6

ALKALOIDS

Alkaloids are classified according to the amino acid that provides both the nitrogen atom and the fundamental portion of the alkaloid skeleton, and these are discussed in turn. Ornithine gives rise to pyrrolidine and tropane alkaloids, lysine to piperidine, quinolizidine, and indolizidine alkaloids, and nicotinic acid to pyridine alkaloids. Tyrosine produces phenylethylamines and simple tetrahydroisoquinoline alkaloids, but also many others in which phenolic oxidative coupling plays an important role, such as modified benzyltetrahydroisoquinoline, phenethylisoquinoline, terpenoid tetrahydroisoquinoline, and Amaryllidaceae alkaloids. Alkaloids derived from tryptophan are subdivided into simple indole, simple β-carboline, terpenoid indole, quinoline, pyrroloindole, and ergot alkaloids. Anthranilic acid acts as a precursor to quinazoline, quinoline and acridine alkaloids, whilst histidine gives imidazole derivatives. However, many alkaloids are not derived from an amino acid core, but arise by amination of another type of substrate, which may be acetate derived, phenylalanine derived, a terpene or a steroid, and examples are discussed. Purine alkaloids are constructed by pathways that resemble those for purines in nucleic acids. Monograph topics giving more detailed information on medicinal agents include belladonna, stramonium, hyoscyamus, duboisia and allied drugs, hyoscyamine, hyoscine and atropine, coca, lobelia, vitamin B$_3$, tobacco, areca, catecholamines, lophophora, curare, opium, colchicum, ipecacuanha, galanthamine, serotonin, psilocybe, rauwolfia, catharanthus, iboga, nux-vomica, ellipticine, cinchona, camptothecin, physostigma, ergot, morning glories, pilocarpus, *Conium maculatum*, ephedra, khat, aconite, *Solanum* alkaloids, caffeine, theobromine and theophylline, coffee, tea, cola, cocoa, mate tea, guarana, saxitoxin, and tetrodotoxin.

The alkaloids are organic nitrogenous bases found mainly in plants, but also to a lesser extent in microorganisms and animals. One or more nitrogen atoms are present, typically as primary, secondary, or tertiary amines, and this usually confers basicity to the alkaloid, facilitating their isolation and purification since water-soluble salts can be formed in the presence of mineral acids. The name alkaloid is in fact derived from alkali. However, the degree of basicity varies greatly, depending on the structure of the alkaloid molecule, and the presence and location of other functional groups. Indeed, some alkaloids are essentially neutral. Alkaloids containing quaternary amines are also found in nature. The biological activity of many alkaloids is often dependent on the amine function being transformed into a quaternary system by protonation at physiological pHs.

Alkaloids are often classified according to the nature of the nitrogen-containing structure, e.g. pyrrolidine, piperidine, quinoline, isoquinoline, indole, etc, though the structural complexity of some examples rapidly expands the number of subdivisions. The nitrogen atoms in alkaloids originate from an amino acid, and, in general, the carbon skeleton of the particular amino acid precursor is also largely retained intact in the alkaloid structure, though the carboxylic acid carbon is often lost through decarboxylation. Accordingly, subdivision of alkaloids into groups based on amino acid precursors forms a rational and often illuminating approach to classification. Relatively few amino acid precursors are actually involved in alkaloid biosynthesis, the principal ones being ornithine, lysine, nicotinic acid, tyrosine, tryptophan, anthranilic acid, and histidine. Building blocks from the acetate, shikimate, or deoxyxylulose phosphate pathways are also frequently incorporated into the alkaloid structures. However, a large group of alkaloids are found to acquire their nitrogen atoms via transamination reactions, incorporating only the nitrogen from an amino acid, whilst the rest of the molecule may be derived
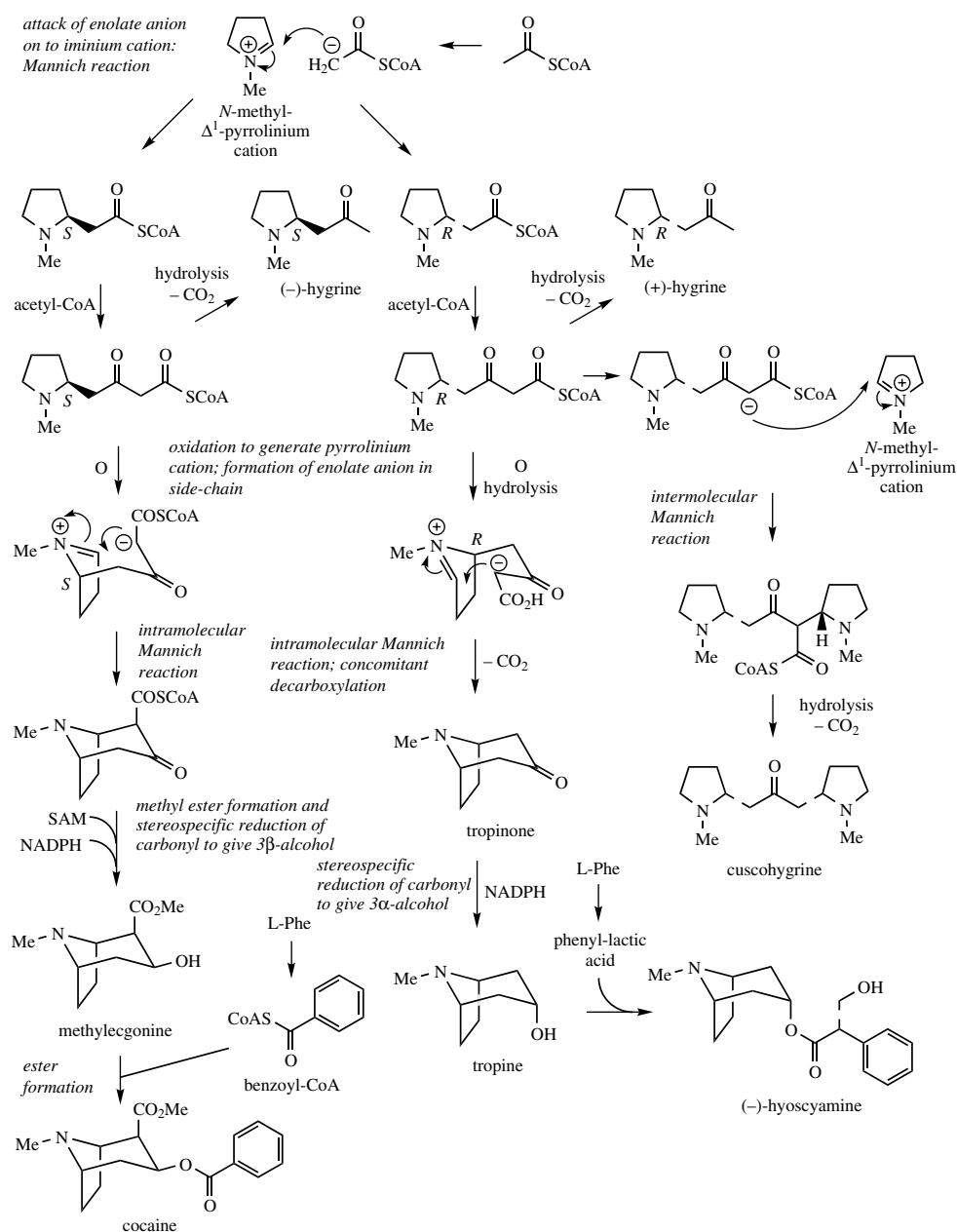
from acetate or shikimate, or may be terpenoid or steroid in origin. The term 'pseudoalkaloid' is sometimes used to distinguish this group.

ALKALOIDS DERIVED FROM ORNITHINE

L-**Ornithine** (Figure 6.1) is a non-protein amino acid forming part of the urea cycle in animals, where it is produced from L-arginine in a reaction catalysed by the enzyme arginase. In plants it is formed mainly from L-glutamate (Figure 6.2). Ornithine contains both δ- and α-amino groups, and it is the nitrogen from the former group which is incorporated into alkaloid structures along with the carbon chain, except for the carboxyl group.

Thus ornithine supplies a C_4N building block to the alkaloid, principally as a pyrrolidine ring system, but also as part of the tropane alkaloids (Figure 6.1). Most of the other amino acid precursors typically supply nitrogen from their solitary α-amino group. However, the reactions of ornithine are almost exactly paralleled by those of L-lysine, which incorporates a C_5N unit containing its ε-amino group (see page 307).

Pyrrolidine and Tropane Alkaloids

Simple pyrrolidine-containing alkaloid structures are exemplified by hygrine and cuscohygrine, found in those plants of the Solanaceae that accumulate medicinally valuable tropane alkaloids such as hyoscyamine or cocaine (see Figure 6.3). The pyrrolidine ring system is formed initially as a Δ^1-pyrrolinium cation (Figure 6.2). PLP-dependent decarboxylation (see page 20) of ornithine gives **putrescine**, which is then methylated to N-methylputrescine. Oxidative deamination of N-methylputrescine by the action of a diamine oxidase (see page 28) gives the aldehyde, and Schiff base (imine) formation produces the N-methyl-Δ^1-pyrrolinium cation. Indeed, the aminoaldehyde in aqueous solution is known to exist as an equilibrium mixture with the

Figure 6.1

Figure 6.2

Figure 6.3

Schiff base. An alternative sequence to putrescine starting from arginine also operates concurrently as indicated in Figure 6.2. The arginine pathway also involves decarboxylation, but requires additional hydrolysis reactions to cleave the guanidine portion.

The extra carbon atoms required for hygrine formation are derived from acetate via acetyl-CoA,

and the sequence appears to involve stepwise addition of two acetyl-CoA units (Figure 6.3). In the first step, the enolate anion from acetyl-CoA acts as nucleophile towards the pyrrolinium ion in a Mannich-like reaction, which could yield products with either *R* or *S* stereochemistry. The second addition is then a Claisen condensation extending the side-chain, and the product is the
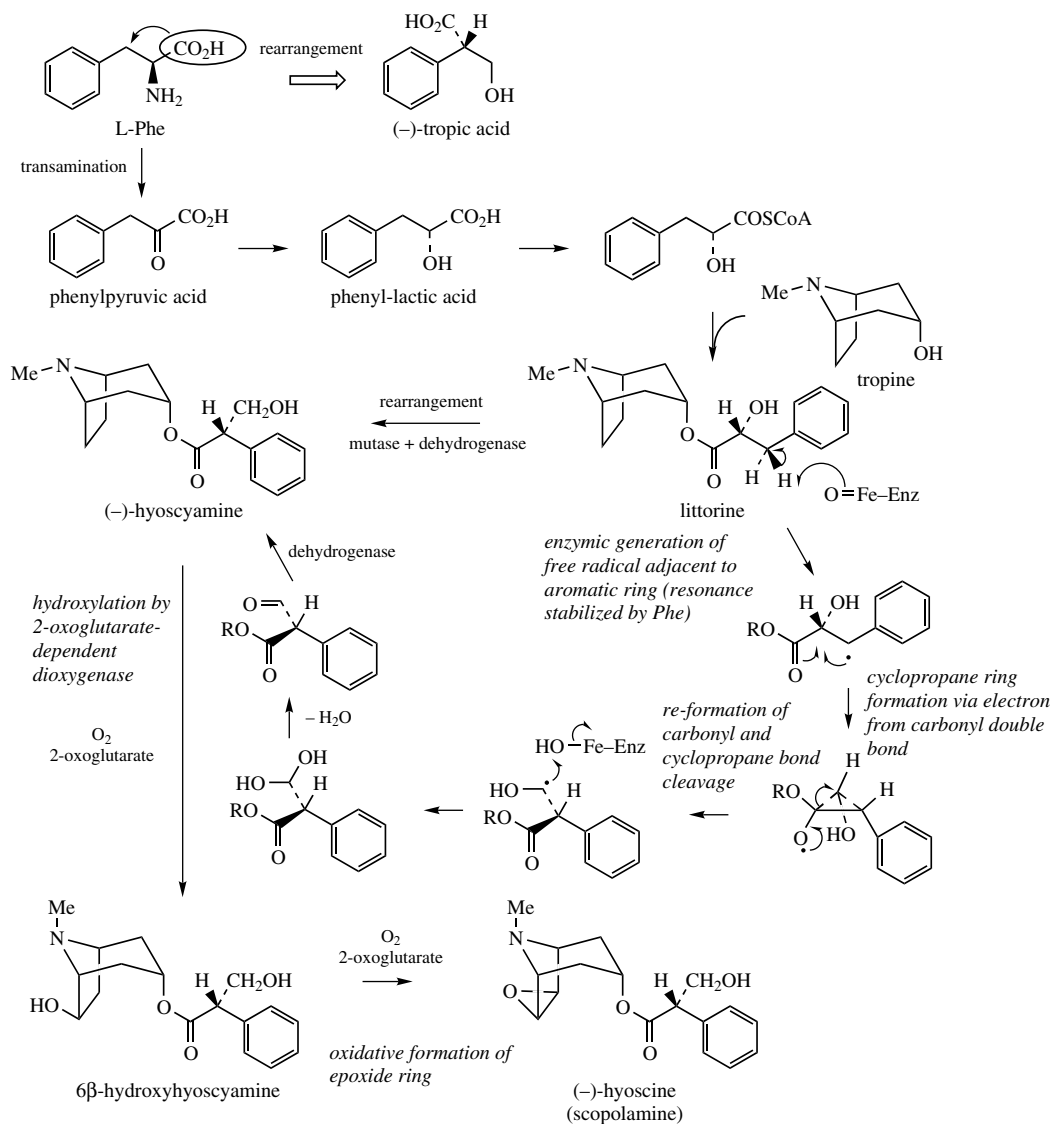
Figure 6.4

2-substituted pyrrolidine, retaining the thioester group of the second acetyl-CoA. **Hygrine** and most of the natural tropane alkaloids lack this particular carbon atom, which is lost by suitable hydrolysis/decarboxylation reactions. The bicyclic structure of the tropane skeleton in **hyoscyamine** and **cocaine** is achieved by a repeat of the Mannich-like reaction just observed. This requires an oxidation step to generate a new Δ^1-pyrrolinium cation, and removal of a proton α to the carbonyl. The *intramolecular* Mannich reaction on the *R* enantiomer accompanied by decarboxylation

generates **tropinone**, and stereospecific reduction of the carbonyl yields **tropine** with a 3α-hydroxyl. Hyoscyamine is the ester of tropine with (S)-**tropic acid** (Figure 6.4), which is derived from L-phenylalanine. A novel rearrangement process occurs in the phenylalanine $\rightarrow$ tropic acid transformation, in which the carboxyl group apparently migrates to the adjacent carbon (Figure 6.4). Phenylpyruvic acid and phenyl-lactic acid have been shown to be involved and tropine becomes esterified with phenyl-lactic acid (as the coenzyme-A ester) to form **littorine**

before the rearrangement occurs. The mechanism of this rearrangement has yet to be proven, though a free radical process (Figure 6.4) with an intermediate cyclopropane-containing radical would accommodate the available data. Further modifications to the tropane skeleton then occur on the ester, and not on the free alcohol. These include hydroxylation to 6β-hydroxyhyoscyamine and additional oxidation allowing formation of an epoxide grouping as in **hyoscine** (**scopolamine**). Both of these reactions are catalysed by a single 2-oxoglutarate-dependent dioxygenase (see page 27). Other esterifying acids may be encountered in tropane alkaloid structures, e.g. tiglic acid in **meteloidine** (Figure 6.5) from *Datura meteloides* and phenyl-lactic acid in littorine, above which is a major alkaloid in *Anthocercis littorea*. Tiglic acid is known to be derived from the amino acid L-isoleucine (see page 197).

The structure of **cuscohygrine** arises by an *intermolecular* Mannich reaction involving a second *N*-methyl-Δ^1-pyrrolinium cation (Figure 6.3).
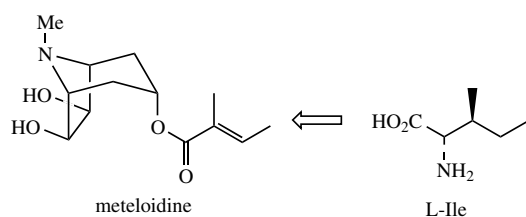
Figure 6.5

Should the carboxyl carbon from the acetoacetyl side-chain not be lost as it was in the formation of tropine, the subsequent intramolecular Mannich reaction will generate a tropane skeleton with an additional carboxyl substituent (Figure 6.3). However, this event is rare, and is only exemplified by the formation of ecgonine derivatives such as **cocaine** in *Erythroxylum coca* (Erythroxylaceae). The pathway is in most aspects analogous to that already described for hyoscyamine, but must proceed through the *S*-enantiomer of the *N*-methylpyrrolidineacetoacetyl-CoA. The ester function is then modified from a coenzyme A thioester to a simple methyl oxygen ester, and **methylecgonine** is subsequently obtained from the methoxycarbonyltropinone by stereospecific reduction of the carbonyl. Note that in this case reduction of the carbonyl occurs from the opposite face to that noted with the tropinone → tropine conversion and thus yields the 3β configuration in ecgonine. **Cocaine** is a diester of ecgonine, the benzoyl moiety arising from phenylalanine via cinnamic acid and benzoyl-CoA (see page 141).

The tropane alkaloids (−)-hyoscyamine* and (−)-hyoscine* are among the most important of the natural alkaloids used in medicine. They are found in a variety of solanaceous plants, including *Atropa belladonna** (deadly nightshade), *Datura stramonium** (thornapple) and other *Datura* species, *Hyoscyamus niger** (henbane), and *Duboisia** species. These alkaloids

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Belladonna

The deadly nightshade *Atropa belladonna* (Solanaceae) has a long history as a highly poisonous plant. The generic name is derived from *Atropos*, in Greek mythology the Fate who cut the thread of life. The berries are particularly dangerous, but all parts of the plant contain toxic alkaloids, and even handling of the plant can lead to toxic effects since the alkaloids are readily absorbed through the skin. Although humans are sensitive to the toxins, some animals, including sheep, pigs, goats, and rabbits, are less susceptible. Cases are known where the consumption of rabbits or birds that have ingested belladonna has led to human poisoning. The plant is a tall perennial herb producing dull-purple bell-shaped flowers followed by conspicuous shiny black fruits, the size of a small cherry. *Atropa belladonna* is indigenous to Central and Southern Europe, though it is not especially common. It is cultivated for drug use in Europe and the United States. The tops of the plant are harvested two or three times per year and dried to give **belladonna** herb. Roots from plants some 3−4 years old are less commonly employed as a source of alkaloids.

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Belladonna herb typically contains 0.3–0.6% of alkaloids, mainly (−)-hyoscyamine (Figure 6.4). Belladonna root has only slightly higher alkaloid content at 0.4–0.8%, again mainly (−)-hyoscyamine. Minor alkaloids including (−)-hyoscine (Figure 6.4) and cuscohygrine (Figure 6.3) are also found in the root, though these are not usually significant in the leaf. The mixed alkaloid extract from belladonna herb is still used as a gastrointestinal sedative, usually in combination with antacids. Root preparations can be used for external pain relief, e.g. in belladonna plasters.

Stramonium

Datura stramonium (Solanaceae) is commonly referred to as thornapple on account of its spikey fruit. It is a tall bushy annual plant widely distributed in Europe and North America, and because of its alkaloid content is potentially very toxic. Indeed, a further common name, Jimson or Jamestown weed, originates from the poisoning of early settlers near Jamestown, Virginia. At subtoxic levels, the alkaloids can provide mild sedative action and a feeling of well-being. In the Middle Ages, stramonium was employed to drug victims prior to robbing them. During this event, the victim appeared normal and was cooperative, though afterwards could usually not remember what had happened. For drug use, the plant is cultivated in Europe and South America. The leaves and tops are harvested when the plant is in flower. **Stramonium** leaf usually contains 0.2–0.45% of alkaloids, principally (−)-hyoscyamine and (−)-hyoscine in a ratio of about 2:1. In young plants, (−)-hyoscine can predominate.

The generic name *Datura* is derived from dhat, an Indian poison used by the Thugs. The narcotic properties of *Datura* species, especially *D. metel*, have been known and valued in India for centuries. The plant material was usually absorbed by smoking. Most species of *Datura* contain similar tropane alkaloids and are potential sources of medicinal alkaloids. In particular, *Datura sanguinea*, a perennial of treelike stature with blood-red flowers, is cultivated in Ecuador, and yields leaf material with a high (0.8%) alkaloid content in which the principal component is (−)-hyoscine. The plants can be harvested several times a year. *Datura sanguinea*, and several other species of the tree-daturas (now classified as a separate genus *Brugmansia*) are widely cultivated as ornamentals, especially for conservatories, because of their attractive large tubular flowers. The toxic potential of these plants is not always recognized.

Hyosycamus

Hyoscyamus niger (Solanaceae), or henbane, is a European native with a long history as a medicinal plant. Its inclusion in mediaeval concoctions and its power to induce hallucinations with visions of flight may well have contributed to our imaginary view of witches on broomsticks. The plant has both annual and biennial forms, and is cultivated in Europe and North America for drug use, the tops being collected when the plant is in flower, and then dried rapidly. The alkaloid content of **hyoscyamus** is relatively low at 0.045–0.14%, but this can be composed of similar proportions of (−)-hyoscine and (−)-hyoscyamine. Egyptian henbane, *Hyoscyamus muticus*, has a much higher alkaloid content than *H. niger*, and although it has mainly been collected from the wild, especially from Egypt, it functions as a major commercial source for alkaloid production. Some commercial cultivation occurs in California. The alkaloid content of the leaf is from 0.35% to 1.4%, of which about 90% is (−)-hyoscyamine.

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Duboisia

Duboisia is a small genus of trees, containing only three species, found in Australia, again from the family Solanaceae. Two of these, *Duboisia myoporoides* and *D. leichhardtii* are grown commercially in Australia for tropane alkaloid production. The small trees are kept as bushes to allow frequent harvesting, with up to 70–80% of the leaves being removed every 7–8 months. The alkaloid content of the leaf is high, up to 3% has been recorded, and it includes (−)-hyoscyamine, (−)-hyoscine, and a number of related structures. The proportion of hyoscyamine to hyoscine varies according to the species used, and the area in which the trees are grown. The hyoscine content is frequently much higher than that of hyoscyamine. Indeed, interest in *Duboisia* was very much stimulated by the demand for hyoscine as a treatment for motion sickness in military personnel in the Second World War. Even higher levels of alkaloids, and higher proportions of hyoscine, can be obtained from selected *D. myoporoides* × *D. leichhardtii* hybrids, which are currently cultivated. The hybrid is superior to either parent, and can yield 1–2.5% hyoscine and 0–1% hyoscyamine. *Duboisia* leaf is an important commercial source of medicinal tropane alkaloids.

The third species of *Duboisia*, *D. hopwoodi*, contains little tropane alkaloid content, but produces mainly nicotine and related alkaloids, e.g. nornicotine (see page 313). Leaves of this plant were chewed by aborigines for their stimulating effects.

Allied Drugs

Tropane alkaloids, principally hyoscyamine and hyoscine, are also found in two other medicinal plants, scopolia and mandrake, but these plants find little current use. Scopolia (*Scopolia carniolica*; Solanaceae) resembles belladonna in appearance, though it is considerably smaller. Both root and leaf materials have been employed medicinally. The European mandrake (*Mandragora officinarum*; Solanaceae) has a complex history as a hypnotic, a general panacea, and an aphrodisiac. Its collection has been surrounded by much folklore and superstition, in that pulling it from the ground was said to drive its collector mad due to the unearthly shrieks emitted. The roots are frequently forked and are loosely likened to a man or woman. Despite the Doctrine of Signatures, which teaches that the appearance of an object indicates its special properties, from a pharmacological point of view, this plant would be much more efficient as a pain-reliever than as an aphrodisiac.

Hyoscyamine, Hyoscine and Atropine

All the above solanaceous plants contain as main alkaloidal constituents the tropane esters (−)-**hyoscyamine** and (−)-**hyoscine**, together with other minor tropane alkaloids. The piperidine ring in the bicyclic tropane system has a chairlike conformation, and there is a ready inversion of configuration at the nitrogen atom so that the *N*-methyl group can equilibrate between equatorial and axial positions (Figure 6.6). An equatorial methyl is strongly favoured provided there are no substituents on the two-carbon bridge, in which case the axial form may predominate. (−)-Hyoscyamine is the ester of tropine (Figure 6.4) with (−)-(S)-tropic acid, whilst (−)-hyoscine contains scopine (Figure 6.8) esterified with (−)-(S)-tropic acid. The optical activity of both hyoscyamine and hyoscine stems from the chiral centre
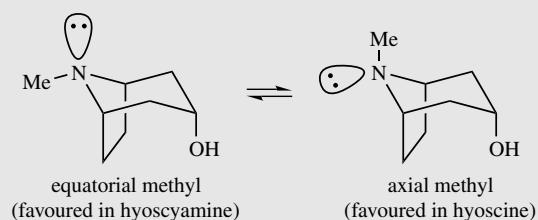
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equatorial methyl
(favoured in hyoscyamine)

axial methyl
(favoured in hyoscine)

Figure 6.6

*base-catalysed or heat-initiated
keto–enol tautomerism*

*double bond of enol and
aromatic ring in conjugation*
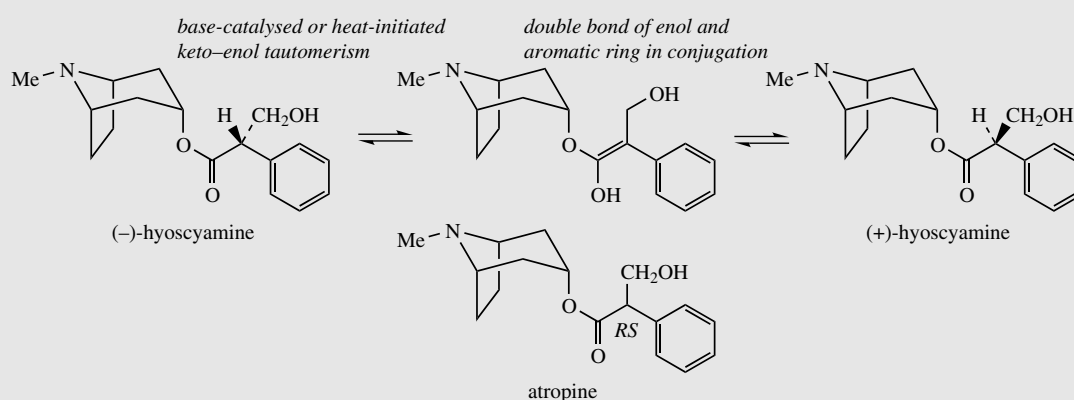
(−)-hyoscyamine

(+)-hyoscyamine

atropine

Figure 6.7

in the acid portion, (*S*)-tropic acid. Tropine itself, although containing chiral centres, is a symmetrical molecule and is optically inactive; it can be regarded as a *meso* structure. The chiral centre in the tropic acid portion is adjacent to a carbonyl and the aromatic ring, and racemization can be achieved under mild conditions by heating or treating with base. This will involve an intermediate enol (or enolate) which is additionally favoured by conjugation with the aromatic ring (Figure 6.7). Indeed, normal base assisted fractionation of plant extracts to isolate the alkaloids can sometimes result in production of significant amounts of racemic alkaloids. The plant material itself generally contains only the enantiomerically pure alkaloids. Hyoscyamine appears to be much more easily racemized than hyoscine. Hydrolysis of the esters using acid or base usually gives racemic tropic acid. Note that littorine (Figure 6.4), in which the chiral centre is not adjacent to the phenyl ring, is not readily racemized, and base hydrolysis gives optically pure phenyl-lactic acid. The racemic form of hyoscyamine is called **atropine** (Figure 6.7), whilst that of hyoscine is called atroscine. In each case, the biological activity of the (+)-enantiomer is some 20–30 times less than that of the natural (−)-form. Chemical hydrolysis of hyoscine in an attempt to obtain the alcohol scopine is not feasible. Instead, the alcohol oscine is generated because of the proximity of the 3α-hydroxyl group to the reactive epoxide function (Figure 6.8).

Probably for traditional reasons, salts of both (−)-hyoscyamine and (±)-hyoscyamine (atropine) are used medicinally, whereas usage of hyoscine is restricted to the

(*Continued*)

hydrolysis

nucleophilic attack of 3α-hydroxyl on to either carbon of epoxide

(−)-hyoscine   scopine   (±)-oscine

Figure 6.8

muscarine   acetylcholine   hyoscyamine
(as conjugate acid)
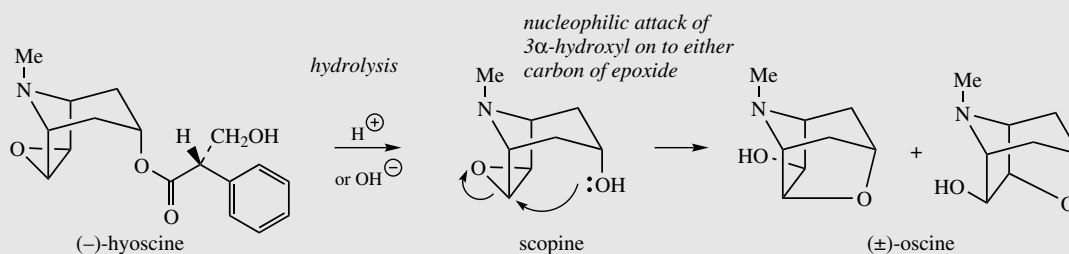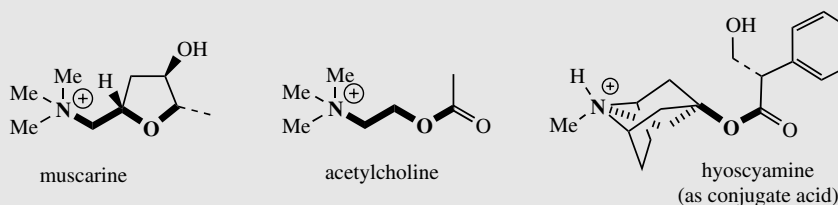
Figure 6.9

natural laevorotatory form. These alkaloids compete with acetylcholine for the muscarinic site of the parasympathetic nervous system, thus preventing the passage of nerve impulses, and are classified as anticholinergics. Acetylcholine binds to two types of receptor site, described as muscarinic or nicotinic, from the specific triggering of a response by the *Amanita muscaria* alkaloid muscarine or the tobacco alkaloid nicotine (see page 314) respectively. The structural similarity between acetylcholine and muscarine (Figure 6.9) can readily be appreciated, and hyoscyamine is able to occupy the same receptor site by virtue of the spatial relationship between the nitrogen atom and the ester linkage (Figure 6.9). The side-chain also plays a role in the binding, explaining the difference in activities between the two enantiomeric forms. The agonist properties of hyoscyamine and hyoscine give rise to a number of useful effects, including antispasmodic action on the gastrointestinal tract, antisecretory effect controlling salivary secretions during surgical operations, and as mydriatics to dilate the pupil of the eye. Hyoscine has a depressant action on the central nervous system and finds particular use as a sedative to control motion sickness. One of the side-effects from oral administration of tropane alkaloids is dry mouth (the antisecretory effect) but this can be much reduced by transdermal administration. In motion sickness treatment, hyoscine can be supplied via an impregnated patch worn behind the ear. Hyoscine under its synonym scopolamine is also well known, especially in fiction, as a 'truth drug'. This combination of sedation, lack of will, and amnesia was first employed in child-birth, giving what was termed 'twilight sleep', and may be compared with the mediaeval use of stramonium. The mydriatic use also has a very long history. Indeed, the specific name *belladonna* for deadly nightshade means 'beautiful lady' and refers to the practice of ladies at court who applied the juice of the fruit to the eyes, giving widely dilated pupils and a striking appearance, though at the expense of blurred vision through an inability to focus. Atropine also has useful antidote action in cases of poisoning caused by cholinesterase inhibitors, e.g. physostigmine and neostigmine (see page 366) and organophosphate insecticides.

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It is valuable to reiterate here that the tropane alkaloid-producing plants are all regarded as very toxic, and that since the alkaloids are rapidly absorbed into the blood stream, even via the skin, first aid must be very prompt. Initial toxicity symptoms include skin flushing with raised body temperature, mouth dryness, dilated pupils, and blurred vision.
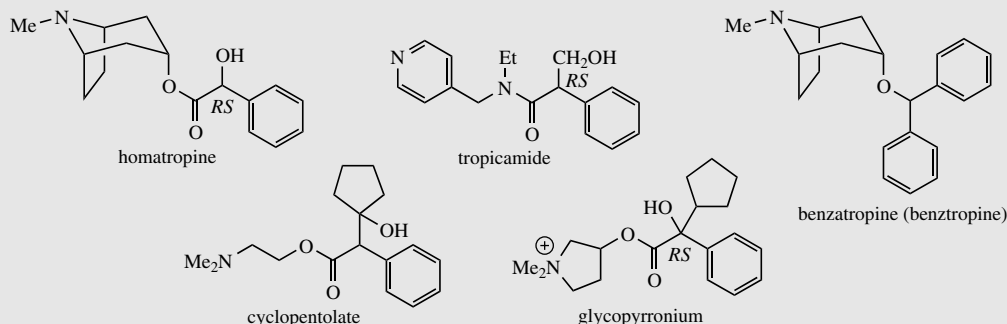

Figure 6.10

Homatropine (Figure 6.10) is a semi-synthetic ester of tropine with racemic mandelic (2-hydroxyphenylacetic) acid and is used as a mydriatic, as are **tropicamide** and **cyclopentolate** (Figure 6.10). Tropicamide is an amide of tropic acid, though a pyridine nitrogen is used to mimic that of the tropane. Cyclopentolate is an ester of a tropic acid-like system, but uses a non-quaternized amino alcohol resembling choline. **Glycopyrronium** (Figure 6.10) has a quaternized nitrogen in a pyrrolidine ring, with an acid moiety similar to that of cyclopentolate. This drug is an antimuscarinic used as a premedicant to dry bronchial and salivary secretions. **Hyoscine butylbromide** (Figure 6.11) is a gastro-intestinal antispasmodic synthesized from (−)-hyoscine by quaternization of the amine function with butyl bromide. The quaternization of tropane alkaloids by *N*-alkylation proceeds such that the incoming alkyl group always
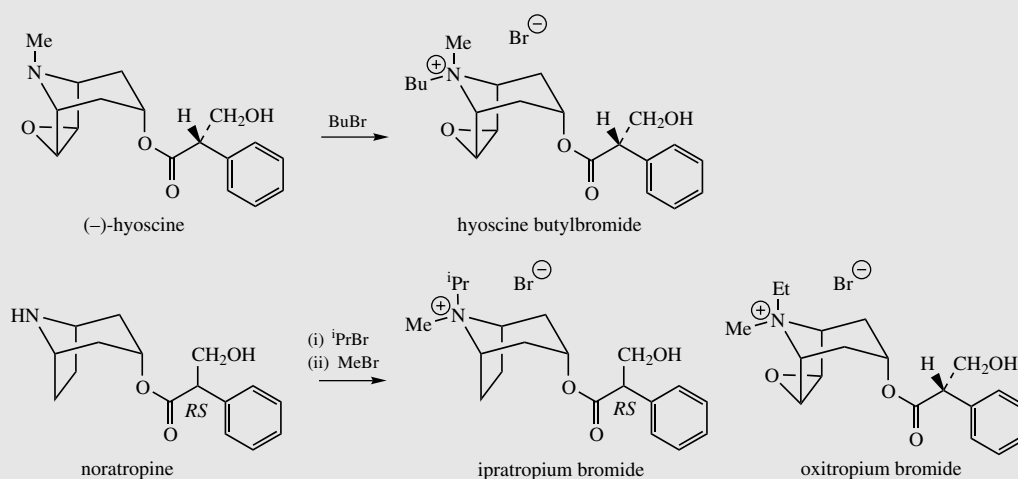
Figure 6.11

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approaches from the equatorial position. The potent bronchodilator **ipratropium bromide** (Figure 6.11) is thus synthesized from noratropine by successive isopropyl and methyl alkylations whilst **oxitropium bromide** is produced from norhyoscine by *N*-ethylation and then *N*-methylation. Both drugs are used in inhalers for the treatment of chronic bronchitis.

Benzatropine (**benztropine**) (Figure 6.10) is an ether of tropine used as an antimuscarinic drug in the treatment of Parkinson's disease. It is able to inhibit dopamine reuptake, helping to correct the deficiency which is characteristic of Parkinsonism.

calystegine A$_3$ calystegine B$_2$
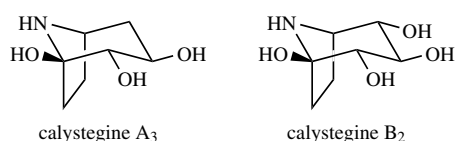
Figure 6.12

are also responsible for the pronounced toxic properties of these plants.

The **calystegines** (Figure 6.12) are a group of recently discovered, water-soluble, polyhydroxy nortropane derivatives that are found in the leaves and roots of many of the solanaceous plants, including *Atropa*, *Datura*, *Duboisia*, *Hyoscyamus*, *Mandragora*, *Scopolia*, and *Solanum*. They were first isolated from *Calystegia sepium* (Convolvulaceae). These compounds, e.g. calystegin A$_3$ and calystegin B$_2$ (Figure 6.12), are currently of great interest as glycosidase inhibitors and have similar potential as the polyhydroxyindolizidines such as castanospermine (see page 310) and the aminosugars such as deoxynojirimycin (see

page 477) in the development of drugs with activity against the AIDS virus HIV. It is likely that these alkaloids are produced by a similar pathway to that which yields tropine, but the stereochemistry of reduction of tropinone (or nortropinone) yields the 3β-alcohol, and further hydroxylation steps are necessary. Examples of tri-, tetra-, and penta-hydroxy calystegines are currently known.

Cocaine (Figure 6.3) is a rare alkaloid restricted to some species of *Erythroxylum* (Erythroxylaceae). *Erythroxylum coca* (coca)* is the most prominent as a source of cocaine, used medicinally as a local anaesthetic, and as an illicit drug for its euphoric properties. Coca also contains significant amounts of **cinnamoylcocaine** (**cinnamylcocaine**) (Figure 6.13), where cinnamic acid rather than benzoic acid is the esterifying acid, together with some typical tropine derivatives without the extra carboxyl, e.g. **tropacocaine** (Figure 6.13). Tropacocaine still retains the 3β-configuration, showing that the stereospecific carbonyl reduction is the same as with the cocaine route, and not as with the hyoscyamine pathway.
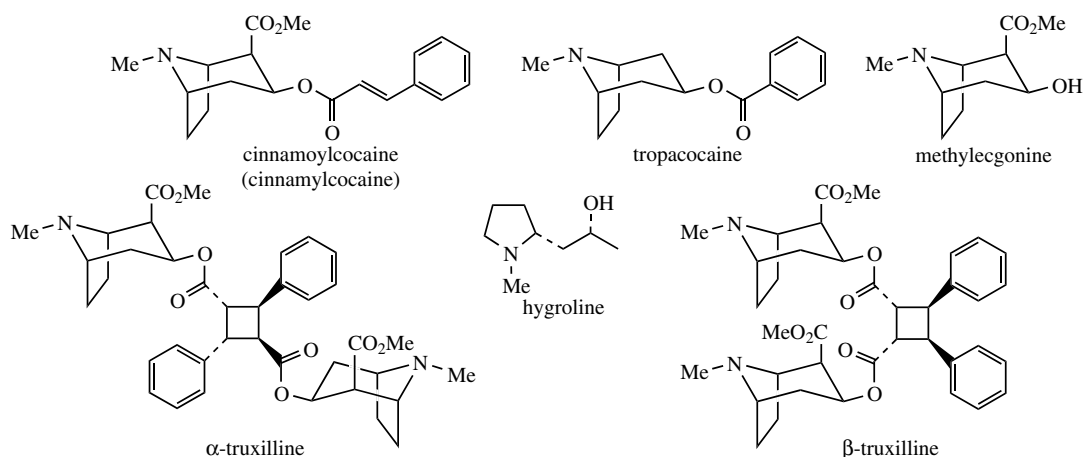

cinnamoylcocaine (cinnamylcocaine)   tropacocaine   methylecgonine

α-truxilline   hygroline   β-truxilline

Figure 6.13

Coca

Coca leaves are obtained from species of *Erythroxylum* (Erythroxylaceae), small shrubs native to the Andes region of South America, namely Colombia, Ecuador, Peru, and Bolivia. Plants are cultivated there, and in Indonesia. Two main species provide drug materials, *Erythroxylum coca* (Bolivian or Huanaco coca) and *E. truxillense* (Peruvian or Truxillo coca). Cultivated plants are kept small by pruning and a quantity of leaves is harvested from each plant three or more times per year.

Coca-leaf chewing has been practised by South American Indians for many years and is an integral part of the native culture pattern. Leaf is mixed with lime, this liberating the principal alkaloid cocaine as the free base, and the combination is then chewed. Cocaine acts as a potent antifatigue agent, and this allows labourers to ignore hunger, fatigue, and cold, enhancing physical activity and endurance. Originally the practice was limited to the Inca high priests and favoured individuals, but became widespread after the Spanish conquest of South America. It is estimated that 25% of the harvest is consumed in this way by the local workers, who may each use about 50 g of leaf per day ($\equiv$ 350 mg cocaine). Only a tiny amount (1–2%) of the coca produced is exported for drug manufacture. The rest contributes to illicit trade and the world's drug problems. Efforts to stem the supply of illicit coca and cocaine have been relatively unsuccessful.

Coca leaf contains 0.7–2.5% of alkaloids, the chief component (typically 40–50%) of which is (−)-cocaine (Figure 6.3), a diester of (−)-ecgonine. Note that although tropine is an optically inactive *meso* structure, ecgonine contains four chiral centres, is no longer symmetrical, and is therefore optically active. Cinnamoylcocaine (cinnamylcocaine), α-truxilline, β-truxilline, and methylecgonine (Figure 6.13) are minor constituents also based on ecgonine. The truxillines contain dibasic acid moieties, α-truxillic and β-truxinic acids, which are cycloaddition products from two cinnamic acid units (Figure 6.14). Other alkaloids present include structures based on φ-tropine (the 3β-isomer of tropine) such as tropacocaine (Figure 6.13) and on hygrine, e.g. hygrine, hygroline (Figure 6.13) and cuscohygrine (Figure 6.3). Cuscohygrine typically accounts for 20–30% of the alkaloid content.

Illegal production of cocaine is fairly unsophisticated, but can result in material of high quality. The alkaloids are extracted from crushed leaf using alkali (lime) and petrol. The petrol extract is then re-extracted with aqueous acid, and this alkaloid fraction is basified and allowed to stand, yielding the free alkaloid as a paste. Alternatively, the hydrochloride or sulphate salts may be prepared. The coca alkaloids are often diluted with carrier to give a
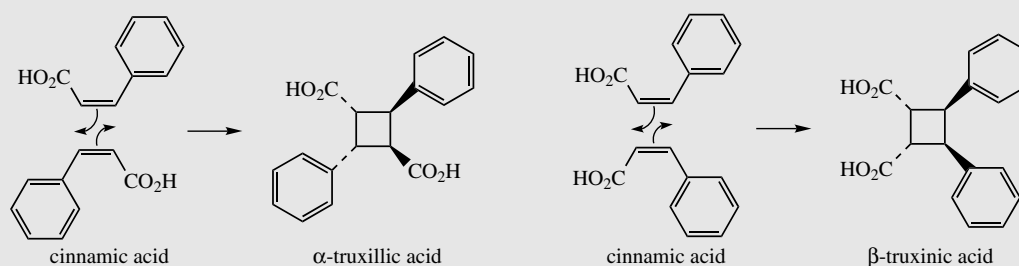

cinnamic acid   α-truxillic acid   cinnamic acid   β-truxinic acid

Figure 6.14

(*Continues*)

(Continued)

preparation with 10–12% of cocaine. The illicit use of cocaine and cocaine hydrochloride is a major problem worldwide. The powder is usually sniffed into the nostrils, where it is rapidly absorbed by the mucosa, giving stimulation and short-lived euphoria through inhibiting reuptake of neurotransmitters dopamine, noradrenaline, and serotonin, so prolonging and augmenting their effects. Regular usage induces depression, dependence, and damage to the nasal membranes. The drug may also be injected intravenously, or the vapour inhaled. For inhalation, the free base or 'crack' is employed to increase volatility. The vaporized cocaine is absorbed extremely rapidly and carried to the brain within seconds, speeding up and enhancing the euphoric lift. Taken in this form, cocaine has proved highly addictive and dangerous. Cocaine abuse is currently a greater problem than heroin addiction, and, despite intensive efforts, there is no useful antagonist drug available to treat cocaine craving and addiction.

In the 1800s, coca drinks were fashionable, and one in particular, Coca-Cola, became very popular. This was originally based on extracts of coca (providing cocaine) and cola (supplying caffeine) (see page 395), but although the coca content was omitted from 1906 onwards, the name and popularity continue.

Medicinally, **cocaine** is of value as a local anaesthetic for topical application. It is rapidly absorbed by mucous membranes and paralyses peripheral ends of sensory nerves. This is achieved by blocking ion channels in neural membranes. It was widely used in dentistry, but has been replaced by safer drugs, though it still has applications in ophthalmic and ear, nose, and throat surgery. As a constituent of Brompton's cocktail (cocaine and heroin in sweetened alcohol) it is available to control pain in terminal cancer patients. It increases the overall analgesic effect, and its additional CNS stimulant properties counteract the sedation normally associated with heroin (see page 332).

The essential functionalities of cocaine required for activity were eventually assessed to be the aromatic carboxylic acid ester and the basic amino group, separated by a lipophilic hydrocarbon chain. Synthetic drugs developed from the cocaine structure have been introduced to provide safer, less toxic local anaesthetics (Figure 6.15). **Procaine**, though little used now, was the first major analogue employed. **Benzocaine** is used topically, but has a short duration of action. **Tetracaine** (**amethocaine**), **oxybuprocaine**, and **proxymetacaine** are valuable local anaesthetics employed principally in ophthalmic work. The ester function can be replaced by an amide, and this gives better stability towards hydrolysis in aqueous solution or by esterases. **Lidocaine** (**lignocaine**) is an example of an amino amide analogue and is perhaps the most widely used local anaesthetic, having rapid action, effective absorption, good stability, and may be used by injection or topically. Other amino amide local anaesthetic structures include **prilocaine**, with similar properties to lidocaine and very low toxicity, and **bupivacaine**, which has a long duration of action. **Ropivacaine**, **mepivacaine**, and **articaine** (**carticaine**) are some recently introduced amide-type local anaesthetics, the latter two being used predominantly in dentistry. **Cinchocaine** is often incorporated into preparations to soothe haemorrhoids.

Lidocaine, although introduced as a local anaesthetic, was subsequently found to be a potent antiarrhythmic agent, and it now finds further use as an antiarrhythmic drug, for treatment of ventricular arrhythmias especially after myocardial infarction. Other cocaine-related structures also find application in the same way, including **tocainide**, **procainamide**, and **flecainide** (Figure 6.15). Tocainide is a primary amine analogue of lidocaine, whilst procainamide is an amide analogue of procaine. In **mexiletene**, a congener of lidocaine, the amide group has been replaced by a simple ether linkage.
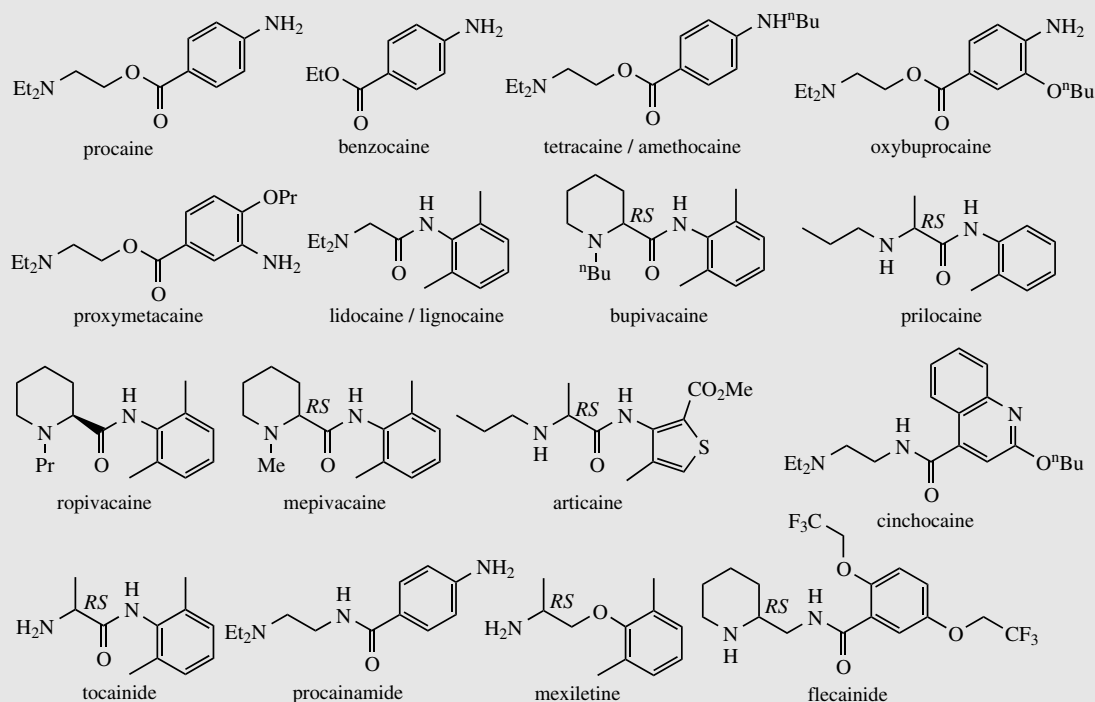
(Continues)

(Continued)

procaine

benzocaine

tetracaine / amethocaine

oxybuprocaine

proxymetacaine

lidocaine / lignocaine

bupivacaine

prilocaine

ropivacaine

mepivacaine

articaine

cinchocaine

tocainide

procainamide

mexiletine

flecainide

Figure 6.15

Anatoxin-*a* (Figure 6.16) is a toxic tropane-related alkaloid produced by a number of cyanobacteria, e.g. *Anabaena flos-aquae* and *Aphanizomenon flos-aquae*, species which proliferate in lakes and reservoirs during periods of hot, calm weather. A number of animal deaths have been traced back to consumption of water containing the cyanobacteria, and ingestion of the highly potent neurotoxin anatoxin-*a*, which has been termed Very Fast Death Factor. Anatoxin-*a* is a powerful agonist at nicotinic acetylcholine receptors, and has become a useful pharmacological probe. The ring system may be regarded as a homotropane, and it has been suggested that the pyrrolidine ring originates from ornithine via putrescine and Δ^1-pyrroline, in a way similar to the tropane alkaloids (Figure 6.16). The remaining carbons may originate from acetate precursors. A remarkable compound with a nortropane ring system has been isolated in tiny amounts from the highly coloured skin of the Ecuadorian poison frog *Epipedobates tricolor*. This compound, called **epibatidine** (Figure 6.17), is exciting considerable interest as a lead compound for analgesic drugs. It is 200–500 times more potent than morphine (see page 331), and does not act by the normal opioid mechanism, but is a specific agonist at nicotinic acetylcholine receptors. Whether or not this structure is ornithine derived remains to be established.

L-Orn

putrescine Δ^1-pyrroline   acetyl-CoA   anatoxin-*a*

Figure 6.16

epibatidine
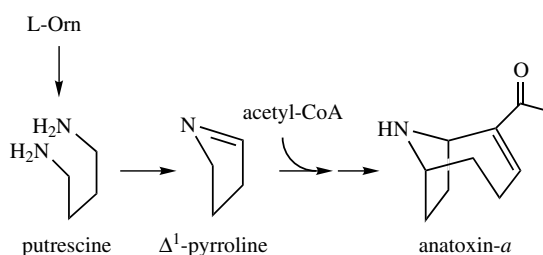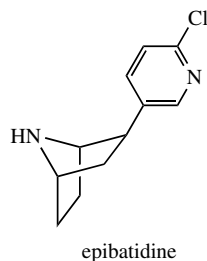
Figure 6.17

Pyrrolizidine Alkaloids

Two molecules of ornithine are utilized in formation of the bicyclic pyrrolizidine skeleton, the pathway (Figure 6.18) proceeding via the intermediate **putrescine**. Because plants synthesizing pyrrolizidine alkaloids appear to lack the decarboxylase enzyme transforming ornithine into putrescine, ornithine is actually incorporated by way of arginine (Figure 6.2). Two molecules of putrescine are condensed in an NAD^+-dependent oxidative deamination reaction to give the imine, which is then converted into **homospermidine** by NADH reduction. On paper, one might predict that one molecule of putrescine is converted by oxidative deamination into the aldehyde, which

condenses with a second putrescine molecule to give the imine, but this mechanism has been proven to be incorrect. The pyrrolizidine skeleton is formed from homospermidine by a sequence of oxidative deamination, imine formation, and an intramolecular Mannich reaction, which exploits the enolate anion generated from the aldehyde. This latter reaction is analogous to that proposed in formation of the tropane ring system (see page 293). A typical simple natural pyrrolizidine structure is that of **retronecine** (Figure 6.18), which can be derived from the pyrrolizidine aldehyde by modest oxidative and reductive steps. The pyrrolizidine skeleton thus incorporates a C_4N unit from ornithine, plus a further four carbons from the same amino acid precursor.

Pyrrolizidine alkaloids have a wide distribution, but are characteristic of certain genera of the Boraginaceae (e.g. *Heliotropium*, *Cynoglossum*, and *Symphytum*), the Compositae/Asteraceae (e.g. *Senecio*) and the Leguminosae/Fabaceae (e.g. *Crotalaria*). The pyrrolizidine bases rarely occur in the free form, but are generally found as esters with rare mono- or di-basic acids, the necic acids. Thus, **senecionine** (Figure 6.18) from *Senecio* species is a diester of retronecine with senecic acid. Inspection of the ten-carbon skeleton
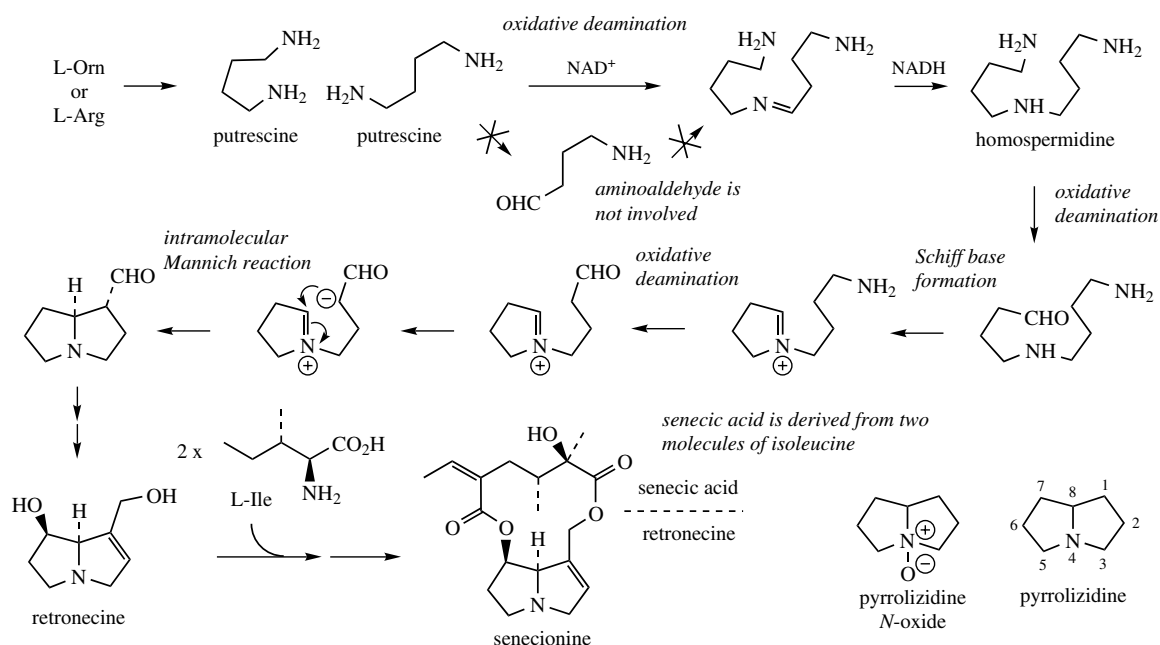
Figure 6.18

of senecic acid suggests it is potentially derivable from two isoprene units, but experimental evidence has demonstrated that it is in fact obtained by incorporation of two molecules of the amino acid L-isoleucine. Loss of the carboxyl from isoleucine supplies a carbon fragment analogous to isoprene units (compare tiglic acid in the tropane alkaloid meteloidine, Figure 6.5). Other necic acid structures may incorporate fragments from valine, threonine, leucine, or acetate. It is also worthy of note that, in general, the pyrrolizidine alkaloids accumulate in the plant as polar *N*-oxides, facilitating their transport, and above all, maintaining them in a non-toxic form. The *N*-oxides are easily changed back to the tertiary amines by mild reduction, as will occur in the gut of a herbivore.

Many pyrrolizidine alkaloids are known to produce pronounced hepatic toxicity and there are many recorded cases of livestock poisoning. Potentially toxic structures have 1,2-unsaturation in the pyrrolizidine ring and an ester function on the side-chain. Although themselves non-toxic, these alkaloids are transformed by mammalian liver

oxidases into reactive pyrrole structures, which are potent alkylating agents and react with suitable cell nucleophiles, e.g. nucleic acids and proteins (Figure 6.19). *N*-oxides are not transformed by these oxidases, only the free bases. The presence of pyrrolizidine alkaloids, e.g. **acetyl-intermedine** and **acetyl-lycopsamine** (Figure 6.20) in medicinal comfrey (*Symphytum officinale*; Boraginaceae) has emphasized potential dangers of using this traditional herbal drug as a remedy for inflammatory, rheumatic, and gastrointestinal disorders. Prolonged usage may lead to liver damage. Caterpillars of the cinnabar moth *Tyria jacobaeae* feed on species of *Senecio* (e.g. ragwort, *S. jacobaea*, and groundsel, *S. vulgaris*) with impunity, building up levels of pyrrolizidine alkaloids in their bodies (in the form of non-toxic *N*-oxides) making them distasteful to predators, and potentially toxic should the predator convert the alkaloids into the free bases. **Indicine-*N*-oxide** (Figure 6.20) from *Heliotropium indicum* (Boraginaceae) demonstrated significant antileukaemic activity in clinical trials but undesirable hepatotoxicity prevented any further development.

Figure 6.19

acetyl-intermedine   acetyl-lycopsamine   indicine-*N*-oxide
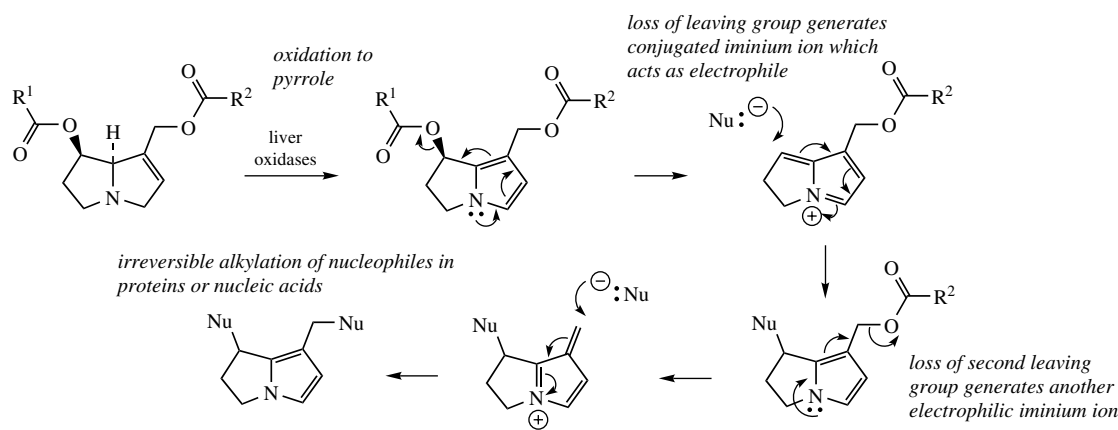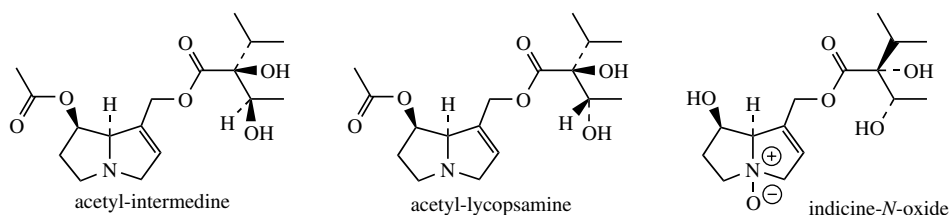
Figure 6.20

The tobacco alkaloids, especially nicotine, are derived from nicotinic acid (see page 311) but also contain a pyrrolidine ring system derived from ornithine as a portion of their structure.

ALKALOIDS DERIVED FROM LYSINE

L-Lysine is the homologue of L-ornithine, and it too functions as an alkaloid precursor, using pathways analogous to those noted for ornithine. The extra methylene group in lysine means this amino acid participates in forming six-membered piperidine rings, just as ornithine provided five-membered pyrrolidine rings. As with ornithine, the carboxyl group is lost, the ε-amino nitrogen rather than the α-amino nitrogen is retained, and lysine thus supplies a C_5N building block (Figure 6.21).
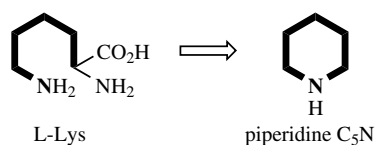
Figure 6.21
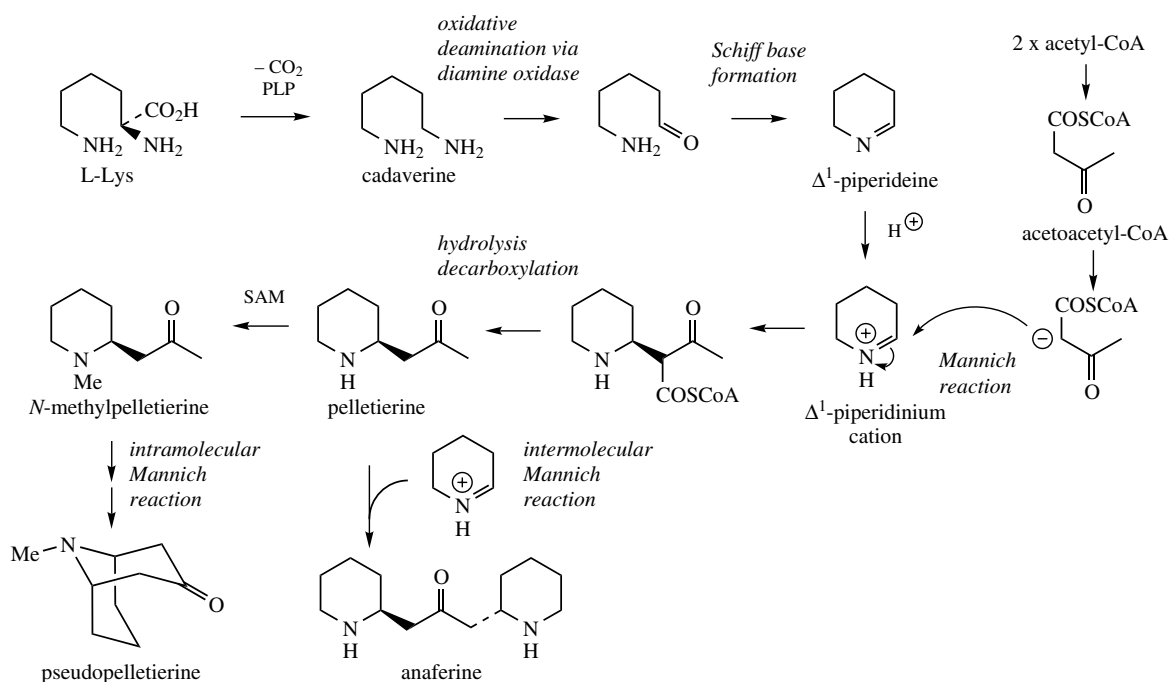
Piperidine Alkaloids

N-**Methylpelletierine** (Figure 6.22) is an alkaloidal constituent of the bark of pomegranate (*Punica granatum*; Punicacae), where it cooccurs with **pelletierine** and **pseudopelletierine** (Figure 6.22), the mixture of alkaloids having activity against intestinal tapeworms. *N*-Methylpelletierine and pseudopelletierine are homologues of hygrine and tropinone respectively, and a pathway similar to Figure 6.3 using the diamine **cadaverine** (Figure 6.22) may be proposed. (The rather distinctive names cadaverine and putrescine reflect early isolations of these compounds from decomposing animal flesh.) In practice, the Mannich reaction involving the Δ^1-piperidinium salt utilizes the more nucleophilic acetoacetyl-CoA rather than acetyl-CoA, and the carboxyl carbon from acetoacetate appears to be lost during the reaction by suitable hydrolysis/decarboxylation reactions (Figure 6.22). **Anaferine** (Figure 6.22) is an analogue of cuscohygrine in which a further piperidine ring is added via an intermolecular Mannich reaction.

Figure 6.22

The alkaloids found in the antiasthmatic plant *Lobelia inflata** (Campanulaceae) contain piperidine rings with alternative C_6C_2 side-chains derived from phenylalanine via cinnamic acid. These alkaloids are produced as in Figure 6.23, in which benzoylacetyl-CoA, an intermediate in the β-oxidation of cinnamic acid (see page 141) provides the nucleophile for the Mannich reaction. Oxidation in the piperidine ring gives a new iminium species, and this can react further with a second molecule of benzoylacetyl-CoA, again via a Mannich reaction. Naturally, because of the nature of the side-chain, the second intramolecular Mannich reaction, as involved in pseudopelletierine biosynthesis, is not feasible. Alkaloids such as

lobeline and **lobelanine** from *Lobelia inflata*, or **sedamine** from *Sedum acre* (Crassulaceae), are products from further *N*-methylation and/or carbonyl reduction reactions (Figure 6.23).

The simple piperidine alkaloid coniine from poison hemlock is not derived from lysine, but originates by an amination process and is discussed on page 381.

The pungency of the fruits of black pepper (*Piper nigrum*; Piperaceae), a widely used condiment, is mainly due to the piperidine alkaloid **piperine** (Figure 6.24). In this structure, the piperidine ring forms part of a tertiary amide structure, and is incorporated via piperidine itself, the reduction product of Δ^1-piperideine (Figure 6.22).
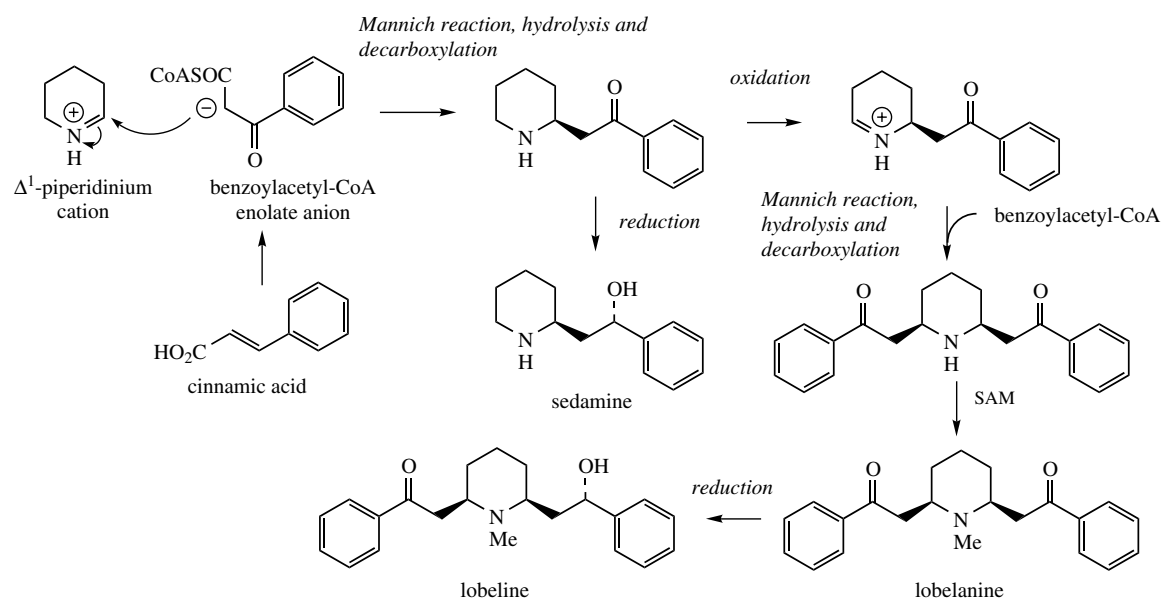
Figure 6.23

Lobelia

Lobelia or Indian tobacco consists of the dried leaves and tops of *Lobelia inflata* (Campanulaceae), an annual herb from the USA and Canada. Lobelia contains about 0.2–0.4% of alkaloids, of which the piperidine derivative lobeline (Figure 6.23) is the chief constituent. Minor alkaloids identified include closely related structures, e.g. lobelanine (Figure 6.23). The North American Indians employed lobelia as an alternative or substitute for tobacco (*Nicotiana tabacum*; Solanaceae), and it is found that lobeline stimulates nicotinic receptor sites in a similar way to nicotine, but with a weaker effect. **Lobeline** has been employed in preparations intended as smoking deterrents. The crude plant drug has also long been used to relieve asthma and bronchitis, though in large doses it can be quite toxic.
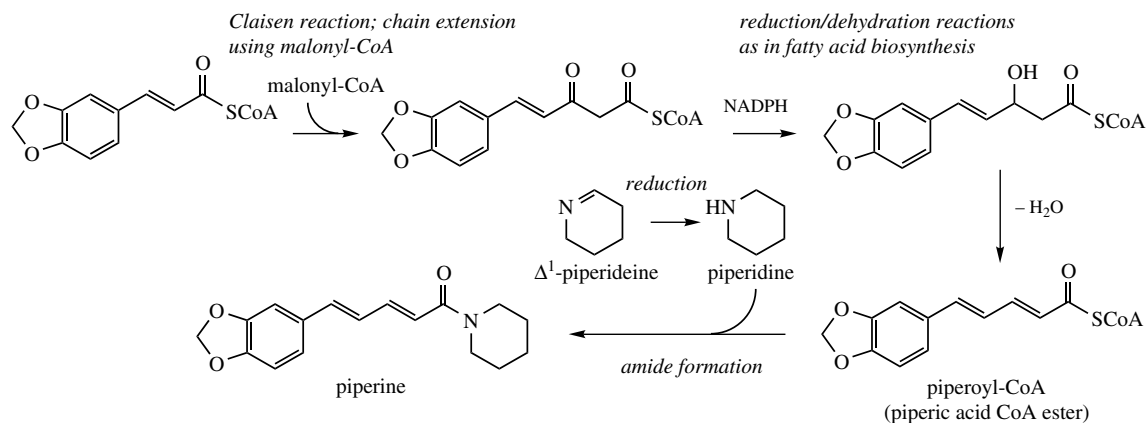
Figure 6.24

The piperic acid portion is derived from a cinnamoyl-CoA precursor, with chain extension using acetate/malonate (compare flavonoids, page 149), and combines as its CoA ester with piperidine.

Quinolizidine Alkaloids

The lupin alkaloids, found in species of *Lupinus* (Leguminosae/Fabaceae), and responsible for the toxic properties associated with lupins, are characterized by a quinolizidine skeleton (Figure 6.25). This bicyclic ring system is closely related to the ornithine-derived pyrrolizidine system, but is formed from two molecules of lysine. **Lupinine** from *Lupinus luteus* is a relatively simple structure very comparable to the basic ring system of the pyrrolizidine alkaloid retronecine (see page 305), but other lupin alkaloids, e.g. **lupanine** and **sparteine** (Figure 6.25) contain a tetracyclic bis-quinolizidine ring system, and are formed by incorporation of a third lysine molecule. Sparteine is also the major alkaloid in broom (*Cytisus scoparius*; Leguminosae/Fabaceae). The alkaloid **cytisine**, a toxic component of *Laburnum* species (Leguminosae/Fabaceae) contains a modified tricyclic ring system, and comparison with the structures of lupanine or sparteine shows its likely relationship by loss of carbon atoms from the tetracyclic system (Figure 6.25). However, the structural similarity of lupinine and retronecine is not fully reflected in the biosynthetic pathways. Experimental evidence shows lysine to be

incorporated into lupinine via **cadaverine**, but the intermediate corresponding to homospermidine is excluded. Δ^1-Piperideine seems to be an important intermediate after cadaverine and the pathway proposed (Figure 6.25) invokes coupling of two such molecules. The two tautomers of Δ^1-piperideine, as *N*-analogues of corresponding carbonyl compounds, are able to couple by an aldol-type mechanism (see page 19). Indeed, this coupling occurs in solution at physiological pHs, though stereospecific coupling to the product shown in Figure 6.25 would require appropriate enzymic participation. Following the coupling, it is suggested that the imine system is hydrolysed, the primary amine group then oxidized, and formation of the quinolizidine ring is achieved by Schiff base formation. **Lupinine** is then synthesized by two reductive steps.

The pathway to **sparteine** and **lupanine** undoubtedly requires participation of another molecule of cadaverine or Δ^1-piperideine. Experimental data are not clear-cut and Figure 6.25 merely indicates how incorporation of a further piperidine ring might be envisaged. Loss of one or other of the outermost rings and oxidation to a pyridone system offers a potential route to **cytisine**.

Quinolizidine alkaloids are mainly found in plants of the Leguminosae/Fabaceae family. They deter or repel feeding of herbivores, and are toxic to them by a variety of mechanisms. A number of plants (*Laburnum*, *Cytisus*, *Lupinus*) containing significant quantities of these alkaloids must be regarded as potentially toxic to humans, and are known to be responsible for human poisoning.
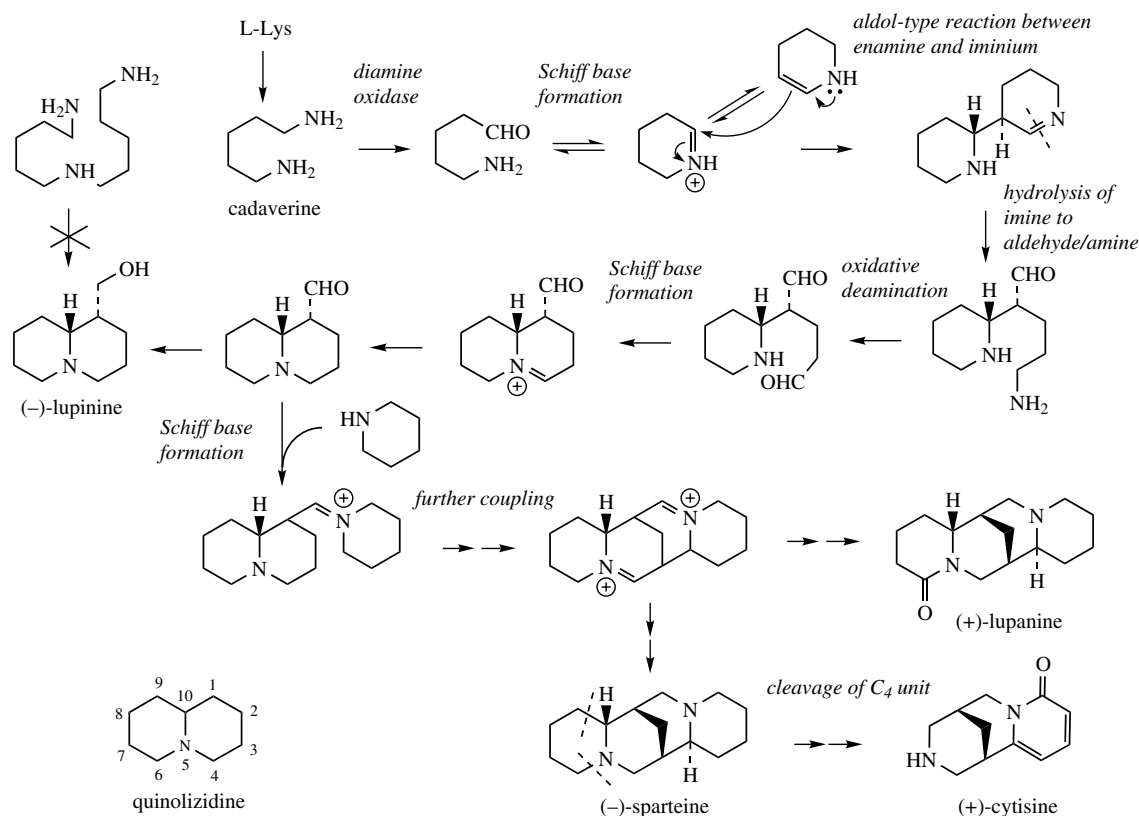
Figure 6.25

The widely planted and ornamental laburnum trees offer a particular risk, since all parts, including the pealike seeds, contain dangerously high amounts of alkaloids. So-called 'sweet lupins' are selected strains with an acceptably low alkaloid content (typically about a quarter of the total alkaloids of 'bitter' strains), which are grown as a high protein crop.

Indolizidine Alkaloids

Indolizidine alkaloids (Figure 6.26) are characterized by fused six- and five-membered rings, with a nitrogen atom at the ring fusion, e.g. **swainsonine** from *Swainsona canescens* (Leguminosae/Fabaceae) and **castanospermine** from the Moreton Bay chestnut *Castanospermum australe* (Leguminosae/Fabaceae). In this respect, they appear to be a hybrid between the pyrrolizidine and quinolizidine alkaloids described above. Although

they are derived from lysine, their origin deviates from the more common lysine-derived structures in that L-**pipecolic acid** is an intermediate in the pathway. Two routes to pipecolic acid are known in nature as indicated in Figure 6.26, and these differ with respect to whether the nitrogen atom originates from the α- or the ε-amino group of lysine. For indolizidine alkaloid biosynthesis, pipecolic acid is formed via the aldehyde and Schiff base with retention of the α-amino group nitrogen. The indolizidinone may then be produced by incorporating a C_2 acetate unit by simple reactions, though no details are known. This compound leads to castanospermine by a sequence of hydroxylations, but is also a branch-point compound to alkaloids such as swainsonine, which have the opposite configuration at the ring fusion. Involvement of a planar iminium ion could account for the change in stereochemistry. Polyhydroxyindolizidines such as swainsonine and castanospermine have demonstrated activity against
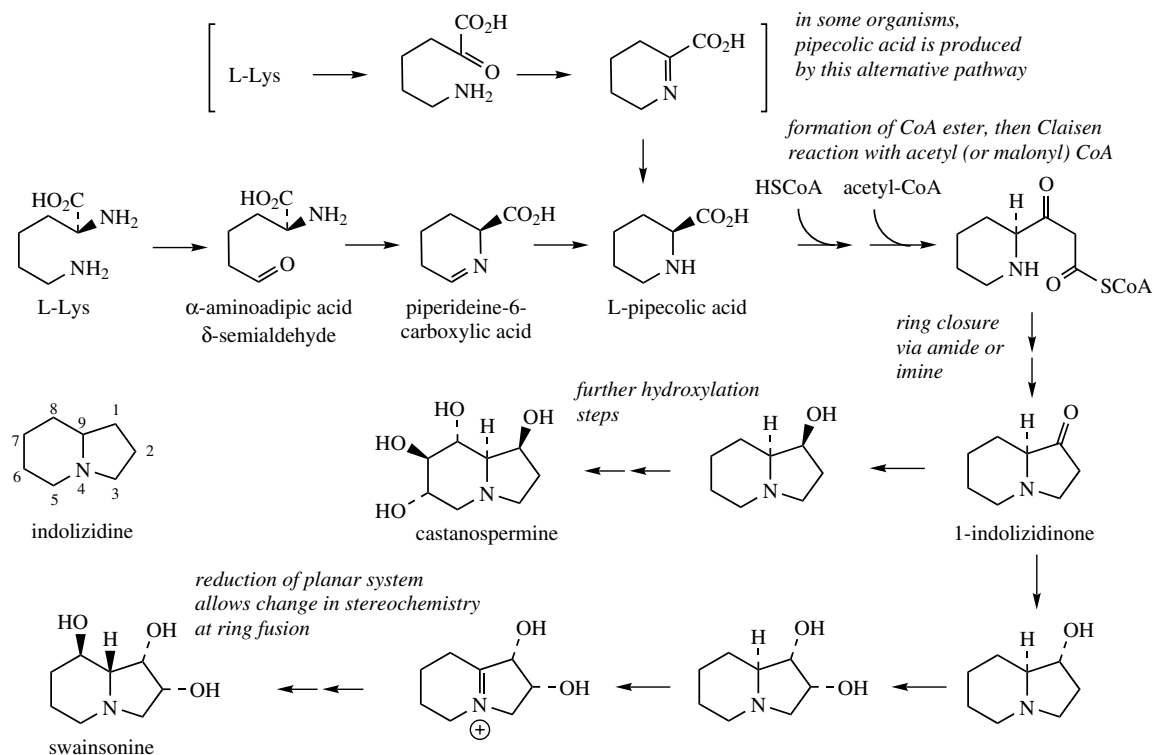
Figure 6.26
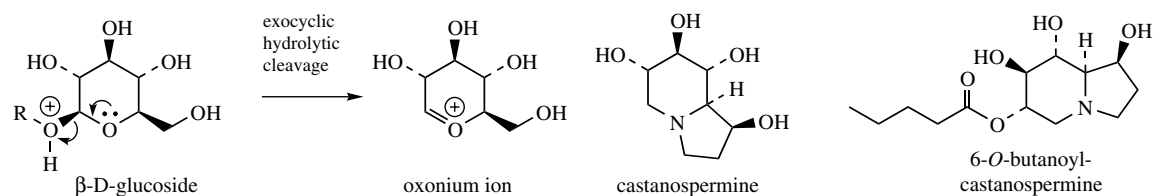
Figure 6.27

the AIDS virus HIV, by their ability to inhibit glycosidase enzymes involved in glycoprotein biosynthesis. The glycoprotein coating is essential for the proliferation of the AIDS virus. This has stimulated considerable research on related structures and their mode of action. The ester 6-*O*-butanoyl-castanospermine (Figure 6.27) is currently in clinical trials as an anti-AIDS agent. There is a strong similarity between castanospermine and the oxonium ion formed by hydrolytic cleavage of a glucoside (Figure 6.27) (see page 30), but there appears to be little stereochemical relationship with some other sugars, whose hydrolytic enzymes are also strongly inhibited. These alkaloids are also toxic to

animals, causing severe gastro-intestinal upset and malnutrition by severely affecting intestinal hydrolases. Indolizidine alkaloids are found in many plants in the Leguminosae/Fabaceae (e.g. *Swainsona*, *Astragalus*, *Oxytropis*) and also in some fungi (e.g. *Rhizoctonia leguminicola*).

ALKALOIDS DERIVED FROM NICOTINIC ACID

Pyridine Alkaloids

The alkaloids found in tobacco* (*Nicotiana tabacum*; Solanaceae) include **nicotine** and

nicotinic acid
(niacin / vitamin B₃)

nicotinamide

trigonelline

nicotine

nornicotine
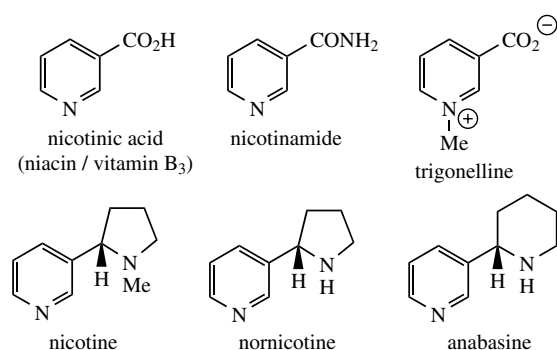
anabasine

Figure 6.28

anabasine (Figure 6.28). The structures contain a pyridine ring together with a pyrrolidine ring (in nicotine) or a piperidine unit (in anabasine),

the latter rings arising from ornithine and lysine respectively. The pyridine unit has its origins in **nicotinic acid** (**vitamin B₃**)* (Figure 6.28), the vitamin sometimes called **niacin**, which forms an essential component of coenzymes such as NAD^+ and $NADP^+$ (see page 24). The nicotinic acid component of nicotinamide is synthesized in animals by degradation of L-tryptophan through the **kynurenine** pathway and **3-hydroxyanthranilic acid** (Figure 6.29) (see also dactinomycin, page 432), the pyridine ring being formed by oxidative cleavage of the benzene ring and subsequent inclusion of the amine nitrogen (Figure 6.29). However, plants such as *Nicotiana* use a different pathway employing glyceraldehyde 3-phosphate and L-aspartic acid precursors (Figure 6.30). The dibasic
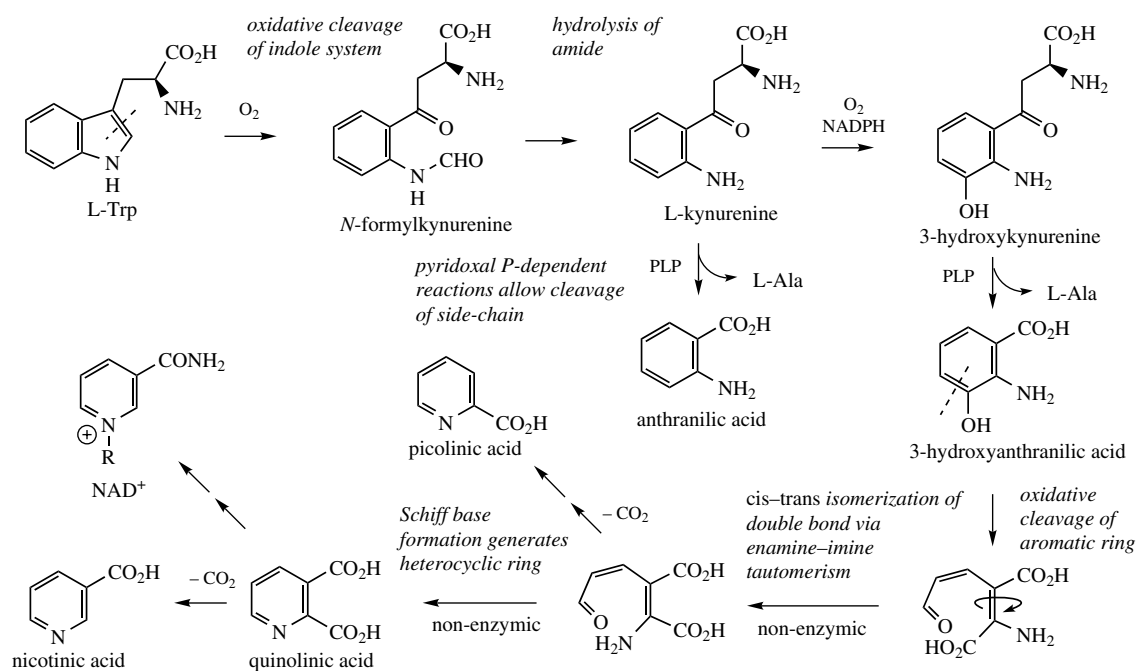
Figure 6.29
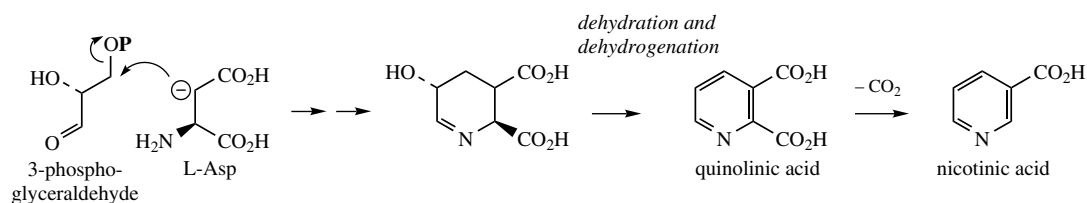
Figure 6.30

Vitamin B₃

Vitamin B₃ (nicotinic acid, niacin) (Figure 6.28) is a stable water-soluble vitamin widely distributed in foodstuffs, especially meat, liver, fish, wheat germ, and yeast. However, in some foods, e.g. maize, it may be present in a bound form, and is not readily available. Diets based principally on maize may lead to deficiencies. The amino acid tryptophan can be converted in the body into nicotinic acid (Figure 6.29), and may provide a large proportion of the requirements. Nicotinic acid is also produced during the roasting of coffee from the decomposition of the N-methyl derivative trigonelline (Figure 6.28). Nicotinic acid is converted into nicotinamide (Figure 6.28), though this compound also occurs naturally in many foods. The term vitamin B₃ is often used for the combined nicotinamide–nicotinic acid complement. In the form of the coenzymes NAD^+ and $NADP^+$, nicotinamide plays a vital role in oxidation–reduction reactions (see page 24), and is the most important electron carrier in primary metabolism. Deficiency in nicotinamide leads to pellagra, which manifests itself in diarrhoea, dermatitis, and dementia. Oral lesions and a red tongue may be more noticeable than the other symptoms. **Nicotinamide** is usually preferred over **nicotinic acid** for dietary supplements since there is less risk of gastric irritation. Both are produced synthetically. It is common practice to enrich many foods, including bread, flour, corn, and rice products.

   Nicotinic acid in large doses can lower both cholesterol and triglyceride concentrations by inhibiting their synthesis.
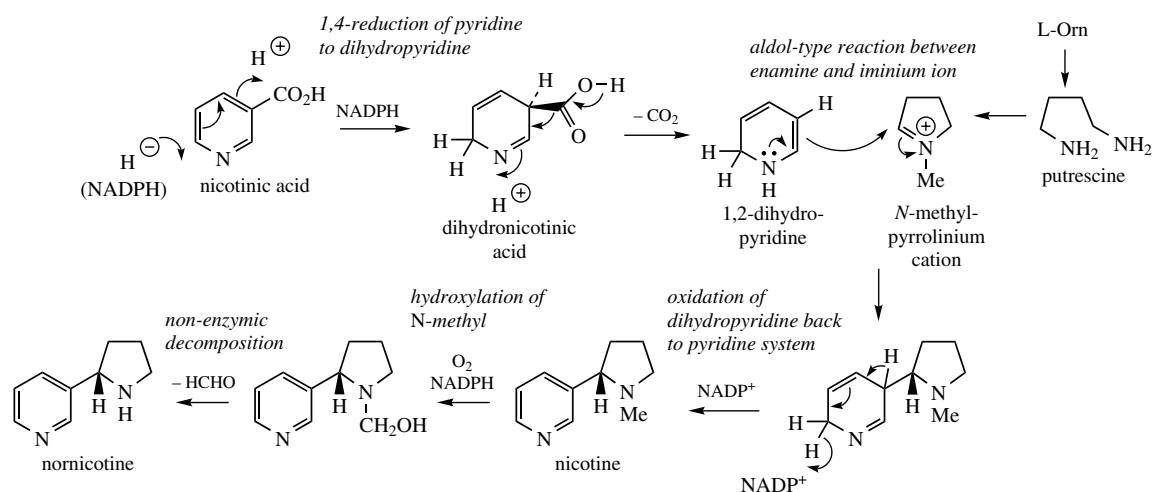
Figure 6.31

acid **quinolinic acid** features in both pathways, decarboxylation yielding nicotinic acid.

   In the formation of **nicotine**, a pyrrolidine ring derived from ornithine, most likely as the N-methyl-Δ^1-pyrrolinium cation (see Figure 6.2) is attached to the pyridine ring of nicotinic acid, displacing the carboxyl during the sequence (Figure 6.31). A dihydronicotinic acid intermediate is likely to be involved allowing decarboxylation to the enamine 1,2-dihydropyridine.

This allows an aldol-type reaction with the N-methylpyrrolinium cation, and finally dehydrogenation of the dihydropyridine ring back to a pyridine gives nicotine. **Nornicotine** is derived by oxidative demethylation of nicotine. **Anabasine** is produced from nicotinic acid and lysine via the Δ^1-piperidinium cation in an essentially analogous manner (Figure 6.32). A subtle anomaly has been exposed in that a further *Nicotiana* alkaloid **anatabine** appears to be derived by

combination of two nicotinic acid units, and the Δ^3-piperideine ring is *not* supplied by lysine (Figure 6.33).

Nicotinic acid undoubtedly provides the basic skeleton for some other alkaloids. **Ricinine** (Figure 6.35) is a 2-pyridone structure and contains a nitrile grouping, probably formed by dehydration of a nicotinamide derivative. This alkaloid is a toxic constituent of castor oil seeds (*Ricinus communis*; Euphorbiaceae), though the toxicity of the seeds results mainly from the polypeptide ricin (see page 434). **Arecoline** (Figure 6.36) is found in Betel nuts (*Areca catechu*: Palmae/Arecaceae)* and is a tetrahydronicotinic acid derivative. Betel nuts are chewed in India and Asia for the stimulant effect of arecoline.
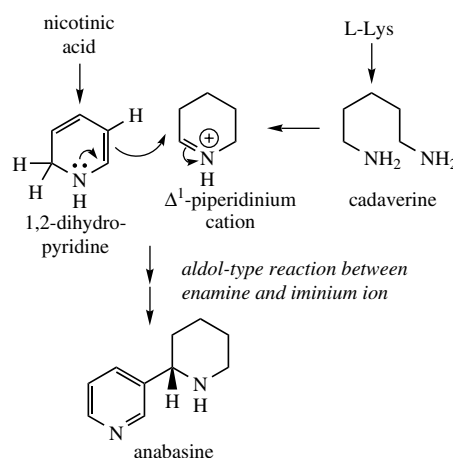
Figure 6.32
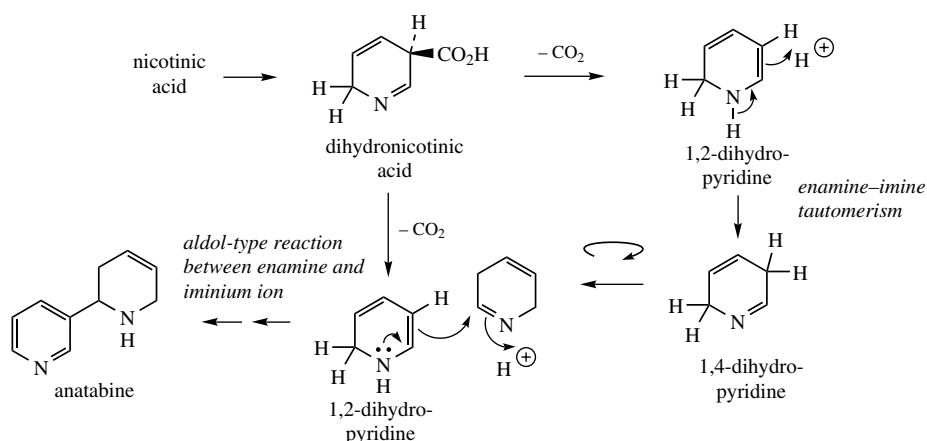
Figure 6.33

Tobacco

Tobacco is the cured and dried leaves of *Nicotiana tabacum* (Solanaceae), an annual herb indigenous to tropical America, but cultivated widely for smoking. Tobacco leaves may contain from 0.6–9% of (−)-nicotine (Figure 6.28), an oily, volatile liquid alkaloid, together with smaller amounts of structurally related alkaloids, e.g. anabasine and nornicotine (Figure 6.28). In the leaf, the alkaloids are typically present as salts with malic and citric acids. Nicotine in small doses can act as a respiratory stimulant, though in larger doses it causes respiratory depression. Despite the vast array of evidence linking tobacco smoking and cancer, the smoking habit continues throughout the world, and tobacco remains a major crop plant. Tobacco smoke contains a number of highly carcinogenic chemicals formed by incomplete combustion, including benzpyrene, 2-naphthylamine, and 4-aminobiphenyl. Metabolism by the body's P-450 system leads to further reactive intermediates, which can combine with DNA and cause mutations. Tobacco smoking also contributes to atherosclerosis, chronic

(*Continues*)

(*Continued*)

bronchitis, and emphysema, and is regarded as the single most preventable cause of death in modern society. **Nicotine** is being used by former smokers who wish to stop the habit. It is available in the form of chewing gum or nasal sprays, or can be absorbed transdermally from nicotine-impregnated patches.
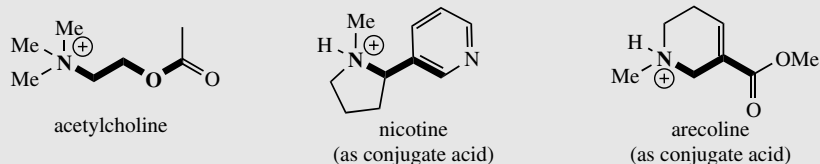

acetylcholine

nicotine
(as conjugate acid)

arecoline
(as conjugate acid)

Figure 6.34

Powdered tobacco leaves have long been used as an insecticide, and nicotine from *Nicotiana tabacum* or *N. rustica* has been formulated for agricultural and horticultural use. The free base is considerably more toxic than salts, and soaps were included in the formulations to ensure a basic pH and to provide a surfactant. Other *Nicotiana* alkaloids, e.g. anabasine and nornicotine, share this insecticidal activity. Although an effective insecticide, nicotine has been replaced by other agents considered to be safer. Nicotine is toxic to man due to its effect on the nervous system, interacting with the nicotinic acetylcholine receptors, though the tight binding observed is only partially accounted for by the structural similarity between acetylcholine and nicotine (Figure 6.34). Recent studies suggest that nicotine can improve memory by stimulating the transmission of nerve impulses, and this finding may account for the lower incidence of Alzheimer's disease in smokers. Any health benefits conferred by smoking are more than outweighed by the increased risk of heart, lung, and respiratory diseases.

nicotinic acid → nicotinamide → ricinine
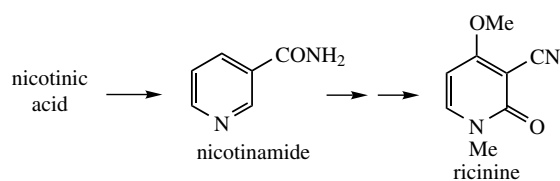
Figure 6.35

ALKALOIDS DERIVED FROM TYROSINE

Phenylethylamines and Simple Tetrahydroisoquinoline Alkaloids

PLP-dependent decarboxylation of L-**tyrosine** gives the simple phenylethylamine derivative

Areca

Areca nuts (betel nuts) are the seeds of *Areca catechu* (Palmae/Arecaceae), a tall palm cultivated in the Indian and Asian continents. These nuts are mixed with lime, wrapped in leaves of the betel pepper (*Piper betle*) and then chewed for their stimulant effect, and subsequent feeling of well-being and mild intoxication. The teeth and saliva of chewers stain bright red. The major stimulant alkaloid is arecoline (up to 0.2%) (Figure 6.36), the remainder of the alkaloid content (total about 0.45%) being composed of related reduced pyridine

(*Continues*)

(*Continued*)

structures, e.g. arecaidine, guvacine (tetrahydronicotinic acid), and guvacoline (Figure 6.36). Arecoline is an agonist for muscarinic acetylcholine receptors (see Figure 6.34), although it possesses a reversed ester profile compared with acetylcholine. **Areco-line** has been employed in veterinary practice as a vermicide to eradicate worms.
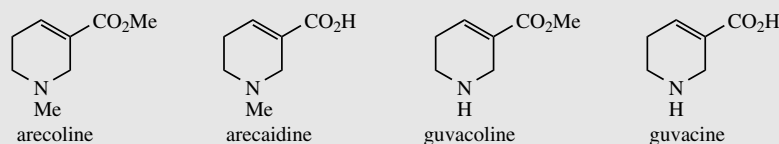

arecoline   arecaidine   guvacoline   guvacine

Figure 6.36

tyramine, which on di-*N*-methylation yields **hordenine**, a germination inhibitory alkaloid from barley (*Hordeum vulgare*; Graminae/Poaceae) (Figure 6.37). More commonly, phenylethylamine derivatives possess 3,4-di- or 3,4,5-tri-hydroxylation patterns, and are derived via **dopamine** (Figure 6.37), the decarboxylation product from L-**DOPA** (L-dihydroxyphenylalanine) (see page 129). Pre-eminent amongst these are the catecholamines* **noradrenaline** (**norepinephrine**), a mammalian neurotransmitter, and **adrenaline** (**epinephrine**), the 'fight or flight' hormone released in animals from the adrenal gland as a result of stress. These compounds are synthesized by successive β-hydroxylation and *N*-methylation reactions on dopamine (Figure 6.37). Aromatic hydroxylation and *O*-methylation reactions in the cactus *Lophophora williamsii** (Cactaceae) convert dopamine into **mescaline** (Figure 6.37), an alkaloid with pyschoactive and hallucinogenic properties. Note that the sequence of hydroxylations and methylations exactly parallel those described for the cinnamic acids (see page 131).
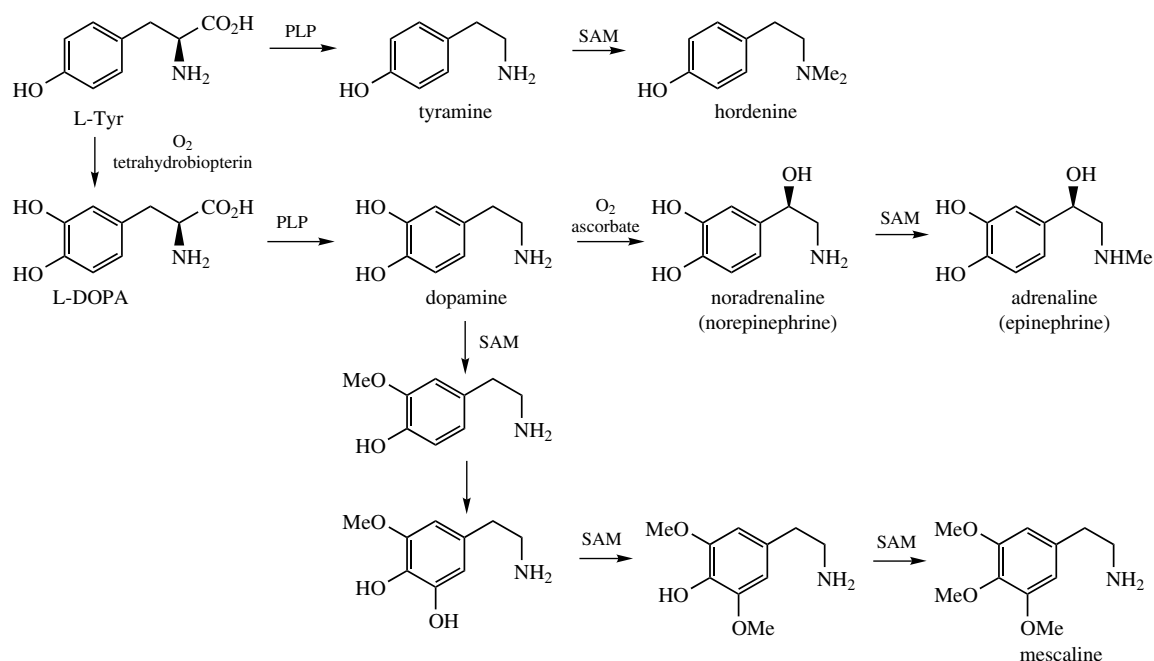
Figure 6.37

Catecholamines

The catecholamines dopamine, noradrenaline (norepinephrine), and adrenaline (epinephrine) are produced in the adrenal glands and nervous tissue and act as neurotransmitters in mammals. Several adrenergic receptors have been identified. α-Receptors are usually excitatory and produce a constricting effect on vascular, uterine, and intestinal muscles. β-Receptors are usually inhibitory on smooth muscle, but stimulatory on heart muscles. **Dopamine** (Figure 6.37) can act on both vascular α_1 and cardiac β_1 receptors, but also has its own receptors in several other structures. In Parkinson's disease, there is a deficiency of dopamine due to neural degeneration, affecting the balance between excitatory and inhibitory transmitters. Treatment with L-**DOPA** (**levodopa**) (Figure 6.37) helps to increase the dopamine levels in the brain. Unlike dopamine, DOPA can cross the blood–brain barrier, but needs to be administered with a DOPA-decarboxylase inhibitor, e.g. **carbidopa** (Figure 6.38), to prevent rapid decarboxylation in the bloodstream. Injections of dopamine or **dobutamine** (Figure 6.38) are valuable as cardiac stimulants in cases of cardiogenic shock. These agents act on β_1 receptors; **dopexamine** (Figure 6.38) is also used for chronic heart failure but acts on β_2 receptors in cardiac muscle.

 Noradrenaline (**norepinephrine**) (Figure 6.37) is a powerful peripheral vasoconstrictor predominantly acting on α-adrenergic receptors, and is useful in restoring blood pressure in cases of acute hypotension. The structurally related alkaloid **ephedrine** (see page 384) may be used in the same way, and synthetic analogues of noradrenaline, e.g. **phenylephrine**, **methoxamine**, and **metaraminol** (Figure 6.38), have also been developed. **Methyldopa** is used to treat hypertension; it is a centrally acting agent that becomes decarboxylated and hydroxylated to form the false transmitter α-methylnoradrenaline, which competes with noradrenaline.

 Adrenaline (**epinephrine**) (Figure 6.37) is released from the adrenal glands when an animal is confronted with an emergency situation, markedly stimulating glycogen breakdown in muscle, increasing respiration, and triggering catabolic processes that result in energy release. Adrenaline interacts with both α- and β- receptors, an α-response being vasoconstriction of smooth muscle in the skin. β-Responses include mediation of cardiac muscle contractions and the relaxation of smooth muscle in the bronchioles of the lung. Injection of adrenaline is thus of value in cases of cardiac arrest, or in allergic emergencies such as bronchospasm or severe allergy (anaphylactic shock). It is not effective orally. A wide range of cardioactive β-adrenoceptor blocking agents (**beta-blockers**) has been developed to selectively bind
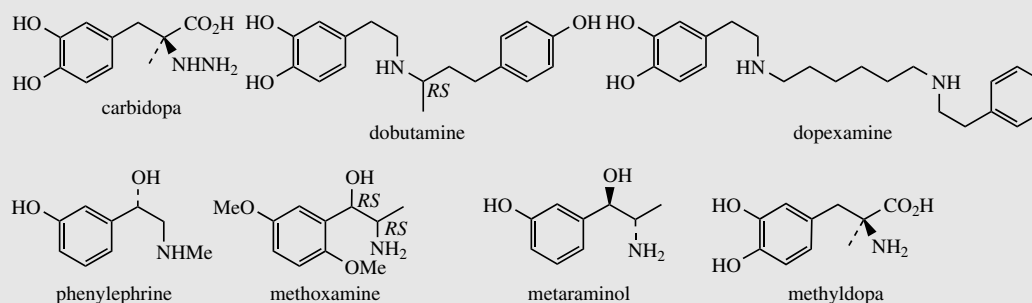

Figure 6.38

(*Continued*)

to β-receptors to control the rate and force of cardiac contractions in the management of hypertension and other heart conditions. The prototype of the beta-blocker drugs is **propranolol** (Figure 6.39), in which the catechol ring system has been modified to a
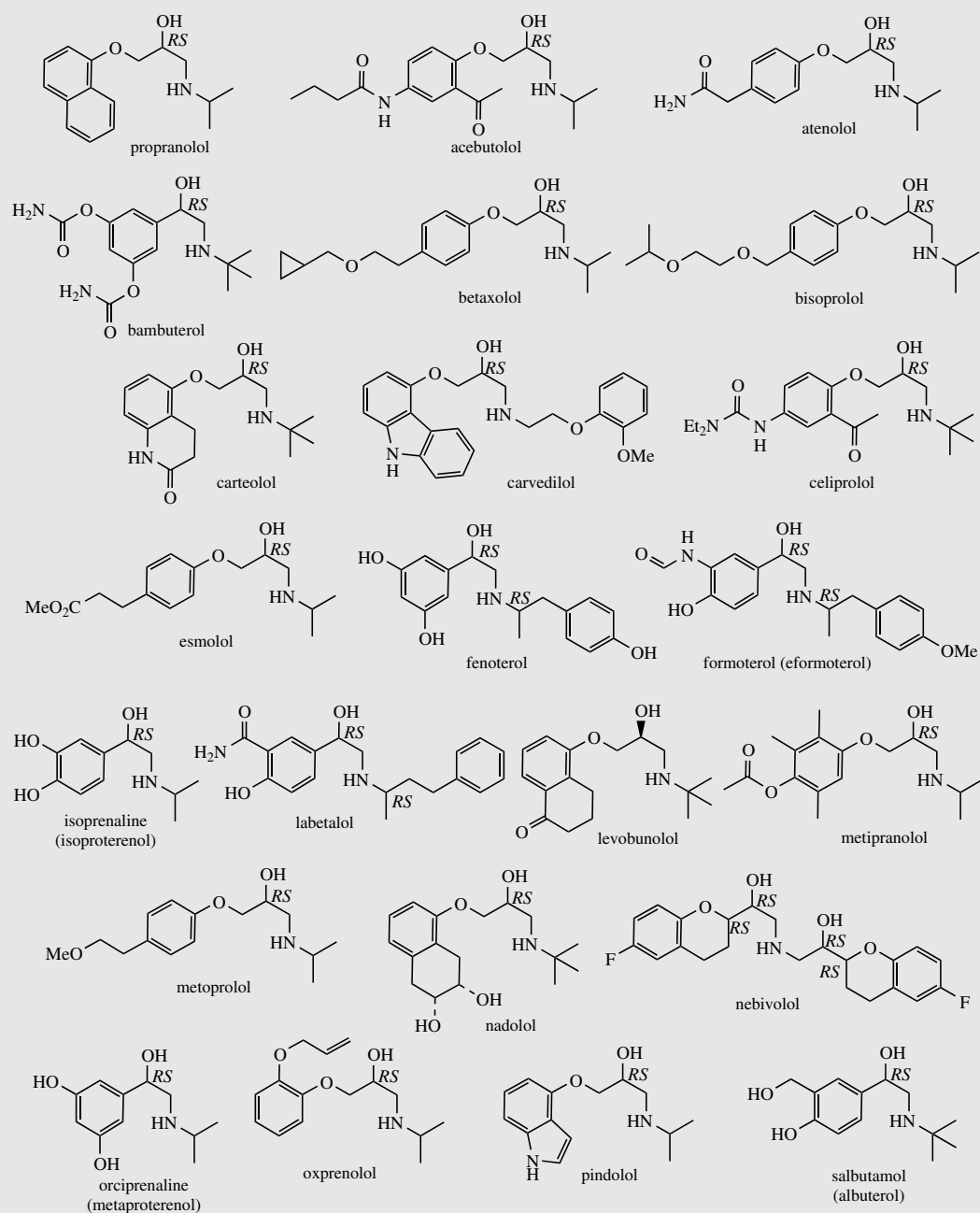

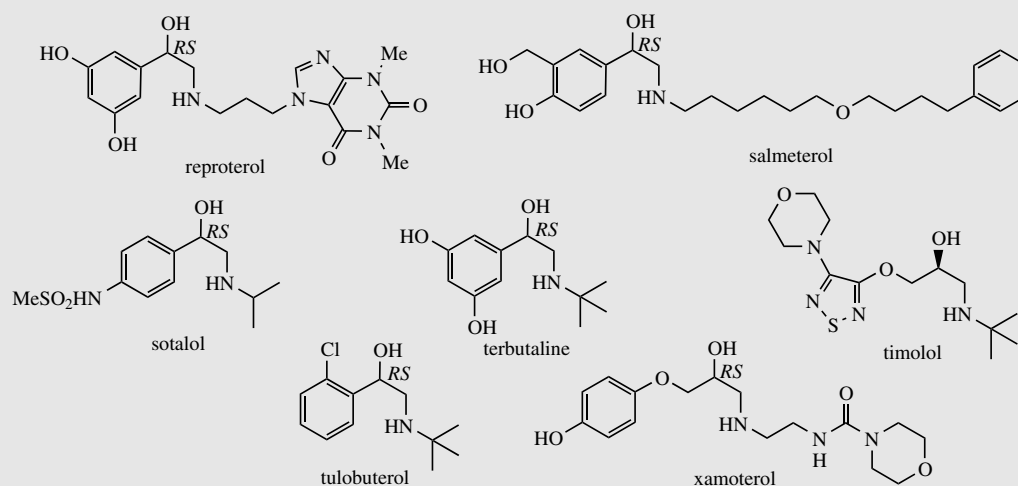**Figure 6.39**   (*continues*)

(*Continues*)

(*Continued*)

Figure 6.39 (*continued*)

naphthalene ether, and a bulky *N*-alkyl substituent has been incorporated. Many structural variants have been produced and there is now a huge, perhaps bewildering, variety of beta-blockers in regular use, with subtle differences in properties and action affecting the choice of drug for a particular condition or individual patient. These are shown in Figure 6.39. **Atenolol**, **betaxolol**, **bisoprolol**, **metoprolol**, **nebivolol**, and to a lesser extent **acebutolol**, have less effect on the β_2 bronchial receptors and are thus relatively cardioselective. Most other agents are non-cardioselective, and could also provoke breathing difficulties. **Esmolol** and **sotalol** are used only in the management of arrhythmias.

Other β-agonists are valuable as antiasthmatic drugs. Important examples include **salbutamol** (**albuterol**) and **terbutaline**, which are very widely prescribed, principally for administration by inhalation at the onset of an asthma attack, but, as with cardioactive beta-blockers, a wide range of agents is in current use (Figure 6.39). These agents are mainly selective towards the β_2-receptors, and supersede the earlier less selective bronchodilator drugs such as **isoprenaline** (**isoproterenol**) and **orciprenaline** (**metaproterenol**) (Figure 6.39). Topical application of a beta-blocker to the eye reduces intra-ocular pressure by reducing the rate of production of aqueous humour. Some drugs in this class, namely **betaxolol**, **carteolol**, **levobunolol**, **metipranolol**, and **timolol**, are thus useful in treating glaucoma. **Propranolol**, **metoprolol**, **nadolol**, and **timolol** also have additional application in the prophylaxis of migraine.

Catecholamine neurotransmitters are subsequently inactivated by enzymic methylation of the 3-hydroxyl (via catechol-*O*-methyltransferase) or by oxidative removal of the amine group via monoamine oxidase. Monoamine oxidase inhibitors are sometimes used to treat depression, and these drugs cause an accumulation of amine neurotransmitters. Under such drug treatment, simple amines such as tyramine in cheese, beans, fish, and yeast extracts are also not metabolized and can cause dangerous potentiation of neurotransmitter activity.

(*Continues*)

Closely-related alkaloids cooccurring with mescaline are **anhalamine**, **anhalonine**, and **anhalonidine** (Figure 6.40), which are representatives of simple tetrahydroisoquinoline derivatives. The additional carbon atoms, two in the case of anhalonidine and anhalonine, and one for anhalamine, are supplied by pyruvate and glyoxylate respectively. In each case, a carboxyl group is
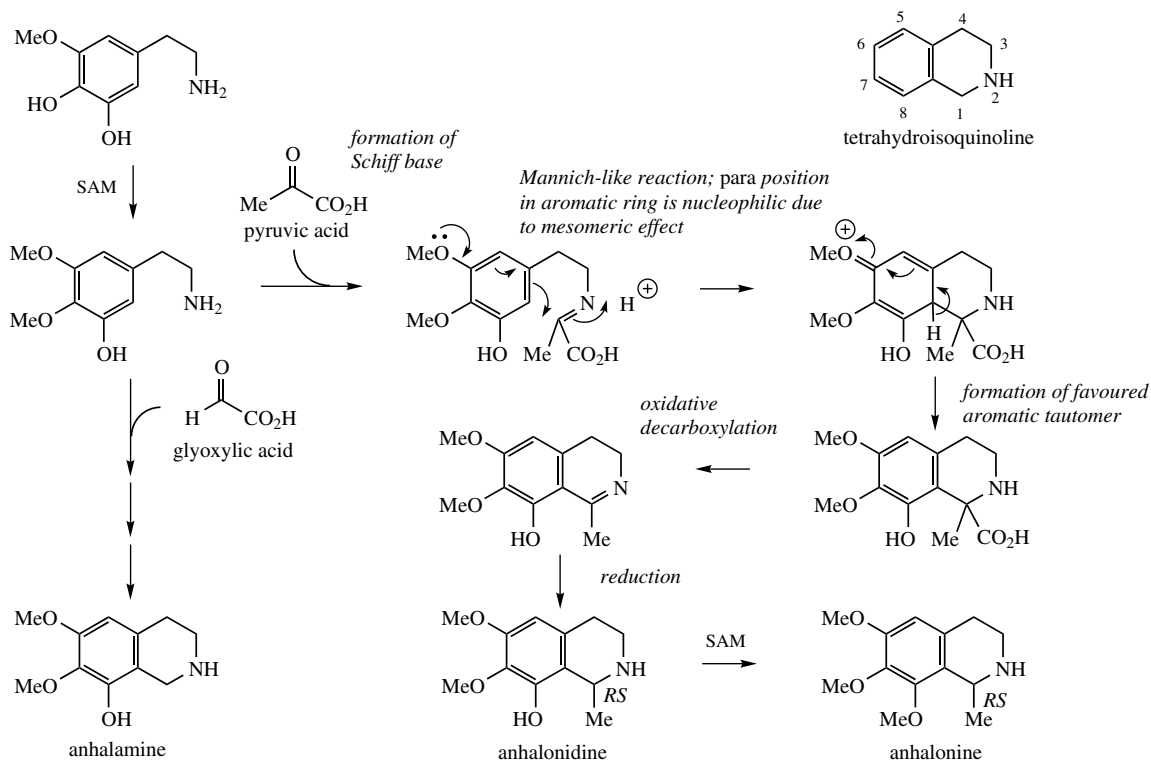

Figure 6.40

lost from this additional precursor. The keto acid pyruvate reacts with a suitable phenylethylamine, in this case the dimethoxy-hydroxy derivative, giving a Schiff base (Figure 6.40). In a Mannich-like mechanism, cyclization occurs to generate the isoquinoline system, the mesomeric effect of an oxygen substituent providing the nucleophilic site on the aromatic ring. Restoration of aromaticity via proton loss gives the tetrahydroisoquinoline, overall a biosynthetic equivalent of the Pictet–Spengler synthesis. The carboxyl group is then removed, not by a simple decarboxylation, but via an unusual oxidative decarboxylation first generating the intermediate imine, reduction finally leading to **anhalonidine** with further methylation giving **anhalonine**. **Anhalamine** is derived from the same phenylethylamine precursor utilizing glyoxylic acid (Figure 6.40).

The chemical synthesis of tetrahydroisoquinolines by the Pictet–Spengler reaction does not usually employ keto acids like pyruvate or aldehyde acids like glyoxylate. Instead, simple aldehydes, e.g. acetaldehyde or formaldehyde, could be used (Figure 6.41, a), giving the same product directly without the need for a decarboxylation step to convert the intermediate tetrahydroisoquinolinecarboxylic acid (Figure 6.41, b). In nature, both routes are in fact found to operate, depending on the complexity of the R group. Thus, the keto acid (route b) is used for relatively simple substrates (R = H, Me) whilst more complex precursors (R = ArCH$_2$, ArCH$_2$CH$_2$, etc) are incorporated via the corresponding aldehydes (route a). The stereochemistry in the product is thus controlled by the condensation/Mannich reactions (route a), or by the final reduction reaction (route b). Occasionally, both types of transformation have been demonstrated in the production of a single compound, an example being the *Lophophora schotti* alkaloid **lophocerine** (Figure 6.42). This requires
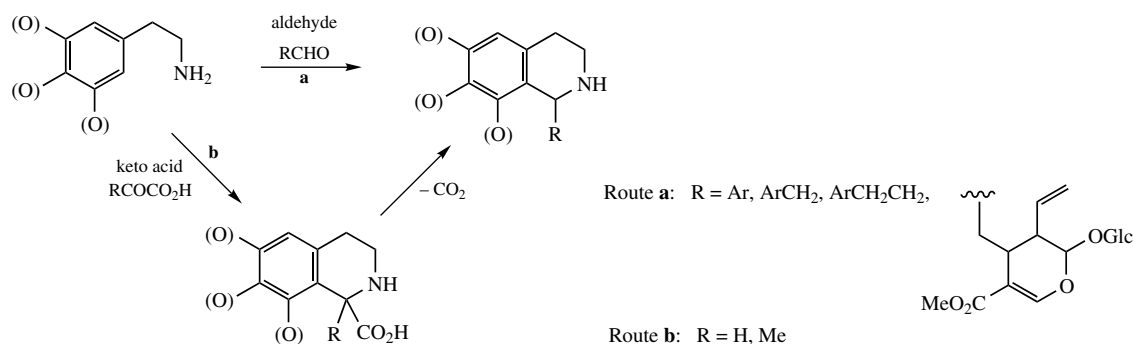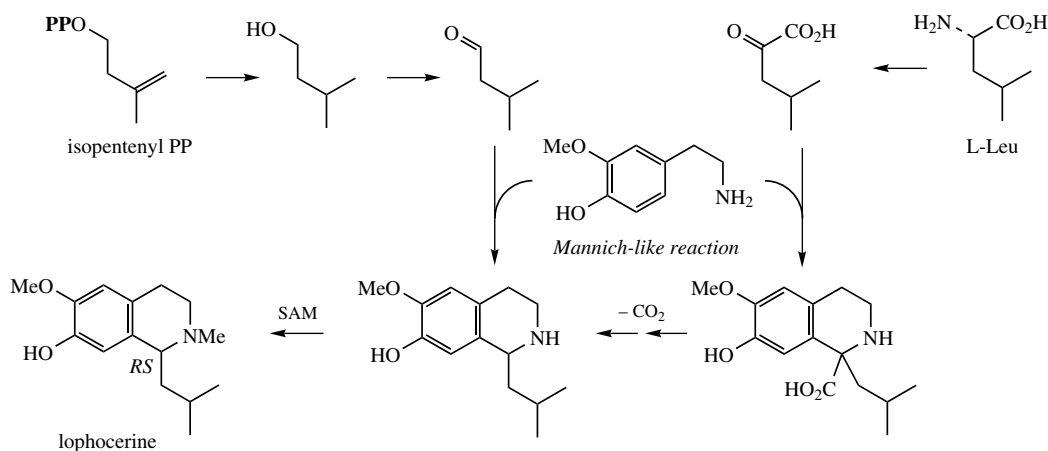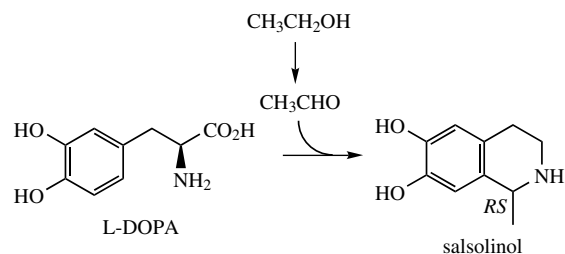

Figure 6.41

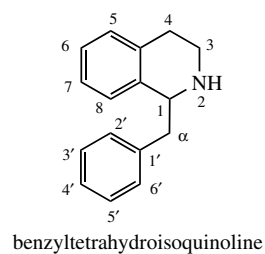
Figure 6.42

Figure 6.43

Figure 6.44

utilization of a C_5 isoprene unit, incorporated via an aldehyde. However, a second route using the keto acid derived from the amino acid L-leucine by transamination has also been demonstrated. The

alkaloid **salsolinol** (Figure 6.43) is found in plants, e.g. *Corydalis* spp. (Papaveraceae), but can also be detected in the urine of humans as a product from dopamine and acetaldehyde combining via
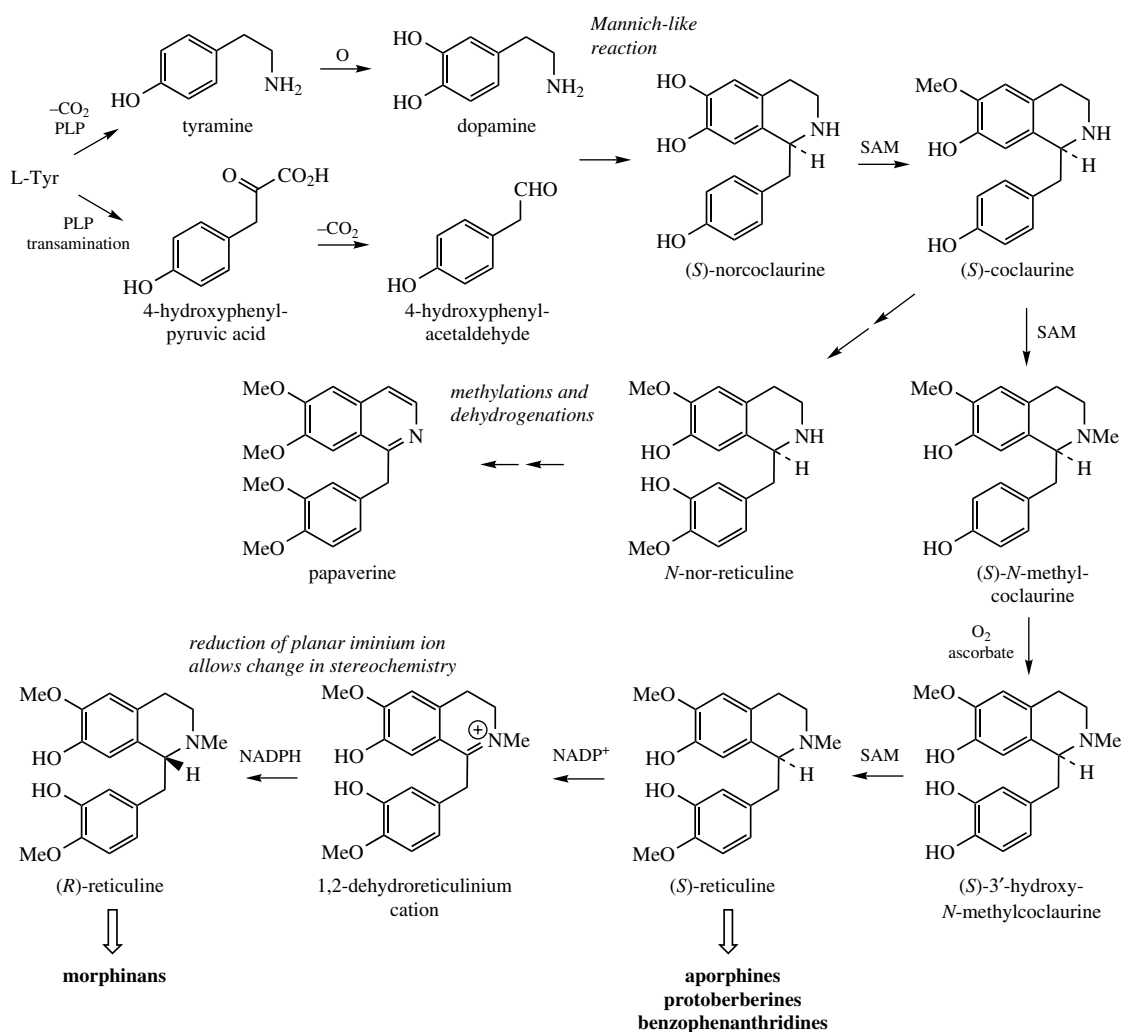

Figure 6.45

a Pictet–Spengler reaction. Acetaldehyde is typically formed after ingestion of ethanol.

Incorporation of a phenylethyl unit into the phenylethylamine gives rise to a benzyltetrahydroisoquinoline skeleton (Figure 6.44), which can undergo further modifications to produce a wide range of plant alkaloids, many of which feature as important drug materials. Fundamental changes to the basic skeleton increase the diversity of structural types as described under 'modified benzyltetrahydroisoqinolines'. Most examples of benzyltetrahydroisoquinoline alkaloids and modified structures contain *ortho* di-oxygenation in each aromatic ring, which pattern is potentially derivable from the utilization of two DOPA molecules. Although two tyrosine molecules are used in the biosynthetic pathway, only the phenylethylamine fragment of the tetrahydroisoquinoline ring system is formed via DOPA, the remaining carbons coming from tyrosine via 4-hydroxyphenylpyruvic acid and 4-hydroxyphenylacetaldehyde (Figure 6.45). The product from the Mannich-like reaction is thus the trihydroxy alkaloid **norcoclaurine**, formed stereospecifically as the (*S*)-enantiomer. The tetrahydroxy substitution pattern is built up by further hydroxylation in the benzyl ring, though *O*-methylation [giving (*S*)-**coclaurine**] and *N*-methylation steps precede this. Eventually,

(*S*)-**reticuline**, a pivotal intermediate to other alkaloids, is attained by *N*-methylation. Surprisingly, some alkaloids, such as the opium alkaloids morphine, codeine, and thebaine (see page 327) are elaborated from (*R*)-reticuline rather than the first-formed (*S*)-isomer. The change in configuration is known to be achieved by an oxidation–reduction process and the intermediate 1,2-dehydroreticulinium ion, as shown in Figure 6.45. **Papaverine**, a benzylisoquinoline alkaloid found in opium (see page 331), is formed from *N*-nor-reticuline by successive *O*-methylations and oxidation in the heterocyclic ring (Figure 6.45).

Structures in which two (or more) benzyltetrahydroisoquinoline units are linked together are readily explained by a phenolic oxidative coupling mechanism (see page 28). Thus, **tetrandrine** (Figure 6.46), a bis-benzyltetrahydroisoquinoline alkaloid isolated from *Stephania tetrandra* (Menispermaceae) is easily recognized as a coupling product from two molecules of (*S*)-*N*-methylcoclaurine (Figure 6.46). The two diradicals, formed by one-electron oxidations of a free phenol group in each ring, couple to give ether bridges, and the product is then methylated to tetrandrine. The pathway is much more likely to follow a stepwise coupling process requiring two oxidative enzymes rather
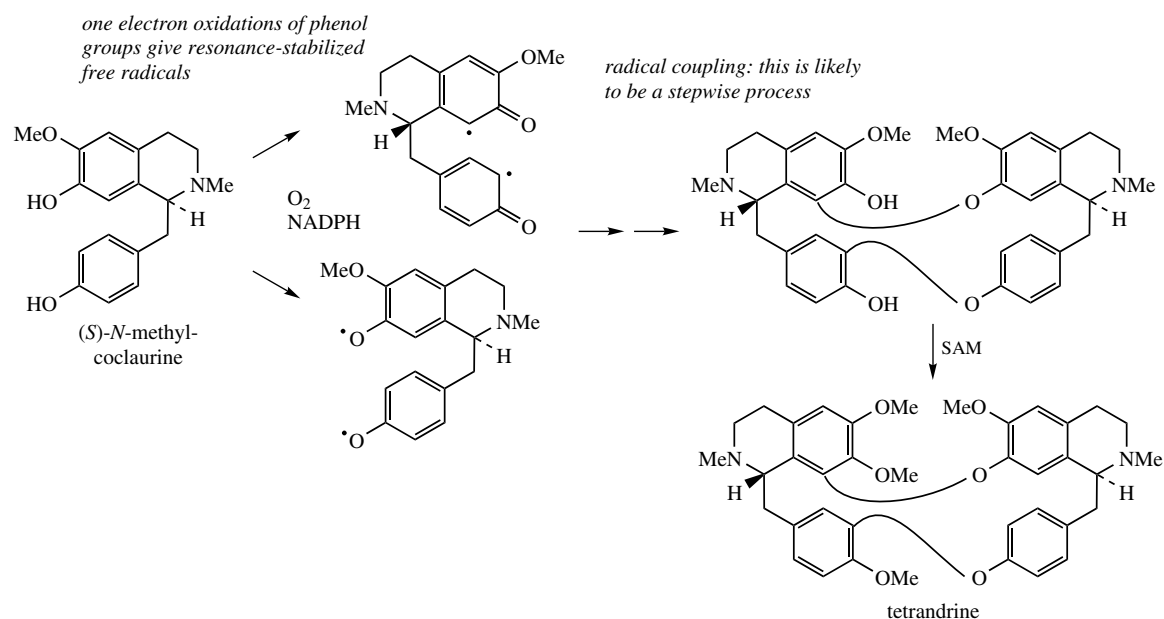

Figure 6.46

than the combined one suggested in Figure 6.46. Tetrandrine is currently of interest for its ability to block calcium channels, and may have applications in the treatment of cardiovascular disorders. By a similar mechanism, **tubocurarine** (Figure 6.47),

the principal active component in the arrow poison curare* from *Chondrodendron tomentosum* (Menispermaceae), can be elaborated by a different coupling of one molecule each of (*S*)- and (*R*)-*N*-methylcoclaurine (Figure 6.47).
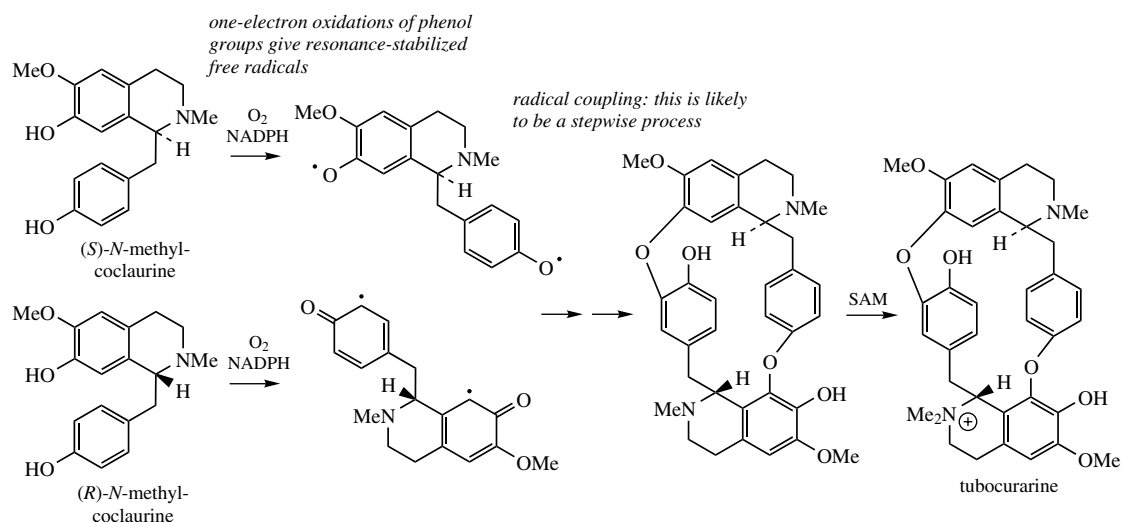

Figure 6.47

Curare

Curare is the arrow poison of the South American Indians, and it may contain as many as 30 different plant ingredients, which may vary widely from tribe to tribe according to local custom. Curare is prepared in the rain forests of the Amazon and Orinoco, and represents the crude dried extract from the bark and stems of various plants. The young bark is scraped off, pounded, and the fibrous mass percolated with water in a leaf funnel. The liquor so obtained is then concentrated by evaporation over a fire. Further vegetable material may be added to make the preparation more glutinous so that it will stick to the arrows or darts. The product is dark brown or black, and tarlike.

In the 1880s, it was found that the traditional container used for curare was fairly indicative of the main ingredients that had gone into its preparation. Three main types were distinguished. Tube curare was packed in hollow bamboo canes, and its principal ingredient was the climbing plant *Chondrodendron tomentosum* (Menispermaceae). Calabash curare was packed in gourds, and was derived from *Strychnos toxifera* (Loganiaceae). Pot curare was almost always derived from a mixture of loganiaceous and menispermaceous plants, and was packed in small earthenware pots. Current supplies of curare are mainly of the menispermaceous type, i.e. derived from *Chondrodendron*.

The potency of curare as an arrow poison is variable and consequently needs testing. A frequently quoted description of this testing is as follows: 'If a monkey hit by a dart is only able to get from one tree to the next before it falls dead, this is ''one-tree curare'', the superior grade. ''Two-tree curare'' is less satisfactory, and ''three-tree curare'' is so weak that it can be used to bring down live animals that the Indians wish to keep in captivity.' Thus, the poison

(*Continues*)

(*Continued*)

does not necessarily cause death; it depends on the potency. Curare is only effective if it enters the bloodstream, and small amounts taken orally give no ill effects provided there are no open sores in the mouth or throat.

Curare kills by producing paralysis, a limp relaxation of voluntary muscles. It achieves this by competing with acetylcholine at nicotinic receptor sites (see page 299), thus blocking nerve impulses at the neuromuscular junction. Death occurs because the muscles of respiration cease to operate, and artificial respiration is an effective treatment prior to the effects gradually wearing off through normal metabolism of the drug. Anticholinesterase drugs such as physostigmine and neostigmine are specific antidotes for moderate curare poisoning. Curare thus found medicinal use as a muscle relaxant, especially in surgical operations such as abdominal surgery, tonsillectomy, etc, where tense muscles needed to be relaxed. Curare was also found to be of value in certain neurological conditions, e.g. multiple sclerosis, tetanus, and Parkinson's disease, to temporarily relax rigid muscles and control convulsions, but was not a curative. However, the potency of curare varied markedly, and supplies were sometimes limited.

The alkaloid content of curare is from 4% to 7%. The most important constituent in menispermaceous curare is the bis-benzyltetrahydroisoquinoline alkaloid (+)-tubocurarine (Figure 6.48). This is a monoquaternary ammonium salt, and is water soluble. Other main alkaloids include non-quaternary dimeric structures, e.g. isochondrodendrine and curine (bebeerine) (Figure 6.48), which appear to be derived from two molecules of (*R*)-*N*-methylcoclaurine, with the former also displaying a different coupling mode. The constituents in loganiaceous curare (from calabash curare, i.e. *Strychnos toxifera*) are even more complex, and a series of 12 quaternary dimeric strychnine-like alkaloids has been identified, e.g. C-toxiferine (toxiferine-1) (see page 359).

Tubocurarine (Figure 6.48) is still extracted from menispermaceous curare and injected as a muscle relaxant in surgical operations, reducing the need for deep anaesthesia. Artificial respiration is required until the drug has been inactivated (about 30 minutes) or antagonized (e.g. with neostigmine). The limited availability of tubocurarine has led to the development of a series of synthetic analogues, some of which have improved characteristics and are now
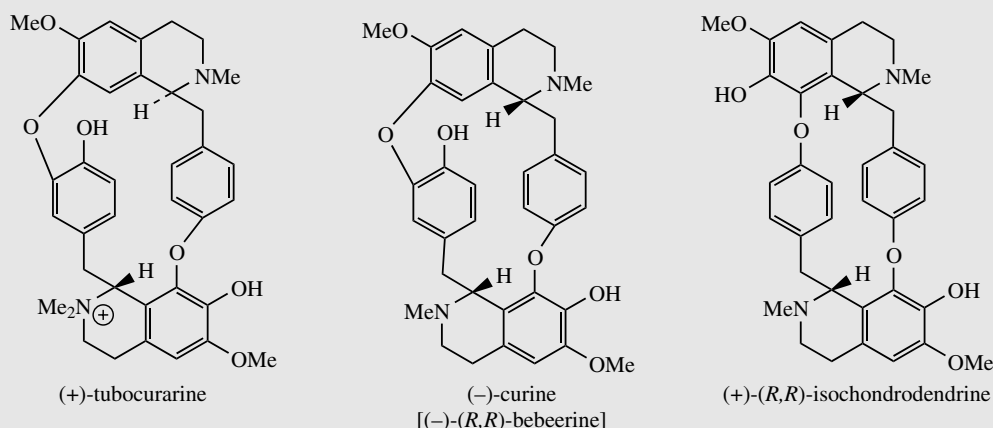

(+)-tubocurarine

(−)-curine
[(−)-(*R*,*R*)-bebeerine]

(+)-(*R*,*R*)-isochondrodendrine

Figure 6.48

(*Continues*)

(*Continued*)

preferred over the natural product. Interestingly, the structure of tubocurarine was originally formulated incorrectly as a diquaternary salt, rather than the monoquaternary salt, and analogues were based on the pretext that curare-like effects might be obtained from compounds containing two quaternary nitrogens separated by a polymethylene chain. This was borne out in practice, and the separation was found to be optimal at about ten carbons.

   Decamethonium (Figure 6.49) was the first synthetic curare-like muscle relaxant, but has since been superseded. In tubocurarine, the two nitrogens are also separated by ten atoms, and at physiological pHs it is likely that both centres will be positively charged. Obviously, the interatomic distance (1.4 nm in tubocurarine) is very dependent on the structure and stereochemistry rather than just the number of atoms separating the centres, but an extended conformation of decamethonium approximates to this distance. **Suxamethonium**
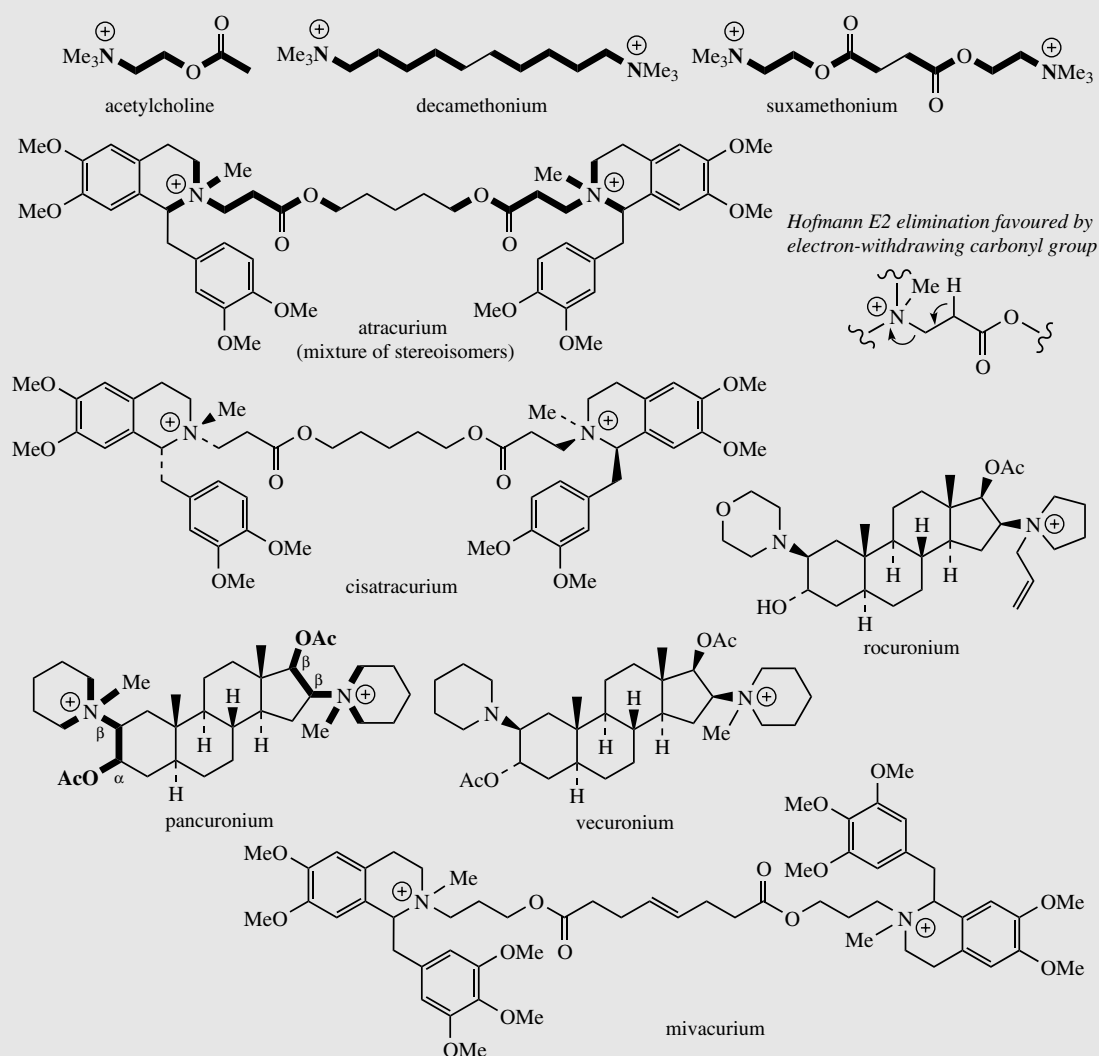

Figure 6.49

(*Continues*)

(*Continued*)

(Figure 6.49) is an effective agent with a very short duration of action, due to the two ester functions, which are rapidly metabolized by an esterase (a pseudocholinesterase) in the body, and this means the period during which artificial respiration is required is considerably reduced. It also has ten-atom separation between the quaternary nitrogens. **Atracurium** (Figure 6.49) is a recent development, containing two quaternary nitrogens in benzyltetrahydroisoquinoline structures separated by 13 atoms. In addition to enzymic ester hydrolysis, atrocurium is also degraded in the body by non-enzymic E2 Hofmann elimination (Figure 6.49), which is independent of liver or kidney function. Normally, this elimination would require strongly alkaline conditions and a high temperature, but the presence of the carbonyl group increases the acidity and thus facilitates loss of the proton, and the elimination can proceed readily under physiological conditions, giving atracurium a half life of about 20 minutes. This is particularly valuable where patients have low or atypical pseudocholinesterase enzymes. Atracurium contains four chiral centres (including the quaternary nitrogens) and is supplied as a mixture of stereoisomers; the single isomer **cisatracurium** has now been introduced. This isomer is more potent than the mixture, has a slightly longer duration of action, and produces fewer cardiovascular side-effects. **Mivacurium** (Figure 6.49) has similar benzyltetrahydroisoquinoline structures to provide the quaternary centres, but the separation has now increased to 16 atoms. In **pancuronium**, separation of the two quaternary centres is achieved by a steroidal skeleton. This agent is about five times as potent as tubocurarine. **Vecuronium** is the equivalent monoquaternary structure, and has the fewest side-effects. **Rocuronium** is also based on a steroidal skeleton, and provides rapid action with no cardiovascular effects.

The toxiferines (see Figure 6.85, page 359) also share the diquaternary character. **Alcuronium** is a semi-synthetic skeletal muscle relaxant containing the dimeric strychnine-like structure and is produced chemically from C-toxiferine (see page 360).

These neuromuscular blocking agents act by occupying nicotinic acetylcholine (Figure 6.49) receptor sites. All the structures have two acetylcholine-like portions, which can interact with the receptor. Where these are built into a rigid framework, e.g. tubocurarine and pancuronium, the molecule probably spans and blocks several receptor sites. Tubocurarine and the heterocyclic analogues are termed non-depolarizing or competitive muscle relaxants. The straight chain structures, e.g. decamethonium and suxamethonium, initially mimic the action of acetylcholine but then persist at the receptor, and are termed depolarizing blocking agents. Thus they trigger a response, a brief contraction of the muscle, which is then followed by a prolonged period of muscular paralysis until the compound is metabolized.

Modified Benzyltetrahydroisoquinoline Alkaloids

The concept of phenolic oxidative coupling is a crucial theme in modifying the basic benzyltetrahydroisoquinoline skeleton to many other types of alkaloid. Tetrandrine (Figure 6.46) and tubocurarine (Figure 6.47) represent coupling of two benzyltetrahydroisoquinoline molecules by ether bridges, but this form of coupling is perhaps less frequent than that involving carbon–carbon bonding between aromatic rings. The principal opium* alkaloids **morphine**, **codeine**, and **thebaine** (Figure 6.50) are derived by this type of coupling, though the subsequent reduction of one aromatic ring to some extent disguises their benzyltetrahydroisoquinoline origins. (*R*)-**Reticuline** (Figure 6.45) is firmly established as the precursor of these morphinan alkaloids.

(*R*)-Reticuline, rewritten as in Figure 6.50, is the substrate for one-electron oxidations via the phenol group in each ring, giving the diradical. Coupling *ortho* to the phenol group in the tetrahydroisoquinoline, and *para* to the phenol in the benzyl substituent, then yields the dienone
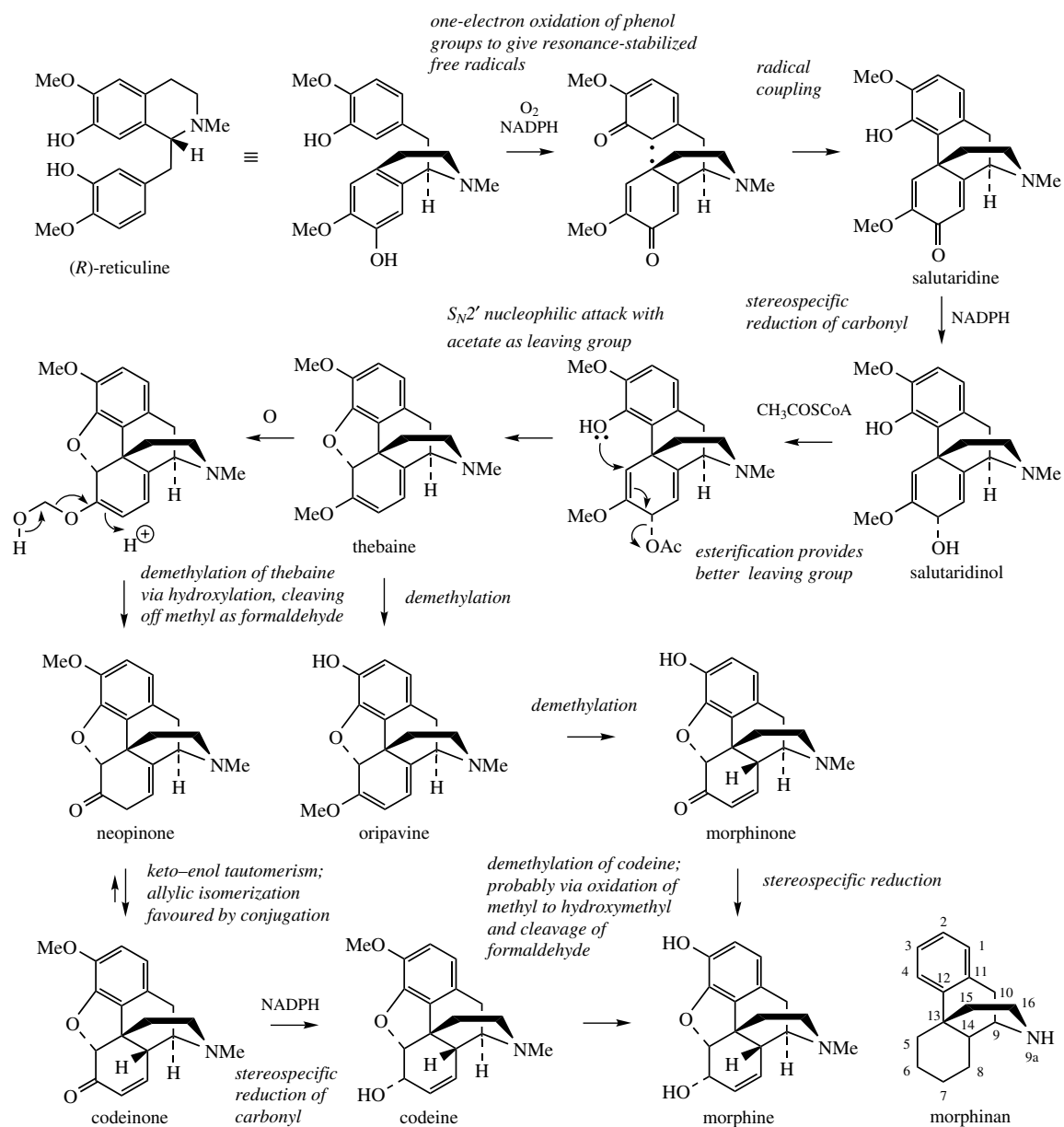
Figure 6.50

salutaridine, found as a minor alkaloid constituent in the opium poppy *Papaver somniferum* (Papaveraceae). Only the original benzyl aromatic ring can be restored to aromaticity, since the tetrahydroisoquinoline fragment is coupled *para* to the phenol function, a position which is already substituted. The alkaloid **thebaine** is obtained by way of **salutaridinol**, formed from salutaridine

by stereospecific reduction of the carbonyl group. Ring closure to form the ether linkage in thebaine would be the result of nucleophilic attack of the phenol group on to the dienol system and subsequent displacement of the hydroxyl. This cyclization step can be demonstrated chemically by treatment of salutaridinol with acid. *In vivo*, however, an additional reaction is used to improve the

nature of the leaving group, and this is achieved by acetylation with acetyl-CoA. The cyclization then occurs readily, and without any enzyme participation. Subsequent reactions involve conversion of thebaine into **morphine** by way of **codeine**, a process which modifies the oxidation state of the diene ring, but most significantly removes two *O*-methyl groups. One is present as an enol ether, removal generating **neopinone**, which gives **codeinone** and then codeine by allylic isomerization and reduction respectively. The last step, demethylation of the phenol ether codeine to the phenol morphine, is the type of reaction only achievable in the laboratory by the use of powerful and reactive demethylating agents, e.g. HBr or BBr$_3$. Because of the other functional groups present, chemical conversion of codeine into morphine is not usually a satisfactory process. However, the enzyme-mediated conversion in *P. somniferum* proceeds smoothly and efficiently. The enzymic demethylations of both the enol ether and the phenol ether probably involve initial hydroxylation followed by loss of the methyl groups as formaldehyde (Figure 6.50).

The involvement of these *O*-demethylation reactions is rather unusual; secondary metabolic pathways tend to increase the complexity of the product by adding methyls rather than removing them. In this pathway, it is convenient to view the methyl groups in reticuline as protecting groups, which reduce the possible coupling modes available during the oxidative coupling process, and these groups are then removed towards the end of the synthetic sequence. There is also some evidence that the later stages of the pathway in Figure 6.50 are modified in some strains of opium poppy. In such strains, thebaine is converted by way of **oripavine** and **morphinone**, this pathway removing the phenolic *O*-methyl before that of the enol ether, i.e. carrying out the same steps but in a different order. The enzymic transformation of thebaine into morphine, and the conversion of (*R*)-reticuline into salutaridinol have also been observed in mammalian tissues, giving strong evidence that the trace amounts of morphine and related alkaloids which can sometimes be found in mammals are actually of endogenous origin rather than dietary.

Opium

Opium is the air-dried milky exudate, or latex, obtained by incising the unripe capsules of the opium poppy *Papaver somniferum* (Papaveraceae). The plant is an annual herb with large solitary flowers, of white, pink, or dull red-purple colour. For opium production, the ripening capsules, which are just changing colour from blue-green to yellow, are carefully incised with a knife to open the latex tubes, but not to cut through to the interior of the capsule. These latex tubes open into one another, so it is not necessary to incise them all. Cuts are made transversely or longitudinally according to custom. The initially white milky latex quickly oozes out, but rapidly turns brown and coagulates. This material, the raw opium, is then removed early the following morning, being scraped off and moulded into balls or blocks. Typically, these are wrapped in poppy leaves and shade-dried. The blocks may be dusted with various plant materials to prevent cohering. Fresh opium is pale to dark brown and plastic, but it becomes hard and brittle when stored.

Opium has been known and used for 4000 years or more. In recent times, attempts have been made at governmental and international levels to control the cultivation of the opium poppy, but with only limited success. In endeavours to reduce drug problems involving opium-derived materials, especially heroin, where extremely large profits can be made from smuggling relatively small amounts of opium, much pharmaceutical production has been replaced by the processing of the bulkier 'poppy straw'. The entire plant tops are harvested and dried, then extracted for their alkaloid content in the pharmaceutical industry. Poppy straw now accounts for most of the medicinal opium alkaloid production, but there is still

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considerable trade in illicit opium. In addition to opium, the opium poppy yields seeds, which are used in baking and are also pressed to give poppy seed oil. The remaining seed cake is used as cattle feed, and it is held that these poppy seed products cover all the growing expenses, with opium providing the profit. Poppy seeds do not contain any significant amounts of alkaloids.

The main producer of medicinal opium is India, whilst poppy straw is cultivated in Turkey, Russia, and Australia. Opium destined for the black market originates from the Golden Triangle (Burma, Laos, and Thailand), the Golden Crescent (Iran, Pakistan, and Afghanistan), and Mexico.

Crude opium has been used since antiquity as an analgesic, sleep-inducer (narcotic), and for the treatment of coughs. It has been formulated in a number of simple preparations for general use, though these are now uncommon. Laudanum, or opium tincture, was once a standard analgesic and narcotic mixture. Paregoric, or camphorated opium tincture, was used in the treatment of severe diarrhoea and dysentery, but is still an ingredient in the cough and cold preparation Gee's linctus. In Dover's powder, powdered opium was combined with powdered ipecacuanha (see page 344) to give a popular sedative and diaphoretic (promotes perspiration) to take at the onset of colds and influenza. Opium has traditionally been smoked for pleasure, but habitual use develops a craving for the drug followed by addiction. An unpleasant abstinence syndrome is experienced if the drug is withdrawn.

In modern medicine, only the purified opium alkaloids and their derivatives are commonly employed. Indeed, the analgesic preparation '**papaveretum** ' (see below), which once contained the hydrochlorides of total opium alkaloids, is now formulated from selected purified alkaloids, in the proportions likely to be found in opium. Although the ripe poppy capsule can contain up to 0.5% total alkaloids, opium represents a much concentrated form and up to 25% of its mass is composed of alkaloids. Of the many (>40) alkaloids identified, some six represent almost all of the total alkaloid content. Actual amounts vary widely, as shown by the following figures: morphine (Figure 6.50) (4–21%); codeine (Figure 6.50) (0.8–2.5%); thebaine (Figure 6.50) (0.5–2.0%); papaverine (Figure 6.45) (0.5–2.5%); noscapine (narcotine) (Figure 6.51) (4–8%); narceine (Figure 6.51; see also Figure 6.63, page 340) (0.1–2%). A typical commercial sample of opium would probably have a morphine content of about 12%. **Powdered opium** is standardized to contain 10% of anhydrous morphine, usually by dilution with an approved diluent, e.g. lactose or cocoa husk powder. The alkaloids are largely combined in salt form with meconic acid (Figure 6.51), opium containing some 3–5% of this material. Meconic acid is invariably found in opium, but, apart from its presence in other *Papaver* species, has not been detected elsewhere. It gives a deep red-coloured complex with ferric chloride, and this has thus been used as a rapid and reasonably specific test for opium. In the
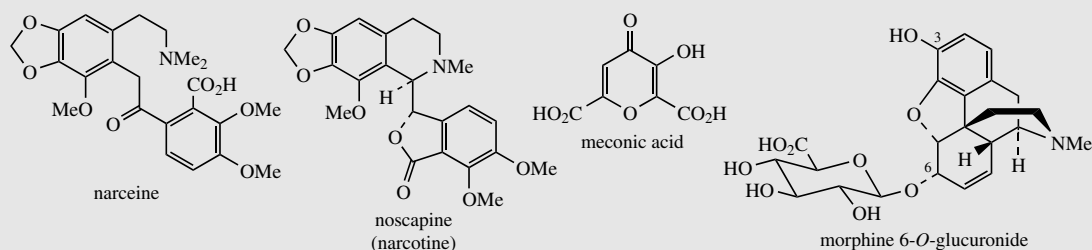

narceine

noscapine
(narcotine)

meconic acid

morphine 6-*O*-glucuronide

Figure 6.51

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past, the urine of suspected opium smokers could also be tested in this way. Of the main opium alkaloids, only morphine and narceine display acidic properties, as well as the basic properties due to the tertiary amine. Narceine has a carboxylic acid function, whilst morphine is acidic due to its phenolic hydroxyl. This acidity can be exploited for the preferential extraction of these alkaloids (principally morphine) from an organic solvent by partitioning with aqueous base.

Morphine (Figure 6.50) is a powerful analgesic and narcotic, and remains one of the most valuable analgesics for relief of severe pain. It also induces a state of euphoria and mental detachment, together with nausea, vomiting, constipation, tolerance, and addiction. Regular users experience withdrawal symptoms, including agitation, severe abdominal cramps, diarrhoea, nausea, and vomiting, which may last for 10–14 days unless a further dose of morphine is taken. This leads to physical dependence, which is difficult to overcome, so that the major current use of morphine is thus in the relief of terminal pain. Although orally active, it is usually injected to obtain rapid relief of acute pain. The side-effect of constipation is utilized in some anti-diarrhoea preparations, e.g. kaolin and morphine. Morphine is metabolized in the body to glucuronides, which are readily excreted. Whilst morphine 3-*O*-glucuronide is antagonistic to the analgesic effects of morphine, morphine 6-*O*-glucuronide (Figure 6.51) is actually a more effective and longer lasting analgesic than morphine, with fewer side-effects.

Codeine (Figure 6.50) is the 3-*O*-methyl ether of morphine, and is the most widely used of the opium alkaloids. Because of the relatively small amounts found in opium, most of the material prescribed is manufactured by semi-synthesis from morphine. Its action is dependent on partial demethylation in the liver to produce morphine, so it produces morphine-like analgesic effects, but little if any euphoria. As an analgesic, codeine has about one-tenth the potency of morphine. Codeine is almost always taken orally and is a component of many compound analgesic preparations. Codeine is a relatively safe non-addictive medium analgesic, but is still too constipating for long-term use. Codeine also has valuable antitussive action, helping to relieve and prevent coughing. It effectively depresses the cough centre, raising the threshold for sensory cough impulses.

Thebaine (Figure 6.50) differs structurally from morphine/codeine mainly by its possession of a conjugated diene ring system. It is almost devoid of analgesic activity, but may be used as a morphine antagonist. Its main value is as substrate for the semi-synthesis of other drugs (see below).

Papaverine (Figure 6.45) is a benzylisoquinoline alkaloid, and is structurally very different from the morphine, codeine, thebaine group of alkaloids (morphinans). It has little or no analgesic or hypnotic properties put possesses spasmolytic and vasodilator activity. It has been used in some expectorant preparations, and in the treatment of gastrointestinal spasms, but its efficacy was not substantiated. It is sometimes used as an effective treatment for male impotence, being administered by direct injection to achieve erection of the penis.

Noscapine (Figure 6.51) is a member of the phthalideisoquinoline alkaloids (see page 339) and provides a further structural variant in the opium alkaloids. Noscapine has good antitussive and cough suppressant activity comparable to that of codeine, but no analgesic or narcotic action. Its original name 'narcotine' was changed to reflect this lack of narcotic action. Despite many years of use as a cough suppressant, the finding that noscapine may have teratogenic properties (i.e. may deform a fetus) has resulted in noscapine preparations being deleted. In recent studies, antitumour activity has been noted from noscapine, which binds to tubulin as do podophyllotoxin and colchicine (see pages 136 and 343), thus arresting cells at mitosis. The chemotherapeutic potential of this orally effective agent merits further evaluation.
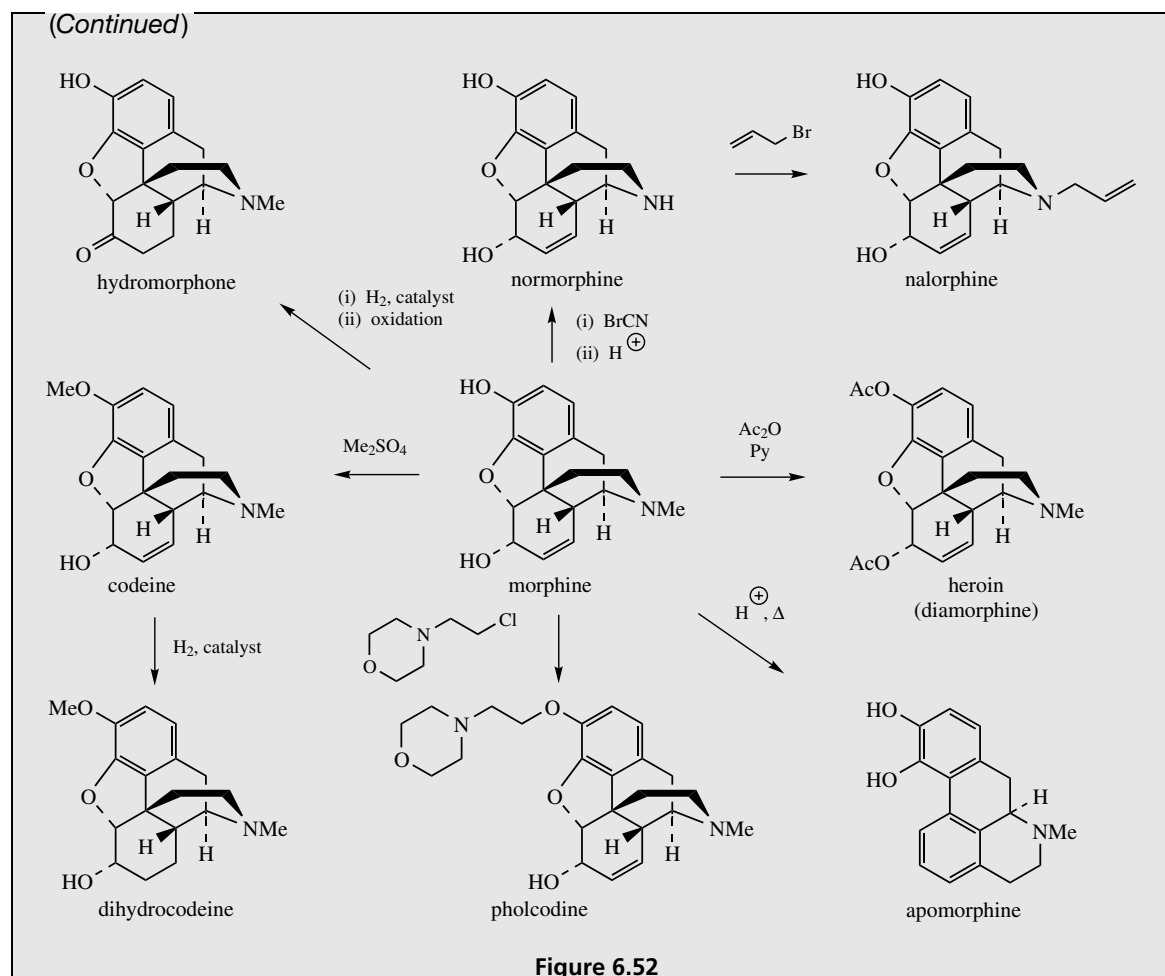
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Figure 6.52

Papaveretum is a mixture of purified opium alkaloids, as their hydrochlorides, and is now formulated to contain only morphine (85.5%), codeine (7.8%), and papaverine (6.7%). It is used for pain relief during operations.

A vast range of semi-synthetic or totally synthetic morphine-like derivatives have been produced. These are collectively referred to as 'opioids'. Many have similar narcotic and pain-relieving properties as morphine, but are less habit forming. Others possess the cough-relieving activity of codeine, but without the analgesic effect. More than 90% of the morphine extracted from opium (or poppy straw) is currently processed to give other derivatives (Figure 6.52). Most of the codeine is obtained by semi-synthesis from morphine, mono-*O*-methylation occurring at the acidic phenolic hydroxyl. Similarly, **pholcodine** (Figure 6.52), an effective and reliable antitussive, can be obtained by alkylation with *N*-(chloroethyl)morpholine. **Dihydrocodeine** (Figure 6.52) is a reduced form of codeine with similar analgesic properties, the double bond not being essential for activity. In **hydromorphone**, the double bond of morphine has been reduced, and in addition the 6-hydroxyl has been oxidized to a ketone. This increases the analgesic effects, but also the side-effects. **Diamorphine**, or **heroin** (Figure 6.52) is merely the diacetate of morphine, and is a highly addictive analgesic and hypnotic. The increased lipophilic

(*Continued*)

character results in better transport and absorption, though the active agent is probably the 6-acetate, the 3-acetate group being hydrolysed by esterases in the brain. Heroin was synthesized originally as a cough suppressant, and though most effective in this role has unpleasant addictive properties, with users developing a psychological craving for the drug. It is widely used for terminal care, e.g. cancer sufferers, both as an analgesic and cough suppressant. The euphoria induced by injection of heroin has resulted in much abuse of the drug, and creation of a world-wide major drug problem.

The *N*-methyl group of morphine can be removed by treatment with cyanogen bromide, then hydrolysis. A variety of *N*-alkyl derivatives, e.g. *N*-allyl-normorphine (**nalorphine**) (Figure 6.52) may be produced by use of appropriate alkyl bromides. Nalorphine has some analgesic activity, but was also found to counter the effects of morphine, and is thus a mixed agonist–antagonist. It is sometimes used as a narcotic antagonist, but is principally regarded as the forerunner of pure opiate antagonists such as naloxone (see below). Treatment of morphine with hot acid induces a rearrangement process, resulting in a highly modified structural skeleton, a representative of the aporphine group of alkaloids (see page 337). The product **apomorphine** (Figure 6.52) has no analgesic properties, but morphine's side-effects of nausea and vomiting are highly emphasized. Apomorphine is a powerful emetic, and can be injected for emergency treatment of poisoning. This is now regarded as dangerous, but apomorphine is also valuable to control the symptoms of Parkinson's disease, being a stimulator of D_1 and D_2 dopamine receptors. Apomorphine's structure contains a dihydroxyphenylethylamine (dopamine) fragment, conferring potent dopamine agonist properties to this agent.

It has been found that a common structural feature required for centrally acting analgesic activity in the opioids is the combination of an aromatic ring, and a piperidine ring which maintain the stereochemistry at the chiral centre as shown in Figure 6.53. The three-dimensional disposition of the nitrogen function to the aromatic ring allows morphine and other analgesics to bind to a pain-reducing receptor in the brain. Several different receptors and groups of receptors are known. The natural agonists include peptides called enkephalins, Met-enkephalin and Leu-enkephalin (Figure 6.53), produced from a larger peptide endorphin (see page 419). The terminal tyrosine residue in the enkephalins is mimicked by portions of
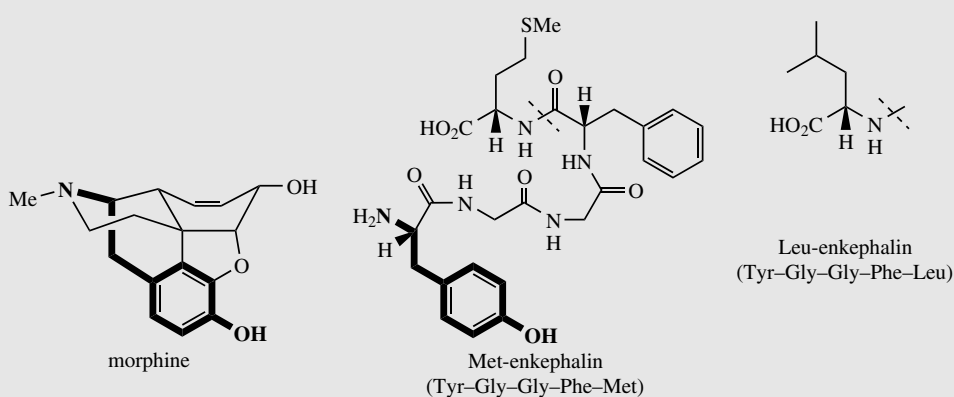

morphine

Met-enkephalin
(Tyr–Gly–Gly–Phe–Met)

Leu-enkephalin
(Tyr–Gly–Gly–Phe–Leu)

Figure 6.53
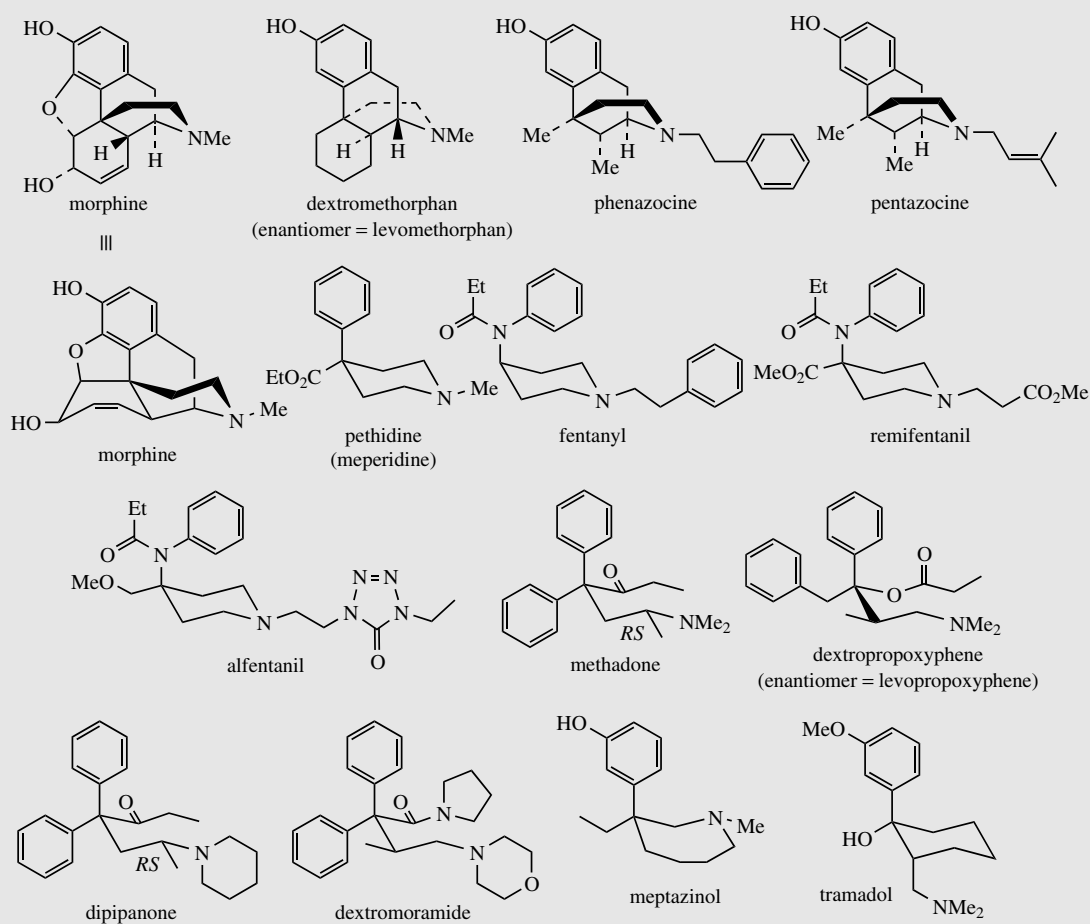
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Figure 6.54

the morphine structure. The enkephalins themselves are rapidly degraded in the body and are unsuitable for drug use.

Some totally synthetic opioid drugs modelled on morphine are shown in Figure 6.54. Removal of the ether bridge and the functionalities in the cyclohexene ring are exemplified in levomethorphan and **dextromethorphan**. Levomethorphan has analgesic properties, whilst both enantiomers possess the antitussive activity of codeine. In practice, the 'unnatural' isomer dextromethorphan is the preferred drug material, being completely non-addictive and possessing no analgesic activity. **Pentazocine** and **phenazocine** are examples of morphine-like structures where the ether bridge has been omitted and the cyclohexene ring has been replaced by simple methyl groups. These drugs are good analgesics and are non-addictive, though pentazocine can induce withdrawal symptoms. Even more drastic simplification of the morphine structure is found in **pethidine** (**meperidine**), one of the most widely used synthetic opiates. Only the aromatic ring and the piperidine systems are retained. Pethidine is less potent than morphine, but produces prompt, short-acting analgesia, and is also less

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constipating than morphine. It can be addictive. **Fentanyl** has a 4-anilino- rather than a 4-phenyl-piperidine structure, and is 50–100 times more active than morphine due to its high lipophilicity and excellent transport properties. **Alfentanil** and **remifentanil** are further variants on the fentanyl structure; all three drugs are rapid-acting and used during oper-ative procedures. The piperidine ring system is no longer present in **methadone**, though this diphenylpropylamine derivative can be drawn in such a way as to mimic the piperidine ring conformation. Methadone is orally active, has similar activity to morphine, but is less euphorigenic and has a longer duration of action. Although it is as potentially addictive as morphine, the withdrawal symptoms are different and much less severe than with other drugs such as heroin, and methadone is widely used for the treatment and rehabilitation of heroin addicts. However, it only replaces one addiction with another, albeit a less dangerous one. **Dextropropoxyphene** mimics the piperidine ring in a rather similar manner, but this agent has only low analgesic activity, about half that of codeine, and finds application in combination formulations with aspirin or paracetamol. The enantiomeric **levopropoxyphene** has antitus-sive activity, but no analgesic properties. **Dipipanone** and **dextromoramide** are structural variants on methadone, and are used for moderate to severe pain; dipipanone is usually administered in combination with an anti-emetic. **Meptazinol** is structurally unlike the other opiate analgesics in that it contains a seven-membered nitrogen heterocycle. It is an effective analgesic, and produces relatively few side-effects with a low incidence of respiratory depres-sion. **Tramadol** is a recent drug claimed to produce analgesia by an opioid mechanism and by enhancement of serotoninergic and adrenergic pathways, with few typical opioid side-effects.
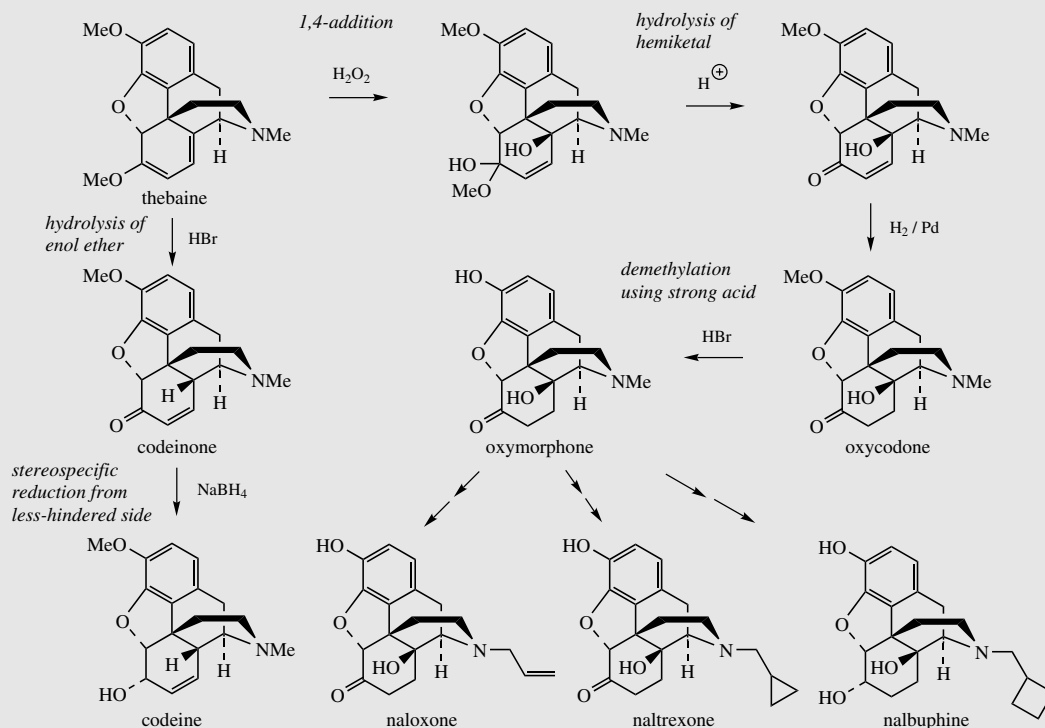

Figure 6.55

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Thebaine, for many years regarded as an unwanted by-product from opium, is now utilized for the semi-synthesis of useful new drugs. On treatment with hydrogen peroxide, the conjugated diene undergoes 1,4-addition, and hydrolysis results in formation of a 4-hydroxy cyclohexenone system (Figure 6.55). Reduction and demethylation lead respectively to **oxycodone** and **oxymorphone**, which are potent analgesics. The conjugated diene system can also be exploited in a Diels–Alder reaction, building on another ring system (Figure 6.56). Some of these adducts have quite remarkable levels of analgesic activity, but are too powerful for human use. Some, e.g. **etorphine** (Figure 6.57), are used in veterinary practice to sedate large animals (elephants, rhinos) by means of tranquillizer darts. Etorphine is some 5000–10 000 times more potent than morphine. **Buprenorphine** (Figure 6.57) is an etorphine analogue with an *N*-cyclopropylmethyl substituent and *tert*-butyl instead of *N*-propyl in the side-chain. This material has both opioid agonist and antagonist properties. Mixed agonist–antagonist properties offer scope for producing analgesia whilst negating the effects of other opioids to which a patient may be addicted. Buprenorphine has a long duration of action, and only low dependence potential, but may precipitate withdrawal symptoms in patients dependent on other opioids. It is now being used as an alternative to methadone in the treatment of opioid dependence. **Nalbuphine** (Figure 6.55), produced semi-sythetically from thebaine, also displays mixed agonist–antagonist properties, and has similar agonist activity as morphine, but produces less side-effects and has less abuse potential. **Naloxone** (Figure 6.55) shows hardly any agonist activity but is a potent antagonist, and is used to treat opiate poisoning, including that in children born to heroin addicts. **Naltrexone** (Figure 6.55)
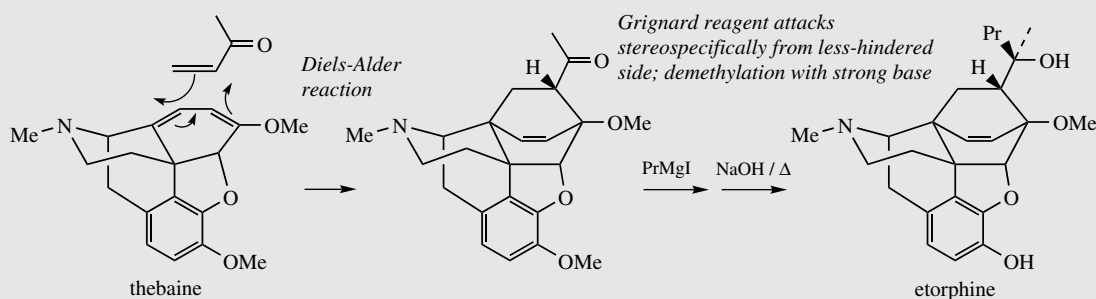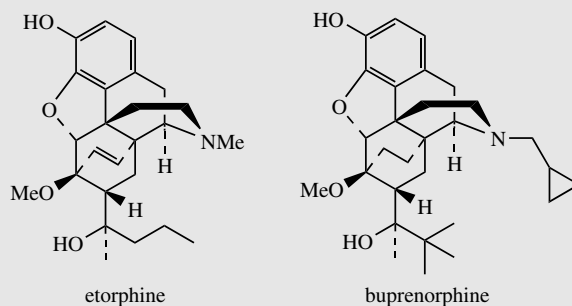

Figure 6.56

Figure 6.57

(*Continues*)

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also has antagonist activity similar to naloxone. These agents are *N*-alkyl derivatives related to oxymorphone/oxycodone.

Thebaine may also be transformed very efficiently into codeine in about 75% yield (Figure 6.55). The two-stage synthesis involves acid-catalysed hydrolysis of the enol ether function to give codeinone (this being the more favoured tautomer of the first-formed β, γ-unsaturated ketone) followed by selective borohydride reduction of the carbonyl. This opens up possibilities for producing codeine (the most widely used of the opium alkaloids) without using morphine. At present, most of the codeine is synthesized by methylation of morphine. The advantage of using thebaine is that the raw material for the pharmaceutical industry could be shifted away from morphine and opium. This might then help in the battle to eliminate illicit morphine production and its subsequent conversion into heroin. Conversion of thebaine into morphine and heroin is much more difficult and low yielding. Thus, there is interest in cultivating *Papaver bracteatum* rather than *P. somniferum*. This plant produces mainly thebaine, no morphine, and only faint traces of codeine. Experiments have shown it has the enzymic activity to convert codeinone into codeine, but it appears to lack enzymes which carry out the late demethylation steps in Figure 6.50. The capsules can produce up to 3% thebaine, but, regrettably, there have been difficulties in making this a commercially viable project, and this idea has not materialized. Other species of *Papaver* seem to lack the enzyme that reduces salutaridine to salutaridinol (Figure 6.50) and they thus do not synthesize morphine-like alkaloids. Remarkably, there is now considerable evidence that various animals, including humans and other mammals, are also able to synthesize morphine and related alkaloids in small amounts. These compounds have been detected in various tissues, including brain, liver, spleen, adrenal glands and skin, and endogenous morphine may thus play a role in pain relief, combining its effects with those provided by the enkephalin peptides.

A minor constituent of *P. somniferum* is the aporphine alkaloid **isoboldine** (Figure 6.58). Other species of poppy, e.g. *Papaver orientale* and *P. pseudoorientale*, are known to synthesize aporphine alkaloids as principal constituents rather than morphinan structures. (*S*)-Isoboldine is readily appreciated to be the product of oxidative coupling of (*S*)-**reticuline**, coupling *ortho* to the phenol group in the tetrahydroisoquinoline, and *para* to the phenol of the benzyl substituent

(Figure 6.58). Some structures, e.g. **isothebaine** (Figure 6.59) from *P. orientale*, are not as easily rationalized. (*S*)-**Orientaline** is a precursor of isothebaine (Figure 6.59). This benzyltetrahydroisoquinoline, with a different methylation pattern to reticuline, is able to participate in oxidative coupling, but inspection of the structures indicates a phenol group is lost in the transformation. The pathway (Figure 6.59) involves an unexpected rearrangement process, however. Thus, oxidative
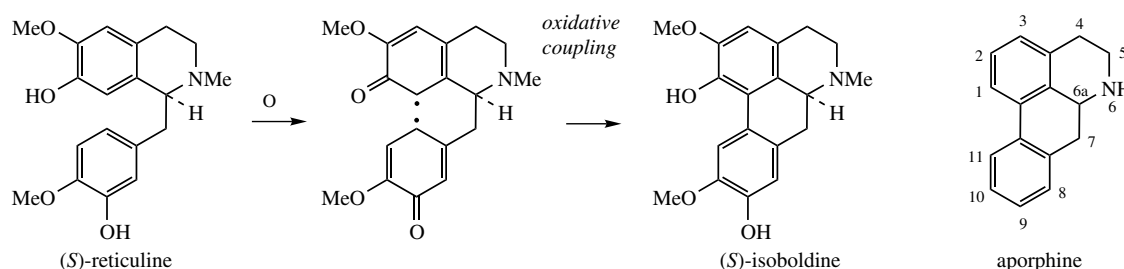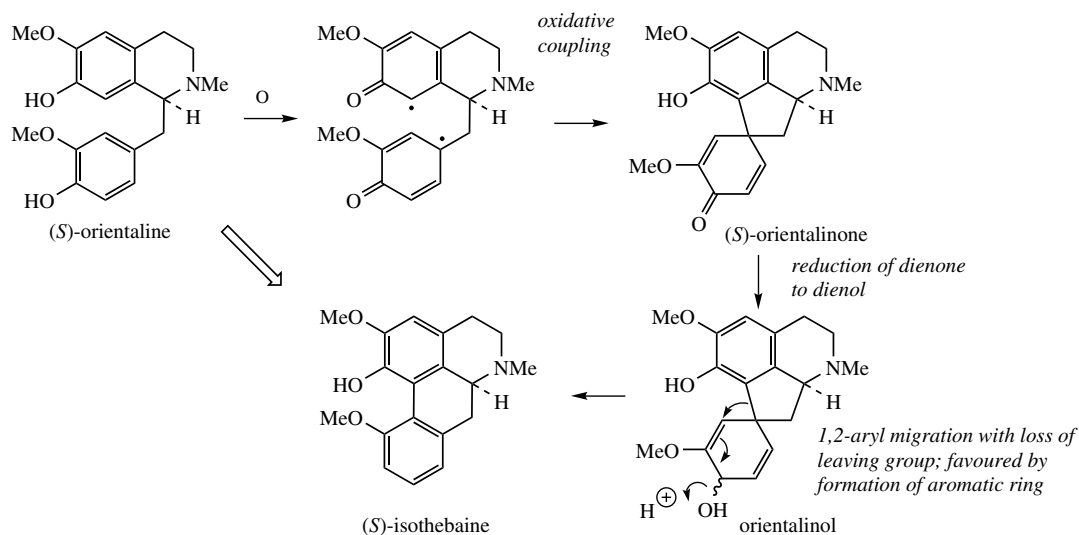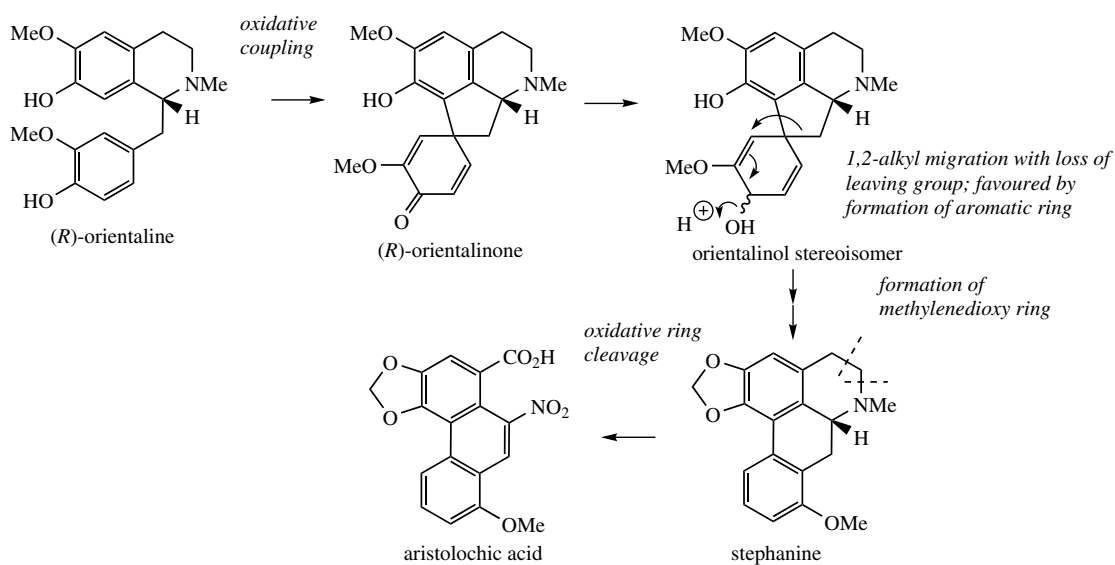

Figure 6.58

Figure 6.59

Figure 6.60

coupling *ortho−para* to the phenol groups gives a dienone **orientalinone** (compare the structure of salutaridine (Figure 6.50)). After reduction of the carbonyl group, a rearrangement occurs, restoring aromaticity and expelling the hydroxyl (originally a phenol group) to produce **isothebaine**. This type of rearrangement, for which good chemical analogies are available, is a feature of many other alkaloid biosynthetic pathways, and occurs

because normal keto−enol tautomerism is not possible for rearomatization when coupling involves positions already substituted. The process is fully borne out by experimental evidence, including the subsequent isolation of orientalinone and orientalinol from *P. orientale*.

Stephanine (Figure 6.60) from *Stephania* species (Menispermaceae) is analogous to isothebaine and shares a similar pathway, though from

(*R*)-**orientaline**. The different substitution pattern in stephanine compared to isothebaine is a consequence of the intermediate dienol suffering migration of the alkyl rather than aryl group (Figure 6.60). **Aristolochic acid** is a novel modified aporphine containing a nitro group and is produced from stephanine by oxidative reactions leading to ring cleavage (Figure 6.60). Aristolochic acid is present in many species of *Aristolochia* (Aristolochiaceae) used in traditional medicine, e.g. snake-root *A. serpentina*. However, because aristolochic acid is now known to be nephrotoxic and to cause acute kidney failure, the use of *Aristolochia* species in herbal medicines, especially Chinese remedies, has been banned in several countries.

The alkaloid **berberine** (Figure 6.61) is found in many members of the Berberidaceae (e.g. *Berberis*, *Mahonia*), the Ranunculaceae (e.g. *Hydrastis*), and other families. Berberine has antiamoebic, antibacterial, and anti-inflammatory properties and plants containing berberine have long been used in traditional medicine. Its tetracyclic skeleton is derived from a benzyl-tetrahydroisoquinoline system with the incorporation of an extra carbon atom, supplied from *S*-adenosylmethionine via an *N*-methyl group (Figure 6.61). This extra skeletal carbon is known as a 'berberine bridge'. Formation of the berberine bridge is readily rationalized as an oxidative process in which the *N*-methyl group is oxidized to an iminium ion, and a cyclization to the aromatic ring occurs by virtue of the phenolic group (Figure 6.62).

The oxidative cyclization process is analogous to the formation of a methylenedioxy group (see page 27), whilst the mechanism of cyclization is exactly the same as that invoked in formation of a tetrahydroisoquinoline ring, i.e. a Mannich-like

reaction (see page 320). The product from the enzymic transformation of (*S*)-**reticuline** is the protoberberine alkaloid (*S*)-**scoulerine**, the berberine bridge enzyme requiring molecular oxygen as oxidant and releasing H_2O_2 as by-product (Figure 6.62). Its role in the cyclization reaction completed, the phenol group in scoulerine is then methylated, and **tetrahydrocolumbamine** is oxidized further to give the quaternary isoquinoline system in **columbamine**. This appears to involve two separate oxidation steps, both requiring molecular oxygen, though H_2O_2 and H_2O are produced in the successive processes. The mechanistic sequence through an iminium ion has been suggested to account for these observations. Finally, **berberine** is produced by transformation of the *ortho*-methoxyphenol to a methylenedioxy group, via the O_2-, NADPH-, and cytochrome P-450-dependent enzyme.

The protoberberine skeleton of scoulerine may be subjected to further modifications, some of which are given in Figure 6.63. Cleavage of the heterocyclic ring systems adjacent to the nitrogen atom as shown give rise to new skeletal types: protopine, e.g. **protopine** from *Chelidonium majus* (Papaveraceae), phthalideisoquinoline, e.g. **hydrastine** from *Hydrastis canadensis* (Ranunculaceae), and benzophenanthridine, e.g. **chelidonine**, also from *Chelidonium majus*. The non-heterocyclic system seen in the opium alkaloid **narceine** from *Papaver somniferum* can be visualized as the result of cleavage of two of these bonds. Some alkaloids of the phthalide type are medicinally important. **Noscapine** (Figure 6.64) is one of the opium alkaloids and although it lacks any analgesic activity it is an effective cough suppressant (see page 331). **Hydrastine** is beneficial as a traditional remedy in the control of uterine bleeding. *Hydrastis* also contains berberine, indicating the
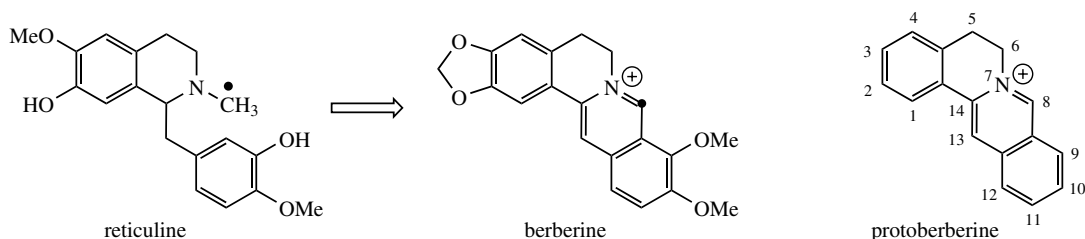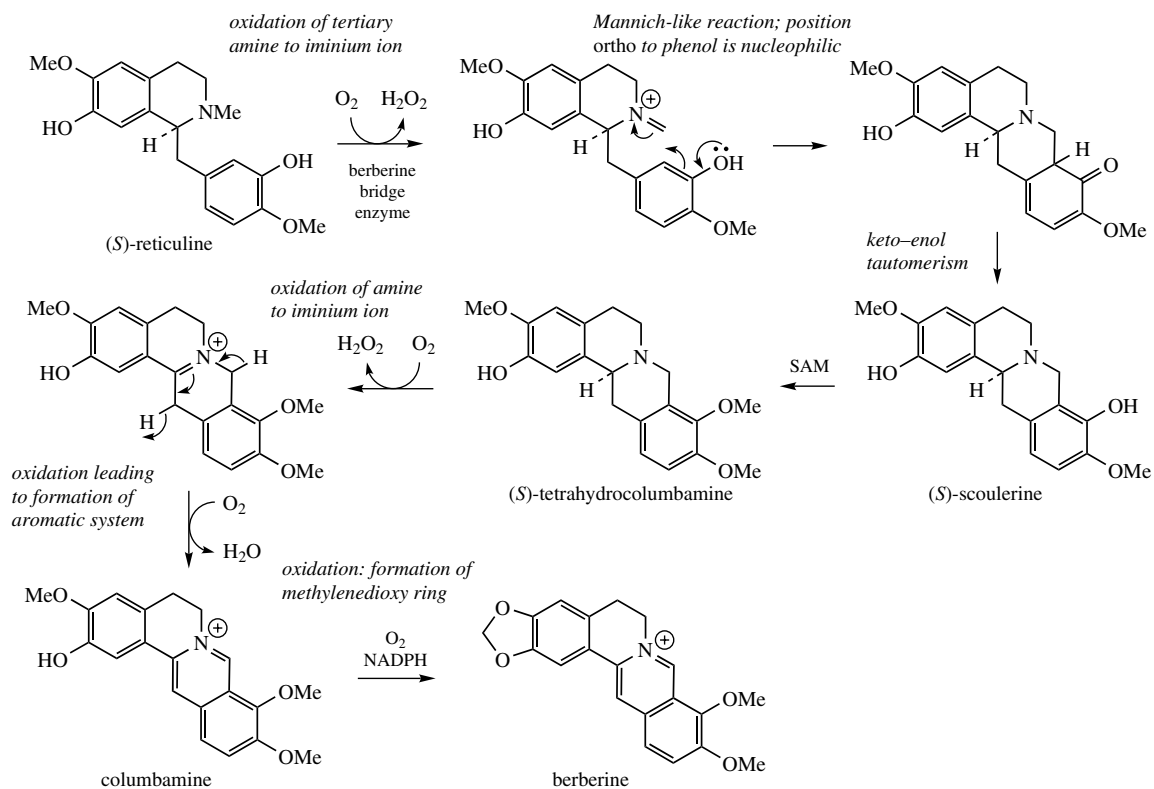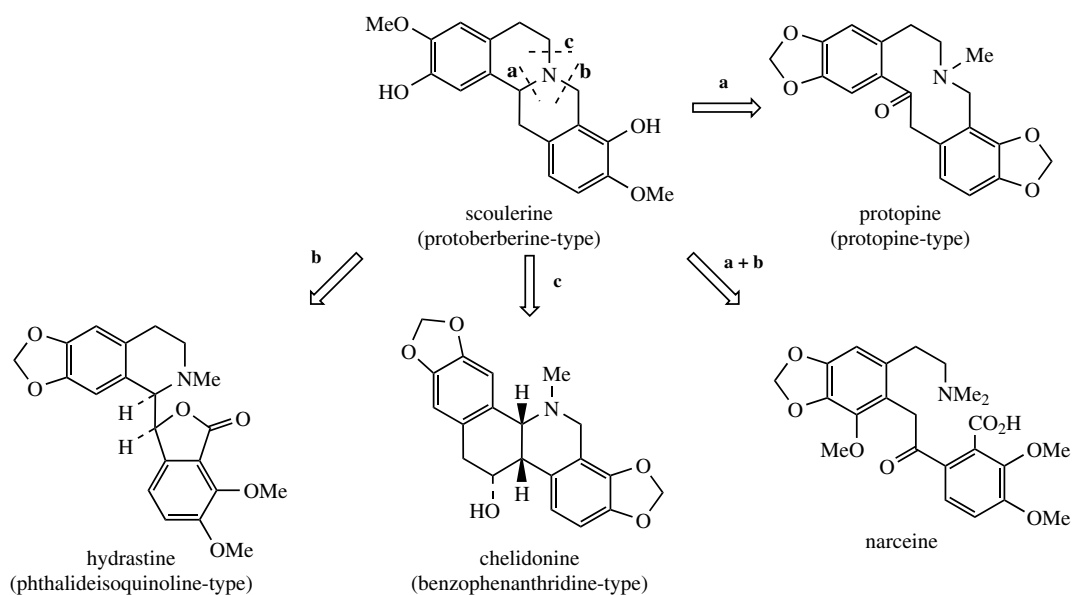

Figure 6.61

oxidation of tertiary
amine to iminium ion

Mannich-like reaction; position
ortho to phenol is nucleophilic

(S)-reticuline

O₂   H₂O₂

berberine
bridge
enzyme

keto–enol
tautomerism

oxidation of amine
to iminium ion

H₂O₂   O₂

SAM

(S)-tetrahydrocolumbamine

(S)-scoulerine

oxidation leading
to formation of
aromatic system

O₂

H₂O

oxidation: formation of
methylenedioxy ring

O₂
NADPH

columbamine

berberine

Figure 6.62

scoulerine
(protoberberine-type)

a

protopine
(protopine-type)

b

c

a + b

hydrastine
(phthalideisoquinoline-type)

chelidonine
(benzophenanthridine-type)
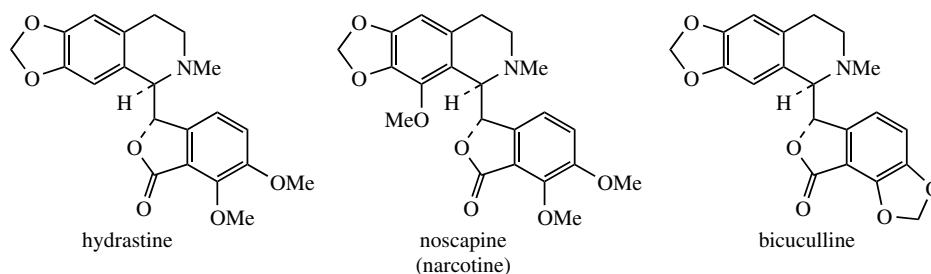
narceine

Figure 6.63

Figure 6.64

close biosynthetic relationship of the two types of alkaloid. **Bicuculline** (Figure 6.64) from species of *Corydalis* and *Dicentra* (Fumariaceae) and its quaternary methiodide have been identified as potent GABA (γ-aminobutyric acid) antagonists and have found widespread application as pharmacological probes for convulsants acting at GABA neuroreceptors.

Phenethylisoquinoline Alkaloids

Several genera in the lily family (Liliaceae) are found to synthesize analogues of the benzyltetrahydroisoquinoline alkaloids, e.g. **autumnaline**

(Figure 6.65), which contain an extra carbon between the tetrahydroisoquinoline and the pendant aromatic rings. This skeleton is formed in a similar way to that in the benzyltetrahydroisoquinolines from a phenylethylamine and an aldehyde (Figure 6.65), but a whole C_6C_3 unit rather than a C_6C_2 fragment functions as the reacting aldehyde. Typically, dopamine (from tyrosine) and 4-hydroxydihydrocinnamaldehyde (from phenylalanine) are involved in the initial condensation, and further hydroxylation and methylation steps then build up the substitution pattern to that of autumnaline. Phenolic oxidative coupling accounts for the occurrence of homoaporphine alkaloids such as **floramultine** and **kreysigine** in
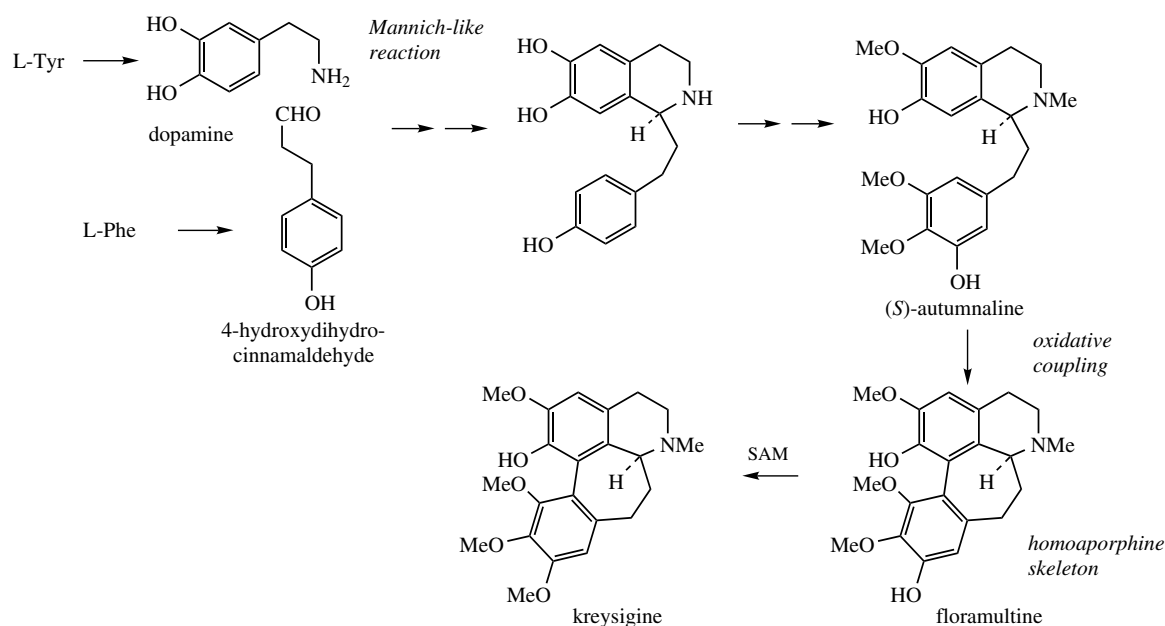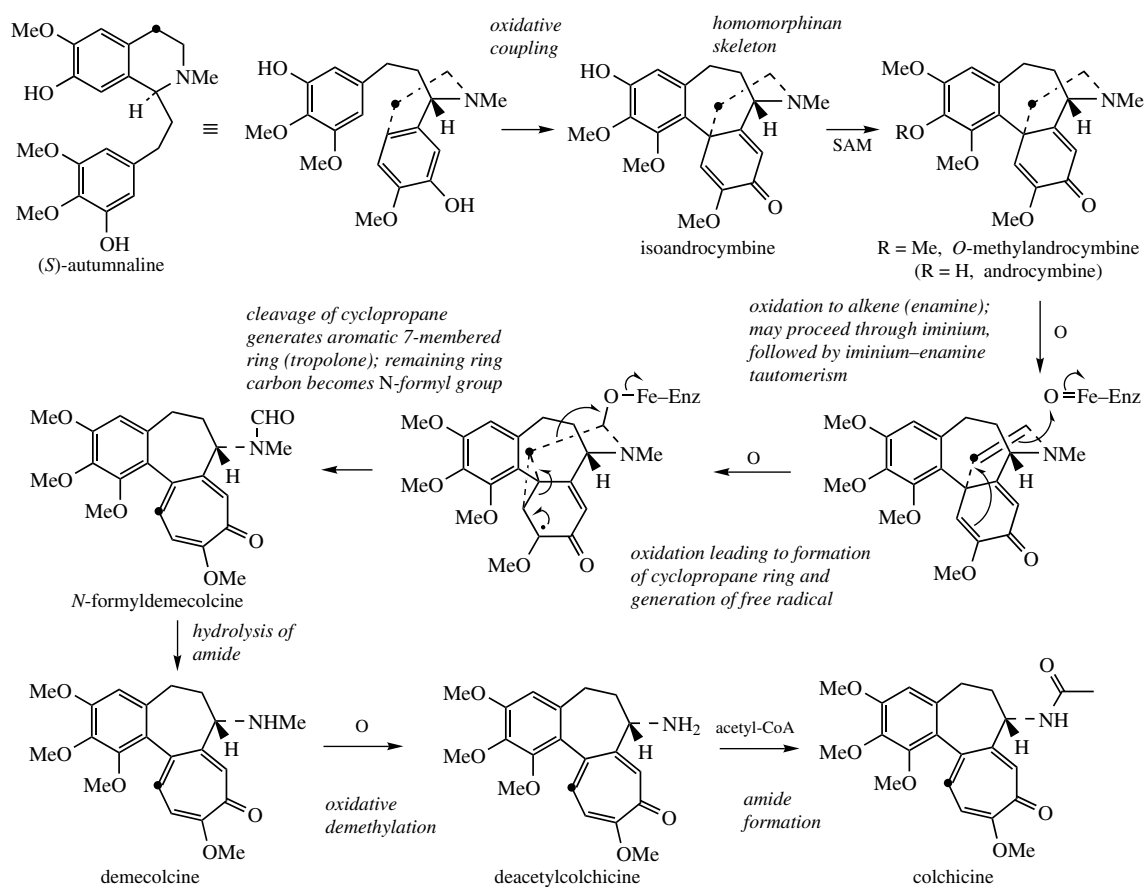

Figure 6.65

Figure 6.66

Kreysigia multiflora (Liliaceae/Convallariaceae). (S)-**Autumnaline** has also been found to act as a precursor for **colchicine** (Figure 6.66), an alkaloid containing an unusual tropolone ring. Colchicine is found in species of *Colchicum**, e.g. *Colchicum autumnale* (Liliaceae/Colchicaceae), as well as many other plants in the Liliaceae. Colchicine no longer has its nitrogen atom in a ring system, and extensive reorganization of the autumnaline structure is thus necessary. The seven-membered tropolone ring was shown by labelling experiments to originate by ring expansion of the tyrosine-derived aromatic ring taking in the adjacent benzylic carbon (Figure 6.66). Prior to these remarkable rearrangements, oxidative coupling of autumnaline in the *para–para* sense features in the pathway giving the dienone **isoandrocymbine**, which has a homomorphinan skeleton (compare salutaridine, Figure 6.50). The isomer **androcymbine** (Figure 6.66) had been

isolated from *Androcymbium melanthioides* (Liliaceae/Colchicaceae), thus giving a clue to the biosynthetic pathway. Methylation follows giving *O*-methylandrocymbine, and it is then proposed that enzymic oxidation to an enamine yields the substrate for ring modification. Experimental labelling studies are then best explained by formation of a cyclopropane ring followed by ring opening to generate the 6π electron aromatic tropolone system, incorporating the original tyrosine benzylic carbon into the seven-membered ring, and also breaking the original phenylethylamine side-chain between the carbons. One carbon is left on the nitrogen as a formyl group, and this can be lost by hydrolysis. **Colchicine** is produced by exchanging the *N*-methyl group for an *N*-acetyl group, by way of an oxidative demethylation followed by acetylation using acetyl-CoA. **Demecolcine** and **deacetylcolchicine** are intermediates in the process.

Colchicum

Colchicum seed and corm are obtained from *Colchicum autumnale* (Liliaceae/Colchicaceae), the autumn crocus or meadow saffron. The plant, though not a crocus, produces crocus-like flowers in the autumn, the leaves not emerging until the spring. It is a native of Europe, is widely cultivated as an ornamental garden plant, and is grown for drug use, mainly in Europe and North Africa. The principal alkaloid is colchicine (Figure 6.66), which occurs to the level of about 0.8% in the seed, and 0.6% in the corm. As an *N*-acetyl derivative, colchicine does not display any significant basicity, and does not form well-defined salts. Demecolcine (*N*-deacetyl-*N*-methylcolchicine) (Figure 6.66) is a minor constituent in both corm and seeds.

Extracts of *Colchicum autumnale*, and later **colchicine** itself, have been used in the treatment of gout, a painful condition in which impaired purine metabolism leads to a build-up of uric acid crystals in the joints. Colchicine is an effective treatment for acute attacks, but it is very toxic, and this restricts its general use. It appears to act primarily as an anti-inflammatory agent, and does not itself affect uric acid metabolism, which needs to be treated with other agents, e.g. a xanthine oxidase inhibitor such as allopurinol. The cytotoxic properties of colchicine and related alkaloid structures from *C. autumnale* led to their being tested as potential anticancer agents, though they still proved too toxic for medicinal use. Colchicine binds to tubulin in the mitotic spindle, preventing polymerization and assembly into microtubules as do podophyllotoxin (see page 136) and vincristine (see page 356), and is a useful biochemical probe. However, the ability of colchicine to act as a mitotic poison is exploited in plant breeding, since the interference with mitosis results in multiplication of chromosomes in the cell nucleus without the process of cell division. Cell division recommences on cessation of treatment. This allows the generation of mutations (polyploids) and possible new varieties of plant. Colchicine is also found in other species of *Colchicum*, as well as many other plants in the Liliaceae (e.g. *Bulbocodium*, *Gloriosa*, *Merendera*, and *Sandersonia*), a group of plants now classified as the family Colchicaceae.

Terpenoid Tetrahydroisoquinoline Alkaloids

The alkaloids found in ipecacuanha*, the dried rhizome and roots of *Cepahaelis ipecacuanha* (Rubiaceae), have a long history of use in the treatment of amoebic dysentery, and provide unusual examples of tetrahydroisoquinoline structures. The principal alkaloids, e.g. **emetine** and **cephaeline** (Figure 6.67), possess a skeleton with two tetrahydroisoquinoline ring systems, plus a further fragment that has its origin in a terpenoid-derived molecule. This terpenoid substrate is the secoiridoid **secologanin** (see page 189), a compound that also features in the biosynthesis of many complex indole alkaloids (see page 350). Secologanin is an aldehyde and can condense with dopamine to give the tetrahydroisoquinoline alkaloid *N*-deacetylisoipecoside (Figure 6.67). **Ipecoside** itself is found in ipecacuanha, though it has

the opposite stereochemistry at C-1 to this biosynthetic intermediate. The secologanin fragment contains an acetal function, which can be restored to its component aldehyde and alcohol fragments by hydrolysis of the glucosidic bond. The newly liberated aldehyde can then bond with the secondary amine to give the quaternary Schiff base. This intermediate is converted into an aldehyde by a sequence of reactions: reduction of iminium, reduction of alkene, plus hydrolysis of ester and subsequent decarboxylation, though not necessarily in that order. The decarboxylation step is facilitated by the β-aldehyde function, shown as an enol in Figure 6.67. Most of the reactions taking place in the secologanin-derived part of the structure are also met in discussions of terpenoid indole alkaloids (see page 350). The resultant aldehyde is now able to participate in formation of a second tetrahydroisoquinoline ring system, by reaction with a second dopamine molecule. Methylation gives **cephaeline** and **emetine**.
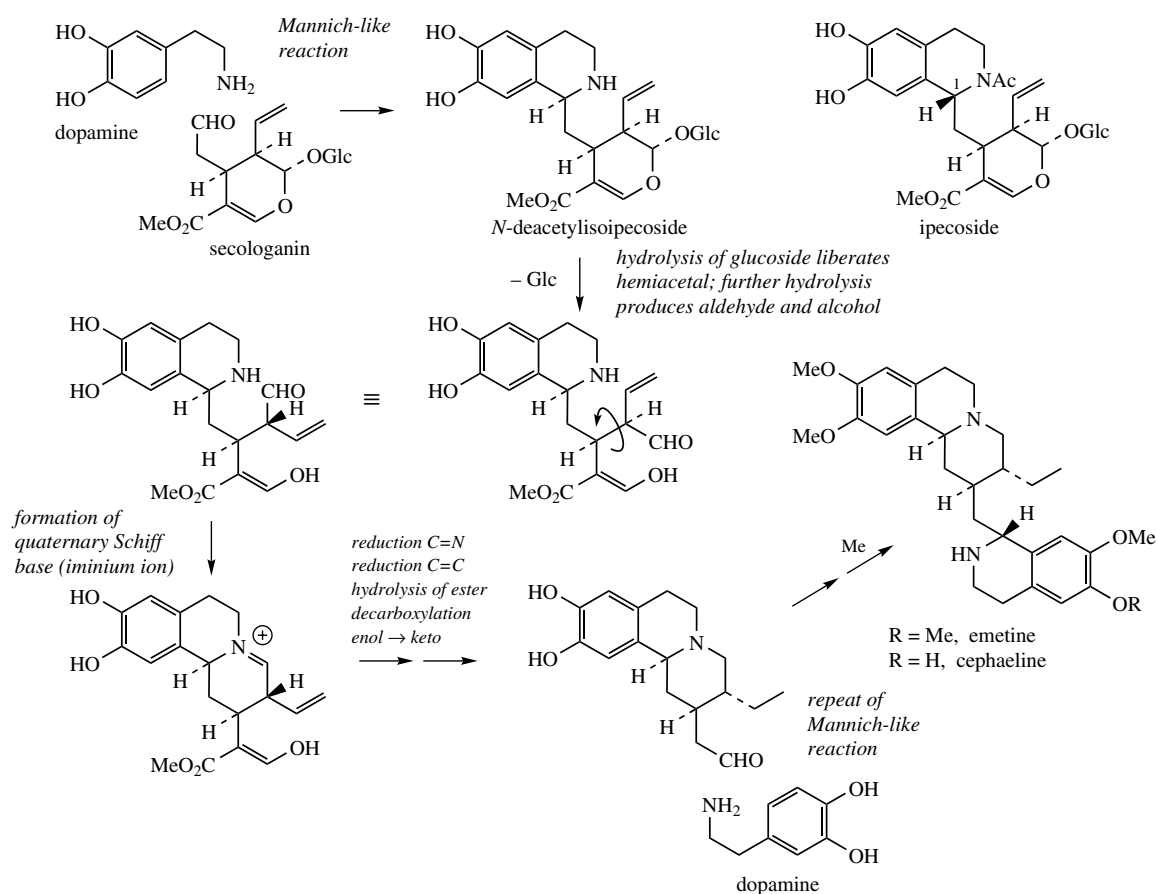
Figure 6.67

Ipecacuanha

Ipecacuanha or **ipecac** is derived from the dried rhizome and roots of *Cephaelis ipecacuanha* or *C. acuminata* (Rubiaceae). These are low straggling shrubs having horizontal rhizomes with prominently ridged roots. *Cephaelis ipecacuanha* yields what is termed Rio or Brazilian ipecac, and is cultivated mainly in Brazil, whilst *C. acuminata* gives Cartagena, Nicaragua, or Panama ipecac, and comes principally from Colombia and Nicaragua. Most of the commercial ipecac now derives from *C. acuminata*. Ipecac is an age-old remedy of the South American Indians, who used it for the treatment of dysentery. More recently it was mixed with powdered opium to give Dover's powder (see page 330), where the ipecac content functioned as a diaphoretic.

Ipecac contains 2–2.5% of alkaloids, the principal ones being emetine and cephaeline (Figure 6.67). Typically, in *C. ipecacuanha* the emetine to cephaeline ratio might be about 2:1, whereas in *C. acuminata* the ratio ranges from about 1:2 to 1:1. Minor alkaloids characterized include psychotrine and *O*-methylpsychotrine (Figure 6.68), which are dehydro variants of cephaeline and emetine respectively.

Both **emetine** and the synthetic **2,3-dehydroemetine** (Figure 6.68) have been useful as anti-amoebics, particularly in the treatment of amoebic dysentery. However, they also cause

(*Continued*)

R = Me, *O*-methylpsychotrine
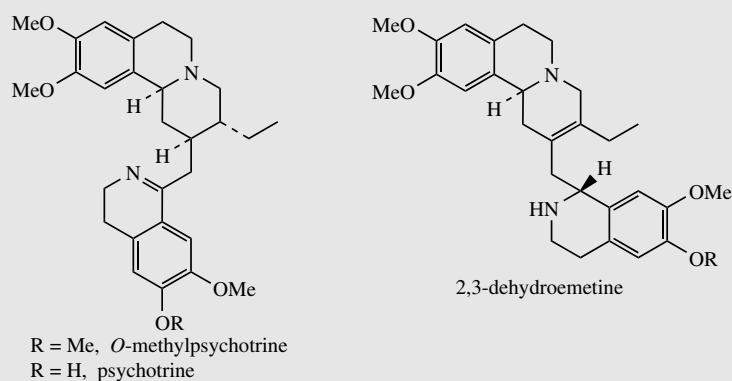R = H, psychotrine

2,3-dehydroemetine

Figure 6.68

nausea, and this has now made other drugs preferable. The emetic action of the alkaloids is particularly valuable though, and the crude drug extract in the form of **ipecacuanha emetic mixture** is an important preparation used for drug overdose or poisoning. The emetic mixture is often a standard component in poison antidote kits. Ipecacuanha also has expectorant activity and extracts are still components of a number of compound expectorant preparations. Emetine has more expectorant and less emetic action than cephaeline, and thus the Brazilian drug is preferred for such mixtures. If required, emetine may be obtained in larger amounts by also methylating the cephaeline component of the plant material.

Emetine and cephaeline are both potent inhibitors of protein synthesis, inhibiting at the translocation stage. They display antitumour and antiviral as well as antiamoebic activity, but are too toxic for therapeutic use. In recent studies, *O*-methylpsychotrine has displayed fairly low effects on protein synthesis, but a quite potent ability to curb viral replication through inhibition of HIV-reverse transcriptase. This may give it potential in the treatment of AIDS.

Amaryllidaceae Alkaloids

Various types of alkaloid structure are encountered in the daffodil family, the Amaryllidaceae, and they can be rationalized better through biosynthesis than by structural type. The alkaloids arise by alternative modes of oxidative coupling of precursors related to **norbelladine** (Figure 6.69), which is formed through combination of 3,4-dihydroxybenzaldehyde with tyramine, these two preursors arising from phenylalanine and tyrosine respectively. Three structural types of alkaloid can be related to **4′-*O*-methylnorbelladine** by different alignments of the phenol rings, allowing coupling *para–ortho* (A), *para–para* (B), or *ortho–para* (C) as shown in Figure 6.69. For **galanthamine**, the dienone formed via oxidative coupling (C) undergoes nucleophilic addition from the phenol group, forming an ether linkage

(compare opium alkaloids, page 328), and the sequence is completed by reduction and methylation reactions. For **lycorine** and **crinine**, although details are not given in Figure 6.69, it is apparent that the nitrogen atom acts as a nucleophile towards the dienone system in a similar manner, generating the new heterocyclic ring systems. Alkaloids such as lycorine, crinine, and galanthamine can undergo further modifications, which include ring cleavage reactions, generating many more variations than can be considered here. The Amaryllidaceae family includes *Amaryllis*, *Narcissus*, and *Galanthus*, and the alkaloid content of bulbs from most members makes these toxic. Lycorine was first isolated from *Lycorus radiata*, but is common and found throughout the family. **Galanthamine** from snowdrops (*Galanthus* species) is currently an important drug material of value in treating Alzheimer's disease.
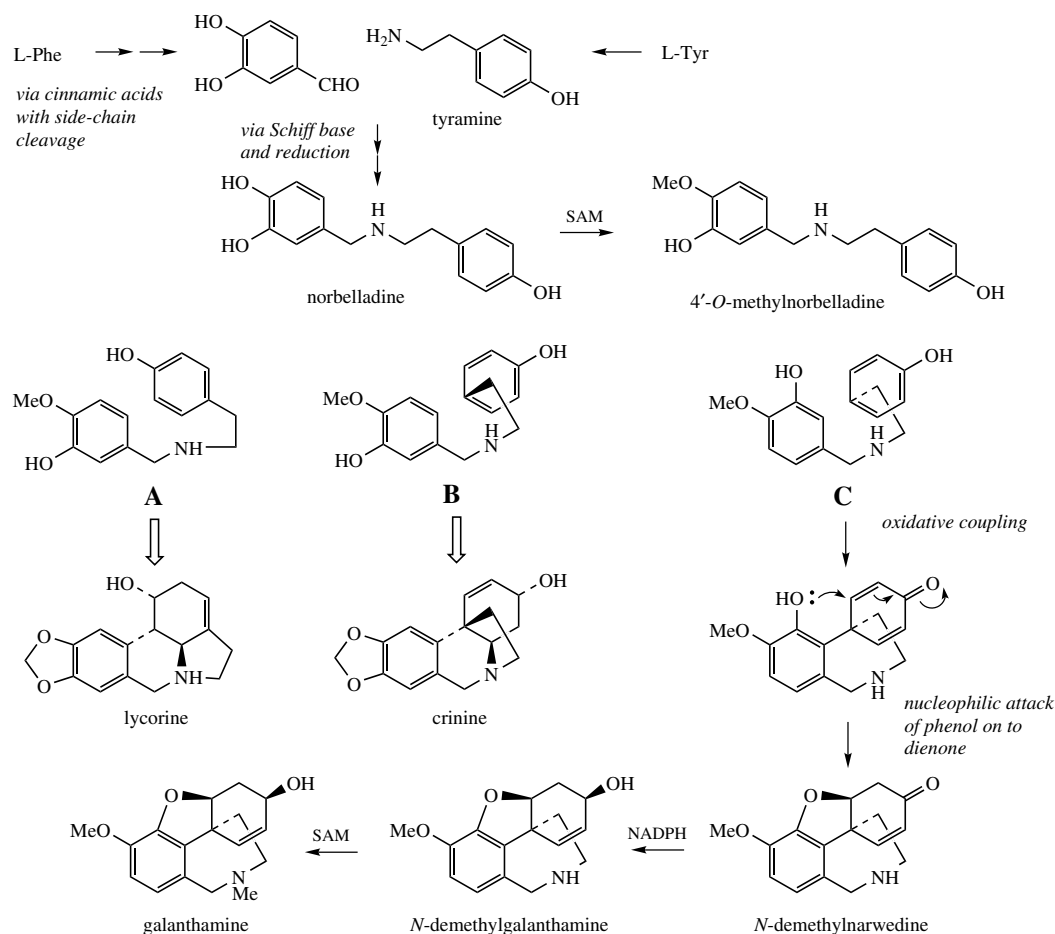
Figure 6.69

Galanthamine

Galantamine (galanthamine) can be isolated from a number of species of the Amaryllidaceae, including snowdrops (*Galanthus* species), daffodils (*Narcissus pseudonarcissus*), and snowflakes (*Leucojum* species), where typical content varies from about 0.05 to 0.2% in the bulbs. It is currently isolated for drug use from the bulbs of wild *Leucojum aestivum* and *Galanthus* species, since commercial synthesis is not economic. Galantamine acts as a competitive cholinesterase inhibitor, and enhances cognitive function in the treatment of Alzheimer's disease by raising acetylcholine levels in brain areas lacking cholinergic neurones. In common with other treatments for Alzheimer's disease, it does not cure the condition, but merely slows the rate of cognitive decline.

ALKALOIDS DERIVED FROM TRYPTOPHAN

L-**Tryptophan** is an aromatic amino acid containing an indole ring system, having its origins in the shikimate pathway (Chapter 4) via anthranilic acid. It acts as a precursor of a wide range of indole alkaloids, but there is also definite proof that major rearrangement reactions can convert the indole ring system into a quinoline ring, thus increasing further

the ability of this amino acid to act as an alkaloid precursor (see page 359).

Simple Indole Alkaloids

Tryptamine and its *N*-methyl and *N,N*-dimethyl derivatives (Figure 6.70) are widely distributed in plants, as are simple hydroxylated derivatives such as **5-hydroxytryptamine (serotonin)**. These are formed (Figure 6.70) by a series of decarboxylation, methylation, and hydroxylation reactions, though the sequences of these reactions are found to vary according to final product and/or

organism involved. 5-Hydroxytryptamine is also found in mammalian tissue, where it acts as a neurotransmitter in the central nervous system. It is formed from tryptophan by hydroxylation and then decarboxylation, paralleling the tyrosine → dopamine pathway (see page 316). In the formation of **psilocin** (Figure 6.70), decarboxylation precedes *N*-methylation, and hydroxylation occurs last. Phosphorylation of the hydroxyl in psilocin gives **psilocybin**. These two compounds are responsible for the hallucinogenic properties of so-called magic mushrooms, which include species of *Psilocybe**, *Panaeolus*, etc.
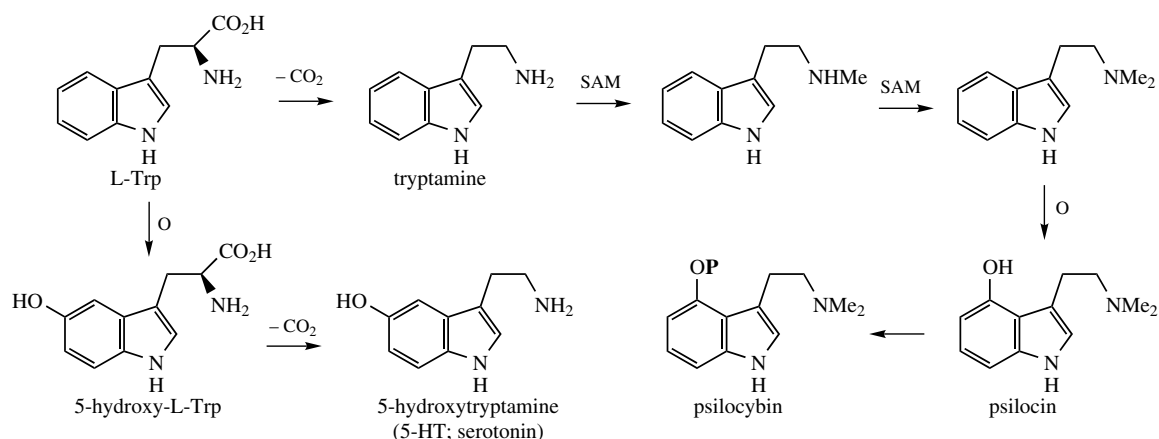

Figure 6.70

5-Hydroxytryptamine (Serotonin)

5-Hydroxytryptamine (5-HT, serotonin) is a monoamine neurotransmitter found in cardiovascular tissue, the peripheral nervous system, blood cells, and the central nervous system. It mediates many central and peripheral physiological functions, including contraction of smooth muscle, vasoconstriction, food intake, sleep, pain perception, and memory, a consequence of it acting on several distinct receptor types. Although 5-HT may be metabolized by monoamine oxidase, platelets and neurons possess a high affinity 5-HT reuptake mechanism. This mechanism may be inhibited by widely-prescribed antidepressant drugs termed selective serotonin re-uptake inhibitors (SSRIS), e.g. fluoxetine (Prozac®), thereby increasing levels of 5-HT in the CNS.

Migraine headaches that do not respond to analgesics may be relieved by the use of an agonist of the 5-HT$_1$ receptor, since these receptors are known to mediate vasoconstriction. Though the causes of migraine are not clear, they are characterized by dilation of cerebral blood vessels. 5-HT$_1$ agonists based on the 5-HT structure in current use include the sulphonamide derivative **sumatriptan**, and the more recent agents **naratriptan**, **rizatriptan**,
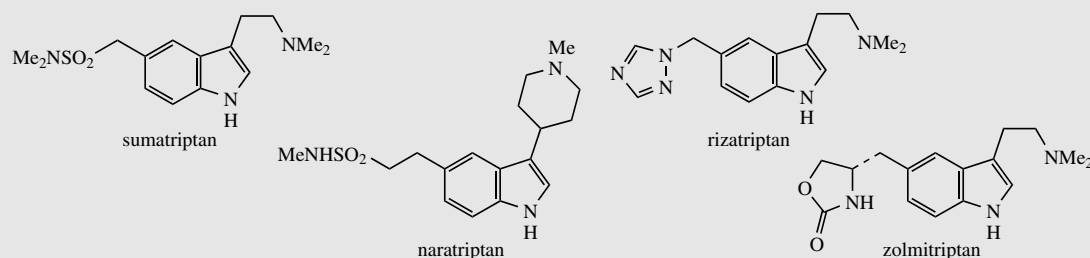
(Continues)

(*Continued*)

Figure 6.71

and **zolmitriptan** (Figure 6.71). These are of considerable value in treating acute attacks. Several of the ergot alkaloids (page 371) also interact with 5-HT receptors.

Psilocybe

The genus *Psilocybe* constitutes a group of small mushrooms with worldwide distribution. It has achieved notoriety on account of hallucinogenic experiences produced following ingestion of several species, particularly those from Mexico, and has led to the description 'magic mushrooms'. Over 80 species of *Psilocybe* have been found to be psychoactive, whereas over 50 species are inactive. More than 30 of the hallucinogenic species have been identified in Mexico, but active species may be found in all areas of the world. *Psilocybe mexicana* has been used by the Mexican Indians in ancient ceremonies for many years, and its history can be traced back to the Aztecs. In temperate regions, *Psilocybe semilanceata*, the liberty cap, is a common species with similar activity. All the psychoactive members of the genus are said to stain blue when the fresh tissue, particularly that near the base of the stalk, is damaged, though the converse is not true. Ingestion of the fungus causes visual hallucinations with rapidly changing shapes and colours, and different perceptions of space and time, the effects gradually wearing off and causing no lasting damage or addiction.

The active hallucinogens, present at about 0.3%, are the tryptamine derivatives psilocybin and psilocin (Figure 6.70), which are structurally related to the neurotransmitter 5-HT, thus explaining their neurological effects. Psilocybin is probably the main active ingredient, and to produce hallucinations a dose of some 6–20 mg is required. In addition to species of *Psilocybe*, these compounds may be found in some fungi from other genera, including *Conocybe*, *Panaeolus*, and *Stropharia*. Misidentification of fungi can lead to the consumers experiencing possible unwanted toxic effects, especially gastro-intestinal upsets, instead of the desired psychedelic visions.
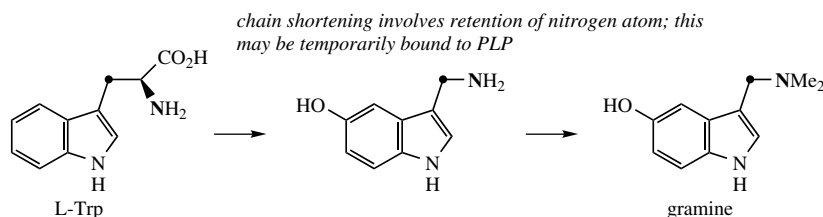

Figure 6.72

Gramine (Figure 6.72) is a simple amine found in barley (*Hordeum vulgare*; Graminae/Poaceae) and is derived from tryptophan by a biosynthetic pathway which cleaves off two carbon atoms, yet surprisingly retains the tryptophan nitrogen atom. Presumably, the nitrogen reacts with a cofactor, e.g. pyridoxal phosphate, and is subsequently transferred back to the indolemethyl group after the chain shortening.

Simple β-Carboline Alkaloids

Alkaloids based on a β-carboline system (Figure 6.73) exemplify the formation of a new six-membered heterocyclic ring using the ethylamine side-chain of tryptamine in a process analogous to generation of tetrahydroisoquinoline alkaloids (see page 320). Position 2 of the indole system is nucleophilic due to the adjacent nitrogen, and can participate in a Mannich/Pictet–Spengler type reaction,

attacking a Schiff base generated from tryptamine and an aldehyde (or keto acid) (Figure 6.73). Aromaticity is restored by subsequent loss of the C-2 proton. (It should be noted that the analogous chemical reaction actually involves nucleophilic attack from C-3, and then a subsequent rearrangement occurs to give bonding at C-2; there is no evidence yet for this type of process in biosynthetic pathways.) Extra carbons are supplied by aldehyes or keto acids, according to the complexity of the substrate (compare tetrahydroisoquinoline alkaloids, page 321). Thus, complex β-carbolines, e.g. the terpenoid indole alkaloid ajmalicine (see page 351), are produced by a pathway using an aldehyde such as secologanin. Simpler structures employ keto acids, e.g. **harmine** (Figure 6.74) incorporates two extra carbons from pyruvate. In such a case, an acid is an intermediate, and oxidative decarboxylation gives the dihydro-β-carboline, from which reduced
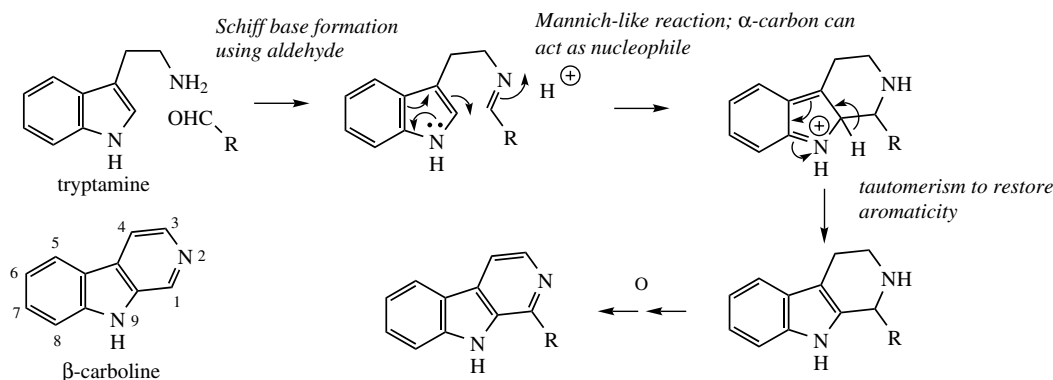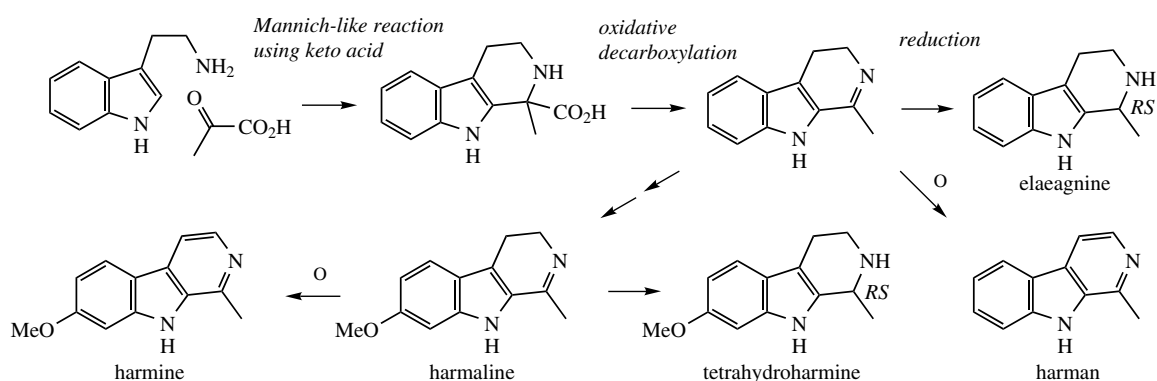

Figure 6.73

Figure 6.74

tetrahydro-β-carboline structures, e.g. **elaeagnine** from *Elaeagnus angustifolia* (Elaeagnaceae), or fully aromatic β-carboline structures, e.g. **harman** and **harmine** from *Peganum harmala* (Zygophyllaceae) are derived (Figure 6.74). The methoxy substitution in the indole system of harmine is introduced at some stage in the pathway by successive hydroxylation and methylation reactions. A sequence from 6-hydroxytryptamine is also feasible. The reported psychoactive properties of the plants *Peganum harmala* and *Banisteriopsis caapi* (Malpighiaceae) is due to the β-carboline alkaloids such as harmine, harmaline, and tetrahydroharmine (Figure 6.74).

Terpenoid Indole Alkaloids

More than 3000 terpenoid indole alkaloids are recognized, making this one of the major groups of alkaloids in plants. They are found mainly in

eight plant families, of which the Apocynaceae, the Loganiaceae, and the Rubiaceae provide the best sources. In terms of structural complexity, many of these alkaloids are quite outstanding, and it is a tribute to the painstaking experimental studies of various groups of workers that we are able to rationalize these structures in terms of their biochemical origins. In virtually all structures, a tryptamine portion can be recognized. The remaining fragment is usually a C_9 or C_{10} residue, and three main structural types are discernable. These are termed the *Corynanthe* type, as in **ajmalicine** and **akuammicine**, the *Aspidosperma* type, as in **tabersonine**, and the *Iboga* type, exemplified by **catharanthine** (Figure 6.75). The C_9 or C_{10} fragment was shown to be of terpenoid origin, and the secoiridoid **secologanin** (see page 189) was identified as the terpenoid derivative, which initially combined with the tryptamine portion of the molecule. Furthermore, the *Corynanthe*, *Aspidosperma*, and *Iboga* groups of alkaloids could
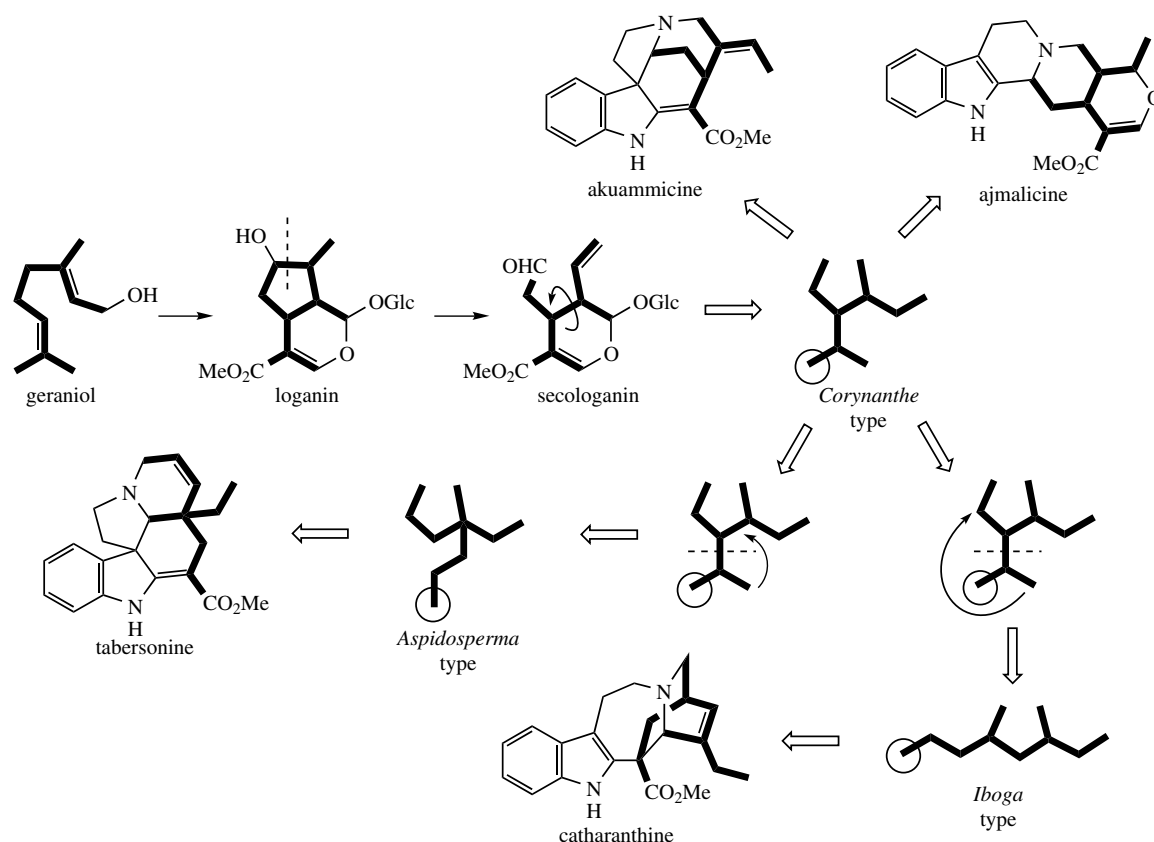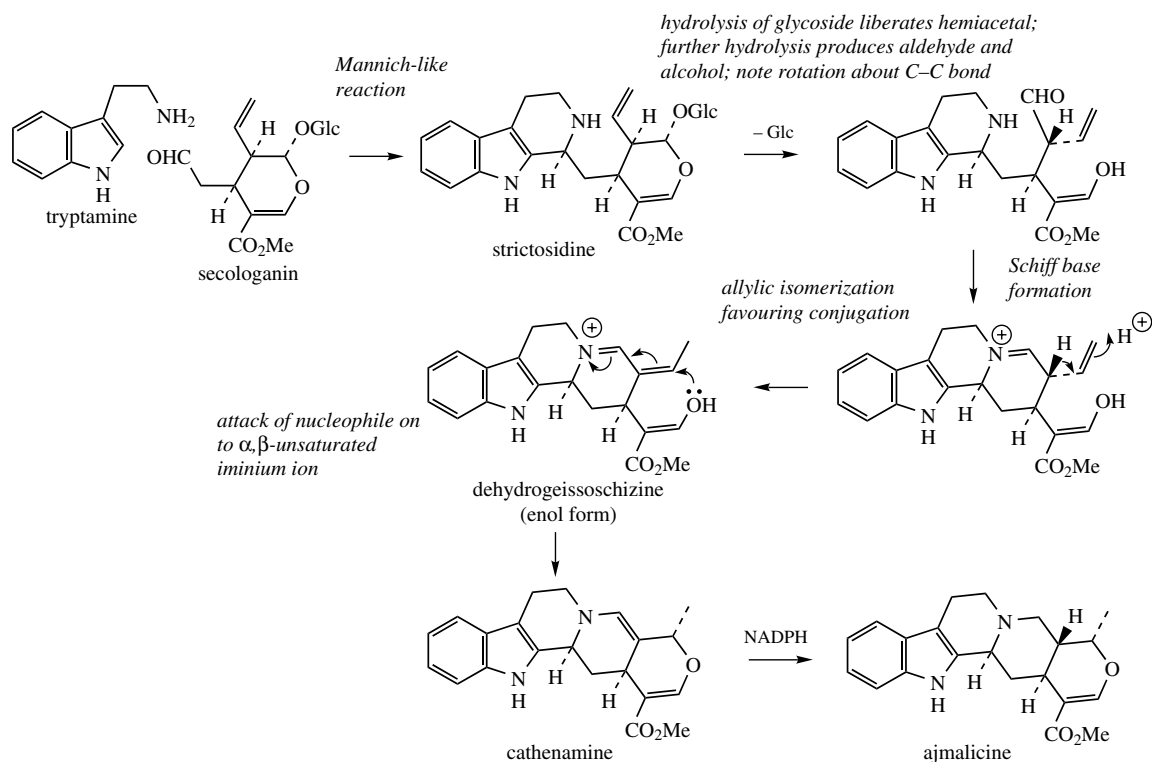

Figure 6.75

Figure 6.76

be related and rationalized in terms of rearrangements occurring in the terpenoid part of the structures (Figure 6.75). Secologanin itself contains the ten-carbon framework typical of the *Corynanthe* group. The *Aspidosperma* and *Iboga* groups could then arise by rearrangement of the *Corynanthe* skeleton as shown. This is represented by detachment of a three-carbon unit, which is then rejoined to the remaining C_7 fragment in one of two different ways. Where C_9 terpenoid units are observed, the alkaloids normally appear to have lost the carbon atom indicated in the circle. This corresponds to the carboxylate function of secologanin and its loss by hydrolysis/decarboxylation is now understandable.

The origins of loganin and secologanin have already been discussed in Chapter 5 (see page 189). Condensation of secologanin with tryptamine in a Mannich-like reaction generates the tetrahydro-β-carboline system and produces **strictosidine** (Figure 6.76). Hydrolysis of the glycoside function allows opening of the hemiacetal, and exposure of an aldehyde group, which can react with

the secondary amine function giving a quaternary Schiff base. These reactions are also seen in the pathway to ipecac alkaloids (see page 343). Allylic isomerization, moving the vinyl double bond into conjugation with the iminium generates **dehydrogeissoschizine**, and cyclization to **cathenamine** follows. Cathenamine is reduced to **ajmalicine** in the presence of NADPH.

Carbocyclic variants related to ajmalicine such as **yohimbine** are likely to arise from dehydrogeissoschizine by the mechanism indicated in Figure 6.77. Yohimbine is found in Yohimbe bark (*Pausinystalia yohimbe*; Rubiaceae) and Aspidosperma bark (*Aspidosperma* species; Apocynaceae) and has been used in folk medicine as an aphrodisiac. It does have some pharmacological activity and is known to dilate blood vessels. More important examples containing the same carbocyclic ring system are the alkaloids found in species of *Rauwolfia**, especially *R. serpentina* (Apocynaceae). **Reserpine** and **deserpidine** (Figure 6.78) are trimethoxybenzoyl esters of yohimbine-like alkaloids, whilst **rescinnamine** is
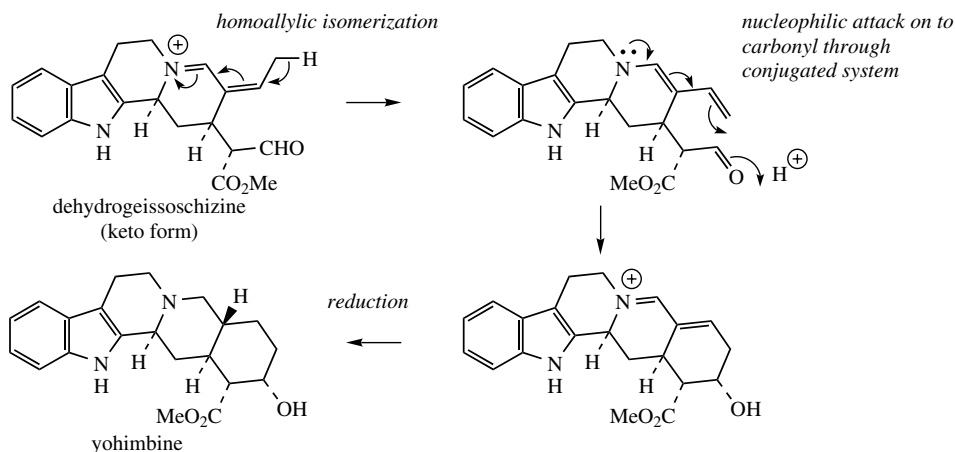
homoallylic isomerization

nucleophilic attack on to carbonyl through conjugated system

dehydrogeissoschizine
(keto form)

reduction

yohimbine

Figure 6.77

R = OMe, reserpine
R = H, deserpidine
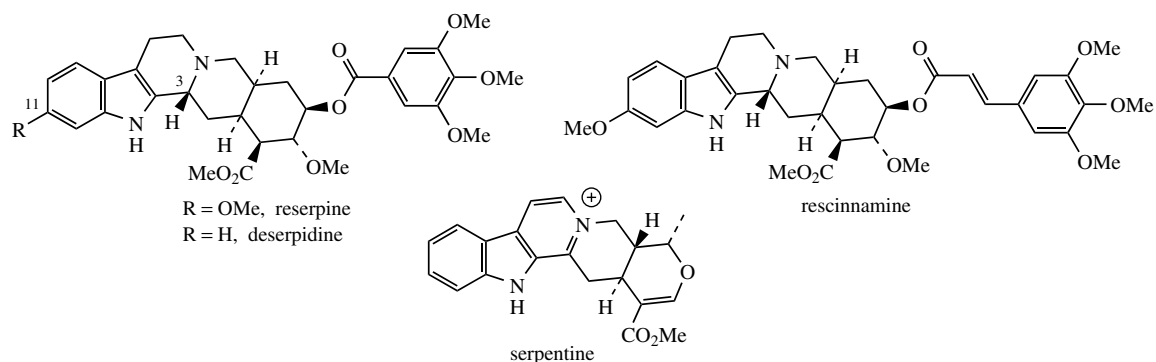
rescinnamine

serpentine

Figure 6.78

Rauwolfia

Rauwolfia has been used in Africa for hundreds of years, and in India for at least 3000 years. It was used as an antidote to snake-bite, to remove white spots in the eyes, against stomach pains, fever, vomiting, and headache, and to treat insanity. It appeared to be a universal panacea, and was not considered seriously by Western scientists until the late 1940s/early 1950s. Clinical tests showed the drug to have excellent antihypertensive and sedative activity. It was then rapidly and extensively employed in treating high blood pressure and to help mental conditions, relieving anxiety and restlessness, and thus initiating the tranquillizer era. The 'cure for insanity' was thus partially justified, and rauwolfia was instrumental in showing that mental disturbance has a chemical basis and may be helped by the administration of drugs.

Rauwolfia is the dried rhizome and roots of *Rauwolfia* (sometimes *Rauvolfia*) *serpentina* (Apocynaceae) or snakeroot, a small shrub from India, Pakistan, Burma, and Thailand. Other species used in commerce include *R. vomitoria* from tropical Africa, a small tree whose leaves after ingestion cause violent vomiting, and *R. canescens* (= *R. tetraphylla*) from India and the

Caribbean. Most of the drug material has been collected from the wild. *Rauwolfia serpentina* contains a wide range of indole alkaloids, totalling 0.7–2.4%, though only 0.15–0.2% consists of desirable therapeutically active compounds, principally reserpine, rescinnamine, and deserpidine (Figure 6.78). Other alkaloids of note are serpentine (Figure 6.78), ajmalicine (Figure 6.76), and ajmaline (see Figure 6.82). Reserpine and deserpidine are major alkaloids in *R. canescens*, and *R. vomitoria* contains large amounts of rescinnamine and reserpine.

Reserpine and **deserpidine** (Figure 6.78) have been widely used as antihypertensives and mild tranquillizers. They act by interfering with catecholamine storage, depleting levels of available neurotransmitters. Prolonged use of the pure alkaloids, reserpine in particular, has been shown to lead to severe depression in some patients, a feature not so prevalent when the powdered root was employed. The complex nature of the alkaloidal mixture means the medicinal action is somewhat different from that of reserpine alone. Accordingly, crude powdered rauwolfia remained an important drug for many years, and selected alkaloid fractions from the crude extract have also been widely used. The alkaloids can be fractionated according to basicity. Thus, serpentine and similar structures are strongly basic, whilst reserpine, rescinnamine, deserpidine and ajmalicine are weak bases. Ajmaline and related compounds have intermediate basicity.

The rauwolfia alkaloids are now hardly ever prescribed in the UK, either as antihypertensives or as tranquillizers. Over a period of a few years, they have been rapidly superseded by synthetic alternatives. Reserpine has also been suggested to play a role in the promotion of breast cancers. Both **ajmalicine** (= raubasine) (Figure 6.76) and **ajmaline** (Figure 6.82) are used clinically in Europe, though not in the UK. Ajmalicine is employed as an antihypertensive, whilst ajmaline is of value in the treatment of cardiac arrhythmias. Ajmalicine is also extracted commercially from *Catharanthus roseus* (see page 357).

a trimethoxycinnamoyl ester. Both reserpine and rescinnamine contain an additional methoxyl substituent on the indole system at position 11, the result of hydroxylation and methylation at a late stage in the pathway. A feature of these alkaloids is that they have the opposite stereochemistry at position 3 to yohimbine and strictosidine. *Rauwolfia serpentina* also contains significant amounts of ajmalicine (Figure 6.76), emphasizing the structural and biosynthetic relationships between the two types of alkaloid.

The structural changes involved in converting the *Corynanthe* type skeleton into those of the *Aspidosperma* and *Iboga* groups are quite complex, and are summarized in Figure 6.79. Early intermediates are alkaloids such as **preakuammicine**, which, although clearly of the *Corynanthe* type, is sometimes designated as *Strychnos* type (compare strychnine, page 358). This is because the *Corynanthe* terpenoid unit, originally attached to the indole α-carbon, is now bonded to the β-carbon, and a new bonding between the rearrangeable C_3 unit and C-α is in place. **Stemmadenine** arises through fission

of the bond to C-β, and then further fission yields a hypothetical intermediate, the importance of which is that the rearrangeable C_3 unit has been cleaved from the rest of the terpenoid carbons. Alkaloids of the *Aspidosperma* type, e.g. **tabersonine** and **vindoline**, and *Iboga* type, e.g. **catharanthine**, then arise from this intermediate by different bonding modes (Figure 6.79).

Many of the experimental studies that have led to an understanding of terpenoid indole alkaloid biosynthesis have been carried out using plants of the Madagascar periwinkle (*Catharanthus roseus**, formerly *Vinca rosea*; Apocynaceae). Representatives of all the main classes of these alkaloids are produced, including **ajmalicine** (*Corynanthe*), **catharanthine** (*Iboga*), and **vindoline** (*Aspidosperma*). The sequence of alkaloid formation has been established initially by noting which alkaloids become labelled as a feeding experiment progresses, and more recently by appropriate enzymic studies. However, the extensive investigations of the *Catharanthus roseus* alkaloids have also been prompted by the anticancer activity
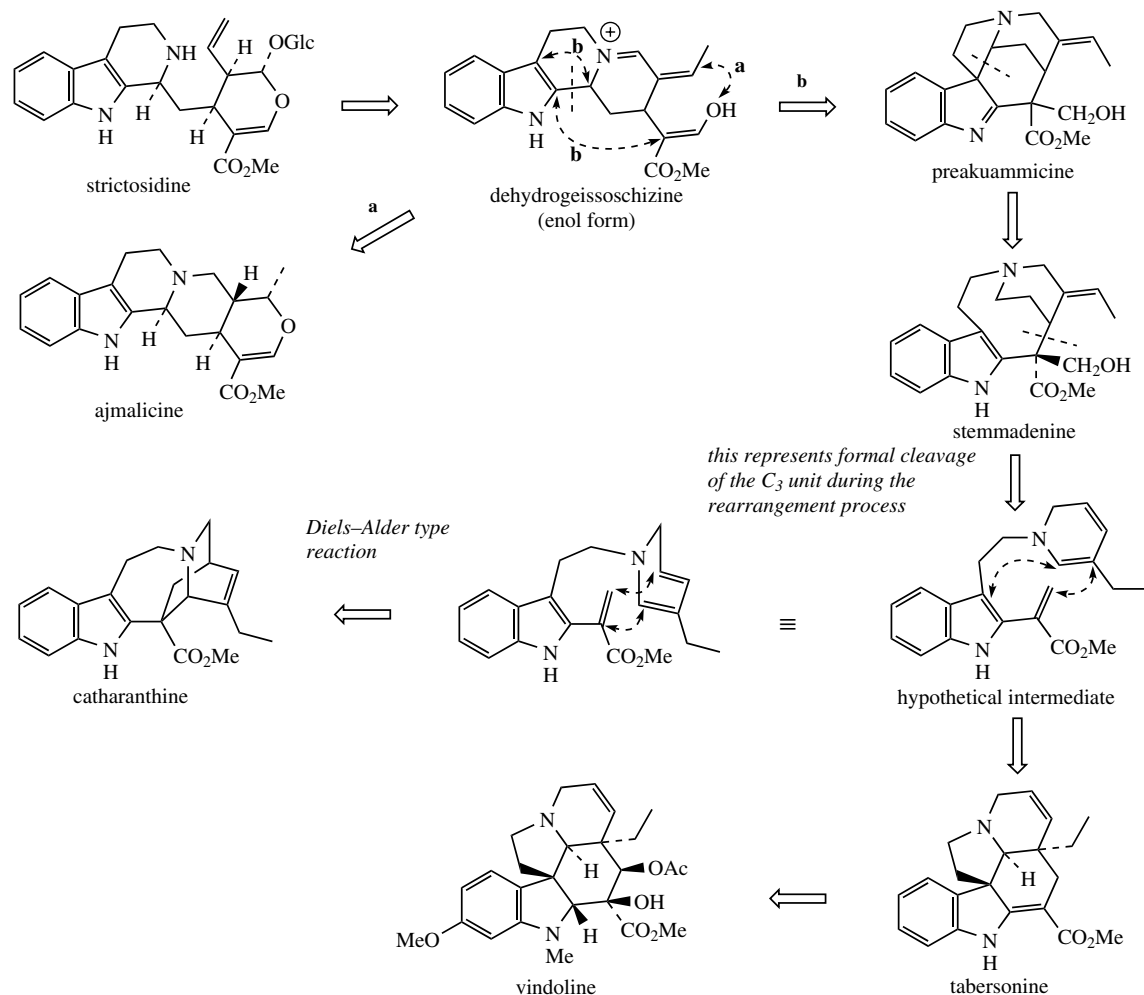
Figure 6.79

detected in a group of bisindole alkaloids. Two of these, **vinblastine** and **vincristine** (Figure 6.80), have been introduced into cancer chemotherapy and feature as some of the most effective anticancer agents available. These structures are seen to contain the elements of catharanthine and vindoline, and, indeed, they are derived by coupling of these two alkaloids. The pathway is believed to involve firstly an oxidative reaction on **catharanthine**, catalysed by a peroxidase, generating a peroxide which loses the peroxide as a leaving group, breaking a carbon–carbon bond as shown (Figure 6.81). This intermediate electrophilic ion is attacked by the nucleophilic vindoline, C-5 of the indole nucleus being suitably activated by the OMe at C-6 and also by the indole nitrogen. The adduct

is then reduced in the dihydropyridinium ring by NADH-dependent 1,4-addition, giving the substrate for hydroxylation. Finally, reduction yields **vinblastine**. **Vincristine**, with its *N*-formyl group rather than *N*-methyl on the vindoline fragment, may be an oxidized product from vinblastine.

Further variants on the terpenoid indole alkaloid skeleton (Figure 6.82) are found in **ibogaine** from *Tabernanthe iboga**, **vincamine** from *Vinca minor*, and **ajmaline** from *Rauwolfia serpentina*. Ibogaine is simply a C_9 *Iboga* type alkaloid, but is of interest as an experimental drug to treat heroin addiction. In a number of European countries, vincamine is used clinically as a vasodilator to increase cerebral blood flow in cases of senility, and ajmaline for cardiac arrhythmias. Ajmaline
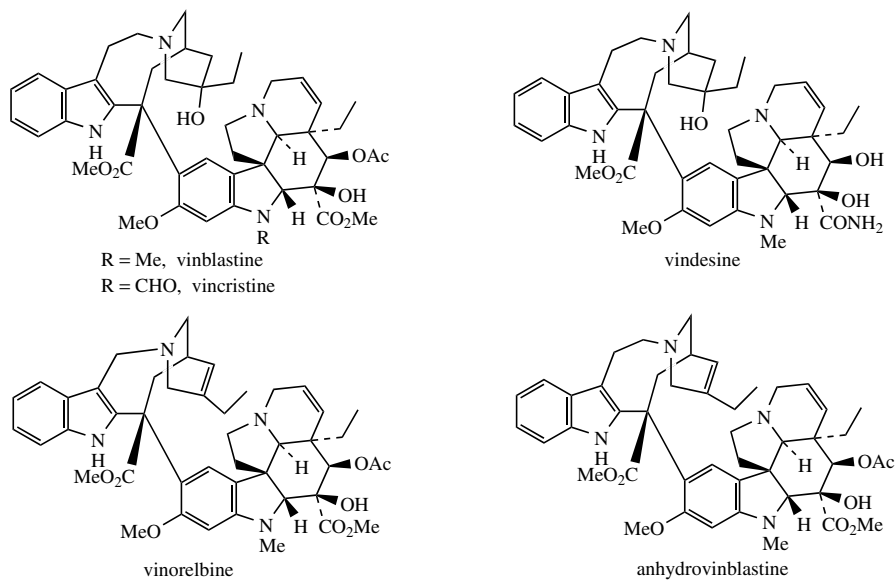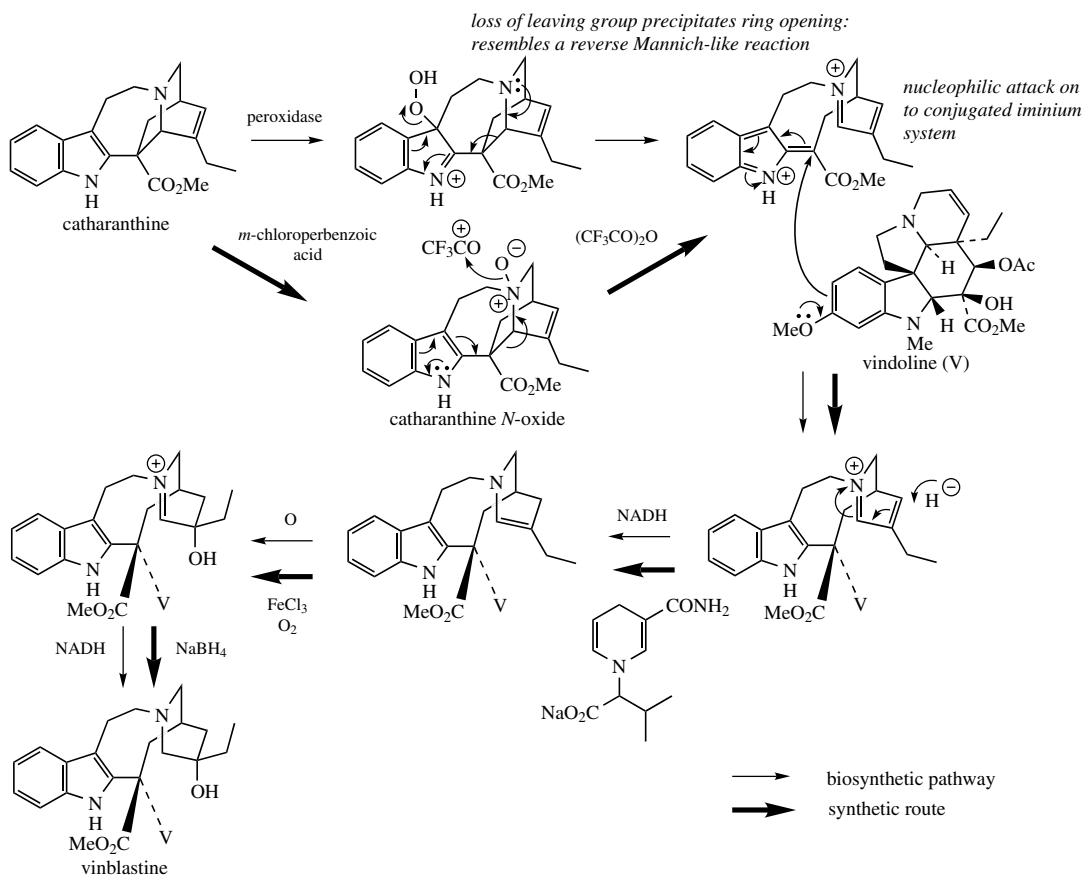
Figure 6.80

Figure 6.81

Catharanthus

The Madagascar periwinkle *Catharanthus roseus* (= *Vinca rosea*) (Apocynaceae) is a small herb or shrub originating in Madagascar, but now common in the tropics and widely cultivated as an ornamental for its shiny dark green leaves and pleasant five-lobed flowers. Drug material is now cultivated in many parts of the world, including the USA, Europe, India, Australia, and South America.

Because of its folklore usage as a tea for diabetics, the plant was originally investigated for potential hypoglycaemic activity. Although plant extracts had no effects on blood sugar levels in rabbits, the test animals succumbed to bacterial infection due to depleted white blood cell levels (leukopenia). The selective action suggested anticancer potential for the plant, and an exhaustive study of the constituents was initiated. The activity was found in the alkaloid fraction, and more than 150 alkaloids have been characterized in the plant. These are principally terpenoid indole alkaloids, many of which are known in other plants, especially from the same family. Useful antitumour activity was demonstrated in a number of dimeric indole alkaloid structures (more correctly bis-indole alkaloids), including vincaleukoblastine, leurosine, leurosidine, and leurocristine. These compounds became known as vinblastine, vinleurosine, vinrosidine, and vincristine respectively, the vin- prefix being a consequence of the earlier botanical nomenclature *Vinca rosea*, which was commonly used at that time. The alkaloids vinblastine and vincristine (Figure 6.80) were introduced into cancer chemotherapy and have proved to be extremely valuable drugs.

Despite the minor difference in structure between vinblastine and vincristine, a significant difference exists in the spectrum of human cancers that respond to the drugs. **Vinblastine** (Figure 6.80) is used mainly in the treatment of Hodgkin's disease, a cancer affecting the lymph glands, spleen, and liver. **Vincristine** (Figure 6.80) has superior antitumour activity compared to vinblastine but is more neurotoxic. It is clinically more important than vinblastine, and is especially useful in the treatment of childhood leukaemia, giving a high rate of remission. Some other cancer conditions, including lymphomas, small cell lung cancer, and cervical and breast cancers, also respond favourably. The alkaloids need to be injected, and both generally form part of a combination regimen with other anticancer drugs. **Vindesine** (Figure 6.80) is a semi-synthetic derivative of vinblastine, which has been introduced for the treatment of acute lymphoid leukaemia in children. **Vinorelbine** (Figure 6.80), an anhydro derivative of 8′-norvinblastine, is a newer semi-synthetic modification obtained from anhydrovinblastine (Figure 6.80), where the indole.C_2N bridge in the catharanthine-derived unit has been shortened by one carbon. It is orally active and has a broader anticancer activity yet with lower neurotoxic side-effects than either vinblastine or vincristine. These compounds all inhibit cell mitosis, acting by binding to the protein tubulin in the mitotic spindle, preventing polymerization into microtubules, a mode of action shared with other natural agents, e.g. colchicine (see page 343) and podophyllotoxin (see page 136).

A major problem associated with the clinical use of vinblastine and vincristine is that only very small amounts of these desirable alkaloids are present in the plant. Although the total alkaloid content of the leaf can reach 1% or more, over 500 kg of catharanthus is needed to yield 1 g of vincristine. This yield (0.0002%) is the lowest of any medicinally important alkaloid isolated on a commercial basis. Extraction is both costly and tedious, requiring large quantities

(*Continues*)

(Continued)

of raw material and extensive use of chromatographic fractionations. The growing importance of vincristine relative to vinblastine as drugs is not reflected in the plant, which produces a much higher proportion of vinblastine. Fortunately, it is possible to convert vinblastine into vincristine by controlled chromic acid oxidation or via a microbiological *N*-demethylation using *Streptomyces albogriseolus*. Considerable effort has been expended on the semi-synthesis of the 'dimeric' alkaloids from 'monomers' such as catharanthine and vindoline, which are produced in *C. roseus* in much larger amounts. Efficient, stereospecific coupling has eventually been achieved, and it is now possible to convert catharanthine and vindoline into vinblastine in about 40% yield. The process used is a biomimetic one, virtually identical to the suggested biosynthetic process, and is also included in Figure 6.81. Catharanthine-*N*-oxide is employed instead of the peroxidase-generated peroxide, and this couples readily in trifluoroacetic anhydride with vindoline in almost quantitative yield. Subsequent reduction, oxidation, and reduction steps then give vinblastine via the same 'biosynthetic' intermediates. It is particularly interesting that the most effective reducing agents for the transformation of the dihydropyridinium compound into the tetrahydropyridine were *N*-substituted 1,4-dihydronicotinamides, simpler analogues of NADH, the natural reducing agent. Excellent yields of anhydrovinblastine (the starting material for vinorelbine production) (Figure 6.80) can also be obtained by electrochemical oxidation of catharanthine/vindoline. These syntheses should improve the supply of these alkaloids and derivatives, and also allow more detailed studies of structure–activity relationships to be undertaken. This group of compounds is still of very high interest, and development programmes for analogues continue.

Ajmalicine (see rauwolfia, page 353) is present in the roots of *Catharanthus roseus* at a level of about 0.4%, and this plant is used as a commercial source in addition to *Rauwolfia serpentina*.

Iboga

The *Iboga* group of terpenoid indole alkaloids takes its name from *Tabernanthe iboga* (Apocynaceae), a shrub from the Congo and other parts of equatorial Africa. Extracts from the root bark of this plant have long been used by indigenous people in rituals, to combat fatigue, and as an aphrodisiac. The root bark contains up to 6% indole alkaloids, the principal component of which is ibogaine (Figure 6.82). Ibogaine is a CNS stimulant, and is also psychoactive. In large doses, it can cause paralysis and respiratory arrest. Ibogaine is of interest as a potential drug for relieving heroin craving in drug addicts. Those who use the drug experience hallucinations from the ibogaine, but it is claimed they emerge from this state with a significantly reduced opiate craving. A number of deaths resulting from the unsupervised use of ibogaine has led to its being banned in some countries.

contains a C_9 *Corynanthe* type unit and its relationship to **dehydrogeissoschizine** is indicated in Figure 6.82. Vincamine still retains a C_{10} *Aspidosperma* unit, and it originates from **tabersonine** by a series of reactions that involve cleavage of bonds to both α and β positions of the indole (Figure 6.82).

Alkaloids like **preakuammicine** (Figure 6.79) and **akuammicine** (Figure 6.75) contain the C_{10} and C_9 *Corynanthe* type terpenoid units respectively. They are, however, representatives of a subgroup of *Corynanthe* alkaloids termed the *Strychnos* type because of their structural similarity to many of the alkaloids found in *Strychnos*
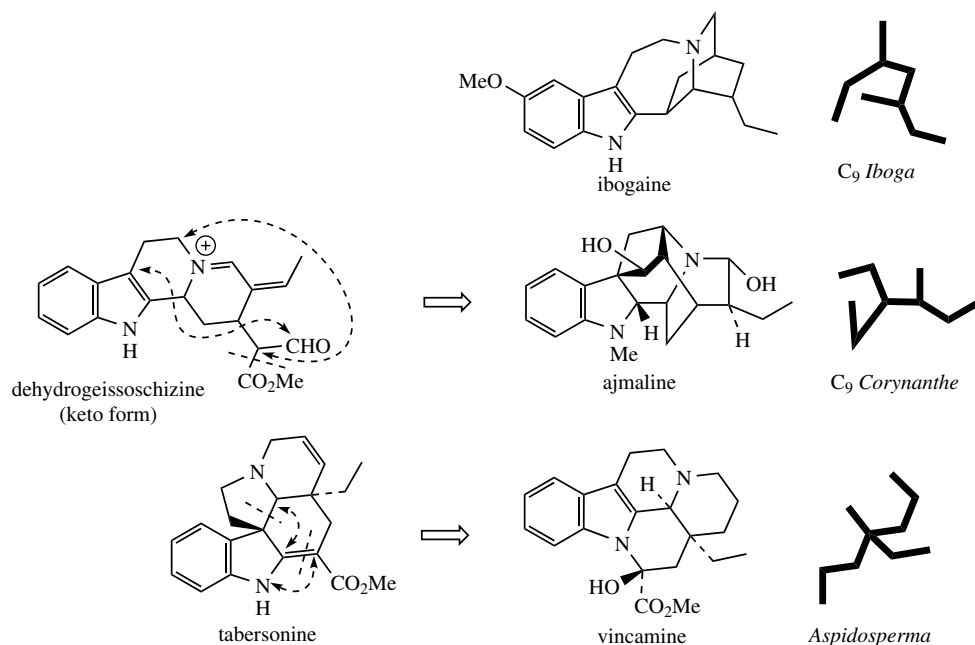
ibogaine

C_9 *Iboga*

dehydrogeissoschizine
(keto form)

ajmaline

C_9 *Corynanthe*

tabersonine

vincamine

Aspidosperma

Figure 6.82

preakuammicine

Wieland–Gumlich aldehyde

acetyl-CoA

*aldol reaction with
acetyl-CoA*

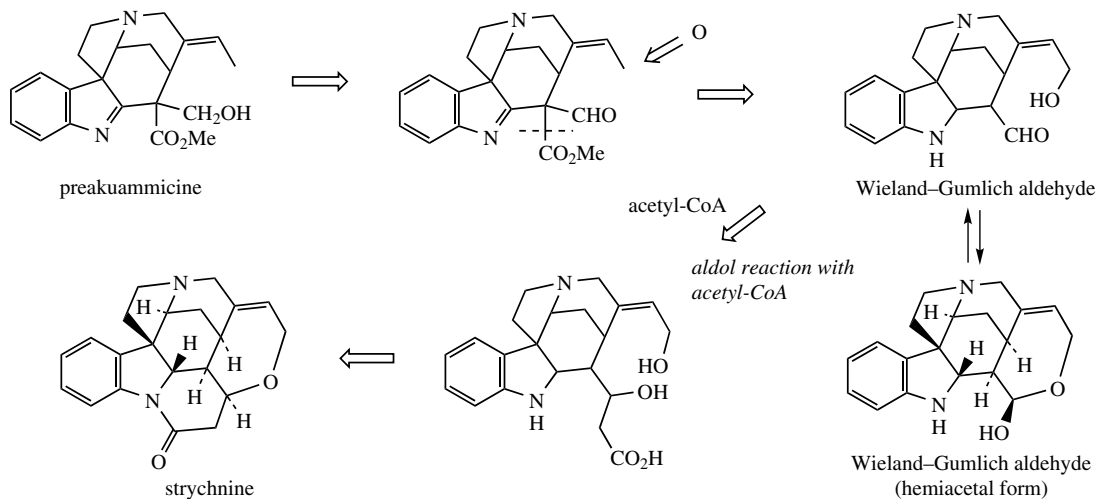strychnine

Wieland–Gumlich aldehyde
(hemiacetal form)

Figure 6.83

species (Loganiaceae), e.g. *S. nux-vomica**, note-worthy examples being the extremely poisonous **strychnine** (Figure 6.83) and its dimethoxy ana-logue **brucine** (Figure 6.84). The non-tryptamine portion of these compounds contains 11 carbons, and is constructed from an iridoid-derived C_9 unit, plus two further carbons supplied from acetate. The pathway to **strychnine** in Figure 6.83 involves loss

of one carbon from a preakuammicine-like struc-ture via hydrolysis/decarboxylation and then addi-tion of the extra two carbons by aldol condensation with the formyl group, complexed as a hemiacetal in the so-called Wieland–Gumlich aldehyde. The subsequent formation of strychnine from this hemi-acetal is merely construction of ether and amide linkages.

Nux-vomica

Nux-vomica consists of the dried ripe seeds of *Strychnos nux-vomica* (Loganiaceae), a small tree found in a wide area of East Asia extending from India to Northern Australia. The fruit is a large berry with a hard coat and a pulpy interior containing three to five flattish grey seeds. These seeds contain 1.5–5% of alkaloids, chiefly strychnine (about 1.2%) and brucine (about 1.6%) (Figure 6.82). **Strychnine** is very toxic, affecting the CNS and causing convulsions. This is a result of binding to receptor sites in the spinal cord that normally accommodate glycine. Fatal poisoning (consumption of about 100 mg by an adult) would lead to asphyxia following contraction of the diaphragm. It has found use as a vermin killer, especially for moles. Its only medicinal use is in very small doses as an appetite stimulant and general tonic, sometimes with iron salts if the patient is anaemic. Brucine is considerably less toxic. Both compounds have been regularly used in synthetic chemistry as optically active bases to achieve optical resolution of racemic acids. Seeds of the related *Strychnos ignatii* have also served as a commercial source of strychnine and brucine.

Of biochemical interest is the presence of quite significant amounts (up to 5%) of the iridoid glycoside loganin (see page 188) in the fruit pulp of *Strychnos nux-vomica*. This compound is, of course, an intermediate in the biosynthesis of strychnine and other terpenoid indole alkaloids.
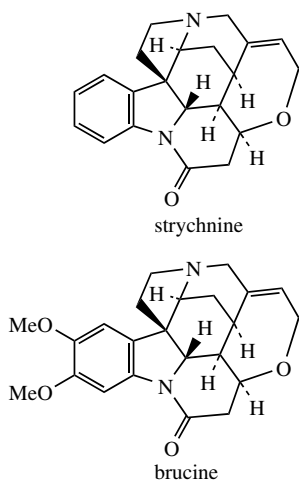

Figure 6.84

The arrow poison curare, when produced from *Chondrodendron* species (Menispermaceae), contains principally the bis-benzyltetrahydroisoquinoline alkaloid tubocurarine (see page 324). Species of *Strychnos*, especially *S. toxifera*, are employed in making loganiaceous curare, and biologically active alkaloids isolated from such preparations have been identified as a series of toxiferines, e.g. **C-toxiferine** (Figure 6.85). The structures appear remarkably complex, but may be envisaged as a combination of two Wieland–Gumlich aldehyde-like molecules (Figure 6.85). The presence of two quaternary nitrogens, separated by an appropriate distance, is responsible for the curare-like activity (compare tubocurarine and synthetic analogues, page 326). **Alcuronium** (Figure 6.85) is a semi-synthetic skeletal muscle relaxant produced from C-toxiferine (see curare, page 327).

Ellipticine* (Figure 6.86) contains a pyridocarbazole skeleton, which is also likely to be formed from a tryptamine–terpenoid precursor. Although little evidence is available, it is suggested that a precursor like **stemmadenine** may undergo transformations that effectively remove the two-carbon bridge originally linking the indole and the nitrogen in tryptamine (Figure 6.86). The remaining C_9 terpenoid fragment now containing the tryptamine nitrogen can then be used to generate the rest of the skeleton. Ellipticine is found in *Ochrosia elliptica* (Apocynaceae) and related species and has useful anticancer properties.

Quinoline Alkaloids

Some of the most remarkable examples of terpenoid indole alkaloid modifications are to be found in the genus *Cinchona** (Rubiaceae), in the alkaloids **quinine**, **quinidine**, **cinchonidine**,
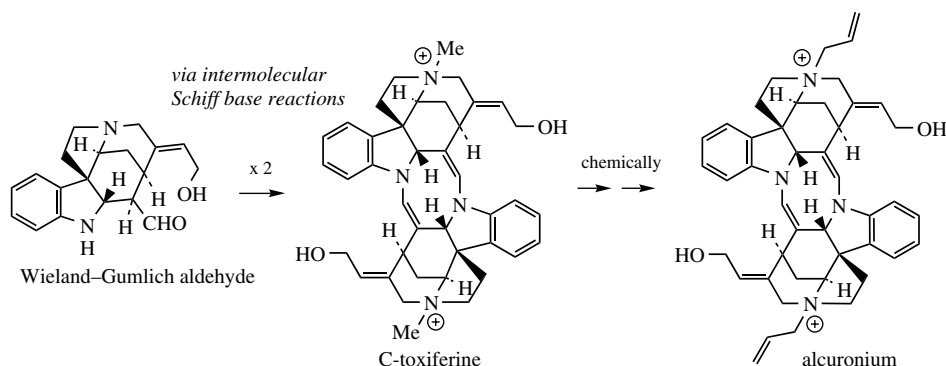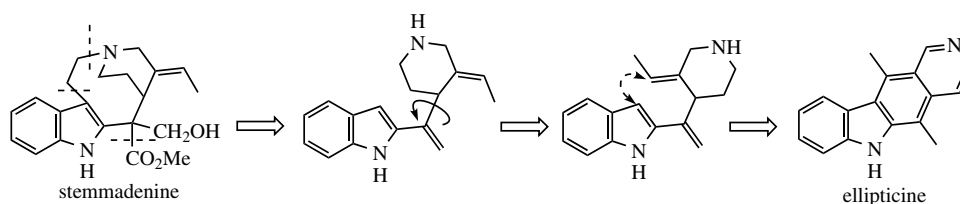
via intermolecular Schiff base reactions

x 2

chemically

Wieland–Gumlich aldehyde

C-toxiferine

alcuronium

Figure 6.85

stemmadenine

ellipticine

Figure 6.86

Ellipticine

Ellipticine (Figure 6.86) and related alkaloids, e.g. 9-methoxyellipticine (Figure 6.87), are found in the bark of *Ochrosia elliptica* (Apocynaceae) and other *Ochrosia* species. Clinical trials with these alkaloids and a number of synthetic analogues showed them to be potent inhibitors of several cancerous disorders, but pre-clinical toxicology indicated a number of side-effects, including haemolysis and cardiovascular effects. Ellipticines are planar molecules that intercalate between the base pairs of DNA and cause a partial unwinding of the helical array. There is a some correlation between the degree of unwinding and the biological properties, those showing the largest unwinding inhibiting the greatest number of cancerous cells. Recent research suggests there may be more than one mechanism of action, however. Ellipticine is oxidized *in vivo* mainly to 9-hydroxyellipticine, which has an increased activity, and it is believed that this may in fact be the active agent. Poor water-solubility of ellipticine and derivatives gave problems in formulation for clinical use, but quaternization of 9-hydroxyellipticine to give the water-soluble 9-hydroxy-2-*N*-methylellipticinium acetate (**elliptinium acetate**) (Figure 6.87) has produced a highly active material, of value in some forms of breast cancer, and perhaps also in renal cell cancer. A variety of such quaternized derivatives is being tested, and some water-soluble *N*-glycosides also show high activity.
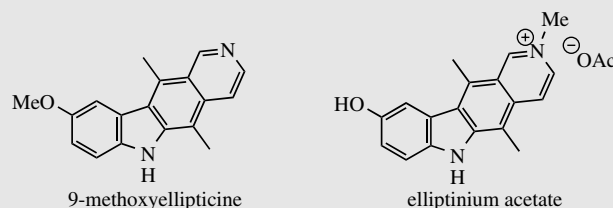

9-methoxyellipticine

elliptinium acetate

Figure 6.87

R = OMe, (–)-quinine
R = H, (–)-cinchonidine

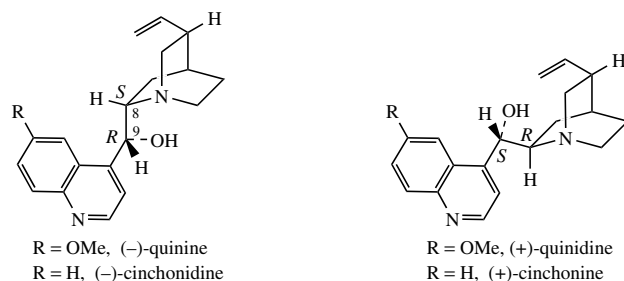R = OMe, (+)-quinidine
R = H, (+)-cinchonine

Figure 6.88

and **cinchonine** (Figure 6.88), long prized for their antimalarial properties. These structures are remarkable in that the indole nucleus is no longer present, having been rearranged into a quinoline system (Figure 6.89). The relationship was suspected quite early on, however, since the indole derivative **cinchonamine** (Figure 6.90) was known
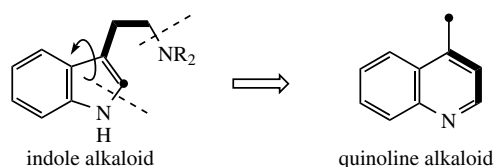

indole alkaloid   quinoline alkaloid

Figure 6.89

strictosidine

cleavage of C–N bond (via iminium) then formation of new C–N bond (again via iminium)

cinchonamine

hydrolysis and decarboxylation

corynantheal

cleavage of indole C–N bond

R = H, cinchonidine
R = OMe, quinine

cinchoninone

epimerization at C-8 via enol

R = H, cinchonine
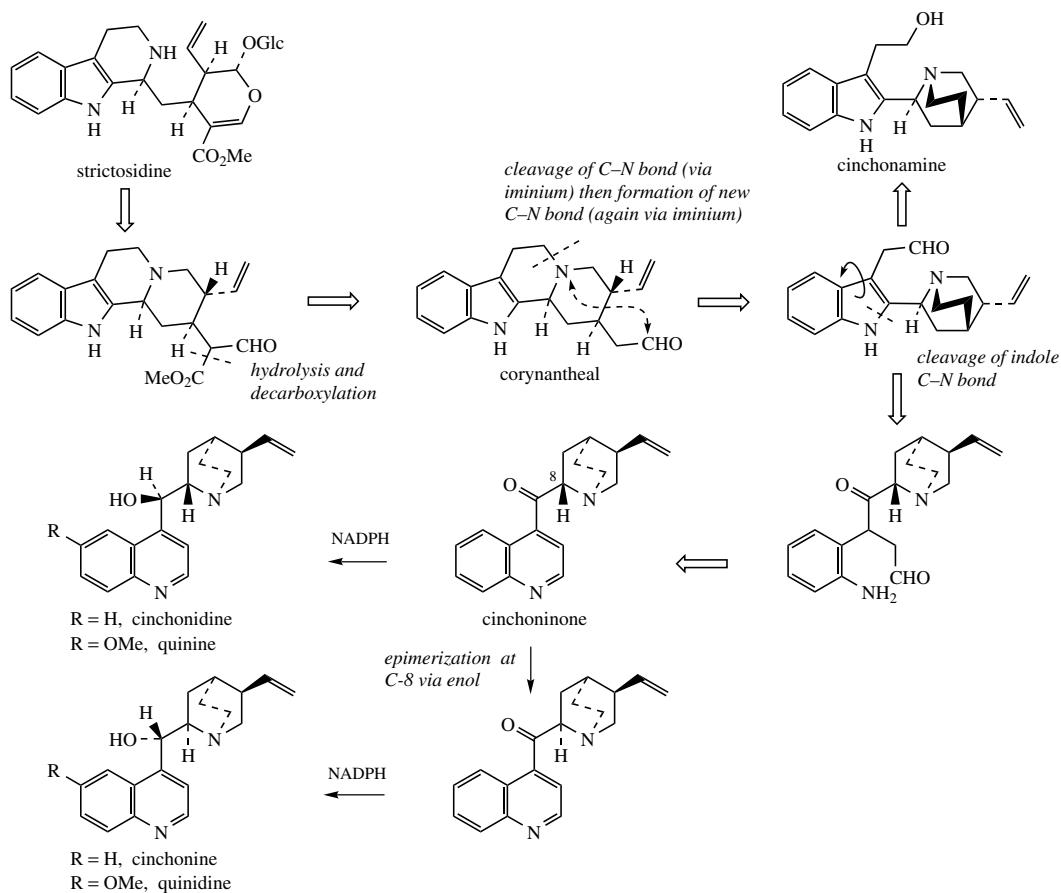R = OMe, quinidine

NADPH

NADPH

Figure 6.90

to co-occur with these quinoline alkaloids. An outline of the pathway from the *Corynanthe*-type indole alkaloids to cinchonidine is shown in Figure 6.90. The conversion is dependent on the reversible processes by which amines plus aldehydes or ketones, imines (Schiff bases), and their reduction products are related in nature. Suitable modification of strictosidine leads to an aldehyde (compare the early reactions in the ajmalicine pathway (Figure 6.76)). Hydrolysis/decarboxylation would initially remove one carbon from the iridoid portion and produce **corynantheal**. An intermediate of the cinchonamine type would then result if the tryptamine side-chain were cleaved adjacent to the nitrogen, and if this nitrogen were then bonded to the acetaldehyde function. Ring opening in the indole heterocyclic ring could generate new amine and keto functions. The new heterocycle would then be formed by combining this amine with the aldehyde produced in the tryptamine side-chain cleavage. Finally, reduction of the ketone gives **cinchonidine** or **cinchonine**. Hydroxylation and methylation at some stage allows biosynthesis of **quinine** and **quinidine**. Quinine and quinidine, or cinchonidine and cinchonine, are pairs of diastereoisomers, which have opposite chiralities at two centres (Figure 6.88). Stereospecific reduction of the carbonyl in cinchoninone can control the stereochemistry adjacent to the quinoline ring (C-9). The stereochemistry at the second centre (C-8) is also determined during the reduction step, presumably via the enol form of cinchoninone (Figure 6.90).

Cinchona

Cinchona bark is the dried bark from the stem and root of species of *Cinchona* (Rubiaceae), which are large trees indigenous to South America. Trees are cultivated in many parts of the world, including Bolivia, Guatemala, India, Indonesia, Zaire, Tanzania, and Kenya. About a dozen different *Cinchona* species have been used as commercial sources, but the great variation in alkaloid content, and the range of alkaloids present, has favoured cultivation of three main species, together with varieties, hybrids, and grafts. *Cinchona succirubra* provides what is called 'red' bark (alkaloid content 5–7%), *C. ledgeriana* gives 'brown' bark (alkaloid content 5–14%), and *C. calisaya* 'yellow' bark with an alkaloid content of 4–7%. Selected hybrids can yield up to 17% total alkaloids. Bark is stripped from trees which are about 8–12 years old, the trees being totally uprooted by tractor for the process.

A considerable number of alkaloids have been characterized in cinchona bark, four of which account for some 30–60% of the alkaloid content. These are quinine, quinidine, cinchonidine, and cinchonine, quinoline-containing structures representing two pairs of diastereoisomers (Figure 6.88). Quinine and quinidine have opposite configurations at two centres. Cinchonidine and cinchonine are demethoxy analogues, but unfortunately use of the *-id-* syllable in the nomenclature does not reflect a particular stereochemistry. Quinine is usually the major component (half to two-thirds total alkaloid content) but the proportions of the four alkaloids vary according to species or hybrid. The alkaloids are often present in the bark in salt combination with quinic acid (see page 122) or a tannin material called cinchotannic acid. Cinchotannic acid decomposes due to enzymic oxidation during processing of the bark to yield a red pigment, which is particularly prominent in the 'red' bark.

Cinchona and its alkaloids, particularly **quinine**, have been used for many years in the treatment of malaria, a disease caused by protozoa, of which the most troublesome is *Plasmodium falciparum*. The beneficial effects of cinchona bark were first discovered in South America in the 1630s, and the bark was then brought to Europe by Jesuit missionaries. Religious intolerance initially restricted its universal acceptance, despite the widespread occurrence of malaria in Europe and elsewhere. The name cinchona is a mis-spelling derived from Chinchon. In an often quoted tale, now historically disproved, the Spanish Countess of Chinchon, wife of the viceroy of Peru, was reputedly cured of malaria by the bark. For

(Continued)

many years, the bark was obtained from South America, but cultivation was eventually established by the English in India, and by the Dutch in Java, until just before the Second World War, when almost all the world's supply came from Java. When this source was cut off by Japan in the Second World War, a range of synthetic antimalarial drugs was hastily produced as an alternative to quinine. Many of these compounds were based on the quinine structure. Of the wide range of compounds produced, **chloroquine**, **primaquine**, and **mefloquine** (Figure 6.91) are important antimalarials. Primaquine is exceptional in having an 8-aminoquinoline structure, whereas chloroquine and mefloquine retain the 4-substituted quinoline as in quinine. The acridine derivative **mepacrine** (Figure 6.91), though not now used for malaria treatment, is of value in other protozoal infections. **Halofantrine** (Figure 6.91) dispenses with the heterocyclic ring system completely, and is based on phenanthrene. At one time, synthetic antimalarials had almost entirely superseded natural quinine, but the emergence of *Plasmodium falciparum* strains resistant to the synthetic drugs, especially the widely used prophylactic chloroquine, has resulted in reintroduction of quinine. Mefloquine is currently active against chloroquine-resistant strains, but, whilst ten times as active as quinine, does produce gastrointestinal upsets and dizziness, and can trigger psychological problems such as depression, panic, or psychosis in some patients. The ability of *P. falciparum* to develop resistance to modern drugs means malaria still remains a huge health problem, and is probably the major single cause of deaths in the modern world. **Chloroquine** and its derivative **hydroxychloroquine** (Figure 6.91), although antimalarials, are also used to suppress the disease process in rheumatoid arthritis.

Quinine (Figure 6.88), administered as free base or salts, continues to be used for treatment of multidrug-resistant malaria, though it is not suitable for prophylaxis. The specific mechanism of action is not thoroughly understood, though it is believed to prevent polymerization of toxic haemoglobin breakdown products formed by the parasite (see artemisinin, page 200). Vastly larger amounts of the alkaloid are consumed in beverages, including vermouth and tonic water. It is amusing to realize that gin was originally added to quinine to make the bitter antimalarial more palatable. Typically, the quinine dosage was up to 600 mg three times a
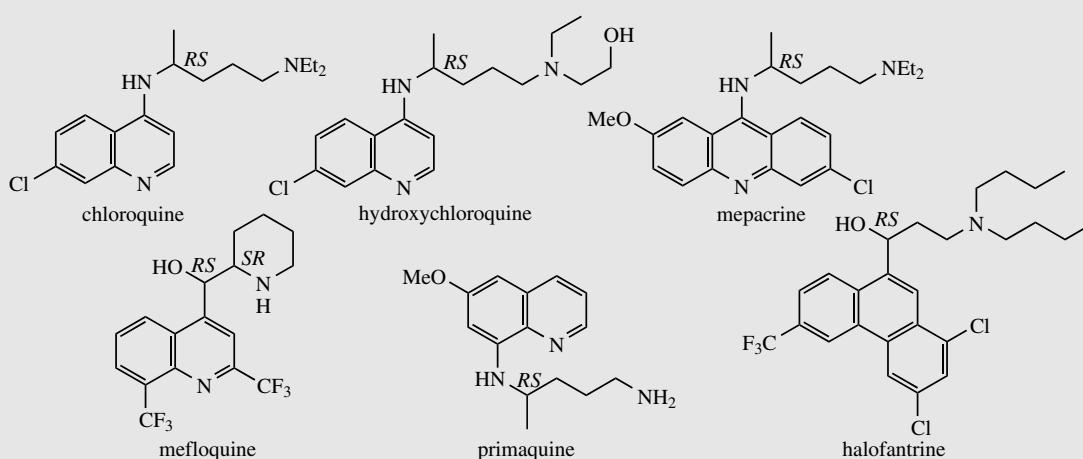

Figure 6.91

(Continued)

day. Quinine in tonic water is now the mixer added to gin, though the amounts of quinine used (about 80 mg l⁻¹) are well below that providing antimalarial protection. Quinine also has a skeletal muscle relaxant effect with a mild curare-like action. It thus finds use in the prevention and treatment of nocturnal leg cramp, a painful condition affecting many individuals, especially the elderly.

Quinidine (Figure 6.88) is the principal cinchona alkaloid used therapeutically, and is administered to treat cardiac arrhymias. It inhibits fibrillation, the uncoordinated contraction of muscle fibres in the heart. It is rapidly absorbed by the gastrointestinal tract and overdose can be hazardous, leading to diastolic arrest.

Quinidine, cinchonine, and cinchonidine also have antimalarial properties, but these alkaloids are not as effective as quinine. The cardiac effect makes quinidine unsuitable as an antimalarial. However, mixtures of total *Cinchona* alkaloids, even though low in quinine content, are acceptable antimalarial agents. This mixture, termed totaquine, has served as a substitute for quinine during shortages. Quinine-related alkaloids, especially quinidine, are also found in the bark of *Remija pendunculata* (Rubiaceae).
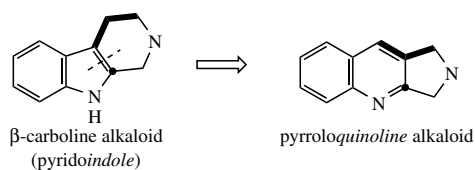

Figure 6.92

Camptothecin* (Figure 6.93) from *Camptotheca acuminata* (Nyssaceae) is a further example of a quinoline-containing structure that is actually derived by modification of an indole system. The main rearrangement process is that the original β-carboline 6−5−6 ring system becomes a 6−6−5 pyrroloquinoline by ring expansion of the indole
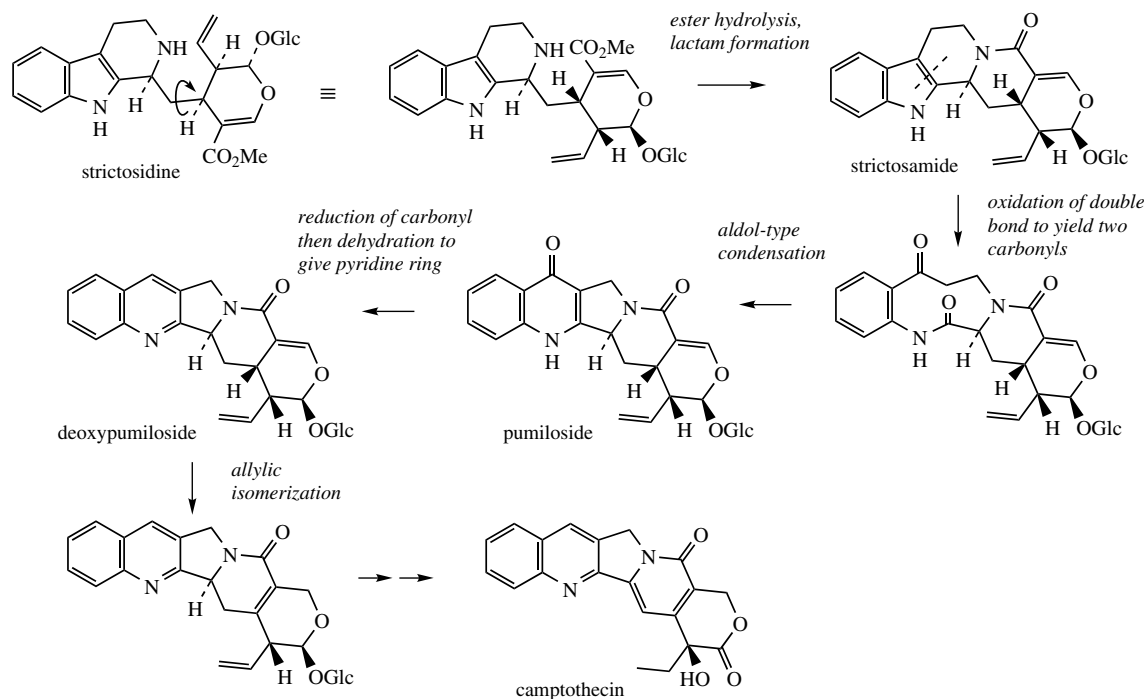

Figure 6.93

heterocycle (Figure 6.92). In camptothecin, the iridoid portion from strictosidine is effectively still intact, the original ester function being utilized in forming an amide linkage to the secondary amine. This occurs relatively early, in that **strictosamide** is an intermediate. **Pumiloside** (also isolated from *C. acuminata*) and **deoxypumiloside** are potential intermediates. Steps beyond are not yet defined, but involve relatively straightforward oxidation and reduction processes (Figure 6.93).

Pyrroloindole Alkaloids

Both C-2 and C-3 of the indole ring can be regarded as nucleophilic, but reactions involving C-2 appear to be the most common in alkaloid biosynthesis. There are examples where the nucleophilic character of C-3 is exploited, however, and the rare pyrroloindole skeleton typified by **physostigmine** (**eserine**) (Figure 6.95) is a likely case. A suggested pathway to physostigmine is by C-3 methylation of tryptamine, followed by ring

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Camptothecin

Camptothecin (Figure 6.93) and derivatives are obtained from the Chinese tree *Camptotheca acuminata* (Nyssaceae). Seeds yield about 0.3% camptothecin, bark about 0.2%, and leaves up to 0.4%. *Camptotheca acuminata* is found only in Tibet and West China, but other sources of camptothecin such as *Nothapodytes foetida* (formerly *Mappia foetida*) (Icacinaceae), *Merilliodendron megacarpum* (Icacinaceae), *Pyrenacantha klaineana* (Icacinaceae), *Ophiorrhiza mungos* (Rubiaceae), and *Ervatmia heyneana* (Apocynaceae) have been discovered. In limited clinical trials camptothecin showed broad-spectrum anticancer activity, but toxicity and poor solubility were problems. The natural 10-hydroxycamptothecin (about 0.05% in the bark of *C. acuminata*) is more active than camptothecin, and is used in China against cancers of the neck and head. Synthetic analogues 9-aminocamptothecin (Figure 6.94) and the water-soluble derivatives **topotecan** and **irinotecan** (Figure 6.94) showed good responses in a number of cancers; topotecan and irinotecan are now available for the treatment of ovarian cancer and colorectal cancer, respectively. Irinotecan is a carbamate pro-drug of 10-hydroxy-7-ethylcamptothecin, and is converted into the active drug by liver enzymes. These agents act by inhibition of the enzyme topoisomerase I, which is involved in DNA replication and reassembly, by binding to and stabilizing a covalent DNA–topoisomerase complex (see page 137). Camptothecin has also been shown to have potentially useful activity against pathogenic protozoa such as *Trypanosoma brucei* and *Leishmania donovani*, which cause sleeping sickness and leishmaniasis respectively. Again, this is due to topoisomerase I inhibition.
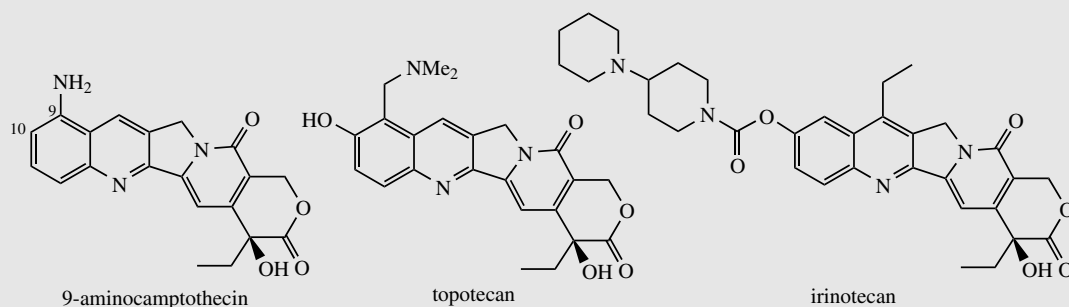

9-aminocamptothecin   topotecan   irinotecan
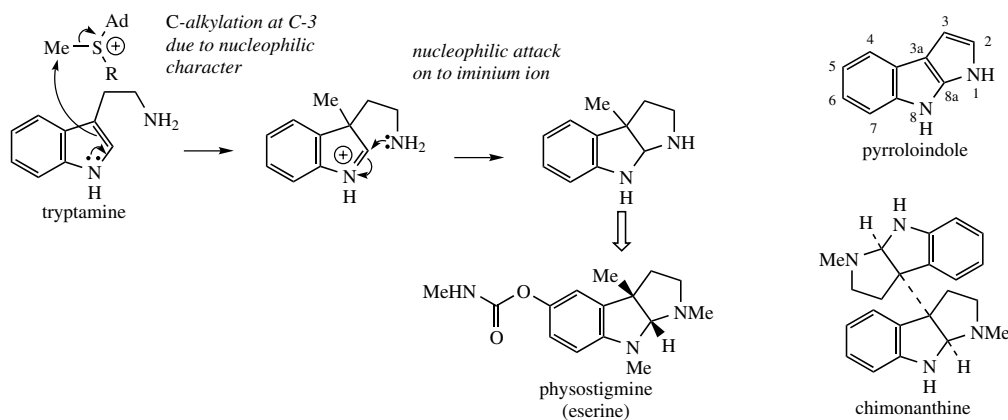
Figure 6.94

Figure 6.95

formation involving attack of the primary amine function on to the iminium ion (Figure 6.95). Further substitution is then necessary. Dimers with this ring system are also known, e.g. **chimonanthine**

(Figure 6.95) from *Chimonanthus fragrans* (Calycanthaceae), the point of coupling being C-3 of the indole, and an analogous radical reaction may be proposed. Physostigmine is found in seeds of

Physostigma

Physostigma venenosum (Leguminosae/Fabaceae) is a perennial woody climbing plant found on the banks of streams in West Africa. The seeds are known as Calabar beans (from Calabar, now part of Nigeria) and have an interesting history in the native culture as an ordeal poison. The accused was forced to swallow a potion of the ground seeds, and if the mixture was subsequently vomited, he/she was judged innocent and set free. If the poison took effect, the prisoner suffered progressive paralysis and died from cardiac and respiratory failure. It is said that slow consumption allows the poison to take effect, whilst emesis is induced by a rapid ingestion of the dose.
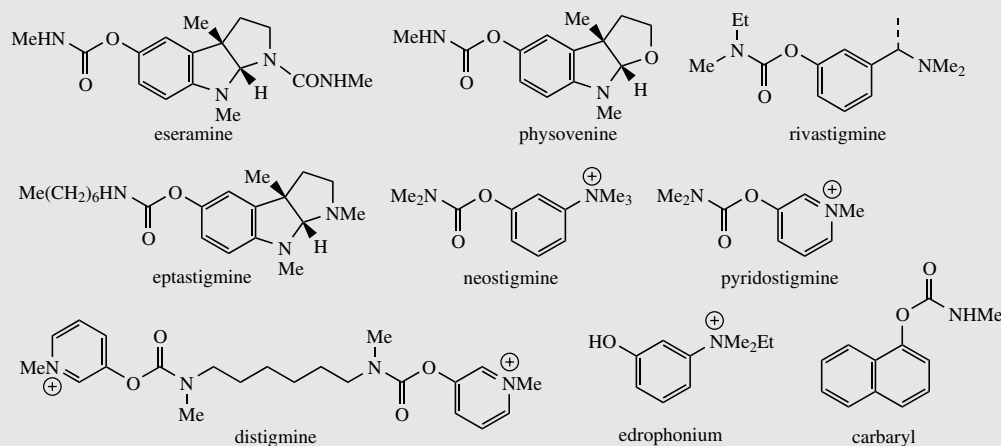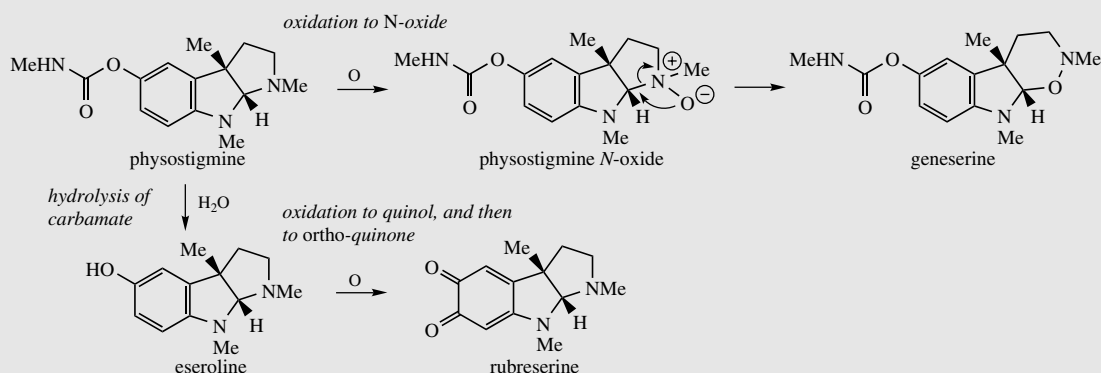

Figure 6.96

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Figure 6.97

The seeds contain several alkaloids (alkaloid content about 1.5%), the major one (up to 0.3%) being physostigmine (eserine) (Figure 6.95). The unusual pyrroloindole ring system is also present in some of the minor alkaloids, e.g. eseramine (Figure 6.96), whilst physovenine (Figure 6.96) contains an undoubtedly related furanoindole system. Another alkaloid, geneserine (Figure 6.97), is an artefact produced by oxidation of physostigmine, incorporating oxygen into the ring system, probably by formation of an *N*-oxide and ring expansion. Solutions of physostigmine are not particularly stable in the presence of air and light, especially under alkaline conditions, oxidizing to a red quinone, rubeserine (Figure 6.97).

Physostigmine (**eserine**) is a reversible inhibitor of cholinesterase, preventing normal destruction of acetylcholine and thus enhancing cholinergic activity. Its major use is as a miotic, to contract the pupil of the eye, often to combat the effect of mydriatics such as atropine (see page 297). It also reduces intraocular pressure in the eye by increasing outflow of the aqueous humour, and is a valuable treatment for glaucoma, often in combination with pilocarpine (see page 380). Because it prolongs the effect of endogenous acetylcholine, physostigmine can be used as an antidote to anticholinergic poisons such as hyoscyamine/atropine (see page 297), and it also reverses the effects of competitive muscle relaxants such as curare, tubocurarine, atracurium, etc (see page 324). Anticholinesterase drugs are also of value in the treatment of Alzheimer's disease, which is characterized by a dramatic decrease in functionality of the central cholinergic system. Use of acetylcholinesterase inhibitors can result in significant memory enhancement in patients, and analogues of physostigmine are presently in use (e.g. **rivastigmine**) or in advanced clinical trials (e.g. eptastigmine (Figure 6.96)). These analogues have a longer duration of action and less toxicity than physostigmine.

The biological activity of physostigmine resides primarily in the carbamate portion, which is transferred to the hydroxyl group of an active site serine in cholinesterase (Figure 6.98). The enzyme is only slowly regenerated by hydrolysis of this group, since resonance contributions reduce the reactivity of the carbonyl in the amide relative to the ester. Accordingly, cholinesterase becomes temporarily inactivated. Synthetic analogues of physostigmine which have been developed retain the carbamate residue, an aromatic ring to achieve binding and to provide a good leaving group, whilst ensuring water-solubility through possession of a quaternary ammonium system. **Neostigmine**, **pyridostigmine**, and **distigmine** (Figure 6.96) are examples of synthetic anticholinesterase drugs used primarily for enhancing neuromuscular transmission in the rare autoimmune condition myasthenia
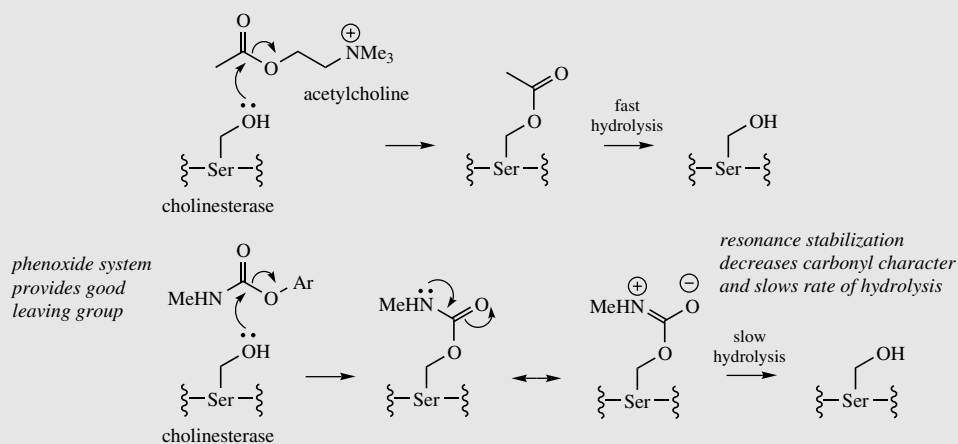
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Figure 6.98

gravis, in which muscle weakness is caused by faulty transmission of nerve impulses. **Edrophonium** is a short-acting competitive blocker of the acetylcholinesterase active site, which is used to help diagnose myasthenia gravis. A number of carbamate insecticides, e.g. carbaryl (Figure 6.96), also depend on inhibition of cholinesterase for their action, insect acetylcholinesterase being more susceptible to such agents than the mammalian enzyme. Physostigmine displays little insecticidal action because of its poor lipid solubility.

*Physostigma venenosum** (Leguminosae/Fabaceae) and has played an important role in pharmacology because of its anticholinesterase activity. The inherent activity is in fact derived from the carbamate side-chain rather than the heterocyclic ring system, and this has led to a range of synthetic materials being developed.

Ergot Alkaloids

Ergot* is a fungal disease commonly found on many wild and cultivated grasses, and is caused by species of *Claviceps*. The disease is eventually characterized by the formation of hard, seedlike 'ergots' instead of normal seeds, these structures,
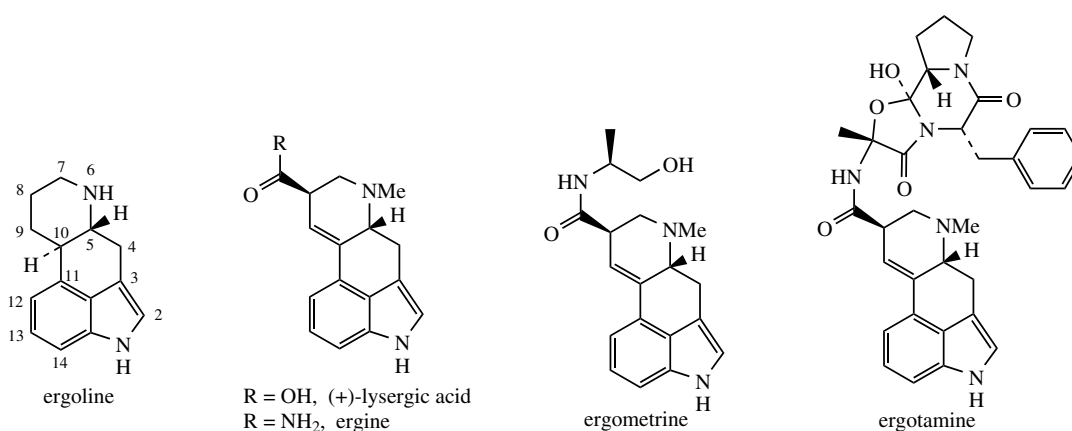

ergoline

R = OH, (+)-lysergic acid
R = NH₂, ergine

ergometrine

ergotamine

Figure 6.99

called sclerotia, forming the resting stage of the fungus. The poisonous properties of ergots in grain, especially rye, for human or animal consumption have long been recognized, and the causative agents are known to be a group of indole alkaloids, referred to collectively as the ergot alkaloids or ergolines (Figure 6.99). Under natural conditions the alkaloids are elaborated by a combination of fungal and plant metabolism, but they can
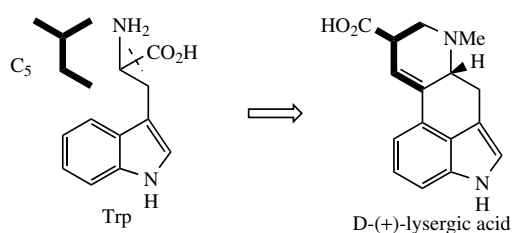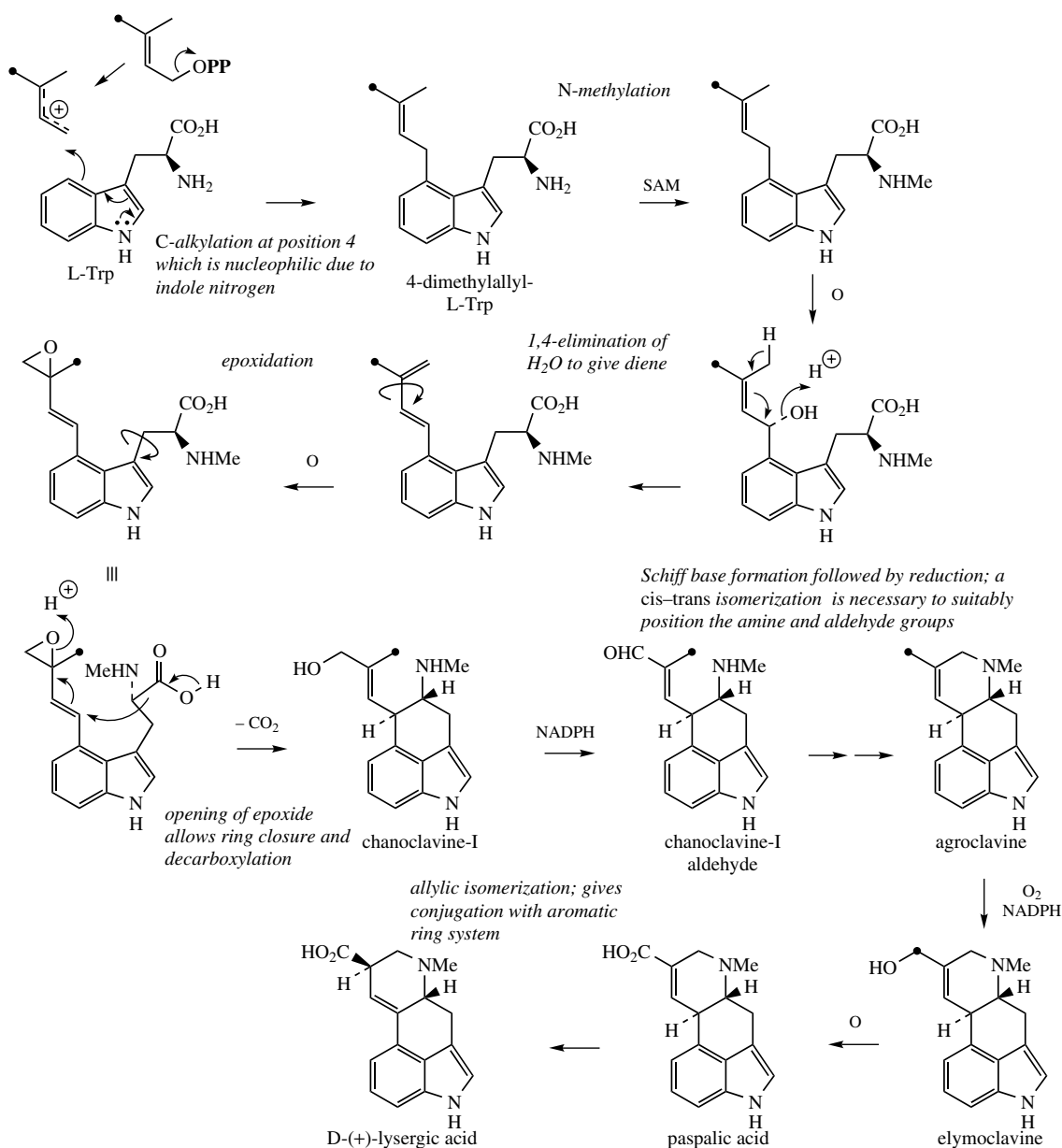

Figure 6.100

Figure 6.101

be synthesized in cultures of suitable *Claviceps* species. Ergoline alkaloids have also been found in fungi belonging to genera *Aspergillus*, *Rhizopus*, and *Penicillium*, as well as *Claviceps*, and simple examples are also found in some plants of the Convolvulaceae such as *Ipomoea* and *Rivea* (morning glories)*. Despite their toxicity, some of these alkaloids have valuable pharmacological activities and are used clinically on a routine basis.

Medicinally useful alkaloids are derivatives of (+)-**lysergic acid** (see Figure 6.99), which is typically bound as an amide with an amino alcohol as in **ergometrine**, or with a small polypeptide structure as in **ergotamine**. The building blocks for lysergic acid are tryptophan (less the carboxyl group) and an isoprene unit (Figure 6.100). Alkylation of tryptophan with dimethylallyl diphosphate gives 4-dimethylallyl-L-tryptophan, which then undergoes *N*-methylation (Figure 6.101). Formation of the tetracyclic ring system of lysergic acid is known to proceed through **chanoclavine-I** and **agroclavine**, though the mechanistic details are far from clear. Labelling studies have established that the

double bond in the dimethylallyl substituent must become a single bond on two separate occasions, allowing rotation to occur as new rings are established. This gives the appearance of *cis–trans* isomerizations as 4-dimethylallyl-L-tryptophan is transformed into chanoclavine-I, and as chanoclavine-I aldehyde cyclizes to agroclavine (Figure 6.101). A suggested sequence to account for the first of these is shown. In the later stages, agroclavine is hydroxylated to **elymoclavine**, further oxidation of the primary alcohol occurs giving **paspalic acid**, and **lysergic acid** then results from a spontaneous allylic isomerization.

Simple derivatives of lysergic acid require the formation of amides; for example, **ergine** (Figure 6.99) in *Rivea* and *Ipomoea* species is lysergic acid amide, whilst **ergometrine** from *Claviceps purpurea* is the amide with 2-aminopropanol. The more complex structures containing peptide fragments, e.g. **ergotamine** (Figure 6.99), are formed by sequentially adding amino acid residues to thioester-bound lysergic acid, giving a linear lysergyl–tripeptide covalently attached to the enzyme complex (Figure 6.102). Peptide formation
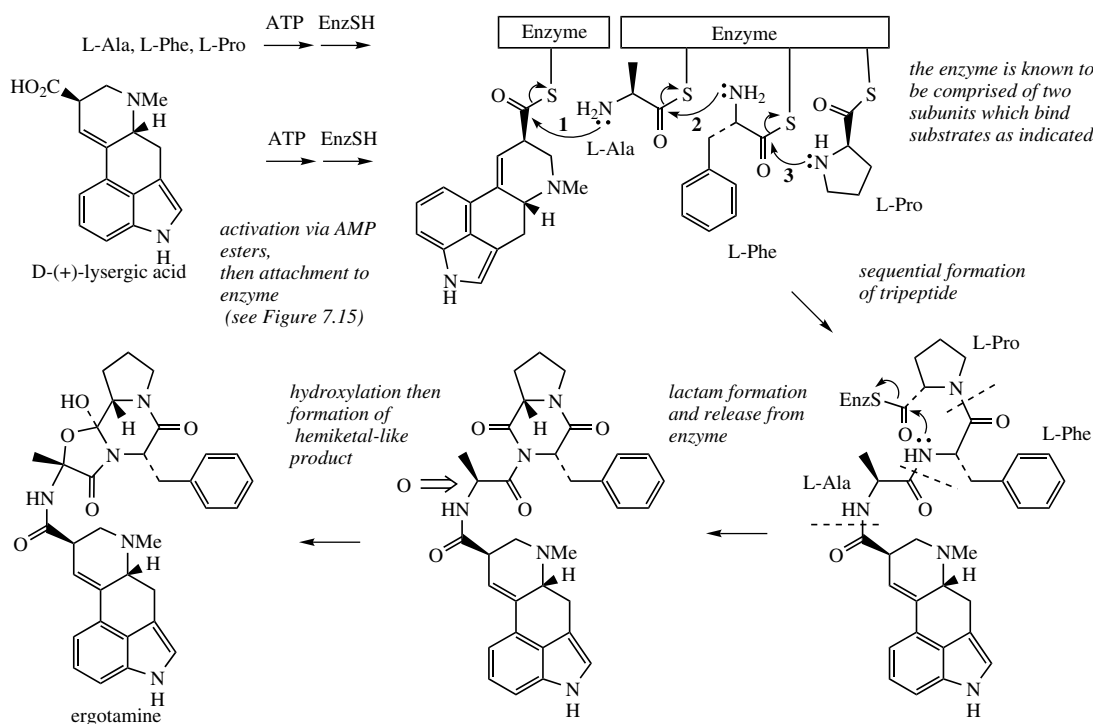

Figure 6.102

involves the same processes seen in the non-ribosomal biosynthesis of peptides, and involves ATP-mediated activation of the amino acids prior to attachment to the enzyme complex through thioester linkages (see page 421). A phosphopantatheine arm is used to enable the growing chain to reach the various active sites (compare fatty acid biosynthesis, page 36). The cyclized tripeptide residue is readily rationalized by the formation of a lactam (amide) which releases the product from the enzyme, followed by generation of a hemiketal-like linkage as shown (Figure 6.102).

Ergot

Medicinal ergot is the dried sclerotium of the fungus *Claviceps purpurea* (Clavicipitaceae) developed on the ovary of rye, *Secale cereale* (Graminae/Poaceae). Ergot is a fungal disease of wild and cultivated grasses, and initially affects the flowers. In due course, a dark sclerotium, the resting stage of the fungus, is developed instead of the normal seed. This protrudes from the seed head, the name ergot being derived from the French word argot – a spur. The sclerotia fall to the ground, germinating in the spring and reinfecting grasses or grain crops by means of spores. Two types of spore are recognized: ascospores, which are formed in the early stages and are dispersed by the wind, whilst later on conidiospores are produced, which are insect distributed. The flowers are only susceptible to infection before pollination. Ergots may subsequently be harvested with the grain and contaminate flour or animal feed. The consumption of ergot-infected rye has resulted in the disease ergotism, which has a long, well documented history.

There are three broad clinical features of ergot poisoning, which are due to the alkaloids present and the relative proportions of each component:

- Alimentary upsets, e.g. diarrhoea, abdominal pains, and vomiting.

- Circulatory changes, e.g. coldness of hands and feet due to a vasoconstrictor effect, a decrease in the diameter of blood vessels, especially those supplying the extremeties.

- Neurological symptoms, e.g. headache, vertigo, convulsions, psychotic disturbances, and hallucinations.

These effects usually disappear on removal of the source of poisoning, but much more serious problems develop with continued ingestion, or with heavy doses of ergot-contaminated food. The vasoconstrictor effect leads to restricted blood flow in small terminal arteries, death of the tissue, the development of gangrene, and even the shedding of hands, feet, or limbs. Gangrenous ergotism was known as St Anthony's Fire, the Order of St Anthony traditionally caring for sufferers in the Middle Ages. The neurological effects were usually manifested by severe and painful convulsions. Outbreaks of the disease in both humans and animals were relatively frequent in Europe in the Middle Ages, but once the cause had been established it became relatively simple to avoid contamination. Separation of the ergots from grain, or the use of fungicides during cultivation of the crop, have removed most of the risks, though infection of crops is still common.

The ergot sclerotia contain from 0.15–0.5% alkaloids, and more than 50 have been characterized. The medicinally useful compounds are derivatives of (+)-lysergic acid (Figure 6.103), and can be separated into two groups, the water-soluble amino alcohol derivatives (up to about 20% of the total alkaloids), and water-insoluble peptide derivatives (up to 80% of the total alkaloids). Ergometrine (Figure 6.103) (also known as ergonovine in the USA and ergobasine in Switzerland) is an amide of lysergic acid and 2-aminopropanol, and is the only significant member of the first group. The peptide derivatives contain a
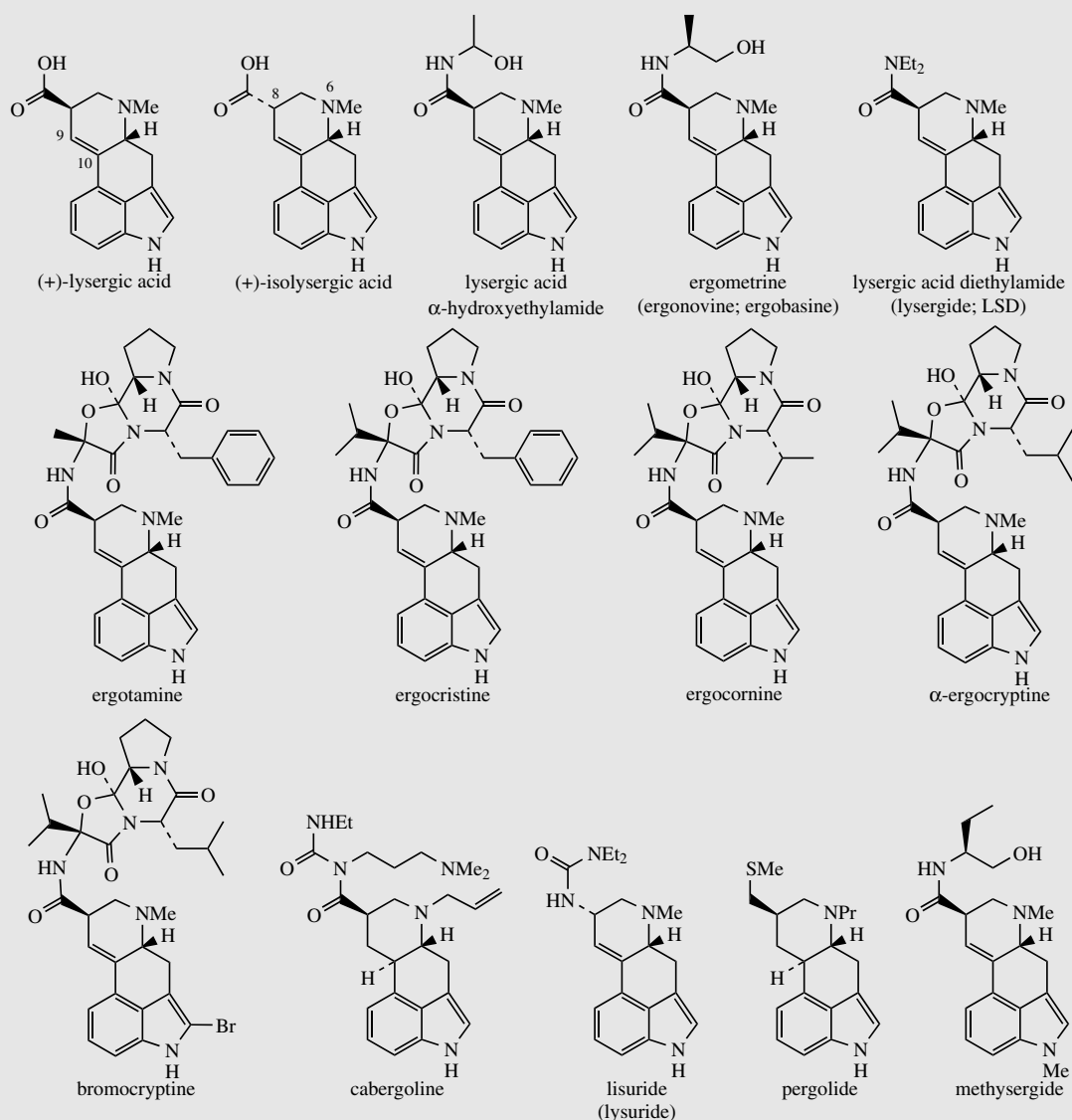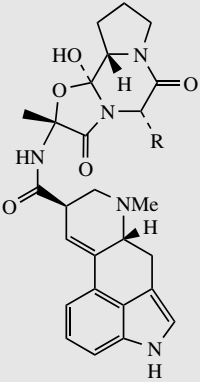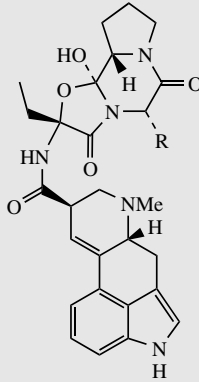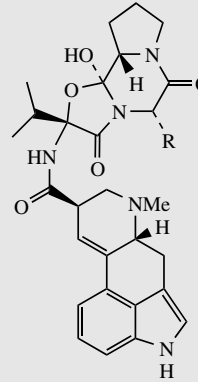
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Figure 6.103

cyclized tripeptide fragment bonded to lysergic acid via an amide linkage. Based on the nature of the three amino acids, these structures can be subdivided into three groups, the ergotamine group, the ergoxine group, and the ergotoxine group (Table 6.1). The amino acids involved are alanine, valine, leucine, isoleucine, phenylalanine, proline, and α-aminobutyric acid, in various combinations (see Figure 6.104). All contain proline in the tripeptide, and one of the amino acids is effectively incorporated into the final structure in the form of an α-hydroxy-α-amino acid. Thus, ergotamine incorporates alanine, phenylalanine, and proline residues in its peptide portion. Hydrolysis gives (+)-lysergic acid, proline, and phenylalanine,
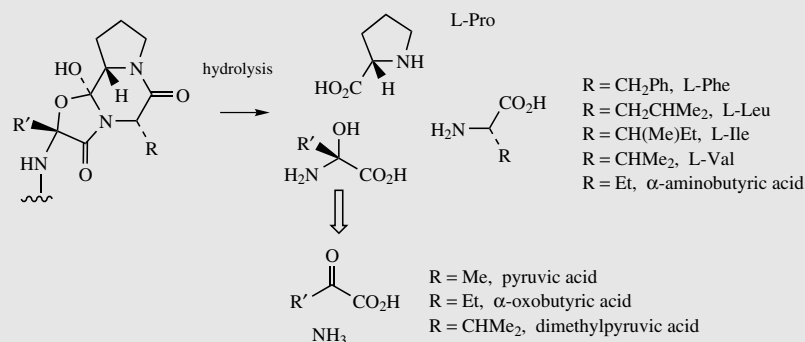
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Table 6.1 Peptide alkaloids in ergot

	ergotamine group	**ergoxine group**	**ergotoxine group**
R = CH$_2$Ph	ergotamine	ergostine	ergocristine
R = CH$_2$CHMe$_2$	ergosine	ergoptine	α-ergocryptine
S R = CH(Me)Et	[β-ergosine]	[β-ergoptine]	β-ergocryptine
R = CHMe$_2$	ergovaline	ergonine	ergocornine
R = Et	ergobine	ergobutine	ergobutyrine

[   ] not yet known in nature

together with pyruvic acid and ammonia, the latter hydrolysis products a consequence of the additional hydroxylation involving alanine (Figure 6.104). Hydrolysis of the ergotoxine group of alkaloids results in the proximal valine unit being liberated as dimethylpyruvic acid (not systematic nomenclature) and ammonia, and the ergoxine group similarly yields α-oxobutyric acid from the α-aminobutyric acid fragment. The alkaloid 'ergotoxine' was originally thought to be a single compound, but was subsequently shown to be a mixture of alkaloids. The proposed structures β-ergosine and β-ergoptine, which complete the combinations shown in Table 6.1, have not yet been isolated as natural products.

R = CH$_2$Ph, L-Phe
R = CH$_2$CHMe$_2$, L-Leu
R = CH(Me)Et, L-Ile
R = CHMe$_2$, L-Val
R = Et, α-aminobutyric acid

R = Me, pyruvic acid
R = Et, α-oxobutyric acid
R = CHMe$_2$, dimethylpyruvic acid

Figure 6.104

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Medicinal ergot is cultivated in the Czech Republic, Germany, Hungary, Switzerland, Austria, and Poland. Fields of rye are infected artificially with spore cultures of *Claviceps purpurea*, either by spraying or by a mechanical process that uses needles dipped in a spore suspension. The ergots are harvested by hand, by machine, or by separation from the ripe grain by flotation in a brine solution. By varying the strain of the fungal cultures, it is possible to maximize alkaloid production (0.4–1.2%), or give alkaloid mixtures in which particular components predominate. Ergots containing principally ergotamine in concentrations of about 0.35% can be cultivated. In recent times, ergot of wheat (*Triticum aestivum*), and the wheat–rye hybrid triticale (*Triticosecale*) have been produced commercially.

Alternatively, the ergot alkaloids can be produced by culturing the fungus. Initially, cultures of the rye parasite *Claviceps purpurea* in fermentors did not give the typical alkaloids associated with the sclerotia, e.g. ergometrine and ergotamine. These medicinally useful compounds appear to be produced only in the later stages of development of the fungus. Instead, the cultures produced alkaloids that were not based on lysergic acid, and are now recognized as intermediates in the biosynthesis of lysergic acid, e.g. chanoclavine-I, agroclavine, and elymoclavine (Figure 6.101). Ergot alkaloids that do not yield lysergic acid on hydrolysis have been termed clavine alkaloids. Useful derivatives based on lysergic acid can be obtained by fermentation growth of another fungal species, namely *Claviceps paspali*. Although some strains are available that produce peptide alkaloids in culture, other strains produce high yields of simple lysergic acid derivatives. These include lysergic acid α-hydroxyethylamide (Figure 6.103), lysergic acid amide (ergine) (Figure 6.99), which is also an acid-catalysed decomposition product from lysergic acid α-hydroxyethylamide, and the $\Delta^{8,9}$-isomer of lysergic acid, paspalic acid (Figure 6.101). Lysergic acid is obtained from the first two by hydrolysis, or from paspalic acid by allylic isomerization. Other alkaloids, e.g. ergometrine and ergotamine, can then be produced semi-synthetically. High yielding fermentation methods have also been developed for direct production of ergotamine and the ergotoxine group of peptide alkaloids.

The pharmacologically active ergot alkaloids are based on (+)-lysergic acid (Figure 6.103), but since one of the chiral centres in this compound (and its amide derivatives) is adjacent to a carbonyl, the configuration at this centre can be changed as a result of enolization brought about by heat or base (compare tropane alkaloids, page 298; again note that enolization is favoured by conjugation with the aromatic ring). The new diastereomeric form of (+)-lysergic acid is (+)-isolysergic acid (Figure 6.103), and alkaloids based on this compound are effectively pharmacologically inactive. They are frequently found along with the (+)-lysergic acid derivatives, amounts being significant if old ergot samples are processed, or unsuitable isolation techniques are employed. In the biologically active lysergic acid derivatives, the amide group occupies an 8-equatorial position, whilst in the inactive iso-forms, this group is axial. However, the axial form is actually favoured because this configuration allows hydrogen-bonding from the amide N–H to the hetrocyclic nitrogen at position 6. Derivatives of (+)-isolysergic acid are named by adding the syllable *-in-* to the corresponding (+)-lysergic acid compound, e.g. ergomet*rin*ine, ergotam*in*ine.

The ergot alkaloids owe their pharmacological activity to their ability to act at α-adrenergic, dopaminergic and serotonergic receptors. The relationship of the general alkaloid structure to those of noradrenaline, dopamine, and 5-hydroxytryptamine (5-HT, serotonin) is shown in Figure 6.105. The pharmacological response may be complex. It depends on the preferred receptor to which the compound binds, though all may be at least partially involved, and whether the alkaloid is an agonist or antagonist.
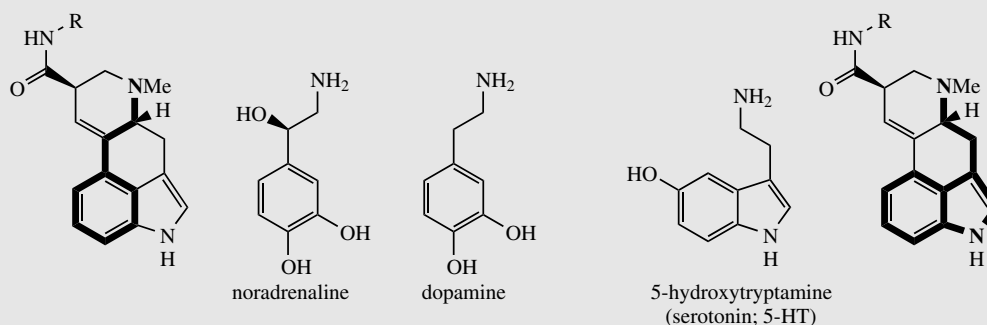
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Figure 6.105

Despite the unpleasant effects of ergot as manifested by St Anthony's Fire, whole ergot preparations have been used since the 16th century to induce uterine contractions during childbirth, and to reduce haemorrhage following the birth. This oxytocic effect (oxytocin is the pituitary hormone that stimulates uterine muscle, see page 415) is still medicinally valuable, but is now achieved through use of the isolated alkaloid ergometrine. The deliberate use of ergot to achieve abortions is dangerous and has led to fatalities.

Ergometrine (**ergonovine**) (Figure 6.103) is used as an oxytocic, and is injected during the final stages of labour and immediately following childbirth, especially if haemorrhage occurs. Bleeding is reduced because of its vasoconstrictor effects, and it is valuable after Caesarian operations. It is sometimes administered in combination with oxytocin itself (see page 415). Ergometrine is also orally active. It produces faster stimulation of uterine muscle than do the other ergot alkaloids, and probably exerts its effect by acting on α-adrenergic receptors, though it may also stimulate 5-HT receptors.

Ergotamine (Figure 6.103) is a partial agonist of α-adrenoceptors and 5-HT receptors. It is not suitable for obstetric use because it also produces a pronounced peripheral vasoconstrictor action. This property is exploited in the treatment of acute attacks of migraine, where it reverses the dilatation of cranial blood vessels. Ergotamine is effective orally, or by inhalation in aerosol form, and may be combined with caffeine, which is believed to enhance its action. The semi-synthetic **dihydroergotamine** is produced by hydrogenation of the lysergic acid $\Delta^{9,10}$ double bond (giving C-10 stereochemistry as in ergoline) and is claimed to produce fewer side-effects, especially digestive upsets.

The 'ergotoxine' alkaloid mixture also has oxytocic and vasoconstrictor activity but is only employed medicinally as the 9,10-dihydro derivatives **dihydroergotoxine** (**co-dergocrine**), a mixture in equal proportions of **dihydroergocornine**, **dihydroergocristine**, and the **dihydroergocryptines** (α- and β- in the ratio 2:1). In the case of these alkaloids, reduction of the double bond appears to reverse the vasoconstrictor effect, and dihydroergotoxine has a cerebral vasodilator activity. The increased blood flow is of benefit in some cases of senility and mild dementia, and helps to improve both mental function and physical performance.

A number of semi-synthetic lysergic acid derivatives act by stimulation of dopamine receptors in the brain, and are of value in the treatment of neurological disorders such as Parkinson's disease. **Bromocriptine** (2-bromo-α-ergocryptine), **cabergoline**, **lisuride** (**lysuride**), and **pergolide** (Figure 6.103) are all used in this way. Bromocriptine and cabergoline find wider use in that they also inhibit release of prolactin by the pituitary (see page 414), and can

(*Continued*)

thus suppress lactation and be used in the treatment of breast tumours. **Methysergide** (Figure 6.103) is a semi-synthetic analogue of ergometrine, having a modified amino alcohol side-chain and an *N*-methyl group on the indole ring. It is a potent 5-HT antagonist and as such is employed in the prophylaxis of severe migraine headaches, though its administration has to be very closely supervised.

Prolonged treatment with any of the ergot alkaloids is undesirable and it is vital that the clinical features associated with ergot poisoning are recognized. Treatment must be withdrawn immediately if any numbness or tingling develops in the fingers or toes. Side-effects will disappear on withdrawal of the drug, but there have been many cases where misdiagnosis has unfortunately led to foot or toe rot, and the necessity for amputation of the dead tissue.

Undoubtedly the most notorious of the lysergic acid derivatives is lysergide (lysergic acid diethylamide or LSD) (Figure 6.103). This widely abused hallucinogen, known as 'acid', is probably the most active and specific psychotomimetic known, and is a mixed agonist–anatagonist at 5-HT receptors, interfering with the normal processes. An effective oral dose is from 30 to 50 μg. It was synthesized from lysergic acid, and even the trace amounts absorbed during its handling were sufficient to give its creator quite dramatic hallucinations. LSD intensifies perceptions and distorts them. How the mind is affected depends on how the user is feeling at the time, and no two 'trips' are alike. Experiences can vary from beautiful visions to living nightmares, sometimes lasting for days. Although the drug is not addictive, it can lead to schizophrenia and there is danger of serious physical accidents occurring whilst the user is under the influence of the drug.

Morning Glories

Lysergic acid derivatives have also been characterized in the seeds of morning glory (*Ipomoea violacea*), *Rivea corymbosa*, and other members of the Convolvulaceae. Such seeds formed the ancient hallucinogenic drug ololiuqui still used by the Mexican Indians in religious and other ceremonies. Extracts from the ground seeds are swallowed and the narcotic and hallucinogenic effects are said to provide contact with the gods. The active constituent has been identified to be principally ergine (lysergic acid amide) (Figure 6.99), and this has an activity about one-20th that of LSD, but is more narcotic than hallucinogenic. The alkaloid content of the seeds is usually low, at about 0.05%, but higher levels (0.5–1.3%) have been recorded. Minor ergot-related constituents include ergometrine (Figure 6.103), lysergic acid α-hydroxyethylamide (Figure 6.103), the inactive isolysergic acid amide (erginine), and some clavine alkaloids.

Since morning glories are widely cultivated ornamentals and seeds are readily available, deliberate ingestion by thrill-seekers has been considerable. Although the biological activity is well below that of LSD, the practice is potentially dangerous.

ALKALOIDS DERIVED FROM ANTHRANILIC ACID

Anthranilic acid (Figure 6.106) is a key intermediate in the biosynthesis of L-tryptophan (see page 126) and so contributes to the elaboration of indole alkaloids. During this conversion, the anthranilic acid residue is decarboxylated, so that only the C_6N skeleton is utilized. However, there are also many examples of where anthranilic acid itself functions as an alkaloid precursor, using processes which retain the full skeleton and exploit the carboxyl (Figure 6.106). It should also be
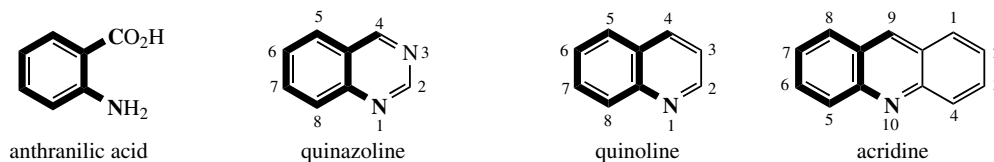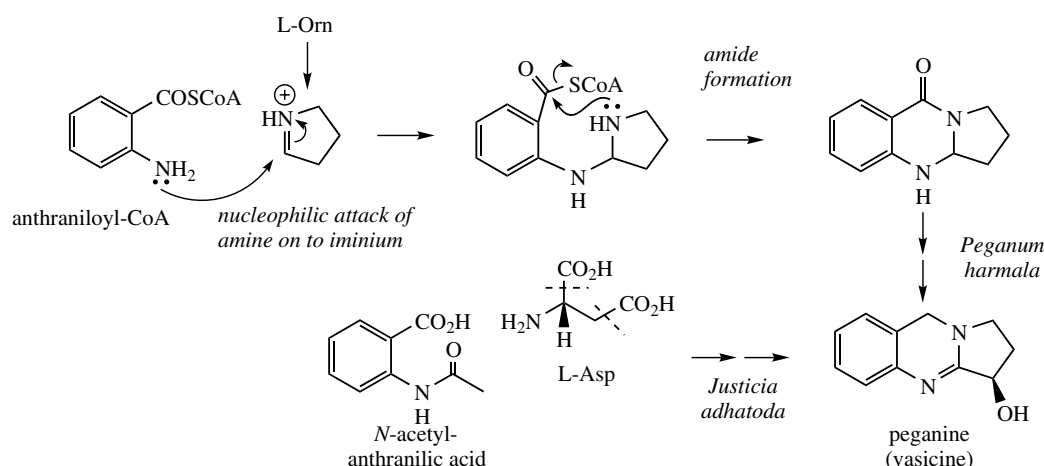
Figure 6.106

Figure 6.107

appreciated that, in mammals, L-tryptophan can be degraded back to anthranilic acid (see page 127), but this is not a route of importance in plants.

Quinazoline Alkaloids

Peganine (Figure 6.107) is a quinazoline alkaloid found in *Peganum harmala* (Zygophyllaceae), where it co-occurs with the β-carboline alkaloid harmine (see page 349). It is also responsible for the bronchodilator activity of *Justicia adhatoda* (*Adhatoda vasica*) (Acanthaceae), a plant used in the treatment of respiratory ailments. As a result, the alternative name **vasicine** is also sometimes used for peganine. Studies in *Peganum harmala* have clearly demonstrated peganine to be derived from anthranilic acid, the remaining part of the structure being a pyrrolidine ring supplied by ornithine (compare Figure 6.1, page 292). The peganine skeleton is readily rationalized as a result of nucleophilic attack from the anthranilate nitrogen on to the pyrrolinium cation, followed by amide formation (Figure 6.107). Remarkably, this

pathway is not operative in *Justicia adhatoda*, and a much less predictable sequence from *N*-acetylanthranilic acid and aspartic acid is observed (Figure 6.107).

Quinoline and Acridine Alkaloids

Alkaloids derived from anthranilic acid undoubtedly occur in greatest abundance in plants from the family the Rutaceae. Particularly well represented are alkaloids based on quinoline and acridine skeletons (Figure 6.106). Some quinoline alkaloids such as quinine and camptothecin have been established to arise by fundamental rearrangement of indole systems and have their origins in tryptophan (see page 359). A more direct route to the quinoline ring system is by the combination of anthranilic acid and acetate/malonate, and an extension of this process also accounts for the origins of the acridine ring system (see Figure 3.47, page 81). Thus, anthraniloyl-CoA (Figure 6.108) can act as a starter unit for chain extension via one molecule of malonyl-CoA, and amide
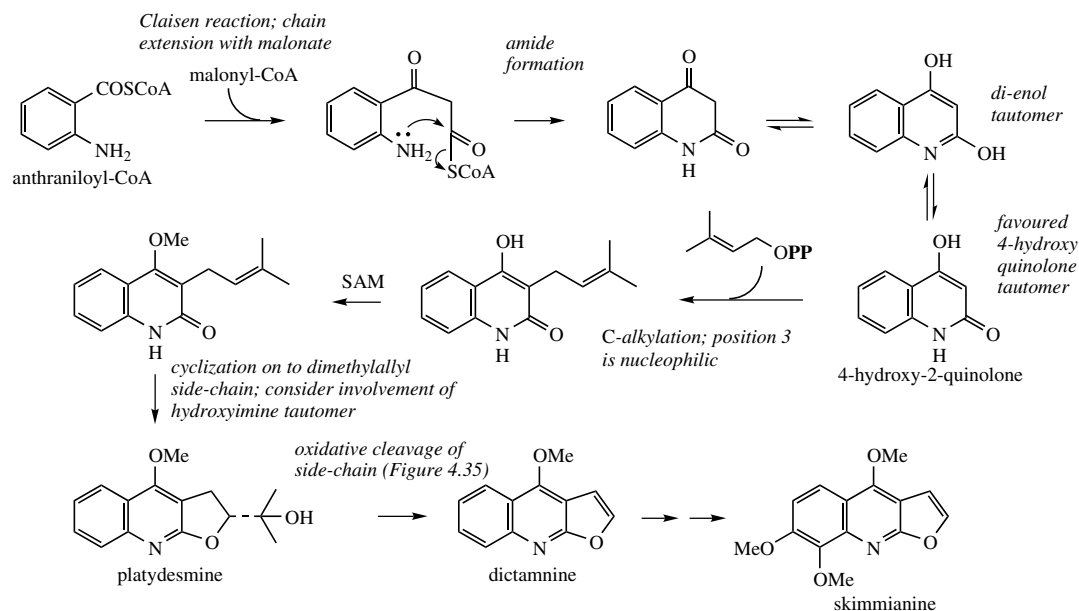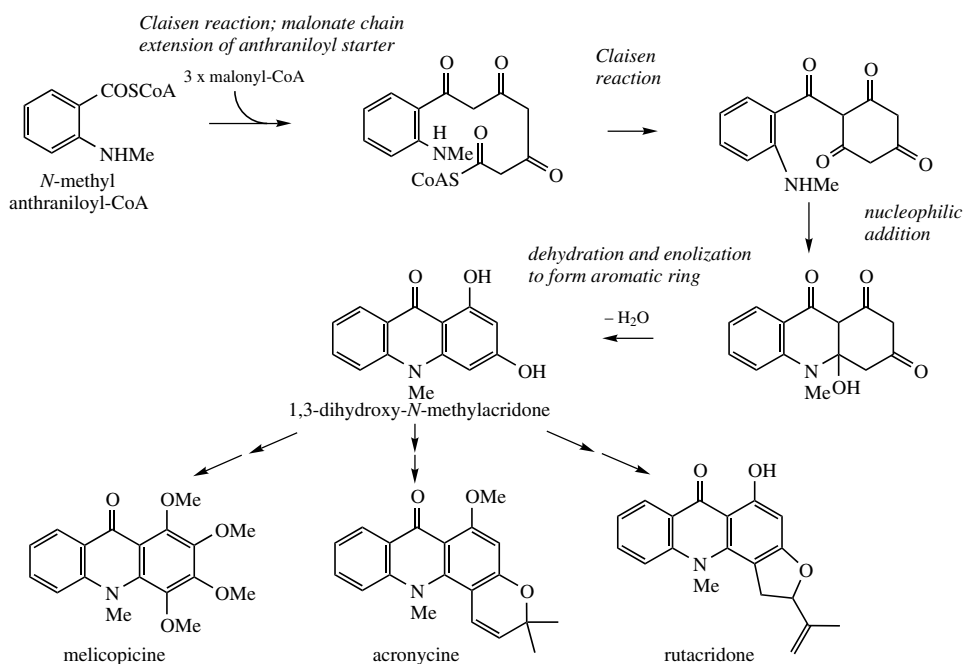
Figure 6.108

Figure 6.109

formation generates the heterocyclic system, which will adopt the more stable 4-hydroxy-2-quinolone form (Figure 6.108). Position 3 is highly nucleophilic and susceptible to alkylation, especially via dimethylallyl diphosphate in the case of

these alkaloids. This allows formation of additional six- and five-membered oxygen heterocyclic rings, as seen with other systems, e.g. coumarins, isoflavonoids, etc (see pages 145, 155). By an analogous series of reactions, the dimethylallyl

derivative can act as a precursor of furoquino-line alkaloids such as **dictamnine** and **skimmianine** (Figure 6.108). These alkaloids are found in both *Dictamnus albus* and *Skimmia japonica* (Rutaceae). To simplify the mechanistic interpretation of these reactions, it is more convenient to consider the di-enol form of the quinolone system.

Should chain extension of anthranilyl-CoA (as the *N*-methyl derivative) incorporate three acetate/malonate units, a polyketide would result (Figure 6.109). The acridine skeleton is then produced by sequential Claisen reaction and C−N linkage by an addition reaction, dehydration, and enolization leading to the stable aromatic tautomer. Again, the acetate-derived ring, with its alternate oxygenation, is susceptible to electrophilic attack, and this can lead to alkylation (with dimethylallyl diphosphate) or further hydroxylation. Alkaloids **melicopicine** from *Melicope fareana*, **acronycine** from *Acronychia baueri*, and **rutacridone** from *Ruta graveolens* (Rutaceae) typify some of the structural variety that may then ensue (Figure 6.109).

ALKALOIDS DERIVED FROM HISTIDINE

Imidazole Alkaloids

The amino acid L-**histidine** (Figure 6.110) contains an imidazole ring, and is thus the likely
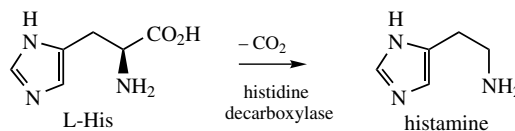
Figure 6.110

presursor of alkaloids containing this ring system. There are relatively few examples, however, and definite evidence linking them to histidine is often lacking.

Histamine (Figure 6.110) is the decarboxylation product from histidine and is often involved in human allergic responses, e.g. to insect bites or pollens. Stress stimulates the action of the enzyme histidine decarboxylase and histamine is released from mast cells (Figure 6.110). Topical antihistamine creams are valuable for pain relief, and oral antihistamines are widely prescribed for nasal allergies such as hay-fever. Major effects of histamine include dilation of blood vessels, inflammation and swelling of tissues, and narrowing of airways. In serious cases, life-threatening anaphylactic shock may occur, caused by a dramatic fall in in blood pressure.

Histidine is a proven precursor of **dolichotheline** (Figure 6.111) in *Dolichothele sphaerica* (Cactaceae), the remaining carbon atoms originating from leucine via isovaleric acid (see page 197). The imidazole alkaloids found in
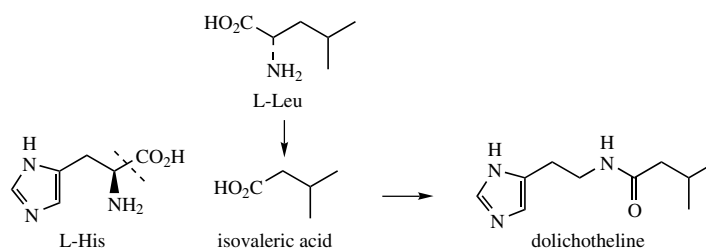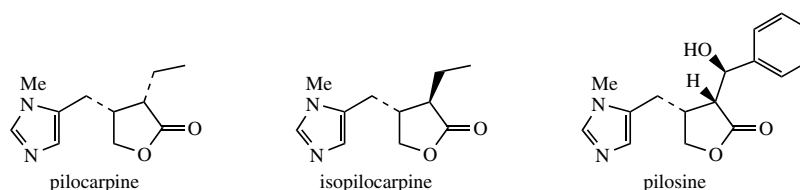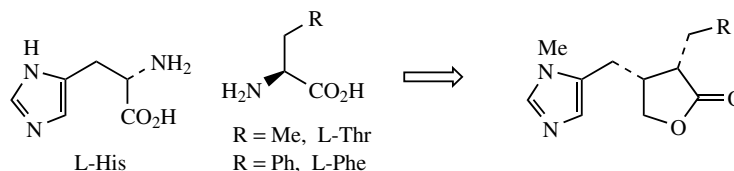
Figure 6.111

Figure 6.112

Figure 6.113

Jaborandi leaves (*Pilocarpus microphyllus* and *P. jaborandi*; Rutaceae)* are also probably derived from histidine, but experimental data are lacking. Jaborandi leaves contain primarily **pilocarpine** and **pilosine** (Figure 6.112). Pilocarpine is valuable in

ophthalmic work as a miotic and as a treatment for glaucoma. Additional carbon atoms may originate from acetate or perhaps the amino acid threonine in the case of pilocarpine, whilst pilosine incorporates a phenylpropane C_6C_3 unit (Figure 6.113).

Pilocarpus

Pilocarpus or jaborandi consists of the dried leaflets of *Pilocarpus jaborandi*, *P. microphyllus*, or *P. pennatifolius* (Rutaceae), small shrubs from Brazil and Paraguay. *Pilocarpus microphyllus* is currently the main source. The alkaloid content (0.5–1.0%) consists principally of the imidazole alkaloid pilocarpine (Figure 6.112), together with small amounts of pilosine (Figure 6.112) and related structures. Isomers such as isopilocarpine (Figure 6.112) and isopilosine are readily formed if base or heat is applied during extraction of the alkaloids. This is a result of enolization in the lactone ring, followed by adoption of the more favourable *trans* configuration rather than the natural *cis*. However, the *iso* alkaloids lack biological activity. The alkaloid content of the leaf rapidly deteriorates on storage.

   Pilocarpine salts are valuable in ophthalmic practice and are used in eyedrops as miotics and for the treatment of glaucoma. Pilocarpine is a cholinergic agent and stimulates the muscarinic receptors in the eye, causing constriction of the pupil and enhancement of outflow of aqueous humour. The structural resemblance to muscarine and acetylcholine is shown in Figure 6.114. Pilocarpine gives relief for both narrow angle and wide angle glaucoma. However, the ocular bioavailability of pilocarpine is low, and it is rapidly eliminated, thus resulting in a rather short duration of action. The effects are similar to those of physostigmine (see page 366) and the two agents are sometimes combined. Pilocarpine is antagonistic to atropine. It has been found that pilocarpine gives relief for dryness of the mouth that results in patients undergoing radiotherapy for mouth and throat cancers. As muscarinic agonists, pilocarpine and analogues are also being investigated for potential treatment of Alzheimer's disease.
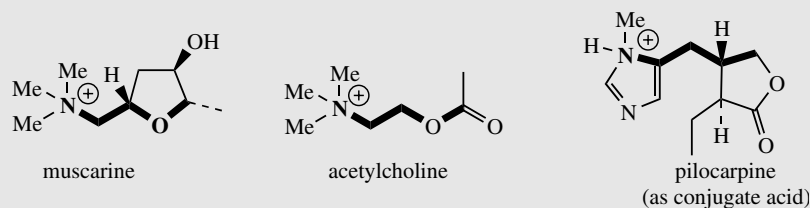

muscarine   acetylcholine   pilocarpine
                                                                       (as conjugate acid)

Figure 6.114

ALKALOIDS DERIVED BY AMINATION REACTIONS

The majority of alkaloids are derived from amino acid precursors by processes that incorporate into the final structure the nitrogen atom together with the amino acid carbon skeleton or a large proportion of it. Many alkaloids do not conform with this description, however, and are synthesized primarily from non-amino acid precursors, with the nitrogen atom being inserted into the structure at a relatively late stage. Such structures are frequently based on terpenoid or steroidal skeletons, though some relatively simple alkaloids also appear to be derived by similar late amination processes. In most of the examples studied, the nitrogen atom is donated from an amino acid source through a transamination reaction with a suitable aldehyde or ketone (see page 20).

Acetate-derived Alkaloids

The poison hemlock (*Conium maculatum**; Umbelliferae/Apiaceae) accumulates a range of simple piperidine alkaloids, e.g. **coniine** and **γ-coniceine** (Figure 6.115). These alkaloids would appear to be related to simple lysine-derived compounds such as pelletierine (see page 307), but, surprisingly, a study of their biosynthetic origins excluded lysine as a precursor, and demonstrated the sequence shown in Figure 6.115 to be operative. A fatty acid precursor, capric (octanoic) acid, is utilized, and this is transformed into the ketoaldehyde by successive oxidation and reduction steps. This ketoaldehyde is then the substrate for a transamination reaction, the amino group originating from L-alanine. Subsequent transformations are imine formation giving the heterocyclic ring of γ-coniceine, and then reduction to **coniine**. **Pinidine** (Figure 6.116) from *Pinus* species is found
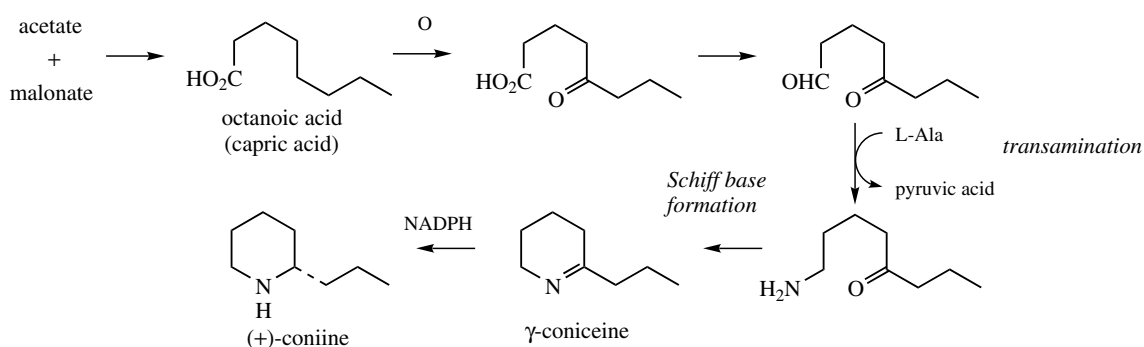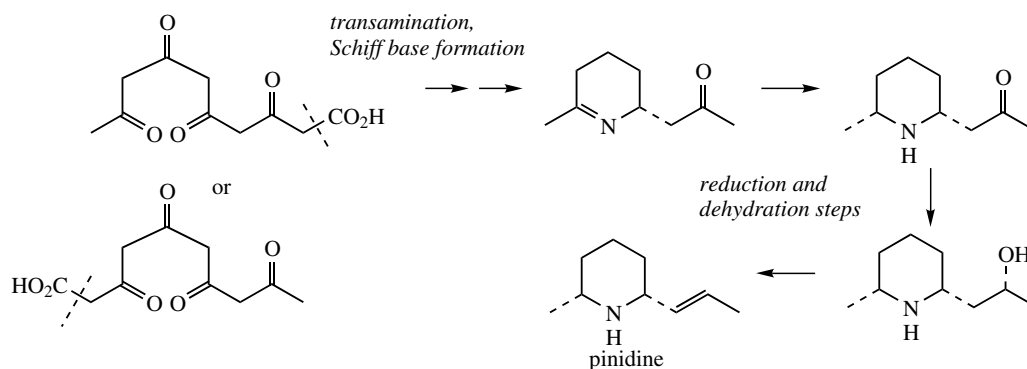

Figure 6.115

Figure 6.116

Conium maculatum

Conium maculatum (Umbelliferae/Apiaceae) or poison hemlock is a large biennial herb indigenous to Europe and naturalized in North and South America. As a common poisonous plant, recognition is important, and this plant can be differentiated from most other members of the Umbelliferae/Apiaceae by its smooth purple-spotted stem. The dried unripe fruits were formerly used as a pain reliever and sedative, but have no medicinal use now. The ancient Greeks are said to have executed condemned prisoners, including Socrates, using poison hemlock. The poison causes gradual muscular paralysis followed by convulsions and death from respiratory paralysis. All parts of the plant are poisonous due to the alkaloid content, though the highest concentration of alkaloids is found in the green fruit (up to 1.6%). The major alkaloid (about 90%) is the volatile liquid coniine (Figure 6.115), with smaller amounts of structurally related piperidine alkaloids, including *N*-methylconiine and γ-coniceine (Figure 6.115).

In North America, the name hemlock refers to species of *Tsuga* (Pinaceae), a group of coniferous trees, which should not be confused with the poison hemlock.

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to have a rather similar origin in acetate, and most likely a poly-β-keto acid. During the sequence outlined in Figure 6.116, the carboxyl group is lost. Note that an alternative folding of the poly-β-keto acid and loss of carboxyl might be formulated.

Phenylalanine-derived Alkaloids

Whilst the aromatic amino acid L-tyrosine is a common and extremely important precursor

of alkaloids (see page 315), L-**phenylalanine** is less frequently utilized, and usually it contributes only carbon atoms, e.g. C_6C_3, C_6C_2, or C_6C_1 units, without providing a nitrogen atom from its amino group (see colchicine, page 342, lobeline, page 308, etc). **Ephedrine** (Figure 6.117), the main alkaloid in species of *Ephedra** (Ephedraceae) and a valuable nasal decongestant and bronchial dilator, is a prime example. Whilst ephedrine contains the same carbon and nitrogen skeleton as seen in phenylalanine, and L-phenylalanine is a
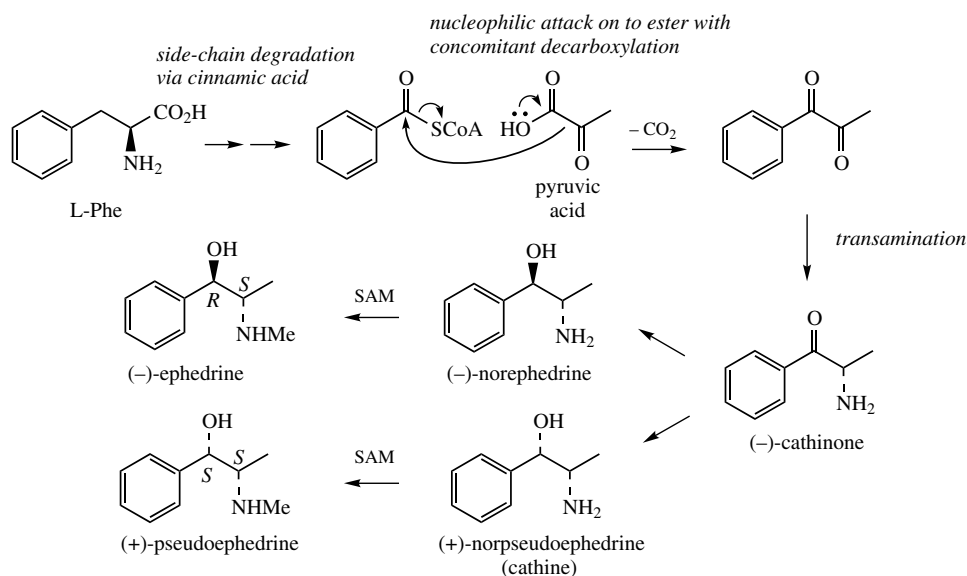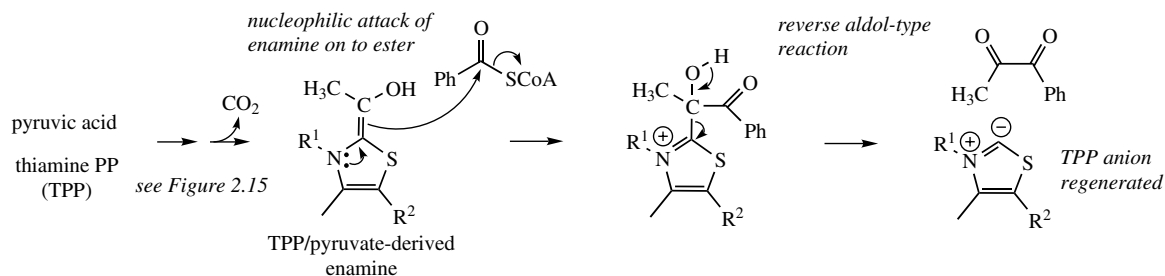

Figure 6.117

Figure 6.118

precursor, only seven carbons, a C_6C_1 fragment, are actually incorporated. It is found that phenylalanine is metabolized, probably through cinnamic acid to benzoic acid (see page 141), and this, perhaps as its coenzyme A ester, is acylated with pyruvate, decarboxylation occurring during the addition (Figure 6.117). The use of pyruvate as a nucleophilic reagent in this way is unusual in secondary metabolism, but occurs in primary metabolism during isoleucine and valine biosynthesis. A thiamine PP-mediated mechanism is suggested (Figure 6.118; compare decarboxylation of pyruvate, page 21, and formation of deoxyxylulose phosphate, page 170). This process yields the diketone, and a transamination reaction would then give **cathinone** (Figure 6.115). Reduction of the carbonyl group from either face provides the diastereomeric **norephedrine** or **norpseudoephedrine** (**cathine**). Finally, *N*-methylation would provide **ephedrine** or **pseudoephedrine** (Figure 6.117). Typically, all four of the latter compounds can be found in *Ephedra* species, the proportions varying according to species. Norpseudoephedrine is also a major constituent of the leaves of khat* (*Catha edulis*; Celastraceae), chewed in African and Arab countries as a stimulant. Most of the CNS stimulant action comes

from the more active cathinone, the corresponding carbonyl derivative. These natural compounds are structurally similar to the synthetic amfetamine/dexamfetamine; (amphetamine/dexamphetamine) (Figure 6.119) and have similar properties.
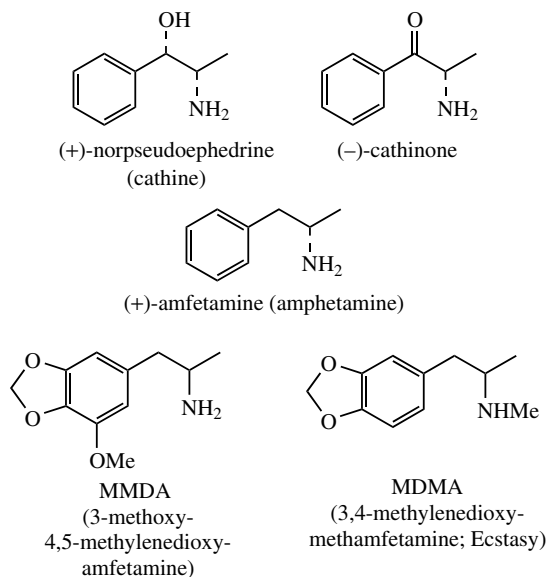

Figure 6.119

Ephedra

Ephedra or Ma Huang is one of the oldest known drugs, having being used by the Chinese for at least 5000 years. It consists of the entire plant or tops of various *Ephedra* species (Ephedraceae), including *E. sinica* and *E. equisetina* from China, and *E. geriardiana*, *E. intermedia* and *E. major* from India and Pakistan. The plants are small bushes with slender aerial stems and minute leaves, giving the appearance of being effectively leafless. The plants typically contain 0.5–2.0% of alkaloids, according to species, and from 30–90%

(*Continues*)

(Continued)

of the total alkaloids is (−)-ephedrine (Figure 6.117). Related structures, including the diastereoisomeric (+)-pseudoephedrine and the demethyl analogues (−)-norephedrine and (+)-norpseudoephedrine (Figure 6.117) are also present. In *E. intermedia*, the proportion of pseudoephedrine exceeds that of ephedrine.

Ephedrine is an indirectly acting sympathomimetic amine with effects similar to noradrenaline (see page 317). Lacking the phenolic groups of the catecholamines, it has only weak action on adrenoreceptors, but it is able to displace noradrenaline from storage vesicles in the nerve terminals, which can then act on receptors. It is orally active and has a longer duration of action than noradrenaline. It also has bronchodilator activity, giving relief in asthma, plus a vasoconstrictor action on mucous membranes, making it an effective nasal decongestant. **Pseudoephedrine** is also widely used in compound cough and cold preparations and as a decongestant. The ephedrine and pseudoephedrine used medicinally are usually synthetic. One commercial synthesis of ephedrine involves a fermentation reaction on benzaldehyde using brewer's yeast (*Saccharomyces* sp.), giving initially an alcohol, then reductive condensation with methylamine yields (−)-ephedrine with very high enantioselectivity (Figure 6.120). The fermentation reaction is similar to that shown in Figure 6.118, in that an activated acetaldehyde bound to TPP is produced by the yeast by decarboxylation of pyruvate, and this unit is added stereospecifically to benzaldehyde in an aldol-like reaction.

The herbal drug ephedra/Ma Huang is currently being traded as 'herbal ecstasy'. Consumption gives CNS stimulation, but in high amounts can lead to hallucinations, paranoia, and psychosis.
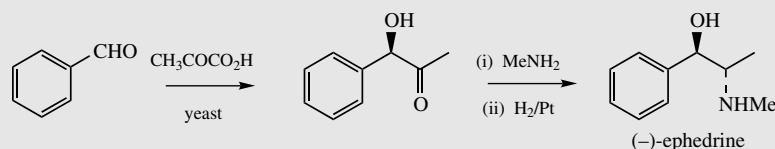

Figure 6.120

Khat

Khat, or Abyssinian tea, consists of the fresh leaves of *Catha edulis* (Celastraceae), a small tree cultivated in Ethiopia, East and South Africa, and the Yemen. The leaves are widely employed in African and Arabian countries, where they are chewed for a stimulant effect. This traditional use alleviates hunger and fatigue, but also gives a sensation of general well-being (compare coca, page 302). Users become cheerful and talkative, and khat has become a social drug. Prolonged usage can lead to hypertension, insomnia, or even mania. Khat consumption may lead to psychological dependence, but not normally physical dependence. There is presently little usage outside of Africa and Arabia, although this is increasing due to immigration from these areas. However, for maximum effects, the leaves must be fresh, and this somewhat restricts international trade. Dried leaves contain up to 1% cathine ((+)-norpseudoephedrine (Figure 6.119)), but young fresh leaves contain (−)-cathinone (Figure 6.119) as the principal CNS stimulant. Cathinone has similar pharmacological properties as the synthetic CNS stimulant (+)-amfetamine/dexamfetamine (amphetamine/dexamphetamine) (Figure 6.119), with a similar potency. Both compounds act by inducing release of catecholamines.

(Continues)

Medicinal use of amfetamine has declined markedly as drug dependence and the severe depression generated on withdrawal have been appreciated. Nevertheless, amfetamine abuse is significant. Amfetamines are taken orally, sniffed, or injected to give a long period of CNS stimulation (hours to days). Users often then take a depressant drug (alcohol, barbiturates, opioids) to terminate the effects. Users rapidly become dependent and develop tolerance. The consumption of khat is not yet restricted in the UK, even though both cathine and cathinone are now controlled drugs. It remains to be seen whether khat will be reclassified and its use restricted in any way. Other amfetamine-like derivatives of note are methoxymethylenedioxyamfetamine (MMDA) and methylenedioxymethamfetamine (MDMA) (Figure 6.119). MMDA is thought to be formed in the body after ingestion of nutmeg (*Myristica fragrans*; Myristicaceae), by an amination process on myristicin (see page 138), and it may be the agent responsible for the euphoric and hallucinogenic effects of nutmeg. MDMA is the illicit drug Ecstasy, a synthetic amfetamine-like stimulant popular among young people. The use of Ecstasy has resulted in a number of deaths, brought about by subsequent heatstroke and dehydration.
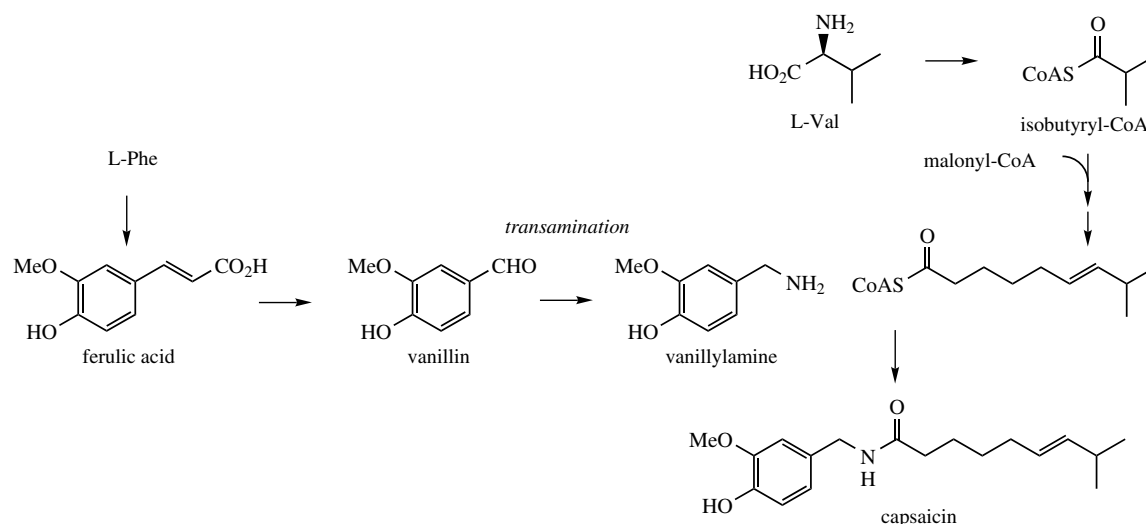

Figure 6.121

The amide **capsaicin** (Figure 6.121) constitutes the powerfully pungent principle in chilli peppers (*Capsicum annuum*; Solanaceae). Apart from its culinary importance, it is also used medicinally in creams to counter neuralgia caused by herpes infections and in other topical pain-relieving preparations. The initial burning effect of capsaicin is found to affect the pain receptors, making them less sensitive. The aromatic portion of capsaicin is derived from phenylalanine through ferulic acid and vanillin (Figure 6.121, compare page 141), this aldehyde being the substrate for

transamination to give vanillylamine. The acid portion of the amide structure is of polyketide origin, with a branched-chain fatty acyl-CoA being produced by chain extension of isobutyryl-CoA. This starter unit is valine derived (see page 197).

Terpenoid Alkaloids

A variety of alkaloids based on mono-, sesqui-, di-, and tri-terpenoid skeletons have been characterized, but information about their formation in nature is still somewhat sparse. Monoterpene alkaloids are in

the main structurally related to iridoid materials (see page 187), the oxygen heterocycle being replaced by a nitrogen-containing ring. **β-Skytanthine** from *Skytanthus acutus* (Apocynaceae) and **actinidine** from *Actinidia polygama* (Actinidiaceae) serve as examples (Figure 6.122). The iridoid loganin, so important in the biosynthesis of terpenoid indole alkaloids (see page 350) and the ipecac alkaloids (see page 343), is not a precursor of these structures, and a modified series of reactions starting from geraniol is proposed (Figure 6.122). The formation of the dialdehyde follows closely elaboration of its stereoisomer in loganin biosynthesis (see page 189). This could then act as a substrate for amination via an amino acid, followed by ring formation as

seen with coniine (see page 381). Reduction and methylation would yield **β-skytanthine**, whereas further oxidation could provide the pyridine ring of **actinidine**. Valerian root (*Valeriana officinalis*; Valerianaceae) (see page 190) is known to contain alkaloids such as that shown in Figure 6.122, as well as iridoid structures. Whilst this alkaloid may be the result of *N*-alkylation on actinidine, an alternative pathway in which tyramine is condensed with the dialdehyde could be proposed. In the latter case, this alkaloid could be regarded as an alkaloid derived from tyrosine, rather than in this group of terpenoid alkaloids.

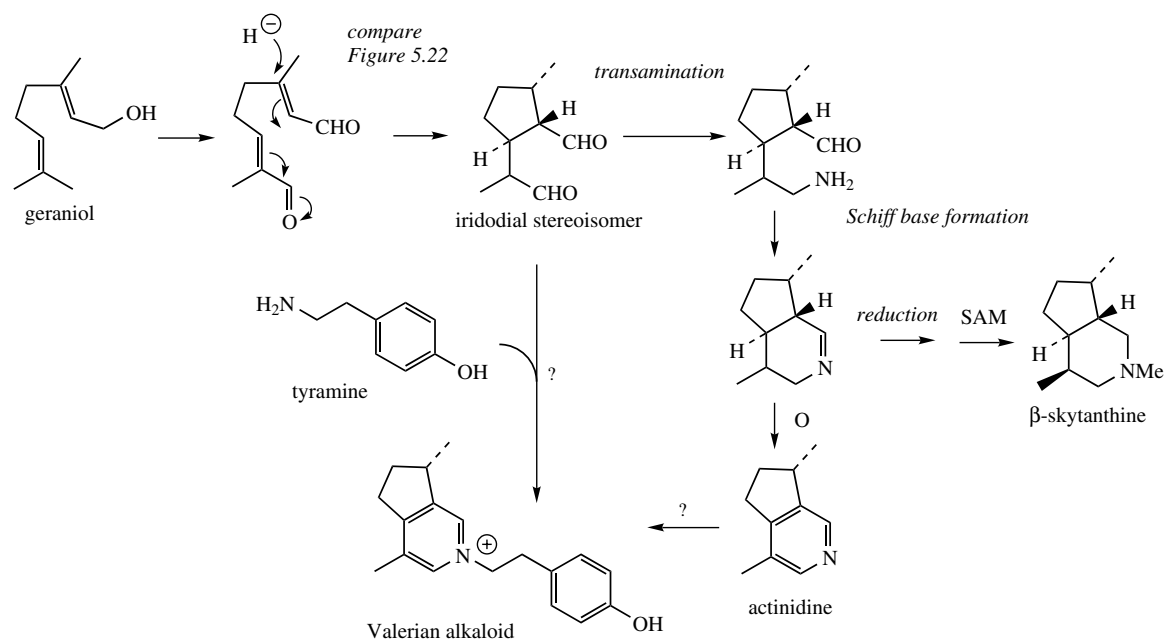**Gentianine** (Figure 6.123) is probably the most common of the monoterpene alkaloids, but it is
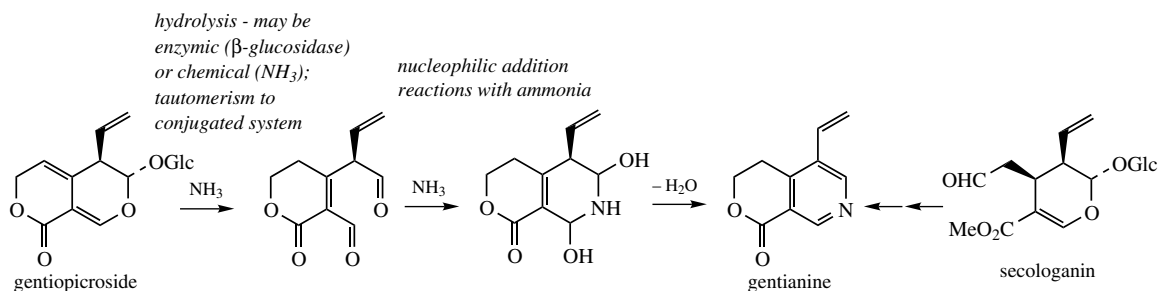

Figure 6.122

Figure 6.123

sometimes formed as an artefact when a suitable plant extract is treated with ammonia, the base commonly used during isolation of alkaloids. Thus, **gentiopicroside** (see page 190) from *Gentiana lutea* (Gentianaceae) is known to react with ammonia to give gentianine (Figure 6.123). Many other iridoid structures are known to react with ammonia to produce alkaloid artefacts. In some plants, gentianine can be found when no ammonia treatment has been involved, and one may speculate that loganin and secologanin may be precursors.

Perhaps the most important examples of terpenoid alkaloids from a pharmacological point of view are those found in aconite* or wolfsbane (*Aconitum* species; Ranunculaceae) and species of *Delphinium* (Ranunculaceae). Whilst *Aconitum*

napellus has had some medicinal uses, plants of both genera owe their highly toxic nature to diterpenoid alkaloids. Aconite in particular is regarded as extremely toxic, due to the presence of **aconitine** (Figure 6.124) and related C_{19} norditerpenoid alkaloids. Species of *Delphinium* accumulate diterpenoid alkaloids such as **atisine** (Figure 6.124), which tend to be less toxic than aconitine. An appreciation of their structural relationship to diterpenes, e.g. *ent*-**kaurene** (see page 208), is given in Figure 6.125, though little experimental evidence is available. It appears feasible that a pre-*ent*-kaurene carbocation undergoes Wagner–Meerwein rearrangements, and that the atisine skeleton is then produced by incorporating an $N-CH_2CH_2-O$ fragment (e.g.
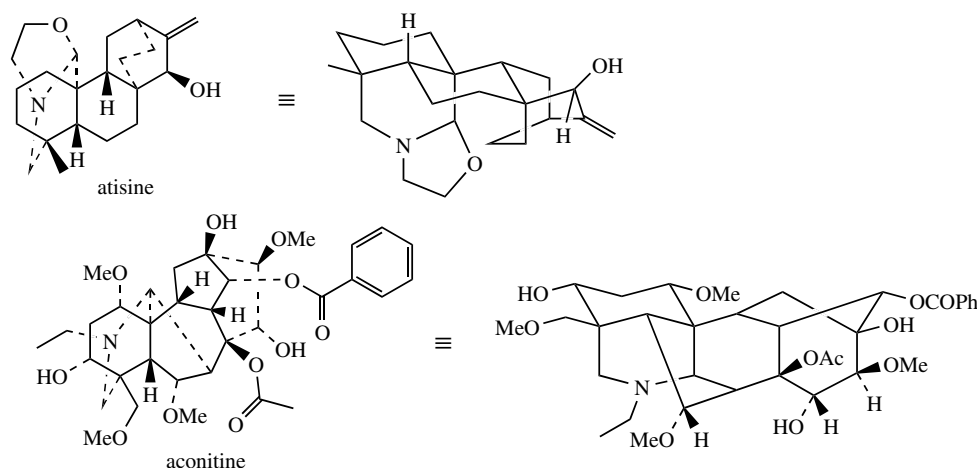

Figure 6.124

Aconite

Aconites, commonly called wolfsbane or monkshood, are species of *Aconitum* (Ranunculaceae), valued ornamental herbaceous plants, grown for their showy blue or purple flowers, which are shaped like a monk's cowl. Their alkaloid content, mainly in the roots, makes them some of the most toxic plants commonly encountered. The dried roots of *Aconitum napellus* were once used, mainly externally for relief of pain, e.g. in rheumatism. The toxic alkaloids (0.3–1.5%) are complex diterpene-derived esters. Aconitine (Figure 6.124) is the principal component (about 30%) and is a diester of aconine with acetic and benzoic acids. Hydrolysis products benzoylaconine and aconine are also present in dried plant material. These alkaloids appear to behave as neurotoxins by acting on sodium channels. All species of *Aconitum* and *Delphinium* are potentially toxic to man and animals and must be treated with caution.
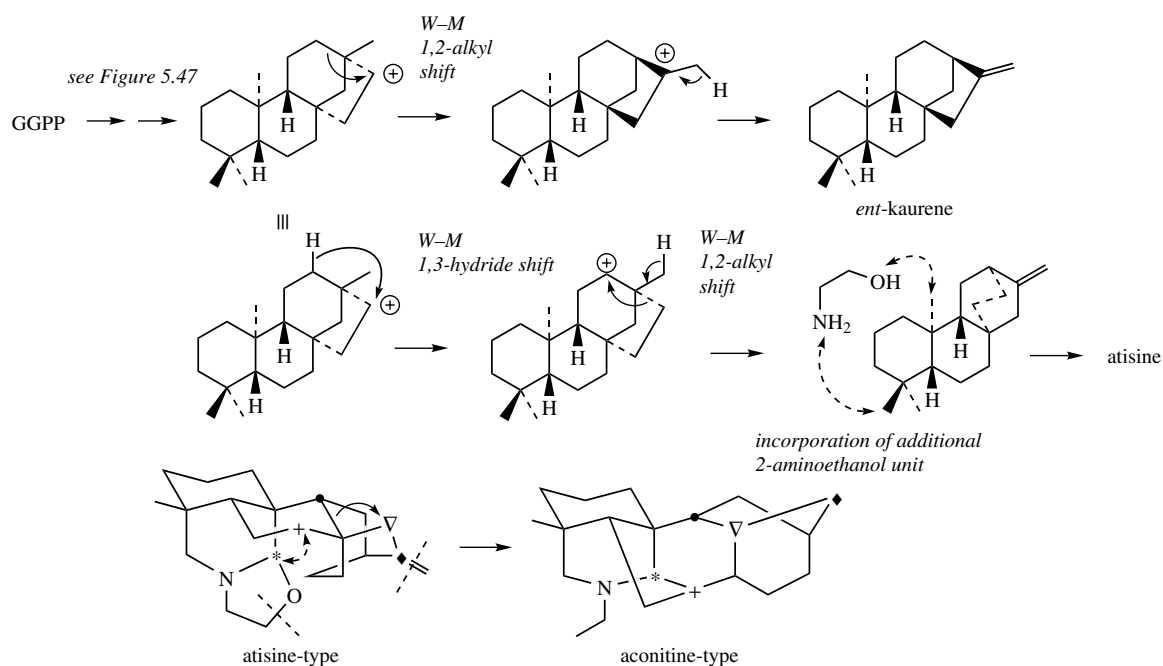
Figure 6.125

from 2-aminoethanol) to form the heterocyclic rings. The aconitine skeleton is probably formed from the atisine skeleton by further modifications as indicated. Note that a rearrangement process converts two fused six-membered rings into a $(7 + 5)$-membered bicyclic system, and that one carbon, that from the exocyclic double bond, is lost.

Steroidal Alkaloids

Many plants in the Solanaceae accumulate steroidal alkaloids based on a C_{27} cholestane skeleton, e.g. **solasodine** and **tomatidine** (Figure 6.126). These are essentially nitrogen analogues of steroidal saponins (see page 240) and have already been briefly considered along with these compounds. In contrast to the oxygen analogues, these compounds all have the same stereochemistry at C-25 (methyl always equatorial), but C-22 isomers do exist, as solasodine and tomatidine exemplify. They are usually present as glycosides which have surface activity and haemolytic properties as do the saponins, but these compounds are also toxic if ingested. **Solasonine** from *Solanum* species and **tomatine** (Figure 6.126) from tomato

(*Lycopersicon esculente*) are typical examples of such glycosides.

As with the sapogenins, this group of steroidal alkaloids is derived from cholesterol, with appropriate side-chain modifications during the sequence (Figure 6.127). Amination appears to employ L-arginine as the nitrogen source, probably via a substitution process on 26-hydroxycholesterol. A second substitution allows 26-amino-22-hydroxycholesterol to cyclize, generating a piperidine ring. After 16β-hydroxylation, the secondary amine is oxidized to an imine, and the spiro-system can be envisaged as the result of a nucleophilic addition of the 16β-hydroxyl on to the imine (or iminium via protonation). Whether the 22R (as in **solasodine**) or 22S (as in **tomatidine**) configuration is established may depend on this reaction.

A variant on the way the cholesterol side-chain is cyclized can be found in **solanidine** (Figure 6.126), which contains a condensed ring system with nitrogen at the bridgehead. Solanidine is found in potatoes (*Solanum tuberosum*), typically as the glycoside **α-solanine** (Figure 6.126). This condensed ring system appears to be produced by a branch from the main pathway to solasodine/
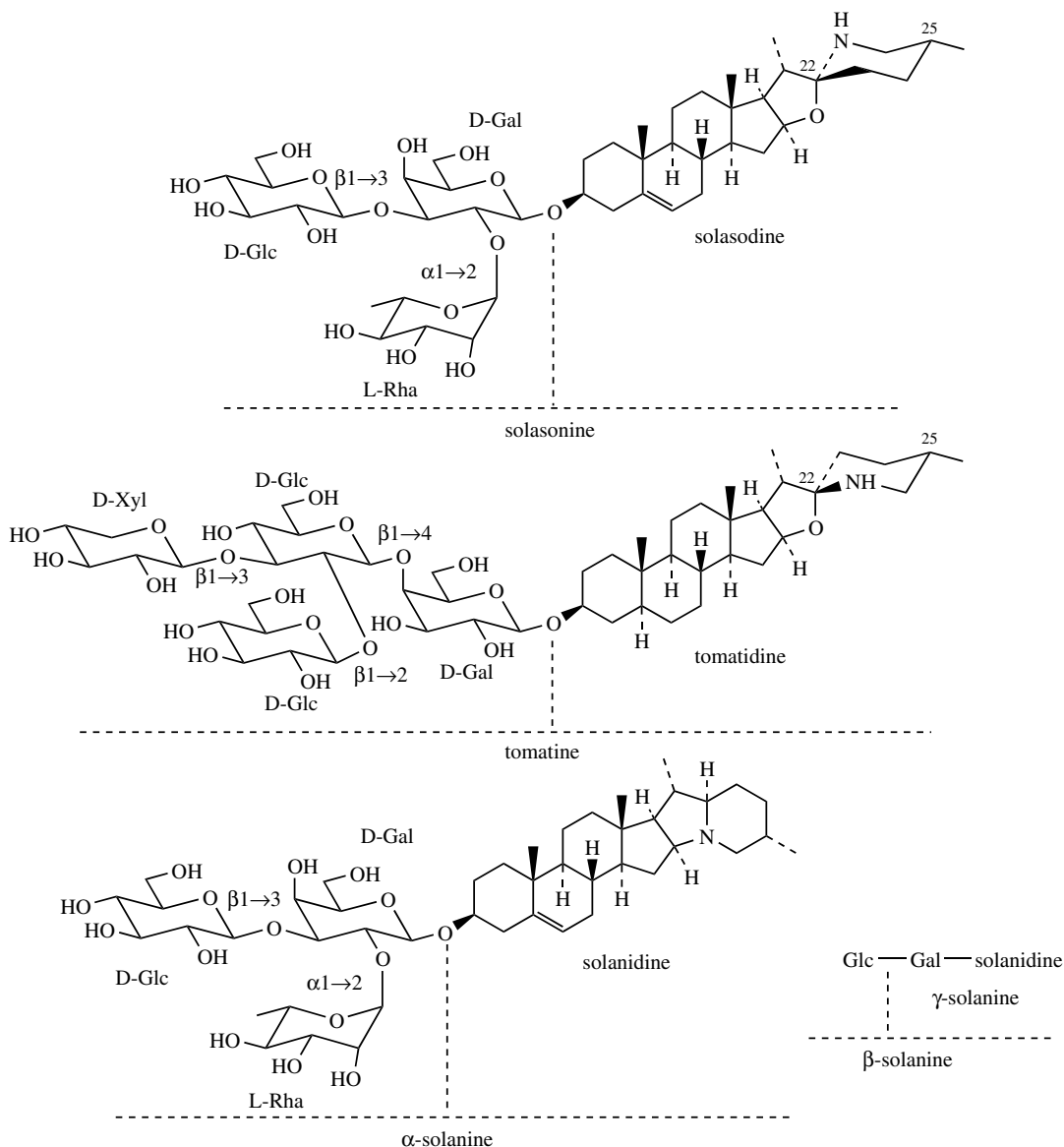
Figure 6.126

tomatidine structures. Thus, a substitution process will allow generation of the new ring system (Figure 6.128).

Since the production of medicinal steroids from steroidal saponins (see page 266) requires preliminary degradation to remove the ring systems containing the original cholesterol side-chain, it is immaterial whether these rings contain oxygen or nitrogen. Thus, plants rich in **solasodine** or **tomatidine** could also be employed for commercial steroid

production. Similarly, other *Solanum* alkaloids* such as **solanidine** with nitrogen in a condensed ring system might also be exploited.

Several plants in the Liliaceae, notably the genus *Veratrum* (Liliaceae/Melanthiaceae), contain a remarkable group of steroidal alkaloids in which a fundamental change to the basic steroid nucleus has taken place. This change expands ring D by one carbon at the expense of ring C, which consequently becomes five-membered.
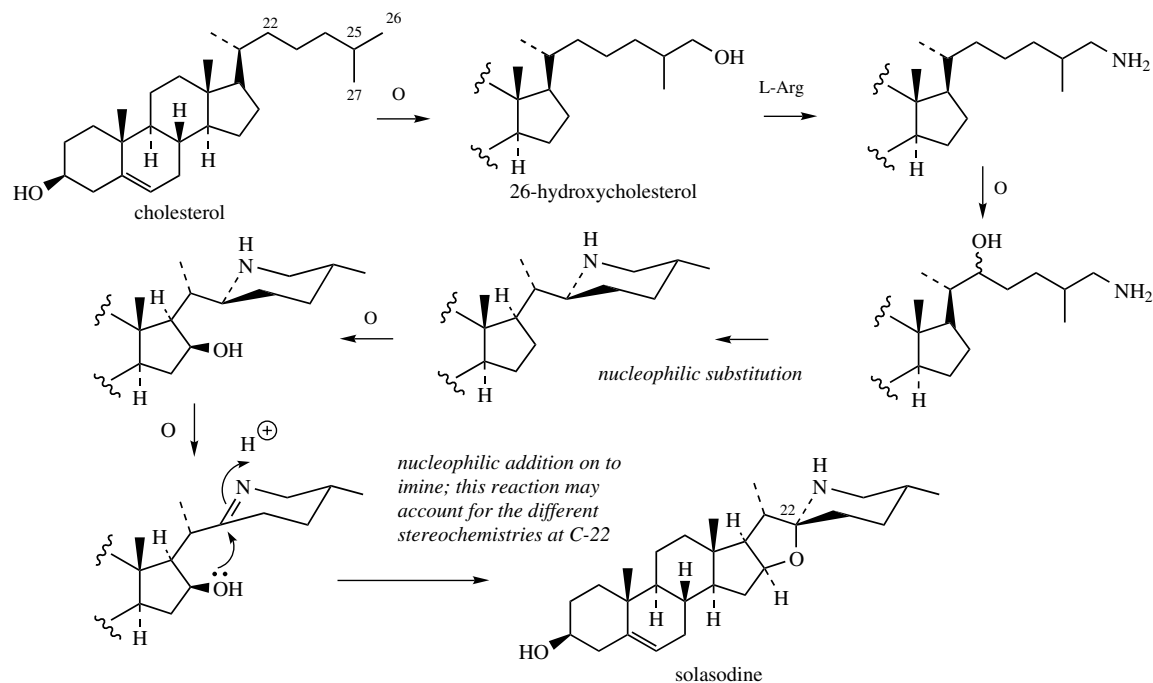
Figure 6.127
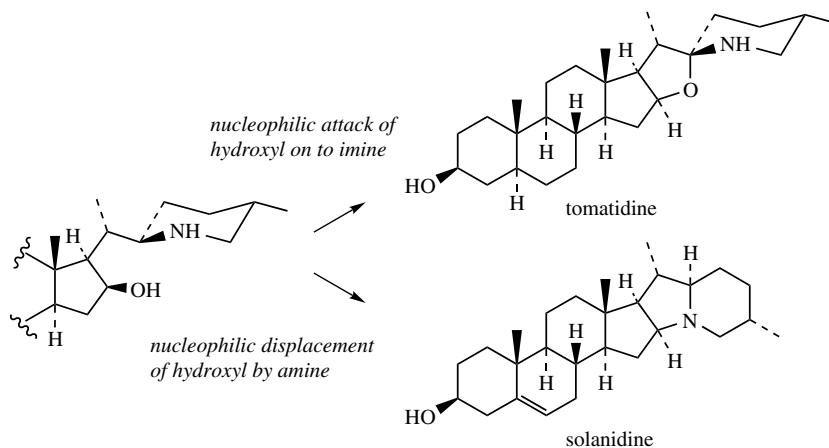
Figure 6.128

The resulting skeleton is termed a C-nor-D-homosteroid in keeping with these alterations in ring size. Cholesterol is a precursor of this group of alkaloids, and a mechanism accounting for the ring modifications is shown in Figure 6.129, where the changes are initiated by loss of a suitable leaving group from C-12. Typical representatives of C-nor-D-homosteroids are **jervine** and **cyclopamine**

(Figure 6.130) from *Veratrum californicum*, toxic components in this plant that are responsible for severe teratogenic effects. Animals grazing on *V. californicum* and some other species of *Veratrum* frequently give birth to young with cyclopia, a malformation characterized by a single eye in the centre of the forehead. The teratogenic effects of jervine, cyclopamine, and cyclopamine

Solanum Alkaloids

Solasodine (Figure 6.126) is a major component in many *Solanum* species, where it is present as glycosides in the leaves, and especially in the unripe fruits. Trial cultivations of a number of species, including *Solanum laciniatum* and *S. aviculare* (indigenous to New Zealand), *S. khasianum* (from India), and *S. marginatum* (from Ecuador), have been conducted in various countries. Alkaloid levels of 1–2% have been obtained, and these plants are especially suitable for long term cultivation if the fruits provide suitable quantities, being significantly easier to cultivate than disogenin-producing *Dioscorea* species. Solasodine may be converted into progesterone by means of the Marker degradation shown in Figure 5.119 (see page 266).
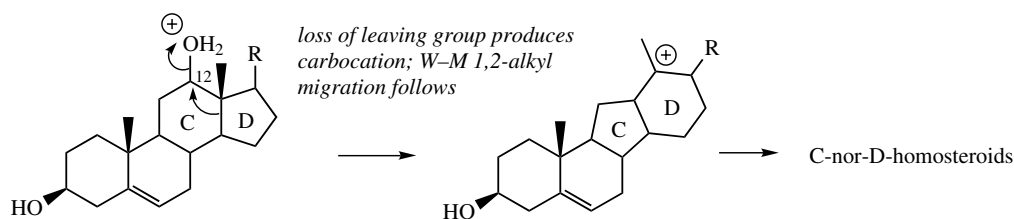

loss of leaving group produces carbocation; W–M 1,2-alkyl migration follows

C-nor-D-homosteroids

Figure 6.129

jervine

cyclopamine

R = H, protoveratrine A
R = OH, protoveratrine B
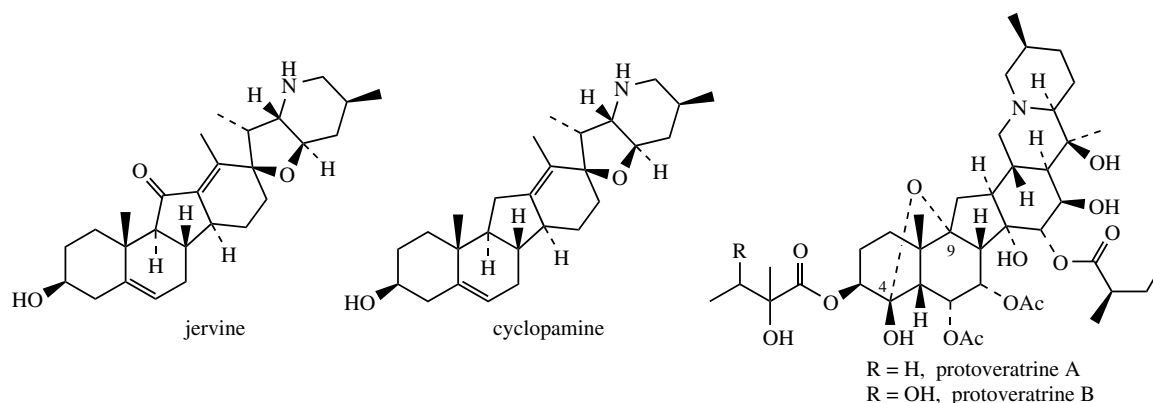
Figure 6.130

glucoside (cycloposine) on the developing fetus have now been well established. Other *Veratrum* alkaloids, especially those found in *V. album* and *V. viride*, have been employed medicinally as hypotensive agents, and used in the same way as *Rauwolfia* alkaloids (see page 352), often in combination with *Rauwolfia*. These medicinal alkaloids, e.g. **protoveratrine A** and **protoveratrine B** (Figure 6.130), which are esters of protoverine, are characterized by fusion of

two more six-membered rings on to the C-nor-D-homosteroid skeleton. This hexacyclic system is extensively oxygenated, and a novel hemiketal linkage bridges C-9 with C-4. Both the jervine and protoverine skeletons are readily rationalized through additional cyclization reactions involving a piperidine ring, probably formed by processes analogous to those seen with the *Solanum* alkaloids (Figure 6.127). These are outlined in Figure 6.131, which suggests the participation of the piperidine
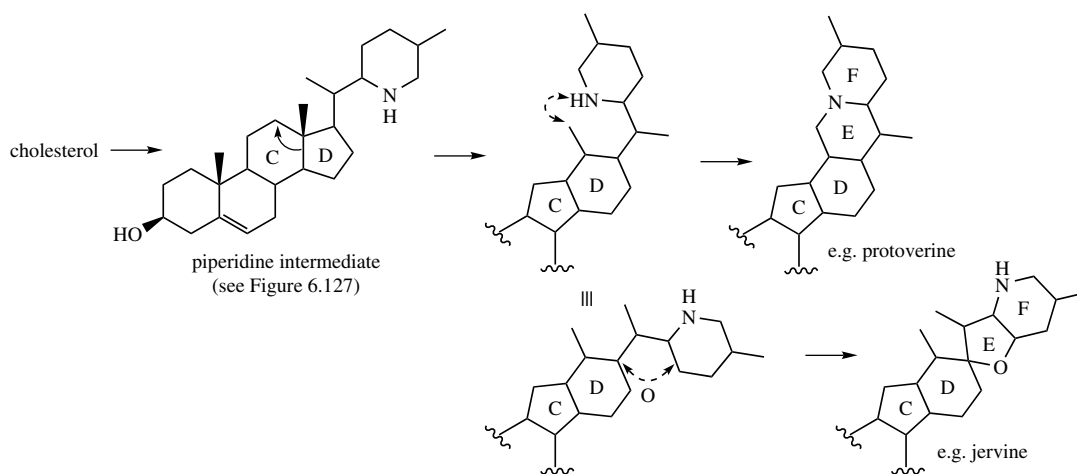
Figure 6.131
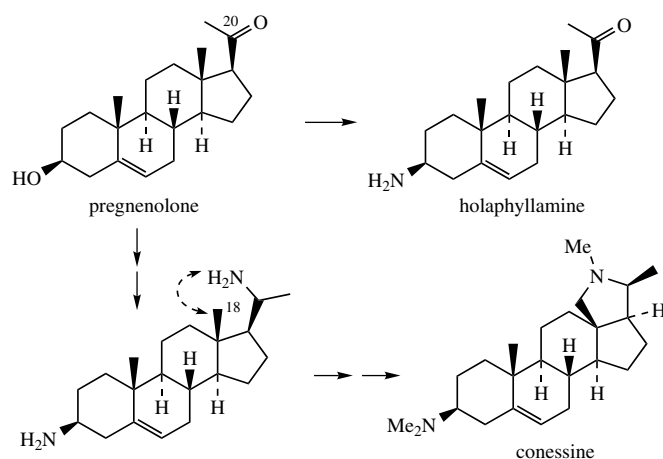
Figure 6.132
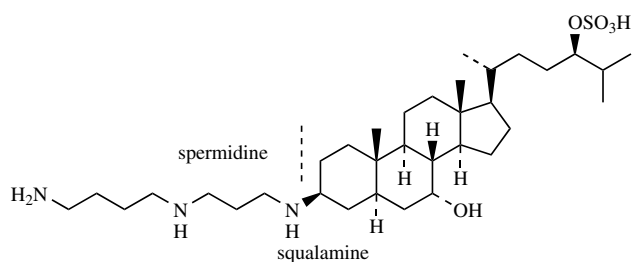
Figure 6.133

intermediate from Figure 6.127. Typically, both types of alkaloid are found co-occurring in *Veratrum* species.

Many steroidal derivatives are formed by truncation of the original C_8 side-chain, and C_{21} pregnane derivatives are important animal hormones (see page 273) or intermediates on the way to other natural steroidal derivatives, e.g. cardioactive glycosides (see page 241). Alkaloids based on a pregnane skeleton are found in plants,

particularly in the Apocynaceae and Buxaceae, and **pregnenolone** (Figure 6.132) is usually involved in their production. **Holaphyllamine** from *Holarrhena floribunda* (Apocynaceae) is obtained from pregnenolone by replacement of the 3-hydroxyl with an amino group (Figure 6.132). **Conessine** (Figure 6.132) from *Holarrhena antidysenterica* is also derived from pregnenolone, and requires two amination reactions, one at C-3 as for holaphyllamine, plus a further one, originally at C-20, probably via the C-20 alcohol. The new ring system in conessine is then the result of attack of the C-20 amine on to the C-18 methyl, suitably activated, of course. The bark of *H. antidysenterica* has long been used, especially in India, as a treatment for amoebic dysentery.

The novel steroidal polyamine **squalamine** (Figure 6.133) has been isolated in very small amounts (about 0.001%) from the liver of the dogfish shark (*Squalus acanthias*), and is

Figure 6.134

Figure 6.135

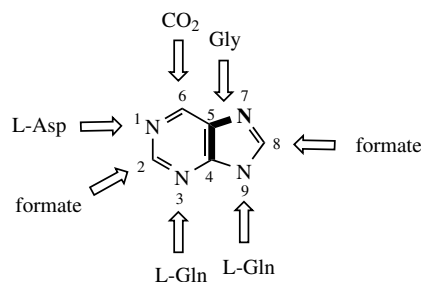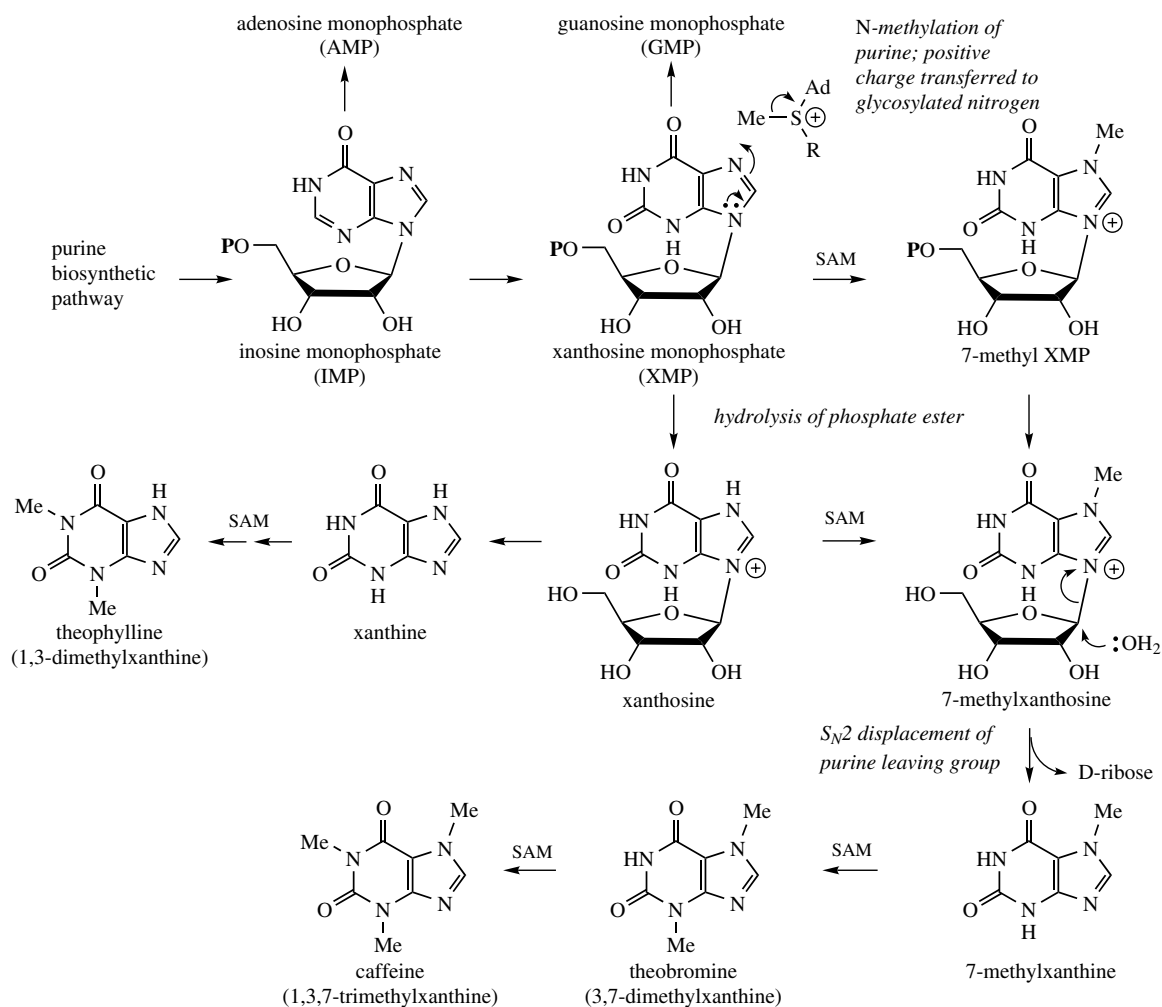attracting attention because of its remarkable antimicrobial activity. This compound is a broad-spectrum agent effective at very low concentrations against Gram-positive and Gram-negative bacteria, and also fungi, protozoa, and viruses including HIV. The sulphated side-chain helps to make squalamine water soluble. The polyamine portion is spermidine, a compound widely distributed in both animals and plants. Related aminosterol derivatives with similar high antimicrobial activity have also been isolated from the liver extracts.

PURINE ALKALOIDS

The purine derivatives **caffeine***, **theobromine***, and **theophylline*** (Figure 6.135) are usually referred to as purine alkaloids. As alkaloids they have a limited distribution, but their origins are very closely linked with those of the purine bases adenine and guanine, fundamental components of nucleosides, nucleotides, and the nucleic acids. Caffeine, in the form of beverages such as tea*, coffee*, and cola* is one of the most widely consumed and socially accepted natural stimulants. It is also used medicinally, but theophylline is

much more important as a drug compound because of its muscle relaxant properties, utilized in the relief of bronchial asthma. Theobromine is a major constituent of cocoa*, and related chocolate products.

The purine ring is gradually elaborated by piecing together small components from primary metabolism (Figure 6.134). The largest component incorporated is glycine, which provides a C_2N unit, whilst the remaining carbon atoms come from formate (by way of N^{10}-formyl-tetrahydrofolate (see page 126)) and bicarbonate. Two of the four nitrogen atoms are supplied by glutamine, and a third by aspartic acid. Synthesis of the nucleotides adenosine 5′-monophosphate (AMP) and guanosine 5′-monophosphate (GMP) is by way of inosine 5′-monophosphate (IMP) and xanthosine 5′-monophosphate (XMP) (Figure 6.135), and the purine alkaloids then branch away through XMP. Methylation, then loss of phosphate, generates the nucleoside **7-methylxanthosine**, which is then released from the sugar. Successive methylations on the nitrogens give **caffeine** by way of **theobromine**, whilst a different methylation sequence can account for the formation of **theophylline**.

Caffeine, Theobromine, and Theophylline

The purine alkaloids caffeine, theobromine, and theophylline (Figure 6.135) are all methyl derivatives of xanthine and they commonly co-occur in a particular plant. The major sources of these compounds are the beverage materials such as tea, coffee, cocoa, and cola, which owe their stimulant properties to these water-soluble alkaloids. They competitively inhibit phosphodiesterase, resulting in an increase in cyclic AMP and subsequent release of adrenaline. This leads to a stimulation of the CNS, a relaxation of bronchial smooth muscle, and induction of diuresis, as major effects. These effects vary in the three compounds. **Caffeine** is the best CNS stimulant, and has weak diuretic action. **Theobromine** has little stimulant action, but has more diuretic activity and also muscle relaxant properties. **Theophylline** also has low stimulant action and is an effective diuretic, but it relaxes smooth muscle better than caffeine or theobromine.

Caffeine is used medicinally as a CNS stimulant, usually combined with another therapeutic agent, as in compound analgesic preparations. **Theobromine** is of value as a diuretic and smooth muscle relaxant, but is not now routinely used. **Theophylline** is an important smooth muscle relaxant for relief of bronchospasm, and is frequently dispensed in slow-release formulations to reduce side-effects. It is also available as **aminophylline** (a more soluble preparation containing theophylline with ethylenediamine) and **choline theophyllinate** (theophylline and choline). The alkaloids may be isolated from natural sources, or obtained by total or partial synthesis.

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It has been estimated that beverage consumption may provide the following amounts of caffeine per cup or average measure: coffee, 30–150 mg (average 60–80 mg); instant coffee, 20–100 mg (average 40–60 mg); decaffeinated coffee, 2–4 mg; tea, 10–100 mg (average 40 mg); cocoa, 2–50 mg (average 5 mg); cola drink, 25–60 mg. The maximal daily intake should not exceed about 1 g to avoid unpleasant side-effects, e.g. headaches, restlessness. An acute lethal dose is about 5–10 g. The biological effects produced from the caffeine ingested via the different drinks can vary, since its bioavailability is known to be modified by the other constituents present, especially the amount and nature of polyphenolic tannins.

Coffee

Coffee consists of the dried ripe seed of *Coffea arabica*, *C. canephora*, *C. liberica*, or other *Coffea* species (Rubiaceae). The plants are small evergreen trees, widely cultivated in various parts of the world, e.g. Brazil and other South American countries, and Kenya. The fruit is deprived of its seed coat, then dried and roasted to develop its characteristic colour, odour, and taste. Coffee seeds contain 1–2% of caffeine and traces of theophylline and theobromine. These are mainly combined in the green seed with chlorogenic acid (see page 132) (5–7%), and roasting releases them and also causes some decomposition of chlorogenic acid to quinic acid and caffeic acid. The nicotinic acid derivative trigonelline is present in green seeds to the extent of about 0.25–1%; during roasting, this is extensively converted into nicotinic acid (vitamin B$_3$, see page 313). Volatile oils and tannins provide odour and flavour. A proportion of the caffeine may sublime off during the roasting process, providing some commercial caffeine. Decaffeinated coffee, containing up to 0.08% caffeine, is obtained by removing caffeine, usually by aqueous percolation prior to roasting. This process provides another source of caffeine.

Tea

Tea is the prepared leaves and leaf buds of *Camellia sinensis* (*Thea sinensis*) (Theaceae), an evergreen shrub cultivated in China, India, Japan, and Sri Lanka. For black tea, the leaves are allowed to ferment, allowing enzymic oxidation of the polyphenols, whilst green tea is produced by steaming and drying the leaves to prevent oxidation. During oxidation, colourless catechins (up to 40% in dried leaf) (see page 150) are converted into intensely coloured theaflavins and thearubigins. Oolong tea is semi-fermented. Tea contains 1–4% caffeine, and small amounts (up to 0.05%) of both theophylline and theobromine. Astringency and flavour come from tannins and volatile oils, the latter containing monoterpene alcohols (geraniol, linalool) and aromatic alcohols (benzyl alcohol, 2-phenylethanol). Theaflavins (see page 151) are believed to act as radical scavengers/antioxidants, and to provide beneficial effects against cardiovascular disease, cancers, and the ageing process generally. Tea leaf dust and waste is a major source of caffeine.

Cola

Cola, or kola, is the dried cotyledon from seeds of various species of *Cola* (Sterculiaceae), e.g. *C. nitida* and *C. acuminata*, trees cultivated principally in West Africa and the West Indies. Seeds are prepared by splitting them open and drying. Cola seeds contain up to 3% caffeine

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and about 0.1% theobromine, partly bound to tannin materials. Drying allows some oxidation of polyphenols, formation of a red pigment, and liberation of free caffeine. Fresh cola seeds are chewed in tropical countries as a stimulant, and vast quantities of dried seeds are processed for the preparation of cola drinks, e.g. Coca-Cola and Pepsi-Cola.

Cocoa

Although cocoa as a drink is now rather unfashionable, it provides the raw material for the manufacture of chocolate and is commercially very important. Cocoa (or cacao) is derived from the roasted seeds of *Theobroma cacao* (Sterculiaceae), a tree widely cultivated in South America and West Africa. The fruits develop on the trunk of the tree, and the seeds from them are separated, allowed to ferment, and are then roasted to develop the characteristic chocolate flavour. The kernels are then separated from the husks, ground up, and processed in various ways to give chocolate, cocoa, and cocoa butter.

Cocoa seeds contain 35–50% of oil (cocoa butter or theobroma oil), 1–4% theobromine and 0.2–0.5% caffeine, plus tannins and volatile oils. During fermentation and roasting, most of the theobromine from the kernel passes into the husk, which thus provides a convenient source of the alkaloid. Theobroma oil or cocoa butter is obtained by hot expression from the ground seeds as a whitish solid with a mild chocolate taste. It is a valuable formulation aid in pharmacy where it is used as a suppository base. It contains glycerides of oleic (35%), stearic (35%), palmitic (26%), and linoleic (3%) acids (see page 44).

Maté Tea

Maté tea is consumed in South America as a stimulant drink. Maté or Paraguay tea consists of the leaves of *Ilex paraguensis* (Aquifoliaceae), South American shrubs of the holly genus. The dried leaf contains 0.8–1.7% caffeine and smaller amounts of theobromine (0.3–0.9%) with little or no theophylline. Considerable amounts (10–16%) of chlorogenic acid (see page 132) are also present.

Guarana

The seeds of the Brazilian plant *Paullinia cupana* (Sapindaceae) are used to make a stimulant drink. Crushed seeds are mixed with water to a paste, which is then sun dried. Portions of this are then boiled with hot water to provide a refreshing drink. The principal constituent, previously called guaranine, has been shown to be identical to caffeine, and the seeds may contain 3–5%. Small amounts of theophylline (0–0.25%) and theobromine (0.02–0.06%) are also present. Guarana is widely available as tablets and capsules, or as extracts, in health food shops where it is promoted to relieve mental and physical fatigue. Labels on such products frequently show the active constituent to be guaranine, but may not indicate that this is actually caffeine.

Saxitoxin and Tetrodotoxin

The structure of **saxitoxin*** (Figure 6.136) contains a reduced purine ring system, but it is not biosynthetically related to the purine alkaloids described above. Not all features of its biosynthetic origin have been established, but the amino acid supplying most of the ring system is known to be L-arginine (Figure 6.136). Acetate and a C_1 unit from methionine are
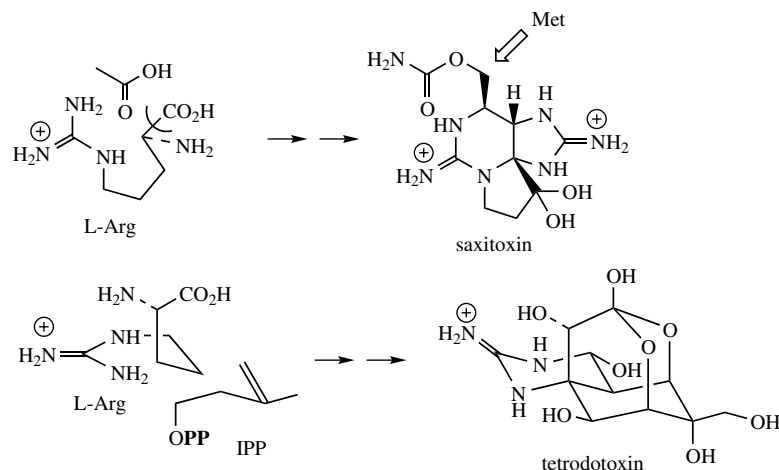
Figure 6.136

also utilized. Saxitoxin contains two highly polar guanidino functions, one of which is provided by arginine, and is a fast acting neurotoxin inhibiting nerve conduction by blocking sodium channels. It is one of a group of marine toxins referred to as paralytic shellfish poisons (PSP) found in a range of shellfish, but ultimately derived from toxic strains of dinoflagellates consumed by the shellfish. Arginine is also a precursor for **tetrodotoxin*** (Figure 6.136), another

marine neurotoxin containing a polar guanidino group. It has been established that the remainder of the carbon skeleton in tetrodotoxin is a C_5 isoprene unit, probably supplied as isopentenyl diphosphate (Figure 6.136). Tetrodotoxin is well known as the toxic principle in the puffer fish (*Tetraodon* species), regarded as delicacy in Japanese cuisine. As potent sodium channel blockers, both saxitoxin and tetrodotoxin are valuable pharmacological tools.

Saxitoxin

Saxitoxin (Figure 6.136) was first isolated from the Alaskan butter clam (*Saxidomus giganteus*) but has since been found in many species of shellfish, especially bivalves such as mussels, scallops, and oysters. These filter feeders consume dinoflagellates (plankton) and can accumulate toxins synthesized by these organisms, particularly during outbreaks known as red tides, when conditions favour formation of huge blooms of the dinoflagellates (see also brevetoxin A, page 109). Species of the dinoflagellate *Gonyaulax* in marine locations, or the cyanobacterium *Aphanizomenon* in freshwater, have been identified among the causative organisms, and the problem is encountered widely in temperate and tropical areas (including Europe, North America, and Japan). Commercial production of shellfish is routinely monitored for toxicity, which will slowly diminish as conditions change and the causative organism disappears from the water. About a dozen natural saxitoxin-related structures have been characterized, and mixtures in various proportions are typically synthesized by a producer, with the possibility that the shellfish may also structurally modify the toxins further. Acute and often fatal poisonings caused by the consumption of contaminated shellfish are termed paralytic shellfish poisoning (PSP), which involves paralysis of the neuromuscular system, death resulting from respiratory failure. Saxitoxin is a cationic molecule, which binds to sodium channels, blocking the influx of sodium ions through excitable nerve membranes,

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and is a valuable pharmacological tool for the study of this process. Saxitoxin and tetrodotoxin (below) are some of the most potent non-protein neurotoxins known, and are active at very low concentrations (μg kg^{-1}).

Tetrodotoxin

Tetrodotoxin (Figure 6.136) is traditionally associated with the puffer fish, *Tetraodon* species, a fish known as fugu, a highly prized delicacy eaten in Japan. Preparation of fugu is a skilled operation in which organs containing the highest levels of toxin, e.g. liver, ovaries, and testes, are carefully separated from the flesh. Even so, deaths from fugu poisoning are not uncommon, and the element of risk presumably heightens culinary appreciation of the fish. As with saxitoxin, tetrodotoxin appears to be produced by microorganisms, and symbiotic marine bacteria, e.g. *Vibrio* species, have been implicated as the synthesizers. In addition to fugu, several other species of fish, newts, and frogs have been found to accumulate tetrodotoxin or related structures. The mode of action of tetrodotoxin is exactly the same as that of saxitoxin above, though there are some subtle differences in the mechanism of binding.

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