THE ALKALOIDS

No other group of natural products has contributed more to medicines and pharmaceutical preparations than the alkaloids. As a group, they display an exceptionally wide array of biological activities and have an equally wide distribution, being present in plants, fungi, bacteria, amphibia, insects, marine animals and man. Plants and fungi rich in these natural products were used by early man to relieve pain, as recreational stimulants or, in religious ceremonies, to enter a psychological state to achieve 'communication' between his ancestors or God. The German pharmacist Karl Friedrich Wilhelm Meissner first coined the term 'alkaloid' in 1818, to describe substances that had alkaline (hence alkaloid) properties. Many alkaloids are, indeed, alkaline in nature (Fig. 6.55) as they possess either a primary, secondary or tertiary amine functional group and the alkaline (basic) properties of these groups may be exploited to aid their extraction and purification (see Chapter 7).

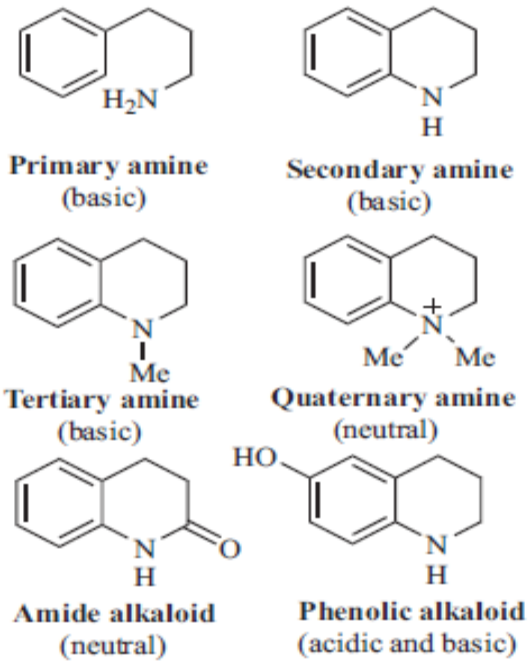


Fig. 6.55

However, some alkaloids exist as quaternary amine salts in which a lone pair of electrons from the nitrogen atom is used to form a bond with another group (e.g. methyl) and, therefore, a positive charge resides on the nitrogen making this group essentially neutral (neither basic nor acidic). Care must, therefore, be taken with the alkali or base definition of alkaloids as some are

neutral, especially the amides (Fig. 6.55),

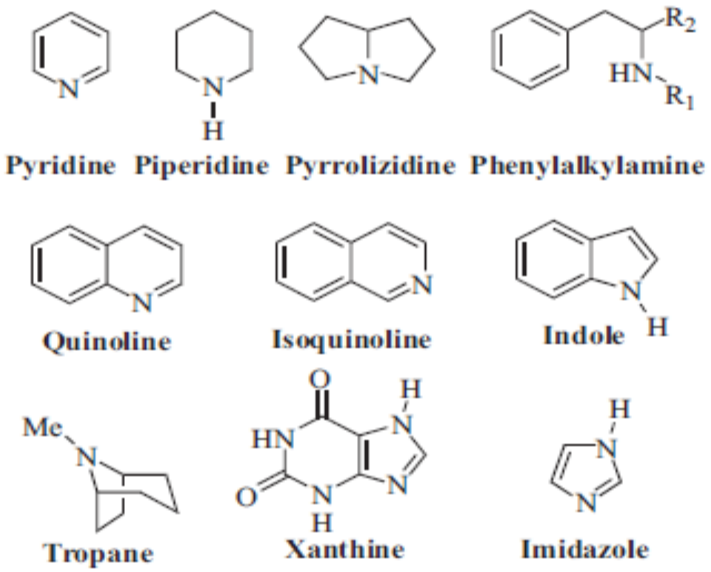


Fig. 6.56

and some alkaloids possess phenolic groups which actually contribute to the acidity of the molecule. Alkaloids may also naturally exist as salts, which are the product of a reaction of a base (alkaloid) and an acid (e.g. sulphuric acid to give the sulphate, or hydrochloric acid to give the hydrochloride). Afurther definition of this group is that they are heterocyclic natural products containing nitrogen, but in our definition we will include compounds that contain nitrogen in an aliphatic chain (e.g. the phenyl-alkylamines; see below). Biosynthetically, the alkaloids are produced from several different amino acids thereby giving rise to a diverse group of fundamental structures (Fig. 6.56). A biosynthetic treatment of this class is outside the scope of this chapter; consequently this group of natural products will be dealt with by alkaloid class.

PYRIDINE, PIPERIDINE AND PYRROLIZIDINE ALKALOIDS

The most widely studied member of the pyridine class is nicotine, the stimulant alkaloidal component of tobacco (Nicotiana tabacum, Solanaceae) (Fig. 6.57), which is responsible for the addictive nature of cigarettes and other tobacco preparations.

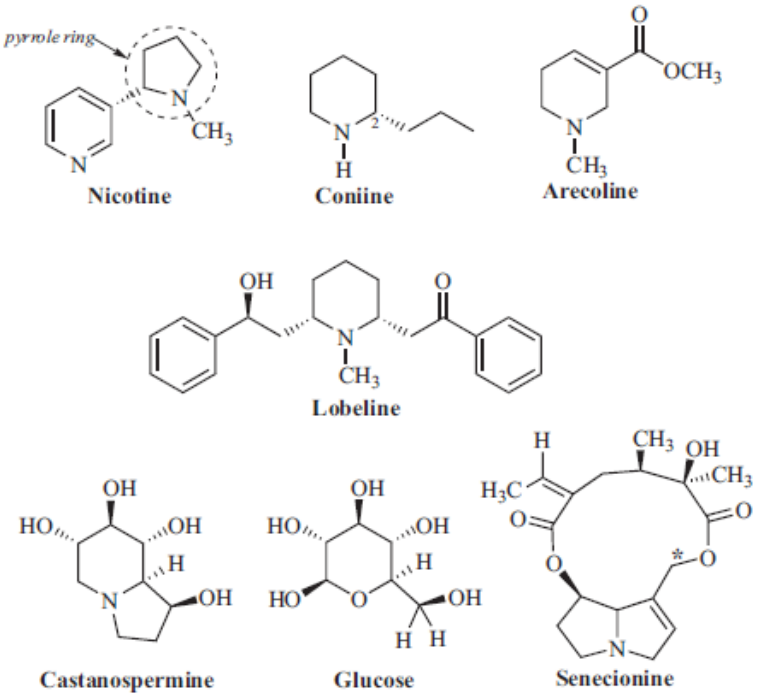


Fig. 6.57

Nicotine is used as a model for addiction to other drugs such as heroin. The compound has a pyrrole ring attached to the pyridine ring. Pharmaceutically, nicotine is formulated into chewing gum as an aid to cessation of smoking in products such as Nicorette. The European plant hemlock (Conium maculatum, Apiaceae) produces the highly poisonous piperidine alkaloid coniine, which has an alkyl (C3) side-chain at the 2-position of the piperidine ring. This plant is famous as it was used to execute the Greek philosopher Socrates who was found guilty of treason and forced to drink a preparation of hemlock. Occasional poisoning with this plant occurs when children use the hollow stems as 'pea shooters' and ingest small quantities of the poison. In the Indian subcontinent, large quantities of betel nuts (Areca catechu, Arecaceae) are consumed by farm workers for their stimulant properties to alleviate fatigue. The nuts are red (due to the presence of tannins), which causes staining of the teeth. These nuts are addictive, the active stimulant component being the piperidine alkaloid arecoline. Like nicotine, arecoline binds to the nicotinic receptors and has a stimulant effect on the CNS. Lobeline is found in the leaves and tops of Lobelia inflata (Campanulaceae),which is also known aswild

tobacco or pukeweed. It has similar effects to those of nicotineandarecoline andhas beenusedas a smoking deterrent. Much work has been done to find alkaloids with activity against HIV of which castanospermine from Castanospermum australe (Fabaceae) is exceptional. This compound is an inhibitor of aglucosidase, an enzymeinvolvedin glycoprotein processing, which is important in the formation of viral coating ,abnormalities of which stop infection of white blood cells. Castanospermine is a polyhydroxylated alkaloid (PHA) and is in fact a sugar analogue (compare with glucose in Fig. 6.57), which explains its activity against the glucosidase enzymes involved in the formation of glycoproteins. The compound is sometimes classified as an indolizidine alkaloid, but, as it also has a piperidine ring system, it is included in this section for convenience. Senecionine is a member of the pyrrolizidine class of alkaloids, which have gained notoriety due to their hepatotoxic properties. These compounds possess a reactive carbon (* in Fig. 6.57), which is readily alkylated by reactive thiol groups present in many enzymes found in the liver. This accounts for the withdrawal of comfrey (Symphytum officinale, Boraginaceae), which has a long history of use as a medicinal plant but also contains these toxic alkaloids. Senecionine occurs in groundsel (Senecio vulgaris, Asteraceae), which is problematic in farms and paddocks where it can cause poisoning of livestock and horses.

PHENYLALKYLAMINE ALKALOIDS

The natural products of this group do not have a cyclic nitrogen atom but have either a free amine or an alkyl-substituted amine. In Chinese medicine, Ma Huang (Ephedra sinica, Ephedraceae) has a long tradition of use as a treatment for colds, asthma and other bronchial conditions. The biologically active component of this species is ephedrine (Fig. 6.58), which possesses CNS stimulatory, vasoconstrictive and bronchodilatory properties. These effects are similar to those of the natural hormone adrenaline (epinephrine), which is

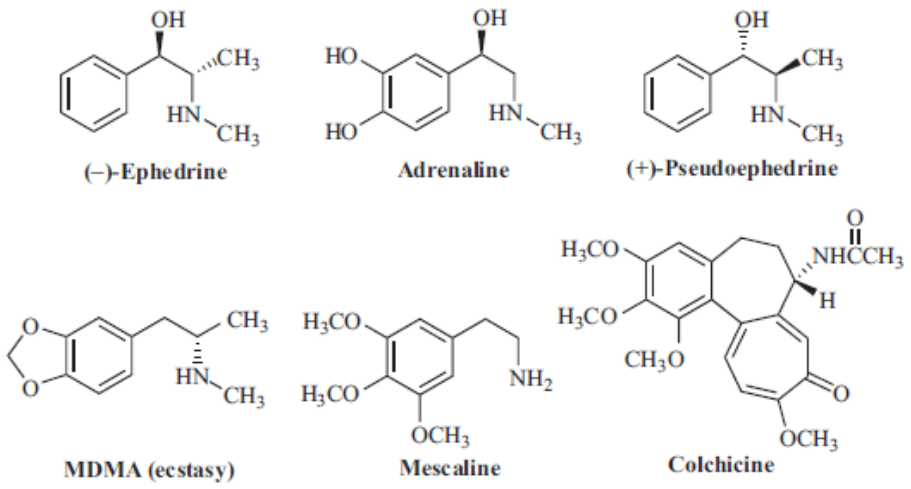


Fig. 6.58

structurally similar (Fig. 6.58). Ephedrine has two stereogenic (chiral) centres and, therefore, has four possible isomers. Injections of (–)-ephedrine are used for severe asthma and life-threatening anaphylactic shock .Another isomer of ephedrine, (þ)-pseudoephedrine, is used in cough preparations such as Sudafed for its bronchodilatory properties. Herbal Ephedra has recently gained notoriety as 'herbal ecstasy', with a number of sources selling plant material over the Internet and in magazines. Claims of the stimulant's 'ecstasy-like' properties are not unfounded due to the high similarity in structure of ephedrine and ecstasy (methylenedioxy-methylamphetamine, MDMA). These herbal preparations are dangerous and should therefore be avoided. The indigenous peoples of central and north Mexico and the south-western USA ingest the dried heads ('buttons') of the cactus (Lophophora williamsii, Cactaceae) as part of their religious ceremonies. This plant material, known as peyote, induces vivid dreams and hallucinations; the biologically active natural product responsible is mescaline, a trimethoxylated phenylethylamine. Ingestion of pure mescaline fails to give the same response as consumption of peyote, which is possibly due to the contribution of other compounds present in the plant material. A compound that is included in this section for convenience is colchicine, an alkaloidal amine from the autumn crocus (Colchicum autumnale, Colchicaceae). This plant was known by the Greek physician Dioscorides and has been widely used on the Arabian Peninsula for centuries in the treatment of gout and it is still used today for this purpose.

However, it is highly cytotoxic and antimitotic, being an inhibitor of microtubule formation.

QUINOLINE ALKALOIDS

The Spanish conquistadors who invaded Peru in the latter part of the 16th century discovered that the indigenous Incas of this area used a preparation of the bark of a rain-forest tree to treat fevers, especially malaria. The Jesuit priests accompanying the invading force collected large amounts of this bark and used it to prevent and treat malaria. The bark was shipped back to Europe where it became known as Jesuit bark or Peruvian bark and gained great fame as a treatment for malaria. The trees responsible for this biological activity are of the genus Cinchona (Rubiaceae), which produce the quinoline alkaloid quinine, first isolated in 1820 by the French pharmacists Pelletier and Caventou (Fig. 6.59).

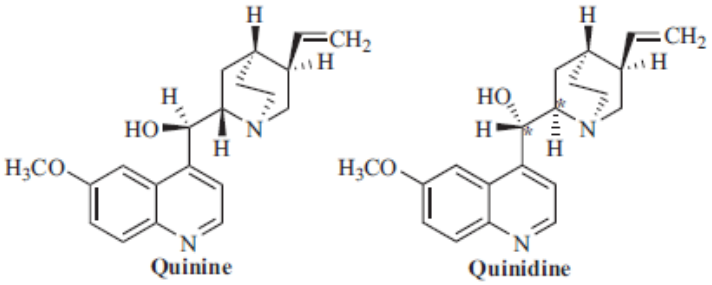


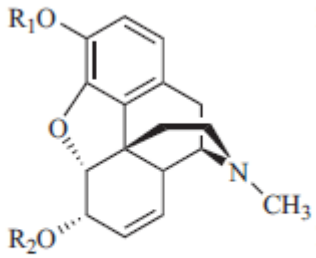
Fig. 6.59

The structure of this compound was not known, however, until 1908 and total synthesis was only achieved in the mid-1940s. The pure compound was used extensively as an antimalarial and was a template for synthetic antimalarials such as quinacrine, chloroquine and mefloquine. Resistance to these agents, particularly chloroquine, has become increasingly widespread, in particular through removal of the antimalarial from the cell by plasmodial membrane-bound efflux mechanisms, resulting in a low intracellular (ineffective) concentration of the drug. Interestingly, quinine is active in many cases against chloroquine-resistant malaria and there has been increased use of this drug. It is thought that quinine and other quinoline antimalarials exert their effects by binding to haem, a degradation product of haemoglobin. This haem– quinoline conjugate is toxic and leads to death of the parasite. In the absence of quinine, haem is converted into a polymeric form known as haemozoin

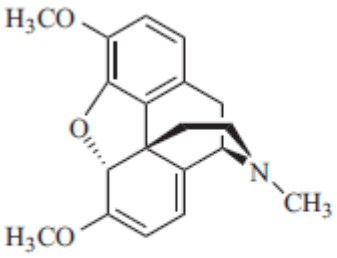
or malaria pigment which is non-toxic. Plasmodia are highly adaptable organisms and at present there is a need for new antimalarials to counter multidrug resistance in Plasmodium falciparum. Quinine also has a use as a treatment for night cramps in the elderly and is added to Indian tonic water where it imparts a bitter taste and a brilliant fluorescence under UV light. Quinidine is an isomer of quinine and has different configuration at the positions marked * in Fig. 6.59. It was observed that patients suffering from malaria who also had atrial fibrillation were cured of arrhythmias by quinine and quinidine. Quinidine is used to treat type I cardiac arrhythmias.

ISOQUINOLINE ALKALOIDS

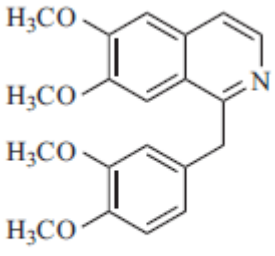
Within the alkaloids as a group, the isoquinolines have had a profound effect on human society as agents for pain relief and as drugs of abuse. In particular, opium, which is rich in morphinane-type isoquinolines, has been used for millennia in the treatment of pain and as a narcotic substance and, arguably, no other substance has caused so much human misery. Opium is the gummy exudate of the unripe capsules of the opium poppy (Papaver somniferum, Papaveraceae) and contains more than 30 alkaloids, of which the major components are morphine, codeine, thebaine, papaverine and noscapine (Fig. 6.60).



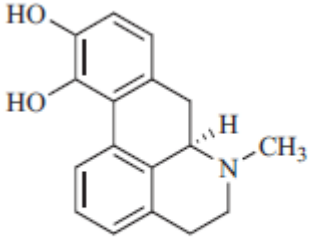
Morphine, $R_1 = R_2 = H$
Heroin, $R_1 = R_2$ = acetyl
Codeine, $R_1 = CH_3$, $R_2 = H$



Thebaine



Papaverine



Apomorphine

Fig. 6.60

The majority of opium, which is produced for illegal drug use, now originates in Afghanistan. When the British conquered the area of Bengal (now eastern India and Bangladesh) in the late 18th century, they discovered an area rich in opium fields and, as at that point in time there was a huge demand for Chinese tea, the opium was therefore used as a form of currency. Unfortunately, the addictive nature of opium was not well known and many Chinese became addicted through smoking the crude drug in opium dens (which were also a part of London life in the 19th century). This generated a huge social problem and resulted in war (opium war) between Britain and China, resulting in China having to cede land (including Hong Kong) to the British. Morphine, derived from the name for the Greek god of sleep Morpheus, possesses both a basic tertiary amine and an acidic phenol functional group. These groups allow morphine to be readily purified by acids and bases; pure morphine was produced in the 1880s and was rapidly recognized as an excellent analgesic when injected (despite its addictive properties). Morphine is readily converted into the drug of abuse, heroin (diamorphine), by acetylation of both hydroxyl groups using acetic anhydride. Much has been written on the destructive nature of heroin as a drug of abuse, but this agent is highly useful in the management of pain, particularly in patients with terminal cancer. Why morphine should dramatically affect analgesia in humans was a mystery until the discovery that we also produce a natural endogenous morphine-like substance (endorphin), which acts at the same site as morphine and is a pentapeptide (Tyr-Gly-Gly-Phe-Met). This molecule, named metenkephalin (met being the terminal methionine residue, and enkephalin being derived from the Greek for ‘in head’) has a portion that shows striking similarity to morphine and explains why both molecules bind to the opiate receptor. Morphine is used as a centrally acting analgesic and as a smooth muscle relaxant. Codeine is the phenolic methyl ether of morphine and is widely used as an over-the-counter analgesic and a cough suppressant. It is formulated with other analgesic agents such as aspirin and paracetamol. Both morphine and codeine are the most important analgesics for the management of moderate to severe pain. A number of semisynthetic morphinanes have been produced as analgesics and cough suppressants; these include pholcodine and dihydrocodeine. Morphine was also used as a template for other analgesic agents including pethidine, which is one of the most widely used synthetic opiates.

Thebaine is the starting point for the synthesis of many agents, including codeine and veterinary sedatives such as etorphine. Papaverine is an antispasmodic and is formulated with some analgesics such as aspirin. It is also used as a treatment for male impotence, and its activity as a Ca2þ channel blocker led to the development of verapamil. Apomorphine is prepared by heating morphine with concentrated hydrochloric acid and has recently been shown to be of use in the treatment of Parkinson's disease as this compound is a dopamimetic. Papaveretum is a total alkaloid extract of opium (containing 85% morphine, 8% codeine and 7% papaverine) from which the minor alkaloid noscapine has been removed as it is genotoxic. Papaveretum is used as a premedication. Indigenous peoples of SouthAmerica use a variety of arrow poison s for hunting purposes ,of which curare is a strong muscle relaxant. This poison is prepared from plants of the family Menispermaceae, notably Chondrodendron tomentosum, which kills by paralysis of the muscles required to breathe. The major active component of this species is the isoquinoline alkaloid tubocurarine, so named because the curare poison was carried in bamboo 'tubes' prior to use (Fig. 6.61). Tubocurarine is a quaternary salt and as a chloride has found use as a muscle relaxant in surgical procedures. The compound was also a template for the development of other muscle relaxants of which atracurium (Tracrium) is an excellent example.
Ipecac (Caephaelis ipecacuanha, Rubiaceae) is a shrub indigenous to Brazil and produces rhizomes (underground stems) that were used by the indigenous peoples to treat diarrhoea. The main alkaloidal components of this species are emetine, psychotrine and cephaeline. Ipecac was used to treat amoebic dysentery, but the side effects (vomiting, nausea and severe gastrointestinal disturbance) stopped its use. However, it is used as an emetic in the form of a syrup to induce vomiting after poisoning and drug overdose. In addition to its emetic and amoebicidal properties, emetine (Fig. 6.61) is an expectorant and is added to many cough medicines.

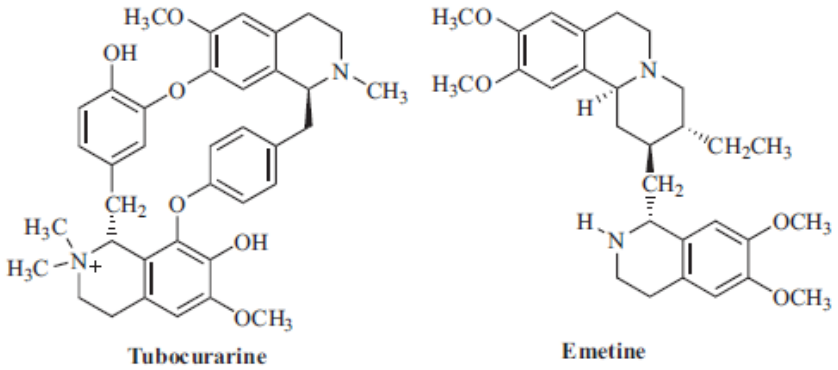


Fig. 6.61

INDOLE ALKALOIDS

Like the isoquinolines, the indole alkaloids are a very important source of bioactive compounds. Snake root (Rauvolfia serpentina, Apocynaceae) is a shrub common to the Indian subcontinent; it has been used as a panacea in the Ayurvedic system of medicine, with uses described for the treatment of snakebite and madness. Reserpine, the major component of this species, was used as an antihypertensive agent, but due to side effects (neurotoxicity, cytotoxicity and depression) it is now not in use (Fig. 6.62). British missionaries working in the Calabar coast area of West Africa (Nigeria and Cameroon) reported that criminal trials were conducted using the Calabar bean (Physostigma venenosum, Fabaceae). The beans of this plant are highly toxic and, when an individual was accused of a crime, they were forced to consume an extract of the bean. This practice was ‘trial by ordeal’ and accounts for the other name for the Calabar bean, the ‘ordeal bean’. Should the individual live then they were innocent of the crime, but death indicated guilt. The margin between innocence and guilt was probably a result of the completeness or incompleteness of extraction of the toxic chemicals from the plant! The toxic component of this species is physostigmine (Fig. 6.62),

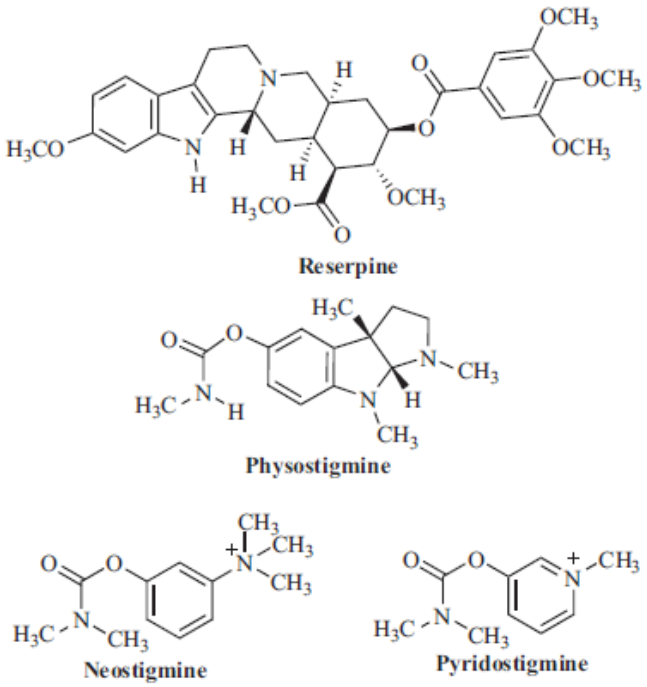


Fig. 6.62

which is an inhibitor of acetylcholinesterase, resulting in an enhancement of the activity of acetylcholine (which is degraded by acetylcholinesterase). There is interest in this compound in the treatment of Alzheimer's disease in which a low concentration of acetylcholine
in the brain is observed. Synthetic compounds based on physostigmine include neostigmine and pyridostigmine, which are used to treat myasthenia gravis, a rare disease characterized by severe muscle weakness. Poisoning through contamination of rye grain by fungi, in particular by Claviceps purpurea, has been described since the Middle Ages. This fungus produces dark-coloured structures (sclerotia) known as ergot on rye plants; these structures are rich in indole alkaloids. The poisoning from ingestion of bread made from contaminated grain is highly unpleasant, with victims complaining of burning, 'fire-like' sensations throughout their extremities and of vivid highly coloured hallucinations. These poisons can cause massive constriction of blood vessels, leading to 'blackened' limbs and gangrene. This condition became known as St Anthony's fire after the saint who spent much of his life meditating in the fire-like heat of the Sinai desert. Because bread was the main staple diet in the Middle Ages, it is likely that this condition was widespread, especially as the damp surroundings in which grain was

kept are conducive to the growth of the fungus. Ergot was used as an obstetric preparation in the 1500s to shorten labour during childbirth. It contains several groups of indole alkaloids such as the ergometrine type, which have simple amide side-chains, and the ergotamine group, which possess complex amino acid derived side-chains (Fig. 6.63). Ergometrine is an oxytocic used to expel the placenta after childbirth or to increase contractions. This compound also acts on the pituitary as well as on the uterine muscles. Ergotamine was first used in the 1920s for the relief of migraine and is still used today. It reduces vasodilation ,which can occur in throbbing migraine headache. The ergot alkaloids were used as a template for the semi-synthesis of bromocriptine, pergolide and cabergolide, which have use in neurological disorders such as Parkinson's disease. Ergot can cause hallucinations, and the hallucinogenic drug of abuse LSD (lysergic acid diethylamide) is structurally related to these compounds (Fig. 6.63).

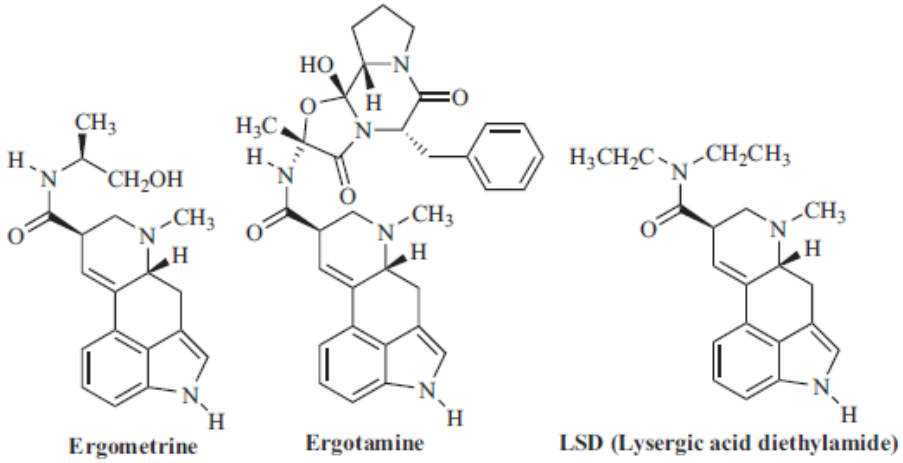


Fig. 6.63

Many of the psychoactive compounds (including LSD) are structurally related to tryptamine, as are the harmine and harmaline alkaloids from Peganum harmala (Syrian Rue, Nitrariaceae) and the yahe´ or ayahuasca preparations (Bansiteriopsis caapi and B. inebrians, Malpighiaceae), which are prepared by Amazonian shamen. Ayahuasca is used as part of the community rituals of some Peruvian groups to preserve their traditional ways and to promote bonding and the establishment of social order. Ibogaine, from iboga (Tabernanthe iboga, Apocynaceae), is hallucinogenic and anticonvulsant, and has recently been studied as a treatment for heroin addiction. Psychoactive indole derivatives are even found in amphibia, notably in the skin of species of the genus Bufo, which produce

bufotenin (Fig. 6.64). Mushrooms of the genera Psilocybe, Panaeolus, Conocybe and Stropharia are known to produce psychoactive substances such as psilocybin, which is a phosphate salt in the fungi and is converted into psilocin in vivo (Fig. 6.64).

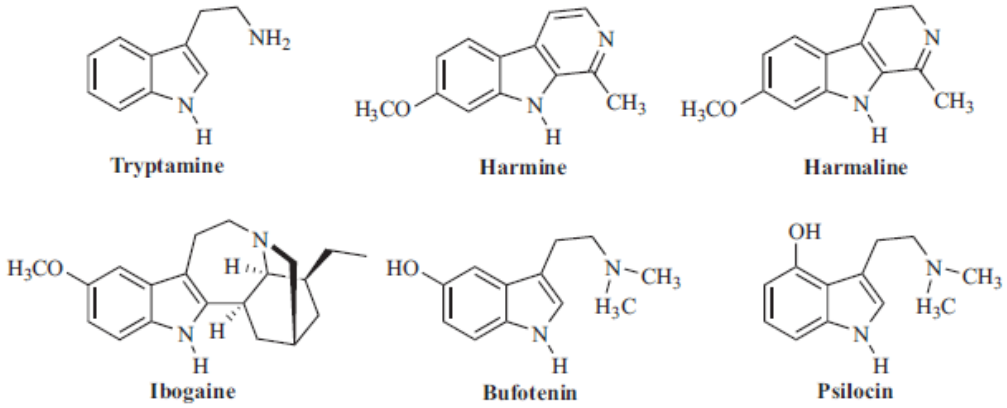


Fig. 6.64

The Aztecs of Mexico revered certain fungi (Psilocybe mexicana, Strophariaceae) as the 'flesh of the Gods' and gave it the name Teonanactl. The reverence for these mushrooms is presumably attributed to the profound hallucinogenic effects they exert, and, in Europe, many related species such as the liberty cap (Psilocybe semilanceata) are collected illegally for recreational abuse. These fungi are colloquially referred to as 'magic mushrooms', but as fungal taxonomy is highly complex there are risks of collecting poisonous species and the outcome may not be 'magic' at all. The most important alkaloids of the indole group are the anticancer agents vincristine and vinblastine from the Madagascar periwinkle (Catharanthus roseus, Apocynaceae). These are complex bisindole (dimeric indole) natural products present in small quantities in the plant material. Vindesine is a semi-synthetic derivative which is also used clinically. These compounds are used for the treatment of Hodgkin's lymphoma, acute leukaemia and some solid tumours (Fig. 6.65) and are dealt with in further detail in Chapter 8. Strychnine and brucine (Fig. 6.66) are intensely bitter indoles from the seeds of nux-vomica or 'vomiting nut' (Strychnos nux-vomica, Loganiaceae), which is a tree indigenous to India.

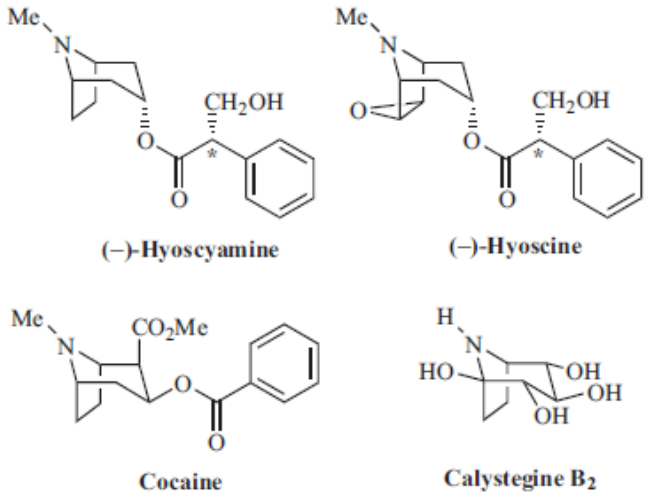


Fig. 6.67

Preparations of nux-vomica were used as a stimulant tonic until the middle of the 20th century. However, these compounds are highly poisonous (strychnine is used as a rodenticide) and they are responsible for occasional poisoning incidents. They are of historical interest only in pharmacy and are now used as research tools.

TROPANE ALKALOIDS

The European plant deadly nightshade (Atropa belladonna, Solanaceae) produces hyoscyamine , which occurs in the plant as a racemic mixture [(þ) and (–) isomers, sometimes denoted (_)] at the chiral centre denoted * in. This mixture is often referred to as atropine. The generic name of the plant refers to Atropos, the ancient Greek Fate who, in mythology, cut the thread of life, and belladonna, meaning beautiful lady in Italian and refers to the use of the juice of the berries of this plant by ladies in the 16th century to dilate the pupils of their eyes which was considered an attractive feature. Hyoscyamine is an anticholinergic and also has been used to treat acute arrhythmias and to dilate the pupil of the eye (a mydriatic) for ophthalmic examinations. Semi-synthetic derivatives are also used (such as tropicamide) that are less longer-acting. Hyoscyamine also occurs in other species of Solanaceae, notably henbane (Hyoscyamus niger) and thornapple (Datura stramonium), together with hyoscine, also known as scopolamine, which is the epoxide derivative of hyoscyamine. Hyoscine iswidely used as a premedication prior to operations to dry up secretions produced by inhalant anaesthetics and reduce nausea caused by the opiates. It is also a component of many travel (motion) sickness preparations. The drug of abuse cocaine comes from the South

American plants Erythroxylum coca and E. truxillense (Erythroxylaceae), which grow at high altitudes in the Andes in Colombia, Peru and Bolivia. As with heroin, this drug causes much misery and is a highly addictive CNS stimulant. Medicinally, cocaine has limited use as a local anaesthetic in ear, nose and throat surgery, and in the control of severe pain for patients with terminal cancer.

The calystegines, typically calystegine B2, are nor-tropane alkaloids ('nor' meaning lacking a carbon) which lack the N-methyl group of the tropanes. These compounds are widely distributed in the plant kingdom, particularly in the plant families Solanaceae and Convolvulaceae, which include a number of fruit and vegetables (e.g. tomatoes). The calystegines are currently of interest as inhibitors of glycosidase enzymes and they may have potential toxicity when ingested.

XANTHINE ALKALOIDS

The xanthine alkaloids are probably the most widely known (and used) group of alkaloids, being constituents of popular daily beverages such as tea (Camellia sinensis, Theaceae) and coffee (Coffea arabica, Rubiaceae). Coffee contains the xanthine (or purine) alkaloid caffeine (1–2%) (Fig. 6.68); typically a cup of instant coffee contains approximately 50 mg of caffeine. The caffeine content is appreciably higher in Turkish or Arabic coffees, which are highly concentrated and may contain up to 300 mg of caffeine per cup. Caffeine is a CNS stimulant and is a component of Proplus, a highly popular product amongst students to counter fatigue and drowsiness. It is also a diuretic and is used in combination with analgesics. Together with caffeine, theophylline and theobromine (Fig. 6.68) are minor components of tea; theobromine also occurs in cocoa (Theobroma cacao, Malvaceae). All three alkaloids differ only in the number and position of methyl substituents around the xanthine ring system. Theophylline is a diuretic and its derivatives (e.g. aminophylline) are used to relax the smooth muscle of the bronchi for relief of asthma.

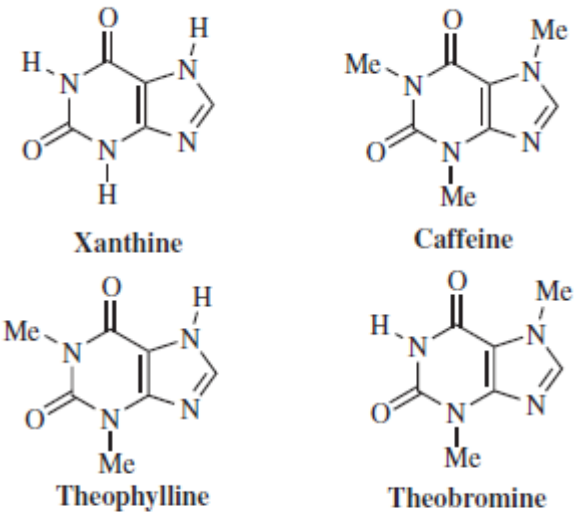


Fig. 6.68

IMIDAZOLE ALKALOIDS

The only member of this class that is of pharmaceutical merit is pilocarpine from jaborandi (Pilocarpus jaborandi, Rutaceae), a tree common to SouthAmerica Pilocarpine is a cholinergic agent and is used to stimulate muscarinic receptors of the eye in the treatment of glaucoma. In the eye, this compound and derivatives (salts such as the hydrochloride and nitrate) cause pupillary constriction (miosis) and relieve eye pressure by facilitating better ocular drainage.

Currently, there is interest in this class of alkaloid as muscarinic agonists in the treatment of Alzheimer's disease.

THE GLYCOSIDES

The glycosides are discussed in a separate section here as they enhance the structural diversity of other natural product classes. The term glycoside is a generic term for a natural product that is chemically bound to a sugar. Thus the glycoside is composed of parts: the sugar and the aglycone. The aglycone may be a terpene, a flavonoid, a coumarin or practically any other natural product. If the aglycone is

a triterpene, it is sometimes referred to as a genin (e.g. protoaescigenin;). Glycosides are very common in nature and provide extra chemical diversity and structural complexity in natural products. There are two basic classes of glycosides: the C-glycosides, in which the sugar is attached to the aglycone through a carbon–carbon bond, and the Oglycosides in which the sugar is connected to the aglycone through an oxygen–carbon bond (Fig. 6.49).

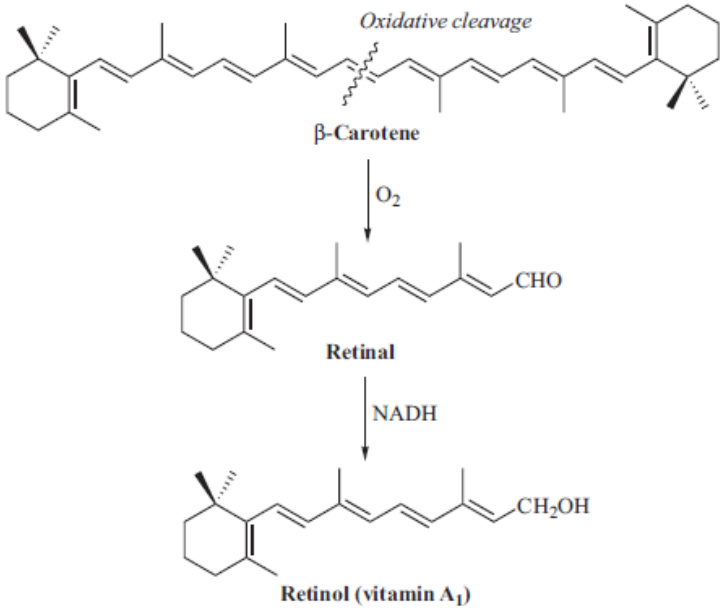


Fig. 6.48

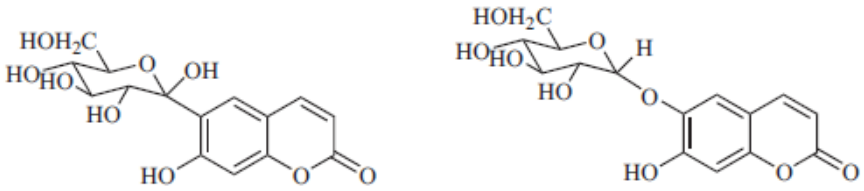


Fig. 6.49

Glycosides are usually more polar than the aglycone, and glycoside formation generally increases water solubility. This may allow the producing organism to transport and store the glycoside more effectively.

CYANIDE GLYCOSIDES

Some glycosides are undoubtedly used by plants as a chemical defence and this is certainly so with the cyanide glycosides. These compounds, in the presence of

enzymes suchasb-glucosidase, lose their sugarportion to form a cyanohydrin which, in the presence of water, can undergo hydrolysis to give benzaldehyde and the highly toxic hydrogen cyanide (HCN) (). Cyanide glycosides such as amygdalin () are present in many species of the genus Prunus, which includes commercially important fruit such as peaches, cherries, plums and apricots. Fortunately, the enzymes that convert these compounds to the cyanohydrins are localized in different parts of the plant or are absent. In the case of sweet almonds (Prunus amygdalus var. dulcis), the enzymes are present but
there are no cyanide glycosides present. Cassava (Manihot esculenta) is consumed widely in Africa as a food-stuff and both the enzymes and cyanide glycosides are present, although extensive boiling of the cassava before eating results in the removal of the toxic HCN. Some cassavas are eaten raw, but it is highly likely that these are chemical races of the plant that lack either the glycosides or the enzymes, so raw cassava should certainly be avoided if there is doubt about the presence of these compounds.

GLUCOSINOLATES

The plant family Brassicaceae includes cabbages, sprouts and the mustards and produces a group of glycosides known as glucosinolates. These are sulphur- and nitrogen-containing glycosides previously referred to as nitrogen mustards.
A common example of this group is sinalbin from white mustard (Sinapis alba), which in the presence of the enzyme myrosinase is converted into a thiohydroximate, which rearranges with the loss of a hydrogen sulphate salt to the isothiocyanate, acrinylisothiocyanate (Fig. 6.51).

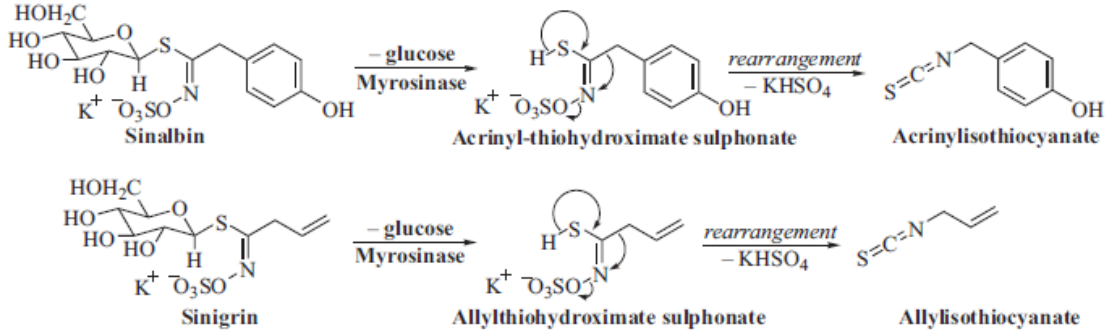


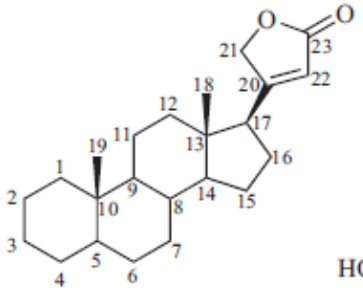
Fig. 6.51

These isothiocyanates are exceptionally pungent and impart a strong aroma tomustards, which can be

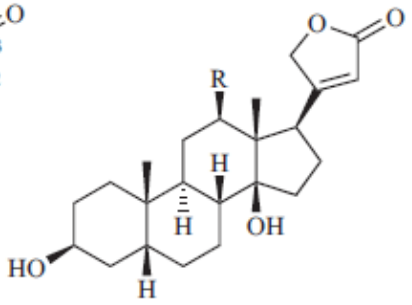
described as hot or even acrid to the taste. In black mustard (Brassica nigra), the simple glucosinolate sinigrin is converted in the same fashion to allylisothiocyanate (Fig. 6.51),which is an oil and far more volatile than acrinylisothiocyanate. The oils derived from mustards are rich in these isothiocyanates and aremildly irritant; they are used medicinally as externally applied treatments for muscular pain.

CARDIAC GLYCOSIDES

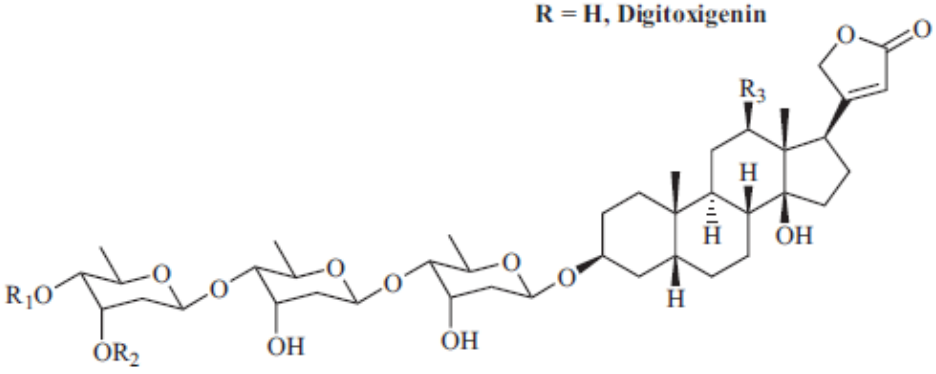
Many plants contain cardioactive or cardiac glycosides, which have a profound effect on heart rhythm. They are commonly found in the genera Convallaria, Nerium, Helleborus and Digitalis. The aglycone portion is steroidal in nature and is sometimes referred to as a cardenolide, being cardioactive and possessing an alkene and an olide (a cyclic ester) (Fig. 6.52). Being ‘steroid-like’, the aglycone (genin) portion is derived from the triterpenes and these compounds may have a wide variety of sugars attached to the steroid portion. The most widely studied plant that contains these compounds is the foxglove (Digitalis purpurea) of the plant family Scrophulariaceae, which was used as long ago as the 18th century for the treatment of heart disease described as ‘dropsy’. The basis of this use was well founded as this plant contains the medicinal agents digoxin and digitoxin (Fig. 6.52).



Cardenolide nucleus

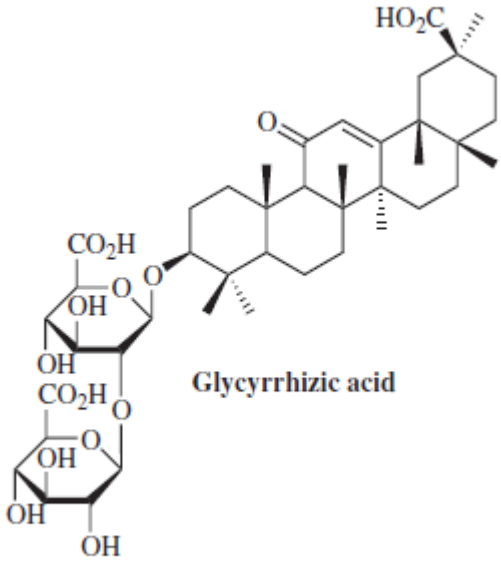


R = OH, Digoxigenin
R = H, Digitoxigenin



$R_1 = R_2 = H, R_3 = OH$, Digoxin
$R_1 = R_2 = R_3 = H$, Digitoxin
R_1 = Glucose, R_2 = Acetyl, $R_3 = OH$, Lanatoside C
R_1 = Glucose, $R_2 = H, R_3 = OH$, Deacetyl-lanatoside C

Fig. 6.52



Glycyrrhizic acid

Fig. 6.53

Digoxin is the most widely used cardiac glycoside in congestive heart failure and is now produced by isolation from the related species Digitalis lanata.

Related cardiac glycosides, which because they are very fast-acting compounds are used in emergencies via the intravenous route, are lanatoside C and deacetyl-lanatoside C. Triterpene glycosides have widespread distribution in plants and are sometimes referred to as saponins as they have soap-like properties and readily form foams. Medicinally important examples include glycyrrhizic acid from liquorice (Glycyrrhiza glabra) (Fig. 6.53),which is used as a treatment for stomach ulcers and the salts of which are intensely sweet. The sugars in Fig. 6.53 are of the glucuronic acid type and are shown as their Fisher projections. Triterpene glycosides are steroid-like in structure and overuse can lead to similar symptoms associated with steroid overuse such as hypertension and thrombosis.

ANTHRAQUINONE GLYCOSIDES

A number of plants that contain anthraquinone or anthrone glycosides (Fig. 6.54) have long been known for their laxative properties. They include cascara (Rhamnus purshiana), aloe (Aloe vera) and senna; the latter is divided into two species (Cassia angustifolia, known as Tinnevelly senna, and Cassia senna, known as Alexandrian senna). Aloe is used as a laxative as well as a treatment for minor burns. It contains a mixture of anthraquinone glycosides of which barbaloin is the major component and is a mixture of 10R and 10S isomers; the purified components are referred to as aloin A and B. The gel or mucilage from aloe is rich in polysaccharides and these anthraquinone glycosides, and is incorporated into creams and ointments to treat abrasions, burns and skin irritation. Cascara was in use in the late 19th century as a laxative by the preparation of the bark of the tree. The main active principle is the diglucoside cascaroside, which, in common with barbaloin, exists as a mixture of epimers at position C10 as cascaroside A (10S) and B (10R). There is little difference in the chemistry of the two senna species. The active constituents are sennosides A and B (Fig. 6.54).

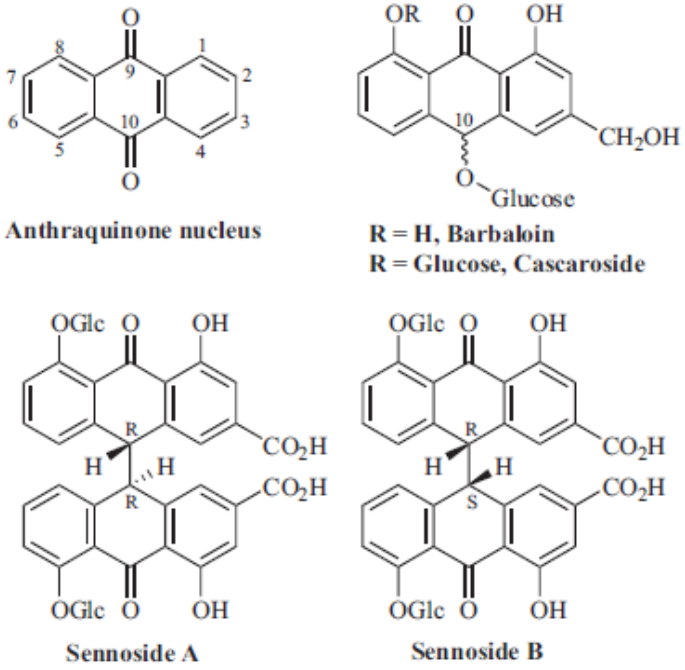
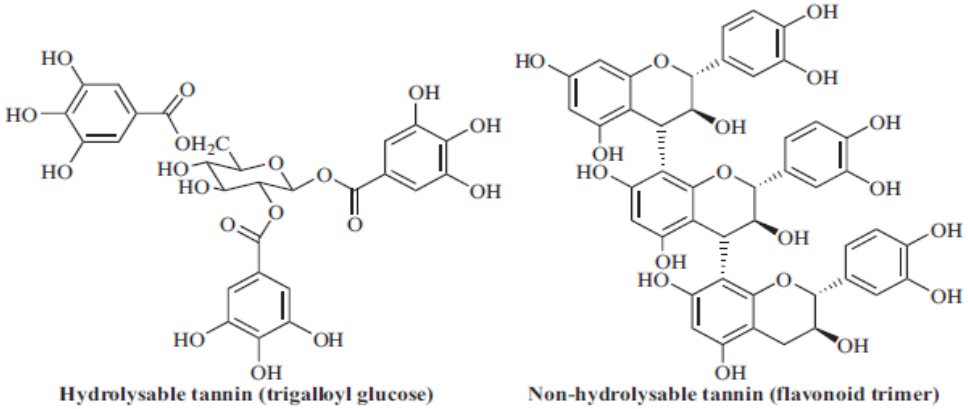


Fig. 6.54

These natural products are dianthrones (dimers) of the anthrone skeleton. The fresh leaves of senna contain glycosides with additional sugar groups present and these are naturally hydrolysed to sennosides A and B. In vivo, the sennosides are then hydrolysed to the dianthrones (lacking the glucose sugars). Senna is widely prescribed for constipation; an example of a marketed product is Senokot.

TANNINS

In addition to the flavonoids, another class of natural products that gives rise to the astringency and bitterness in plants and food are the tannins. This group comprises water-soluble polyphenolic compounds, which may have a high molecular weight. They are broadly divided into two groups: the hydrolysable tannins, which are formed by the esterification of sugars (e.g. glucose) with simple phenolic acids that are shikimate-derived (e.g. gallic acid), and the non-hydrolysable tannins, which are sometimes referred to as condensed tannins, that occur due to polymerization (condensation) reactions between flavonoids (Fig. 6.27). As their name suggests, the hydrolysable tannins may be hydrolysed with base to simple acids and sugars. A key feature of tannins is their ability to bind to proteins, and they have been used to tan leather, clarify beer and as astringent preparations in pharmacy. They have a very wide distribution in the plant kingdom and may be produced by a plant as a feeding deterrent, as their binding to proteins may reduce the dietary value of the plant as a food. Tannic acid is a mixture of gallic acid esters of glucose and is obtained from nutgall, which is an abnormal growth of the tree Quercus infectoria produced by insects. These growths (galls) are harvested and extracted with solvents (ether and water); the aqueous layer is collected and evaporated to yield tannic acid, which is further purified and used as a topical preparation for cold sores.



Hydrolysable tannin (trigalloyl glucose)

Non-hydrolysable tannin (flavonoid trimer)

Fig. 6.27

THE TERPENES

The terpenes are very widespread in nature and occur in most species, including man. They are sometimes referred to as isoprenes because a common recurring motif in their structure (the branched repeatingC5 unit, the isopentane skeleton) is similar to isoprene (Fig. 6.28). Terpenes (hemiterpenes, monoterpenes and sesquiterpenes) contribute to many of the aromas associated with plants and range in complexity from simple C5 units (hemiterpenes) up to the polyisoprenes, which include latex, leaf waxes and rubber. Terpenes are derived from a number of extensive reactions between two C5 units [dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP)] (Fig. 6.28); the products of these reactions will, therefore, have multiples of five carbons.

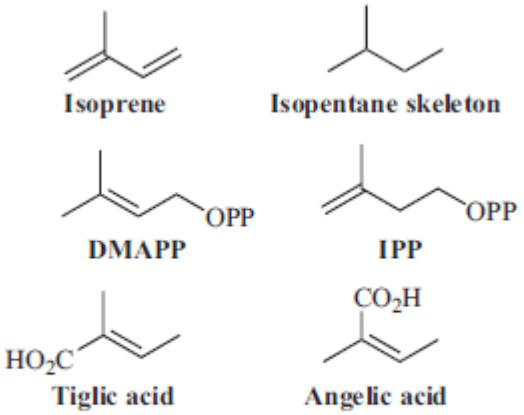


Fig. 6.28

DMAPP and IPP are biosynthesized from two sources (mevalonic acid or deoxyxylulose phosphate). The terpenes are a perfect example of a natural product class that is highly structurally diverse, has many members that are chiral and have extensive functional group chemistry. The simplest are the hemiterpenes (C5) produced by modification

reactions to either DMAPP or IPP and include simple acids such as the structural isomers tiglic acid and angelic acid (Fig. 6.28), which form esters with many natural products. The monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), triterpenes and steroids (C30-derived) and the tetraterpenes (carotenoids, C40) are all important medicinally and thus will be dealt with in more detail.

MONOTERPENES (C10)

Together with the phenylpropenes, the monoterpenes are major constituents of the volatile oils that are common in plants and which contribute to their aroma. This group of compounds has highly characteristic odours and tastes and is used widely in the food and cosmetic industries in flavourings and perfumes. Monoterpenes are present in the leaf glands of plants and in the skin and peel of fruit (in particular Citrus spp.). The reasons for the presence of these compounds in the exterior organs of the plant are due to the many complex interactions that plants have with other organisms: some monoterpenes are insect attractants (to aid pollination), others have a broad spectrum of antimicrobial activity to inhibit growth and invasion by bacteria and fungi (e.g. thymol). Volatile oils in plants are highly complex and their analysis by gas chromatography (GC) can show the presence of hundreds of individual components, many of which are monoterpenoid. These oils are highly prized in the perfume industry; plants such as jasmine are cultivated and the monoterpene-rich oils harvested for the production of popular fragrances. Monoterpenes may be either aliphatic (acyclic or straight chain) or cyclic (saturated, partially unsaturated or fully aromatic) compounds. These natural products usually possess functional groups such as ethers, hydroxyls, acids, aldehydes, esters or ketone moieties, and are generally highly volatile and fat-soluble (lipophilic). Biosynthetically, the monoterpenes are produced by the

reaction between DMAPP and IPP in the presence of the enzyme prenyltransferase (Fig. 6.29).

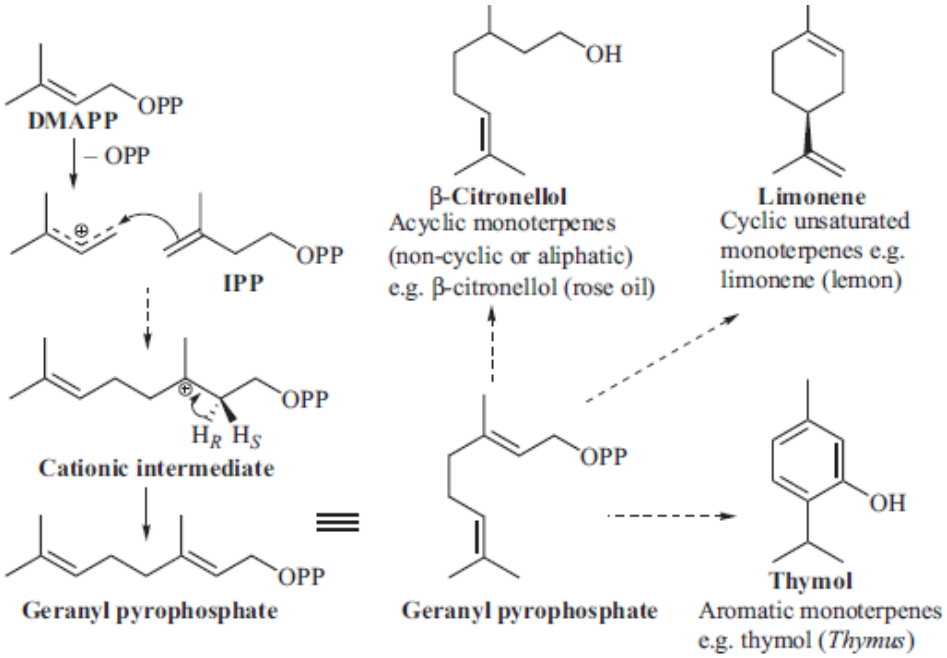


Fig. 6.29

The first step of this reaction is thought to be the ionization of DMAPP to a cation (through the loss of pyrophosphate), which is then attacked by the double bond of IPP to generate a further cationic intermediate. Loss of a proton from the carbon neighbouring the cation (resulting in double bond formation) occurs in a stereospecific fashion (the R proton is lost) and this generates geranyl pyrophosphate (a C10 unit). Geranyl pyrophosphate can then undergo many reactions to generate the variety of monoterpenes observed, such as simple modification to give the acyclic monoterpene b-citronellol, which is a component of rose oil. Geranyl pyrophosphate can be cyclized to give cyclic monoterpenes, which may be fully saturated, partially unsaturated or fully aromatic products of which menthol, piperitone and carvacrol are examples,

respectively (Fig. 6.30).

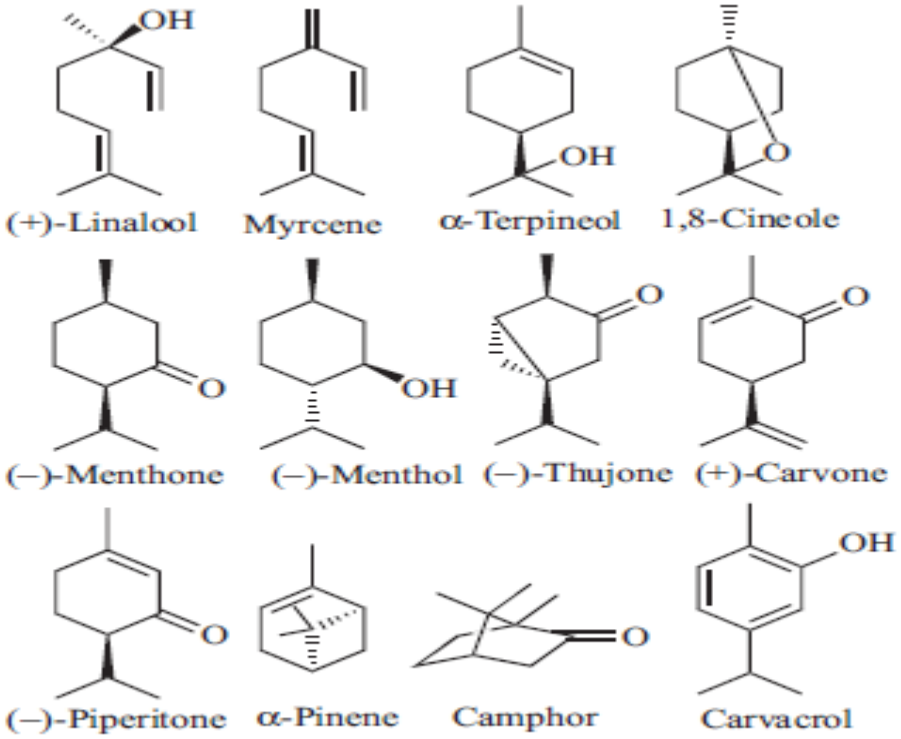


Fig. 6.30

As with the polyketides, some key features of monoterpenes (and terpenes in general) are the presence of stereochemical centres (chiral centres) and wide ranging functional group chemistry. The extensive structural diversity of this group is astounding considering that all of the monoterpenes are derived from just one C10 unit, geranyl pyrophosphate. Linalool, a major constituent of coriander oil (Coriandrum sativum), is used as a flavouring and carminative. Myrcene, which is present in hop oil, is also used as a flavouring. Tea tree oil (from Melaleuca alternifolia) has been used by the indigenous peoples of Australia as a treatment for skin infections; a main ingredient of this volatile oil is the tertiary hydroxylated monoterpene a-terpineol. 1,8-Cineole, the structurally related ether, also has antibacterial properties and comes from species of Eucalyptus that are in the same plant family as Melaleuca, the Myrtaceae. Menthol and menthone

are major constituents of oils of plants belonging to the genus Mentha (Lamiaceae); in particular, peppermint (Mentha _ piperita) is used as a flavouring and carminative tea, and menthone is included in some pharmaceutical preparations as a nasal decongestant. Thujone has a cyclopropane ring as a functional group and is a constituent of Artemisia absinthium, an extract of which was used as an anthelmintic by the French army, hence the common name for this plant, wormwood. The liqueur absinthe was prepared by making an alcoholic extract of wormwood; this was highly popular amongst artists and literati in 19th century France. Unfortunately, high doses of this beverage induce hallucinations and the drink is addictive (not just the alcohol), and these effects led to the term ‘absinthism’ to describe the side effects associated with absinthe. Due to these problems, the production of absinthe was banned in 1915. Carvone is derived from dill (Anethum graveolens) and caraway oils (Carum carvi),which have use as calming ingredients in gripe water preparations .a-Pinene, which has a cyclobutane ring system, is the major constituent of juniper oil (Juniperus communis), which is antiseptic and used in aromatherapy and as a flavouring. Oil from Cinnamomum camphora (Lauraceae) is produced by the steam distillation of the wood and is rich in camphor, which is antiseptic and used in soaps. Although oils from plants such as caraway, coriander, dill, peppermint and eucalyptus are widely used as flavouring agents and perfumes for many preparations (including foods, cosmetics and pharmaceuticals), at present not a great deal is known about the biological activity of the monoterpene components present in these complex mixtures. Natural oils have a very specific aroma, which accounts for the preference to buy these complex natural mixtures rather than cheaper synthetic alternatives. They are produced by steam distillation (see Chapter 7) and, unless much is known about

the stability of the oil components, care must be taken using this technique as some monoterpenes are thermolabile (i.e. they decompose on heating). The analysis of these complex mixtures is usually performed by GC or the combined technique of gas chromatography–mass spectrometry (GC-MS), which utilizes the separating power of GC with MS to yield the molecular ions of components of a mixture, and in some cases fragmentation information which can aid in determining the structure of these components. The perfume industry has a great interest in monoterpene mixtures and uses preparative GC to separate and isolate individual components, which a highly qualified perfumer then smells to find compounds with a distinctive, novel or unusual aroma that can be blended with other volatiles to give a popular fragrance. The iridoids are monoterpenes derived from the iridane skeleton, which is derived from geranyl pyrophosphate and, when oxidized, produces the iridoid skeleton (Fig. 6.31).

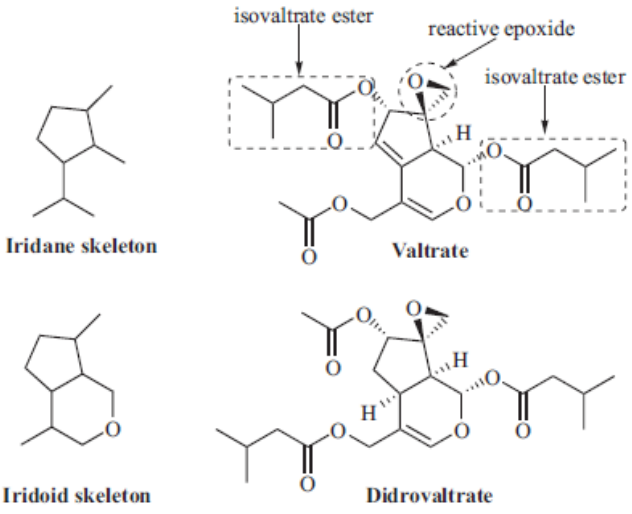


Fig. 6.31

These natural products are normally esterified and are common in the plant families Lamiaceae, Gentianaceae and Valerianaceae. The compounds are highly oxygenated and the esters are often derived from hemiterpenes; for example, valeric acid is esterified to form valtrate and

didrovaltrate. These compounds come from valerian (Valeriana officinalis, Valerianaceae), which was used as a sedative for the treatment of ‘shell shock’, a condition with which troops serving in the First World War were afflicted following extensive barrage by high explosive shells. This class of iridoids is often referred to as the valepotriates; they are highly functional, possessing isovalerate esters and an epoxide group that is possibly responsible for the in vitro cytotoxicity of valtrate and didrovaltrate. It is still not known exactly which class of compounds is responsible for the sedative activity, although the iridoids are widely regarded as the active components. However, it has been suggested that gaminobutyric acid (GABA), which is present in aqueous extracts of valerian, contributes to the sedative activity. Valerian also contains a number of small acids, such as isovaleric acid, that are structurally similar to GABA; these may, therefore, contribute to the sedative action of this herb extract. Valerian is commonly found in herbal remedies to improve sleep and is often used in conjunction with extracts from hops (Humulus lupulus) (e.g. in the preparation Valerina Night-Time).

SESQUITERPENES (C15)

These natural products have properties similar to those of the monoterpenes, are constituents of many of the volatile oils and in some cases are broadly antimicrobial and anti-insecticidal, therefore contributing to the overall chemical defence of the producing organism. The starting unit for these compounds is farnesyl pyrophosphate (FPP), which is produced by the reaction of GPP (the monoterpene precursor) with a molecule of IPP (Fig. 6.32).

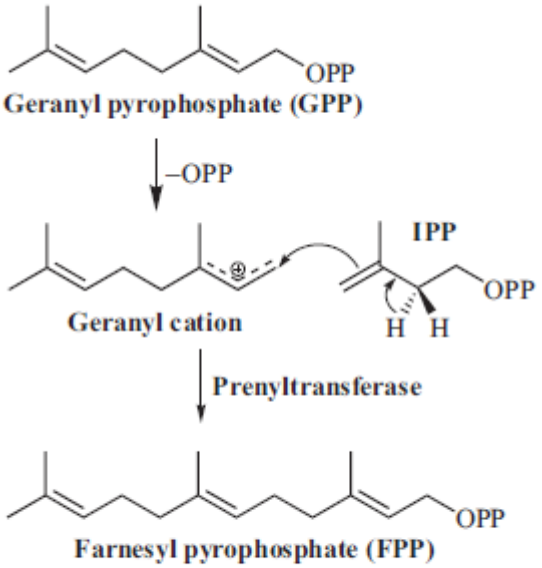


Fig. 6.32

The reaction is analogous to that for the formation of the monoterpenes in which a cationic intermediate is formed that reacts with IPP with elimination of a hydrogen ion.

As with the monoterpenes, FPP can cyclize to form linear (acyclic) and cyclic sesquiterpenes. A key feature of these metabolites is their ability to undergo extensive elaboration chemistry, where they are highly functionalized, thus giving rise to the high structural diversity seen within this group of natural products. It is not always easy to see that these complex, functional, cyclic chiral compounds are derived from FPP due to these elaboration reactions. However, if the C15 skeleton of FPP is compared to arteannuin B, it can be seen how even complex structures are constructed (Fig. 6.33).

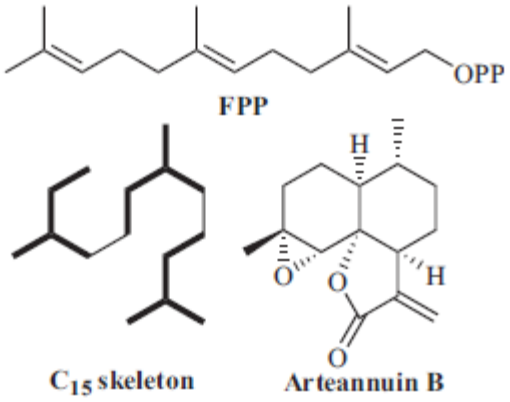


Fig. 6.33

The most important sesquiterpene from the pharmaceutical perspective is the antimalarial product artemisinin (Fig. 6.34)

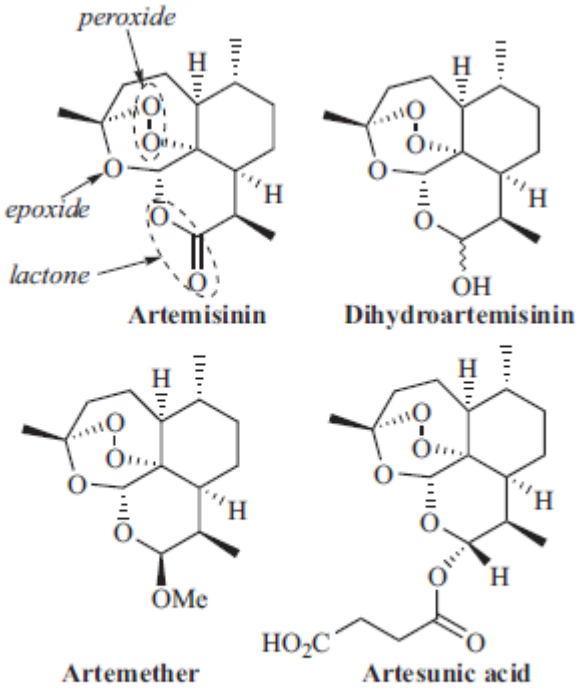
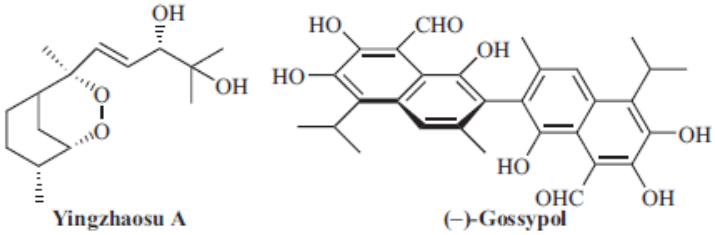


Fig. 6.34

from sweet wormwood (Artemisia annua, Asteraceae). This herb is widely distributed throughout Europe but also has a long history of use for the treatment of fevers and malaria in China where the drug is known as Qinghao. Artemisinin has a number of interesting features, including

an ether, a lactone (cyclic ester) and an unusual peroxide functional group. The peroxide is essential for the antimalarial activity and much work has been done to enhance the solubility of the compound whilst retaining the biological activity. Artemether, the methyl ether of dihydroartemisinin (which possesses an acetal functional group), is used for the treatment of chloroquine-resistant and multidrug-resistant Plasmodium falciparum under the trademark Paluther. Artesunic acid (a succinic acid derivative marketed as Artesunate) is more water-soluble than artemether and is hydrolysed in vitro to dihydroartemisinin. These compounds are very lipid-soluble, are rapidly absorbed into the central nervous system (CNS) and, therefore, may have potential in treating cerebral malaria. It has been proposed that these peroxides complex to the iron atom of haem (which is produced by the degradation of haemoglobin) resulting in the formation of oxy radicals. These radicals may then re-arrange to generate carboncentred radicals, which can attack biomolecules such as DNAand proteins leading to parasite death. Interestingly, another Chinese medicinal plant used for treating malaria, Artabotrys uncinatus (Annonaceae), also contains a series of sesquiterpene peroxides (typically, yingzhaosu A; Fig. 6.35),



Yingzhaosu A (–)-Gossypol

Fig. 6.35

which are responsible for the antimalarial activity. In China, studies have been conducted into cottonseed oil (Gossypium hirsutum), which has been shown to have contraceptive effects and restrict fertility in men and women when incorporated into the diet. In men, the oil has been shown to alter sperm maturation, motility and inhibit enzymes necessary

for fertilization. In women, inhibition of implantation has been observed. The active component is the bis-sesquiterpene (sesquiterpene dimer) (–)-gossypol, which exists in the plant with the (þ)- isomer. These compounds are optically active due to restricted rotation around the bond that joins the two naphthalene ring systems. Studies show that the antifertility effect is reversible after stopping administration, provided that the treatment has not been prolonged.

DITERPENES

There are few examples of C20 diterpenes as drugs, but a former best-selling antitumour agent, paclitaxel, is based on this class of natural products. These compounds are complex in structure and, until the use of multidimensional nuclear magnetic resonance (NMR) spectroscopy, the structure elucidation of these compounds (along with other higher terpenes, e.g. triterpenes) was not routine. NMR has made the structure determination of these compounds readily achievable, even if only 1–2 mg of natural product is available, and it is likely that more examples of this class will become drug candidates in the future. Historically, plants producing diterpenes that contain a nitrogenatom(the so-called diterpene alkaloids), such as Aconitum sp. And Delphinium sp., have been used for a number of illnesses, including decongestants; however, these compounds (e.g. aconitine) are highly toxic and preparations containing these plants are no longer used. Members of the diterpene class are formed by the reaction of farnesyl pyrophosphate (FPP), a C15 unit, with isopentenyl pyrophosphate (IPP), the C5 unit that is the common building block for all of the terpenes. The first step of this reaction is the formation of a farnesyl allylic cation (analogous to the other examples of terpenes seen) which then reacts with IPP with stereospecific loss of a proton, resulting in the formation of geranyl geranyl pyrophosphate (GGPP). Depending on how GGPP folds and cyclizes, a very large number of products may result .

Loss of a proton from an allylic methyl . and migration of bonds to form a bicyclic structure results in the formation of labdadienyl pyrophosphate (LDPP), which is a member of the labdane class of diterpenes of which sclareol from the clary sage (Salvia sclarea, Lamiaceae) is widely used in the perfumery industry. Sclareol is generated by hydrolysis of LDPP. If the exomethylene of LDPP reacts with a proton to form a cationic intermediate, this may undergo a series of Wagner– Meerwein hydride and methyl shifts . These reactions are sometimes referred to as 1,2- shifts (indicating a movement of a group from a position to a neighbouring carbon) or NIH shifts (after the National Institutes of Health, where this reaction was studied). The hydride on C9 migrates to C8, the methyl on C10 migrates to C9, the hydride on C5 migrates to C10, the b-methyl on C4 migrates to C5 and, finally, a proton is lost at C3 resulting in the formation of a C3-C4 double bond. This series of migrations yields clerodadienyl pyrophosphate (CDPP; a clerodane diterpene) with many members of this class; for example, hardwickiic acid which possesses a furan ring (produced by oxidation and cyclization of the six-carbon side-chain at C9) and a carboxylic acid (produced by oxidation of C20). An important facet of these Wagner–Meerwein shifts is the inversion of stereochemistry at the chiral centres where migration has occurred. For example, in LDPP, the methyl at C10 is b (coming up out of the plane of the page), whereas the corresponding group in CDPP is an a hydrogen (going down into the plane of the page).

GGPP can cyclize to give an extraordinarily wide range of diterpene groups,. It is important to understand that, once a simple skeleton has been produced, a wide array of further elaboration reactions can occur, resulting in the highly complicated natural products of this class (e.g. paclitaxel;. This antitumour diterpene was discovered in 1971 by Monroe Wall and Mansukh Wani at the Research Triangle Institute as

part of a programme funded by the National Cancer Institute. This compound is dealt with in further detail in Chapter 8. It was not until the 1980s that further work on the mode of action of this compound prompted its development and release onto the US market in 1993 under the trade name Taxol for the treatment of ovarian cancers. Paclitaxel is present in the bark of the Pacific yew (Taxus brevifolia, Taxaceae), a slow growing tree from the forests of north-west Canada and the USA that takes 100 years before it can be exploited for processing. The wood of T. brevifolia is not suitable for timber production and was in danger of replacement by faster growing conifers, but this practice has been stopped. The yield of paclitaxel is also low (0.01–0.02%) as it takes three 100-yearold trees to produce 1 g of the drug. Thus, with a course of treatment being 2 g, it was quickly realized that the supply of paclitaxel had to come from another source. Taxus brevifolia produces a wide range of taxane diterpenes, and related compounds are also found in the common English yew, Taxus baccata. Paclitaxel belongs to a small class of taxanes that possess a four-membered ether (also called an oxirane) and a complex nitrogen-containing ester side-chain; both of these functional groups are essential for antitumour activity. The solution to the problem of low concentration of the drug came from the knowledge that related compounds, such as baccatin III and 10-deacetylbaccatin III , were present in greater concentrations than paclitaxel and could be converted to paclitaxel by simple reactions. Most importantly, 10-deacetylbaccatin III is also present in the needles (leaves) of the faster growing English yew (T. baccata) at a higher concentration (0.1%) and, unlike the bark, the needles can be harvested without destroying the tree. This is an example of a renewable resource, which is an important concept in natural product chemistry, for, if a biologically active compound is developed into a drug, then large-scale production is always necessary. This is not problematic if a compound

from a plant can be synthesized (semi- or fully synthesized) or produced by cell culture. Another route to this compound is to extract a mixture of taxanes and use enzymes that specifically cleave ester groups from the taxane nucleus, resulting in a higher concentration of 10-deacetylbaccatin. It has also been shown that Taxomyces andreanae, a fungus that lives in close association with the yew tree, produces small concentrations of paclitaxel in fermentation culture. It is possible that the fungus has inherited the gene from the tree (or vice versa), which allows the organism to produce paclitaxel. Another fungus that has been isolated from the Himalayan yew tree (Taxus wallachiana) is Pestalotiopsis microspora, which produces higher concentrations of paclitaxel than T. andreanae. Taxol is now produced by large scale plant cell culture fermentation. Docetaxel (Taxotere), a related semi synthetically produced taxane diterpene, is also used clinically for the treatment of ovarian cancers and has a modified side-chain to that of paclitaxel.

TRITERPENES

The triterpenes are C30-derived terpenoids with an exceptionally wide distribution, including man, plants, fungi, bacteria, soft corals and amphibia. The triterpenes include some very important molecules, such as the steroids (e.g. testosterone), which are degraded triterpenes with many important functions in mammals, notably as sex hormones. Other types include the sterols (e.g. b-sitosterol), which are common tetracyclic steroidal alcohols with ubiquitous distribution in plants, the pentacyclic triterpenes such as glycyrrhetic acid found in liquorice and the limonoids (e.g. limonin), which are highly oxidized bitter principles present in the Citrus plant family (Rutaceae) (Fig. 6.40).

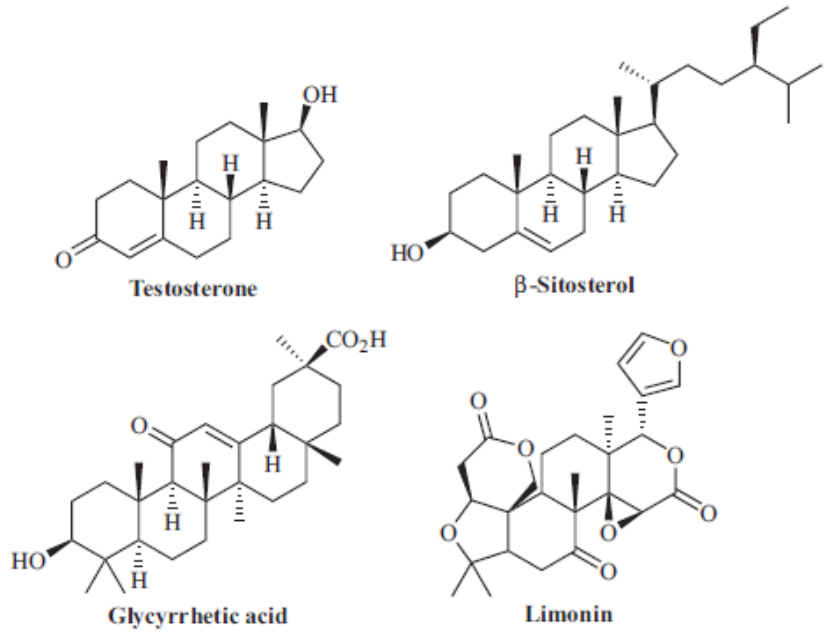


Fig. 6.40

Triterpenes are also components of resins and resinous exudates from plants (e.g. frankincense and myrrh); myrrh is derived from the Arabic word for bitter, a characteristic which many triterpenes display. These resins are common from trees belonging to the plant family Burseraceae (which includes the myrrh-producing Commiphora sp.) and are produced following damage to the tree as a physical barrier to attack by fungi and bacteria. Additionally, many of the terpenoid components of these resins have high antimicrobial activity, either killing potentially invasive microbes, slowing their growth until the tree has repaired the damage or providing a physical barrier toward further invasion. Their biosynthesis starts with the reaction between two molecules of farnesyl pyrophosphate (FPP) to form the true precursor of all triterpenes, squalene . Squalene is then enzymatically epoxidized to squalene epoxide which, when folded in a particular conformation such as the ‘chair-boat-chair-boat’ conformation, can cyclize to give sterol intermediate 1 which is the precursor of the steroids and sterols . This

intermediate can undergo a series of Wagner–Meerwein shifts to give lanosterol, a common component of plants
and of wool fat. Oxidation and loss of methyls at positions C4 and C14, introduction of a C5-C6 double bond (oxidation) and loss of two double bonds (one at C8-C9 and one in the side-chain) would result in the formation of cholesterol. Cholesterol is the main animal sterol, a component of cell membranes and gallstones, and control of the levels of this sterol is important in the management of heart disease. The basic steroid nucleus and numbering of the ring system depicting the A, B, C and D rings is given for cholesterol . Other common sterols include the phytosterols (plant sterols) b-sitosterol and stigmasterol (which differs from b-sitosterol only by the presence of a double bond at position C22-C23), which are widespread in plants, and ergosterol, which is ubiquitous in fungi as a cell wall component .

There is a great need for steroids in the pharmaceutical industry and this is met by using the plant sterol diosgenin from the wild yam (Dioscorea sp.). Diosgenin also occurs naturally as a glycoside (a sugar is attached at the hydroxyl position) and without the sugar the compound is referred to as a genin. Unlike the other plant sterols mentioned, the side-chain that is normally present at position C17 has been formed into two ring structures. Diosgenin can be converted into progesterone via a chemical process known as the Marker degradation, which gives access to many important steroids such as testosterone (a male sex hormone) and oestradiol (a female sex hormone) which has had the A ring aromatized, resulting in the loss of a methyl group from C10 . Another semi-synthetic compound that lacks this methyl is the oral contraceptive norethisterone, which has an unusual acetylene group at position C17. One of the most widely used steroids in pharmaceutical preparations is the anti-inflammatory drug hydrocortisone (cortisol). This compound has an hydroxyl group at C11 which is introduced into the molecule in a

stereospecific manner in fermentation culture using fungi of the genus Rhizopus. If squalene is folded in a different conformation (chair-chair-chair-boat), then cyclization mediated by a cyclase enzyme results in the formation of a different intermediate, sterol intermediate II, which is the precursor of the pentacyclic triterpenes . Migrationof theC16-C17bondto satisfy thepositive charge results in the formation of sterol intermediate III. Thismay undergo several rearrangements to give different triterpene skeletons. Pathway 1 involves formation of a bond between C18 and CX, resulting in a positive charge on CY (through removal of one pair of electrons from the double bond to form the C18-CX bond). This may be satisfied by a series of Wagner–Meerwein methyl and hydride shifts with loss of a proton from C12 resulting in a C12 double bond. This pathway gives us the ursane-type triterpenes of which a-amyrin is an example, possessing a double bond in position C12 (referred to as a D12 ursene) . Pathway 2 occurs through the formation of a C18-CY bond, which leaves a positive charge on CX which is stabilized by the two methyls attached to it. This intermediate may then lose a hydrogen ion from one of these methyls to forming a neutral double bond and the lupane skeleton (pathway a), or the bond between CY and CZ may migrate to CX, giving a carbocation at CY. Wagner–Meerwein migrations and loss of a hydrogen ion from C12 forming a double bond gives the oleanane triterpene skeleton, of which b-amyrin is typical, again possessing a double bond at C12. This compound may be referred to as a D12 oleanene. Pentacyclic triterpenes are common in plants and herbal remedies such as horse chestnut (Aesculus hippocastanum) and liquorice (Glycyrrhiza glabra). Examples such as protoaescigenin, baringtogenol (both from horse chestnut) and glycyrrhetic acid (liquorice) (Fig. 6.46)

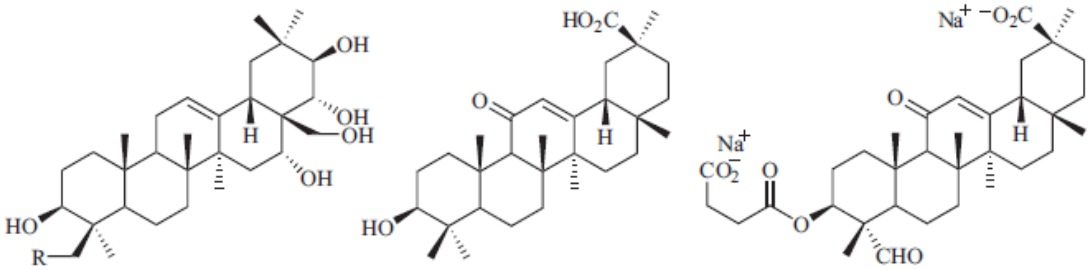


Fig. 6.46

have a high degree of functionality and chirality, and usually occur in the plant material in the form of glycosides. Horse chestnut is used as an anti-inflammatory and antibruising remedy and liquorice has a long history of use as an anti-inflammatory (anti-ulcer) agent. Carbenoxolone sodium is a semi-synthetic derivative of glycyrrhetic acid that is widely prescribed for the treatment of gastric ulcers.

TETRATERPENES (C40)

The final class of terpenoids thatwill be dealt with are the tetraterpenes, which are C40 natural products derived from the reaction of two molecules of geranyl geranylpyrophosphate (C20).Members of this class are sometimes referred to as carotenes or carotenoids because of their occurrence in the carrot (Daucus carota). As with the flavonoids, the tetraterpenes are highly pigmented natural products and are responsible for the very bright colours of certain plants, in particular the orange of carrots due to b-carotene, and the brilliant red colour of tomatoes (Lycopersicon esculentum) and peppers (Capsicum anuum), which is due to lycopene and capsanthin, respectively . These compounds are highly conjugated and strongly UV light absorbing, and are involved in photosynthesis as light accessory pigments. They are widely distributed in plants and may also act as a protection factor against UV light damage. Because of their high colouration they are employed as colouring agents in foods, pharmaceuticals and

cosmetics. The tetraterpenes are strong antioxidants, being preferentially oxidized over biological molecules such as nucleic acids and proteins. It is thought that many disease states such as certain cancers and heart disease are exacerbated by species that cause oxidation; therefore, the presence of these compounds may retard the development of such diseases. The presence of lycopene in the diet has been shown to reduce the incidence of prostate cancer in men and it is likely that the tetraterpenes have high dietary significance and are important in cancer chemoprevention. The tetraterpenes are precursors of vitamin A1 (retinol), a deficiency of which results in a reduction in sight efficiency through changes to the cornea and conjunctiva. Vitamin A1 occurs naturally in fish liver oils, carrots, green and yellow vegetables, and dairy products. It is biosynthesized by the oxidative cleavage of b-carotene to retinal, which is then reduced to retinol (vitamin A1) . Vitamin A preparations are also used to treat nappy rash, skin irritations and minor burns; vitamin A acid (retinoic acid) and vitamin A palmitate are used as treatments for acne.