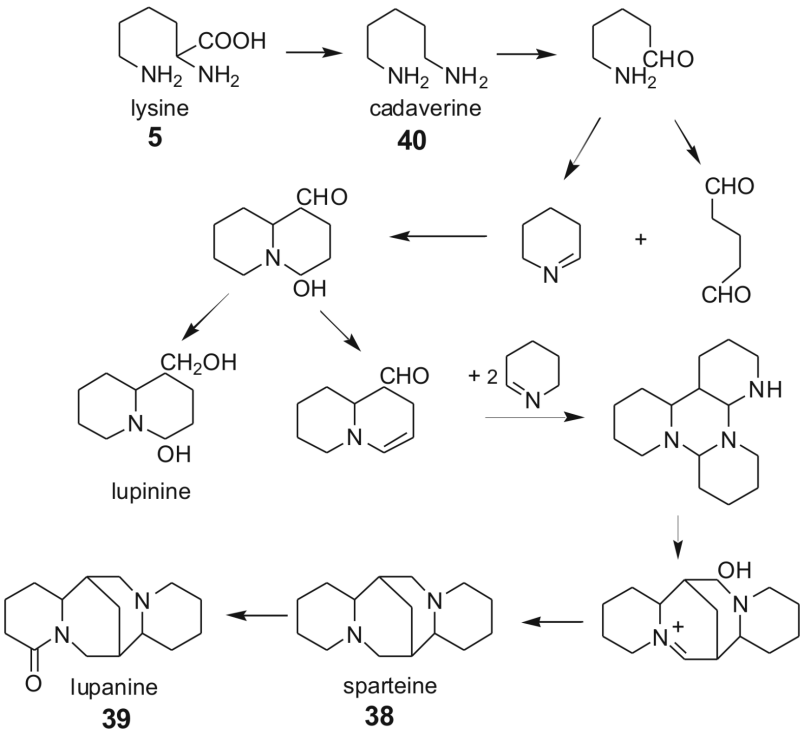


Fig. 12. *The biosynthesis of the lupin alkaloids.*

twenty first century tobacco had become one of the most widely grown of the non-food commercial crops. Smoking tobacco calms the nerves and induces relaxation but it is highly addictive and prolonged use can cause lung cancer and serious respiratory disease. The tobacco plant is an annual with thick stems and leaves arranged in a spiral. The leaves and stems are covered with glands which exude a sticky substance and each plant produces 20–30 leaves suitable for tobacco manufacture. It requires plenty of sunshine and a temperature of around 25°C for maximum growth. Ornamental varieties of the plant are also grown throughout the world for their flowers which are highly scented especially at night.

Pure nicotine produces instantaneous death when ingested in only small quantities, the fatal dose to man being 40–60 mg. Symptoms produced by plant poisoning are irregular, weak heart action, vomiting and unconsciousness followed by death. The alkaloid can be absorbed through the skin and there have been cases of nicotine poisoning through prolonged contact of tobacco leaves with damp skin. Children playing with old tobacco pipes have also

suffered nicotine poisoning. Due to its popularity as an horticultural and agricultural insecticide, nicotine was once one of the most common causes of accidental poisoning by alkaloids. It has also been used to commit suicide and as a homicidal agent. Anabasine has similar effects.

The tobacco alkaloids, nicotine (**41**), anabasine (**42**) and anatabine (**43**) are biosynthesised from nictotinic acid (**29**) as shown in Figure 13. Isotropic tracer analysis has shown that the pyrrolidine ring of nicotine is biosynthesised from ornithine (**28**) through the formation of the *N*-methylpyrrolinium salt (**44**).

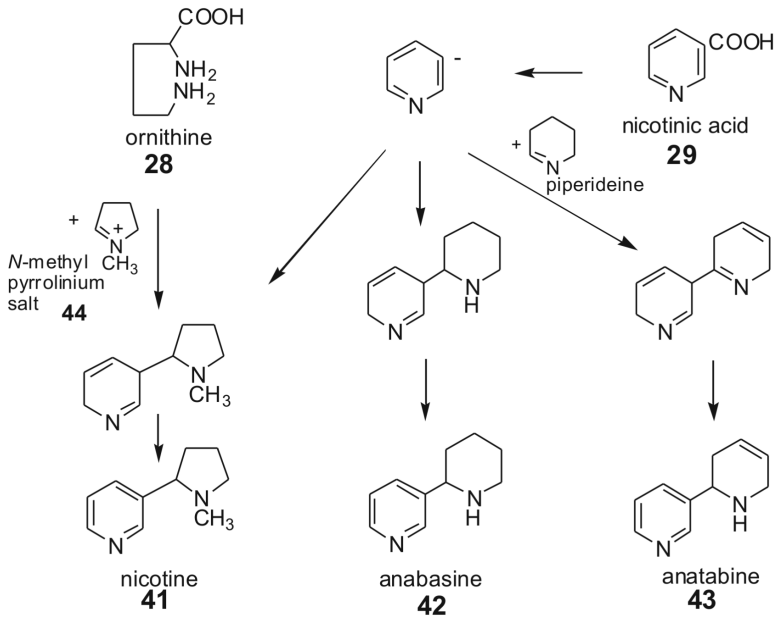


Fig. 13. *The biosynthesis of the tobacco alkaloids.*

Alkaloids biosynthesised from tyrosine

Tyrosine (**23**) is the precursor of many alkaloids of which the benzylisoquinoline derivatives are pharmacologically the most important.

The benzylisoquinoline alkaloids

Numerous benzylisoquinoline alkaloids occur in the related orders Magnoliales, Ranunculales, Aristoliales and Papaverales. Morphine (**45**) accumulates in the latex of the opium poppy (*Papaver*

somniferum, Papaveraceae, Plate 5), particularly in the unripe capsule. Its concentration has been found to vary considerably, being greatest in the early morning. The only other plant found to contain morphine is the closely related *P. setigerum*, while codeine occurs in another related species, *P. peaoniflorum*. Thebaine and papaverine, however, occur much more widely in the *Papaver* genus.

The opium poppy is native to the Middle East and vast quantities are grown in Afghanistan for extraction of the drug. It is an annual with showy flowers, which can vary in colour in the white/pink/purple range. The stems are erect and solid, reaching 3–4 ft and the greyish leaves clasp the stems. Large seed heads are produced with numerous small seeds. These do not contain alkaloids and are used as a decoration, particularly of bread products. Oil is also extracted from the seeds.

Morphine (**45**), codeine (**46**) and papaverine (**47**) are important drugs while thebaine (**48**), although of no pharmacological use, is easily converted to codeine. In man morphine is both narcotic and analgesic. It is one of the oldest narcotics, being referred to as the 'joy plant' by the Sumerians in 4000 BC. It is used to relieve prolonged pain, especially of terminal patients. The brain contains discrete opiate receptors and morphine imitates the action of enkephalins, painkillers naturally produced by the brain. The drug has also been used to treat many diseases from coughs to diarrhoea.

Plate 5 *Opium poppy (Papaver somniferum); en.wikipedia.org/wiki/Opium_poppy*

Morphine affects the central nervous system, causing reduced powers of concentration and lessening feelings of fear, anxiety and hunger, thus leading to a state of contentment. It is also highly addictive and addicts of the drug become both tolerant and physically dependent on its effects. Needing ever-increasing amounts, and at the same time becoming tolerant of otherwise toxic doses, their habit usually leads to a life of degradation and criminality. Abrupt withdrawal causes extremely unpleasant symptoms and can result in death. Overdoses of morphine cause slowing of the respiration which eventually ceases altogether and the patient falls into a deep sleep which leads to death. Morphine constricts the pupils of the eyes and addicts are characterised by their pin-point pupils. As a dilute tincture known as laudanum, morphine was commonly taken by ladies in the eighteenth and nineteenth centuries to combat headache and period pain, but many became dependant on the medicine.

The synthetic derivative of morphine, heroin is the most dangerous of all the drugs of addiction and it has been banned from medical use in many countries, although in Britain its use is allowed for the relief of pain in terminal cancer patients. Morphine has been used to dope horses as it acts as a stimulant in these animals. Repeated attempts have been made to modify the morphine molecule so that it retains its analgesic powers but is not addictive, but there has been little success. A derivative, etorphine has an analgesic potency 10 000 times that of morphine and has been used as a sedative for large animals. Elephants can be rendered immobile by as little as 2 mg administered in a syringe fired as a dart.

Codeine has weaker analgesic powers but is much less addictive than morphine. It is also less toxic and does not slow the respiration. Combined with aspirin, codeine was used in many brands of analgesic tablets but has been largely superseded by drugs such as paracetamol and ibuprofin. Codeine has also been included in cough mixtures as it suppresses the urge to cough.

Papaverine is a muscle relaxant and is used to treat spasms and asthma. It is a coronary vasodilator and is prescribed in some forms of heart disease.

Although benzylisoquinoline alkaloids occur to some extent in all *Papaver* species, animals generally do not have access to sufficient of the plants to cause poisoning. Symptoms which have been observed in poppy poisoning include gastroenteristis and nervous excitement.

Isotopic tracer analysis has shown that norlaudanosoline (**49**) is the precursor of these alkaloids and that this compound is

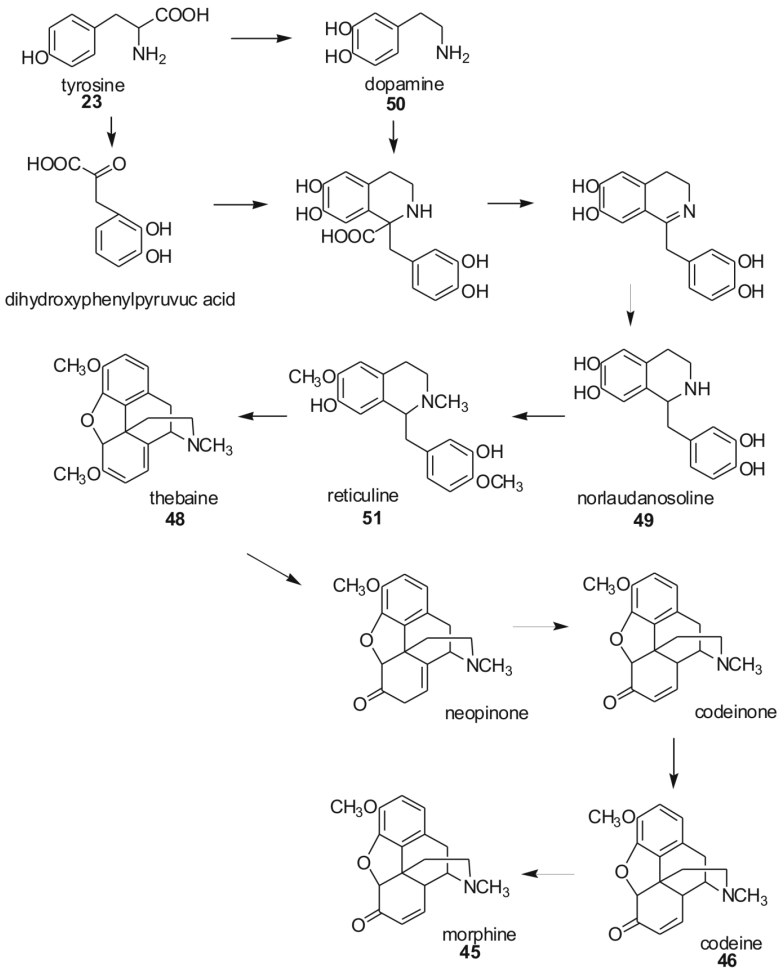


Fig. 14. *The biosynthesis of the poppy alkaloids.*

biosynthesised entirely from tyrosine (**23**) through the intermediate formation of dopamine (**50**) (Figure 14). The opium alkaloids, thebaine (**48**), codeine (**46**) and morphine (**45**) are biosynthesised from norlaudanosoline through the intermediate formation of reticuline (**51**) as shown in Figure 14. Thebaine is the precursor of codeine, which is then converted to morphine. Papaverine (**47**), another opium alkaloid, is also biosynthesised from norlaudosoline but through the intermediate formation of norreticuline (**52**), a compound in which the heterocyclic ring is not methylated as it is in reticuline (Figure 15).

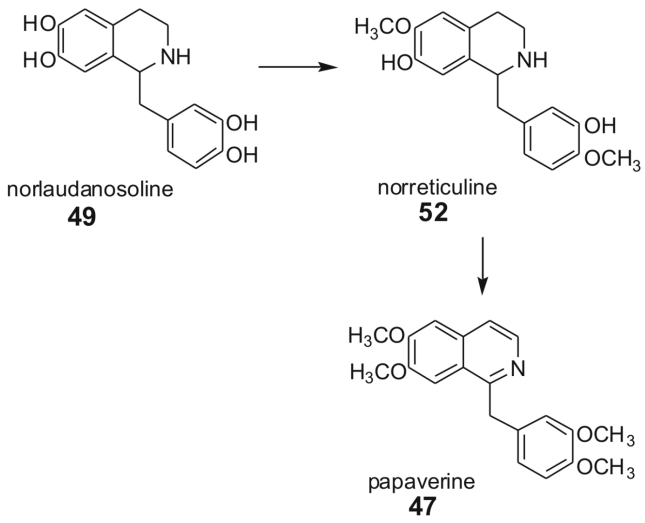


Fig. 15. *The biosynthesis of papaverine.*

Alkaloids biosynthesised from tyrosine and phenylalanine

The phenanthridine alkaloids

Phenylalanine (**22**) and tyrosine (**23**) and are precursors of the phenanthridine alkaloids which are characteristic of the Amaryllidaceae family. Members of the Amarillidaceae are monocotyledons and are characterised by their bulbs from which the strap-like leaves emerge. The flowers are often showy and highly scented and have been popular cultivated plants for centuries.

Although alkaloids occur in the leaves, stems and flowers, it is generally the bulbs which are the most toxic. Human poisoning has occurred through the bulbs of daffodils (*Narcissus* sp.) being mistaken for onions, while pigs and cattle have been poisoned when fed the bulbs of daffodils and snowdrops (*Galanthus* sp.). In Africa the highly toxic *Buphane disticha* has been used to prepare arrow poisons.

Lycorine (**53**) causes vomiting, diarrhoea, and general collapse. Death is due to paralysis of the central nervous system.

Isotopic tracer analysis has shown that norbelladine (**54**) is the precursor and that this is then methylated to *O*-methylnorbelladine (**55**) before conversion to lycorine. Galanthamine (**56**) and several other Amaryllidaceae alkaloids result from the twisting of the aromatic ring derived from tyrosine (Figure 16).

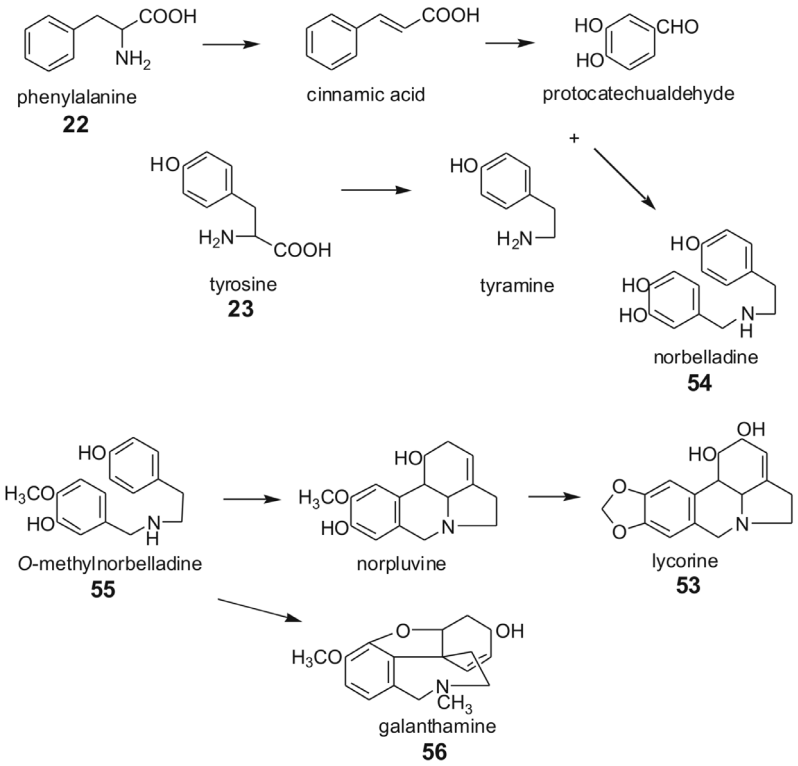


Fig. 16. *The biosynthesis of the Amaryllidaceae alkaloids.*

Alkaloids biosynthesised from tryptophan

Tryptophan (**57**) is the precursor of a large number of indole alkaloids which range from simple compounds such as serotonin (**58**) through physostigmine (**59**) to the highly complex dimers such as vincaleucoblastine (**66**).

The simple indole alkaloids

The simple indole alkaloids occur in a large number of plants belonging to widely varying families. The majority have such a low toxicity that they can be considered non-poisonous, especially in the concentrations occurring in plants. Many of the simple alkaloids are tryptamine (**60**) derivatives and one of the simplest, serotonin (**58**) is thought to act with histamine in producing the intense pain and itching caused by the stinging hairs of several plants including stinging nettles (*Urtica* spp., Urticaceae). The biosynthesis of serotonin is shown in Figure 17.

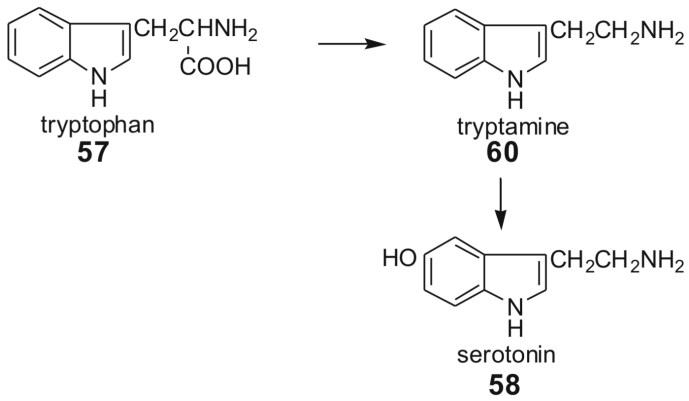
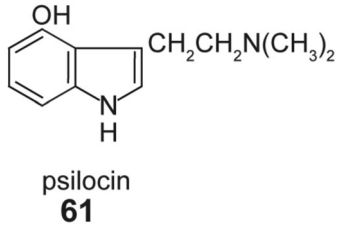


Fig. 17. *The biosynthesis of seratonin.*

Serotonin is produced naturally by the body and is one of the compounds in the brain that influences behaviour and its lack can cause depression. Other tryptamine derivatives are hallucinogens such as psilocin (**61**) found in some mushrooms, especially the South American *Psilocybe* (Agaricaceae).



Physostigmine

Physostigmine (**59**) is the main alkaloid of the Calabar bean (*Physostigma venenosum*, Leguminosae). It is also present in some other *Physostigma* species and in *Hippomane* (Euphorbiaceae). The Calabar bean is native to tropical Africa and is a perennial climber similar to the runner bean but with a stem woody at the base. It can reach a height of 50 ft. The pea-like flowers are pink or purple and the large seed pods contain three or four brown seeds.

As the specific name of the Calabar bean suggests, physostigmine is highly toxic causing vomiting, diarrhoea, spasms, circulatory collapse and paralysis of the lower limbs. Death is due to

respiratory failure or paralysis of the heart. This alkaloid is an inhibitor of acetylycholinesterase, an enzyme which destroys acetylcholine once this compound has been used to transmit nerve impulses. Thus physostigmine causes an abnormally high concentration of acetylcholine at those sites in the nervous system where it is normally released. As an antiacetylcholinesterase medically physostigmine has been used to reverse the effects of muscle relaxants and it also reduces blood pressure and slows the pulse. The alkaloid contracts the pupils of the eye and has been used in dilute solutions to treat glaucoma.

The seeds of the Calabar bean constitute one of the most notorious ordeal poisons of West Africa. Ordeal poisons were used to determine the guilt or innocence of a suspect. Generally, if the suspects vomited immediately after taking the poison they were considered innocent, otherwise they died and were therefore guilty. Those that were lucky enough to vomit before absorption of the poison lived, otherwise even the innocent died. Some tribes would administer an antidote to those supposedly innocent. Missionaries tried very hard to stamp out trial by ordeal but even today it is thought to persist in some of the more isolated regions, although banned by law in all countries.

Physostigmine (**59**) is biosynthesised from tryptophan (**57**) through the intermediate eseroline (**62**) as shown in Figure 18.

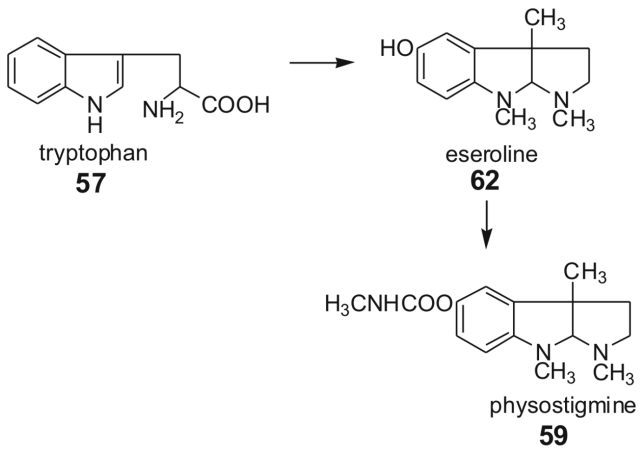


Fig. 18. *The Biosynthesis of physostigmine.*

The complex indole alkaloids

Over 600 bases classified as complex indole alkaloids have been isolated from plants belonging to the Apocynaceae, Loganiaceae and Rubiaceae families. Where isotopic tracer analysis has been carried out it has been shown that the indole nucleus invariably originates from tryptophan (**57**). The remainder of the molecule is derived from mevalonic acid (**63**) through the formation of loganin (**64**) and the resulting alkaloid falls into one of four structural types, corynanthe, strychnine, aspidosperma or iboga (Figure 19). The important medicinal plant Madagascar periwinkle (*Catharanthus roseus*, Apocynaceae, Plate 6) contains all four types which are biosynthesised in this plant from the precursor geissoschizine (**65**) as shown in Figure 20. The Madagascar periwinkle grows wild in Africa and is cultivated throughout the tropics for its pretty pink or white flowers which sometimes have a dark pink centre. The flowers have square petals typical of all periwinkles. It is a drought resistant herb with woody stems and narrow leaves which curl up in drought to minimise water loss.

The alkaloids in *C. roseus* have only a low toxicity and have been used in native medicines for centuries. These extracts are hypotensive and have limited antibiotic activity. The *bis*-indole dimers, particularly vincaleucoblastine (**66**), known as the drug vinblastine, and leurocristine (**67**), known as vincristine are important anticancer drugs. Vinblastine is used in the treatment of Hodgkin's disease and choriocarcinoma, while vincristine is an antileukaemic drug. These drugs also occur in the periwinkles *Vinca major* and *V. minor* (Apocynaceae).

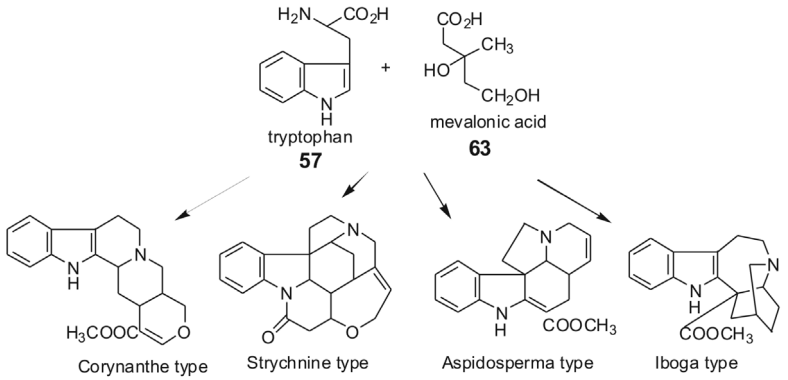
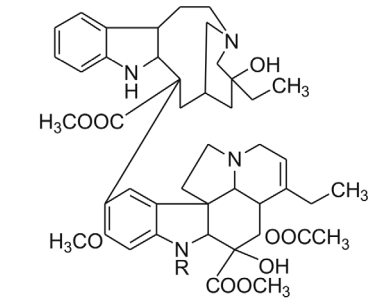


Fig. 19. *Biosynthesis of the complex indole alkaloids.*



R = CH_3, vinceucoblastine **66**

R = CHO, leurocristine **67**

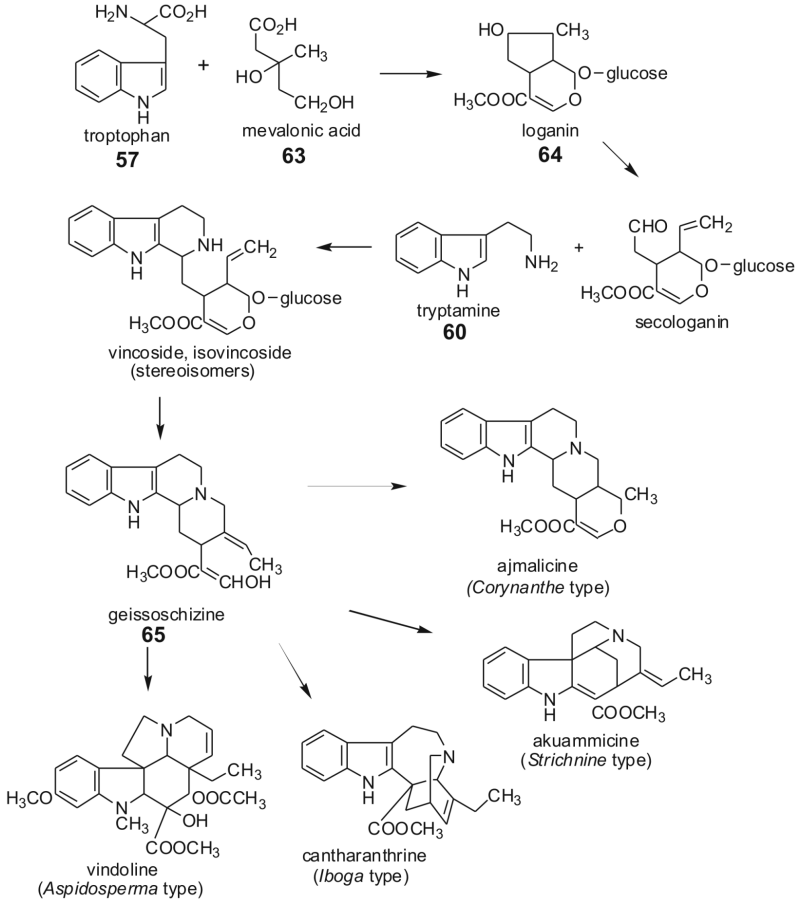


Fig. 20. *The biosynthesis of the Madagascar periwinkle alkaloids.*

Plate 6 *Madagascar periwinkle (Catharanthus roseus);*

Strychnine

Strychnine (**68**) is found in some *Strychnos* species (Loganiaceae) and was first isolated from the Indian tree *Strychnos nux vomica* but has since been found in toxic amounts in other *Strychnos* species. *S. nux vomica* is a medium sized tree native to south-east Asia with green or orange fruits. Strychnine is extracted from the seeds.

The alkaloid is highly toxic, 30–60 mg being sufficient to kill a man. It is a stimulant producing mental and muscular activity and overdoses cause characteristic violent convulsions, five or six of which are sufficient to cause death, which is due to respiratory failure. However, strychnine is one of the few poisons whose effects can be counteracted after absorption. The barbiturate drugs act as antidotes, but it is also imperative that the patient be kept still and quiet. Strychnine has been used medicinally to counteract morphine stupor and overdoses of depressant drugs such as sleeping pills and sometimes in the treatment of *delirium tremens* (alcoholism).

Strychnine (**68**) is biosynthesised from tryptophan (**57**) and loganin (**64**) through the precursor geissoschizine (**65**) (Figure 21).

Quinine

Quinine (**69**) occurs in some *Cinchona* species, particularly *C. pubescens* (Rubiaceae). *Cinchona* species are trees native to South America and are cultivated in many tropical regions. The leaves of *C. pubescens* are mainly green but with the occasional characteristic red leaf. Quinine is extracted from the bark.

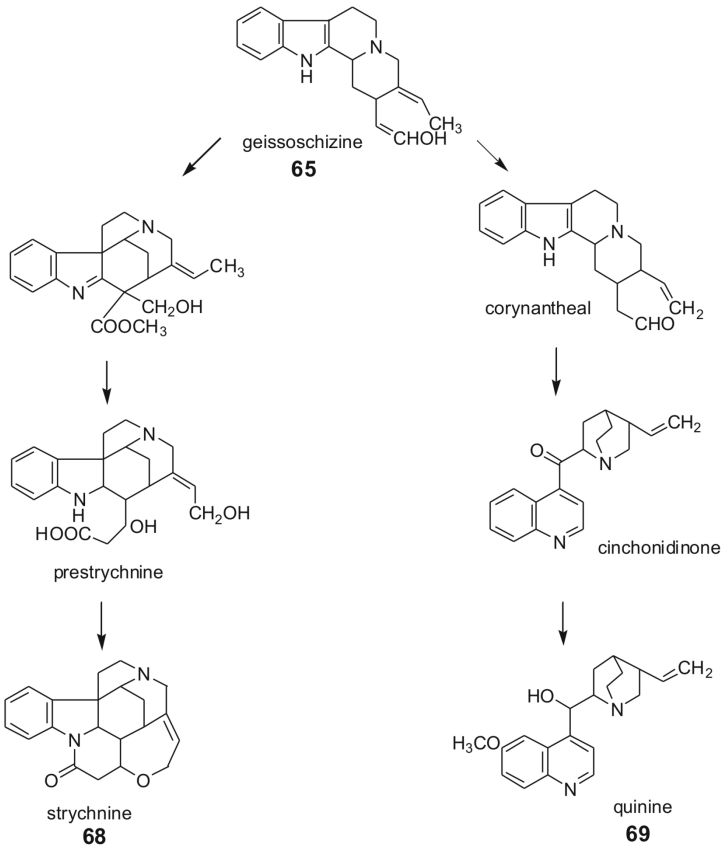


Fig. 21. *The biosynthesis of strichnine and quinine.*

Quinine is a febrifuge and an effective antimalarial drug used particularly in cases resistant to other drugs, but although its toxicity is very low, prolonged use has resulted in blindness and deafness and it can cause allergic reactions. It has also been used to give a bitter taste to soft drinks such as tonic water.

Although a quinoline derivative, quinine is biosynthesised from tryptophan (**57**) and loganin (**64**) through the intermediate formation of geissoschizine (**65**) as shown in (Figure 21).

Cardiac glycosides

Cardiac glycosides or cardenolides are compounds formed between steroids and sugars and, as their name suggests, they act upon the heart. Plants contain a vast variety of steroids but only those containing twenty three or twenty four carbon atoms show

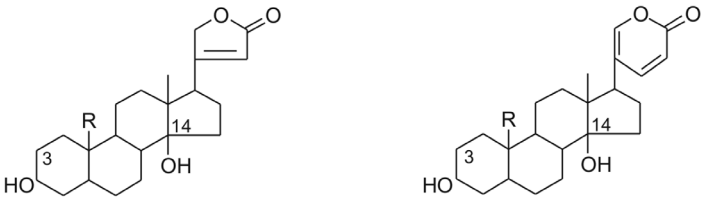


Fig. 22. *Ring structure of cardenolides and bufadienolides.*

cardiac activity (Figure 22), the latter being known as bufadienolides as they were first isolated from toad (*Bufa*) poisons.

All cardiac glycosides are toxic in overdoses, the potency of the compound depending on the sugar component as well as the steroid. Many have been or are still used in orthodox medicine to treat various forms of heart disease. Cardiac glycosides occur in many plant families but are particularly characteristic of the Apopcynacea, Asclepiadaceae and Scrophulariacea and have been isolated from both tropical and temperate species, the best known of the latter being digitoxin from the foxglove (*Digitalis purpurea*, Scrophulariaceae, Plate 7).

Plant steroids are biosynthesised from mevalonic acid (**63**) through the intermediates cholesterol (**70**) and pregnenolone (**71**) (Figure 23). Mevalonic acid is biosynthesised from acetyl Co-enzyme A by the acetate-mevalonate pathway. Cholesterol, the green pigmentation in plants which catalyses photosynthesis, is the product of a complex series of reactions involving the phos-

Table 4 *Some cardiac glycosides*

Cardiac glycoside	Sugar	Occurrence
Ouabain	Rhamnose	*Acocanthera schimperi*, *Strophanthus gratus*
Oleandrin	Oleandrose	*Nerium oleander* (oleander)
Cymarin	Cymarose	*Apocynum cannabinum* (dogbane)
Digitoxin	Digitoxose	*Digitalis purpurea* (foxglove)
Convallatoxin	Rhamnose	*Convallaria majalis* (lily-of-the-valley) *Ornithogalum umbellatum* (star of Bethlehem)

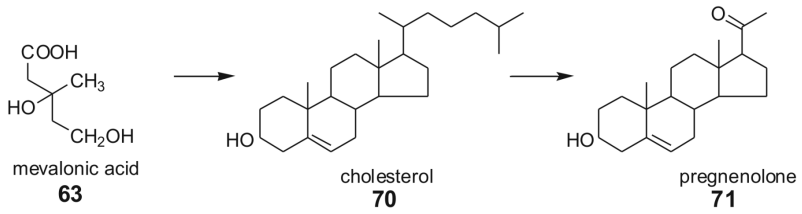
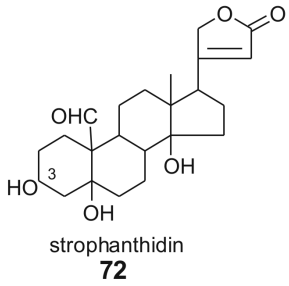


Fig. 23. *General biosynthesis of the C_{21} steriods.*

phorylation of mevalonic acid by ATP (adenosine triphosphate) and the enzyme, mevalonic acid kinase.

In plants, the steroid aglycone is linked to one or more sugars through the hydroxyl group at C-3 and these sugars are often rare and not found linked to any other type of genin except pregnenolone derivatives. Convallatoxin, the rhamnoside of strophanthidin (**72**), is the most toxic of all the C_{23} cardiac glycosides. It occurs in the leaves and flowers of lily-of-the-valley (*Convallaria majalis*, Liliaceae). The hydroxyl group at position 14 is characteristic of all cardenolides, being essential for heart activity.



Cardiac glycosides act on cell membranes by inhibiting the enzyme, ATPase which results in a disturbance of cellular cation concentrations, sodium accumulating while potassium is lost. A decreased heart rate with an increased heart beat intensity results with overdoses leading to heart stoppage.

Digitoxin

Digitoxin (**73**), the active ingredient of digitalis is found in many species of foxgloves particularly *Digitalis purpurea* (Plate 7). Foxgloves are perennials or biennials found throughout Europe. The flowers are tubular and in the case of *D. purpurea*, purple, pink or occasionally white.

***Plate** 7 Foxglove (purple flowers) (Digitalis purpurea); Kohler's Medicinal Plants (1887)*

Digitoxin is the main component of digitalis which has been used over the centuries to treat certain types of heart conditions, particularly congestive heart failure. It acts by slowing the heart rate and producing a strong heartbeat. The digitoxin molecule consists of the steroid digitoxigenin combined with the rare sugar digitoxose. It is biosynthesised from pregnenolone (**71**) by the pathway shown in Figure 24.

Other cardiac glycosides

Ouabain and convallatoxin are amongst the most toxic of the naturally occurring cardenolides. Ouabain, the rhamnoside of ouabagenin (**74**) occurs in tropical *Acocanthera* and *Strophanthus* species (Apocynacea). Ouabain has been used as an arrow poison by African tribes for thousands of years and is still used today in the poaching of wild animals or for acts of homicide. It is usually

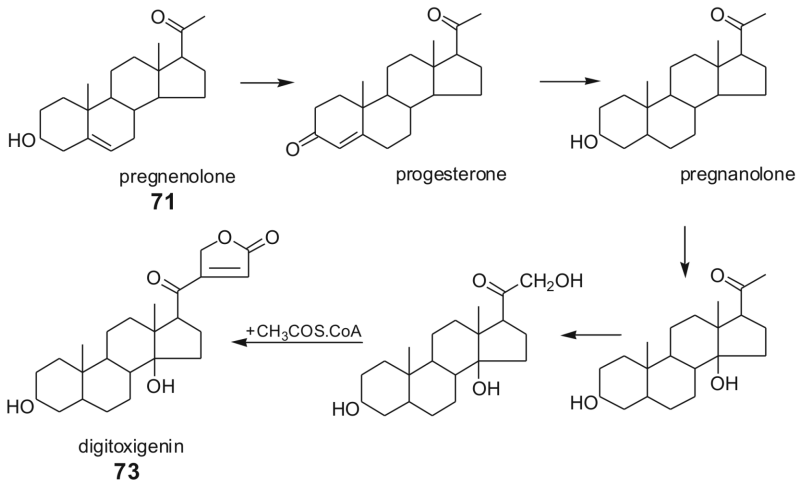
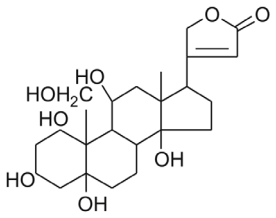


Fig. 24. *The biosynthesis of digitoxigenin.*

extracted from *A. longiflora* and *A. schimperi* (Plate 8), generally from the wood, but all parts of the plants are toxic except the ripe fruit. Ouabain concentration is at its highest during the dry season. Acocanthera species occur widely in Africa. They are evergreen shrubs or small trees with shiny leaves. The flowers are scented, pink or white and occur in clusters in the axils of the leaves. The fruits have edible flesh.



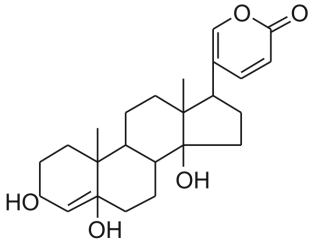
Ouabain is also present in *Strophanthus gratus* seeds, while the related strophanthin obtained from the seeds of *S. hispidus* and *S. kombe* has been used in native medicine for heart problems. Strophanthus species occur at lower altitudes throughout tropical Africa. They are climbing plants with attractive, characteristic flowers whose petals end in long streamers.

Ouabain is only toxic if injected directly into the bloodstream, when it acts quickly killing a large animal in minutes. The lack of toxicity of most cardiac glycosides if ingested orally is probably due

Plate 8 *Acocanthera schimperi; en.wikipedia/wiki/Acocanthera_schimperi*

to the bulk of the molecule and its highly hydroxylated nature, both of which prevent absorption into the bloodstream.

The C_{24} bufadienolides only occur in the Ranunculacea (buttercup) and Liliaceae families in species which do not synthesise cardenolides. Scillarenin (**75**) from the white squill (*Scilla maritima*, Liliaceae) has found some use in the treatment of heart disease but in general the bufadienolides are too toxic to be used medicinally.



scillarenin
75

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