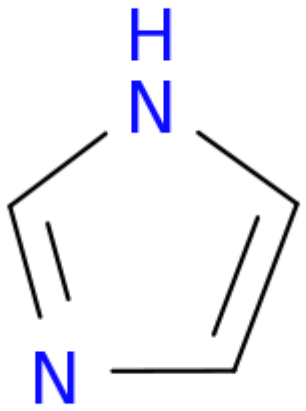
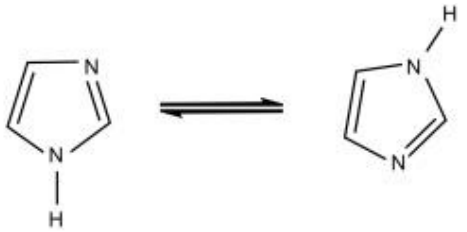
Alkaloids. Medicinal plants and raw materials containing isoquinoline, quinolizidine, quinoline, indole derivatives.

Medicinal plants containing imidazole derivatives

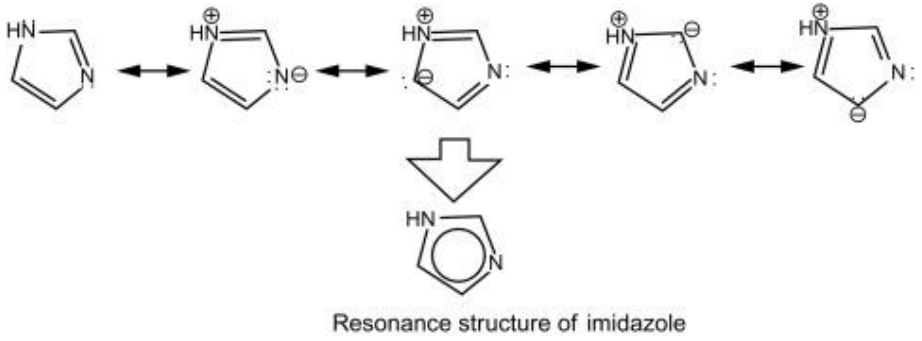
- Imidazole is a heterocyclic aromatic organic compound. This ring system is present in important biological building blocks such as histidine and histamine.



Imidazoles can act as bases and as a weak acids.
Imidazole exists in two tautomeric forms with a hydrogen atom moving between the two nitrogens.



Tautomerism of imidazole
structure at 4 and 5 position



Resonance structure of imidazole

The most important plant of this group is *Pilocarpus jaborandi.*

Medicinal raw material: Jaborandi Leaf - Jaborandi folium

Producing plants: Pilocarpus Jaborandi

Pilocarpus microphyllus

Pilocarpus pinnatifolius

Pilocarpus racemosuv

Family: Rutaceae

Pilocarpus jaborandi is a species of flowering plant in the family *Rutaceae*, native to northeast Brazil.

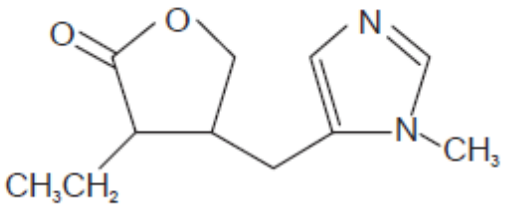
The shrub grows from 4 to 5 feet high; the bark is smooth and greyish; the flowers are thick, small and reddish-purple in colour, springing from rather thick, separate stalks about 1/4 inch long. The leaves are large compound, pinnate with an odd terminal leaflet, with two to four pairs of leaflets.

History

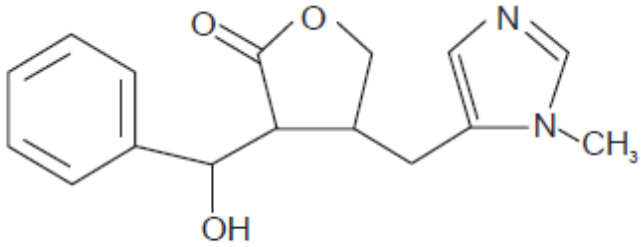
Dr. Coutinho in 1874 sent the plant to Europe from Pernambuco, hence the name Pernambuco jaborandi or *Pilocarpus jaborandi*. Later, Byasson in 1875 showed its alkaloidal nature and further Gerrard and Hardy isolated the main alkaloid ilocarpine.

Chemical Constituents

The drug contains imidazole alkaloids among, which pilocarpine is most important. Other alkaloids are isopilocarpine, pilocarpidine, pilosine, pseudopilocarpine and isopilosine. The range of total alkaloids in different species is between 0.5% and 1%.



Pilocarpine



Pilosine

Chemical Test

1. To the drug containing pilocarpine, small quantities of dilute sulphuric acid, hydrogen peroxide solution, benzene and potassium chromate solution is added and shaken, organic layer gives bluish-violet colour and yellow colour appears in aqueous layer.

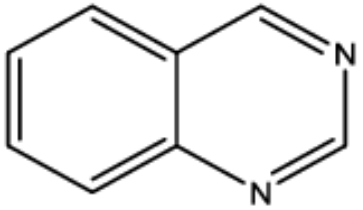
Uses

Pilocarpine is antagonistic to atropine, stimulating the nerve endings paralysed by that drug, and contracting the pupil of the eye. Its principal use is as a owerful and rapid diaphoretic. It induces also free salivation and excites most gland secretions, some regarding it as a galactagogue.

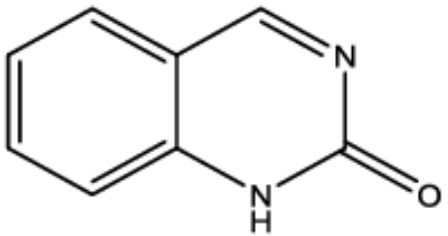
It is also used in ophthalmic practice in the treatment of glaucoma.

Medicinal plants and raw materials containing quinazoline alkaloids

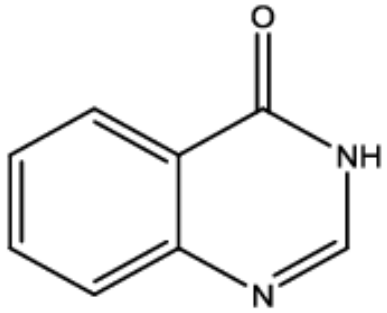
This group of alkaloids consists of a small number of compounds.compounds. The alkaloids are based on quinazoline, which contains a number of substituents.



quinazoline



quinazolin-2(1*H*)-one



quinazolin-4(3*H*)-one

Medicinal raw material: wild rue herb -
Pegani harmalae herba
Producing plants: Peganum harmala L.
Family: Zygophyllaceae

Peganum harmala, commonly called **wild rue**, **Syrian rue**, **African rue**, **esfand** or **espand**, or **harmel**, (among other similar pronunciations and spellings) is a perennial, herbaceous plant, with a woody underground rootstock

Habitus

It is a perennial, herbaceous, suffrutescent, hemicryptophyte plant, which dies off in the winter, but regrows from the rootstock the following spring. It can grow to about 0.8 m (3 ft) tall, but normally it is about 0.3 m (1 ft) tall. The entire plant is hairless (glabrous). Plants are bad tasting and smell foul when crushed.

Stems

Numerous erect to spreading stems grow from the crown of the root-stock in the spring, these branch in a corymbose fashion.

Roots

The roots of the plant can reach a depth of up to 6.1 m (20 ft), if the soil where it is growing is very dry. The roots can grow to 2 cm (0.8 in) thick.

Leaves

The leaves are alternate, sessile, and have bristly, 1.5–2.5 mm (0.06–0.10 in) long stipules at the base. The leaf blade is dissected/forked twice or more into three to five thin, linear to lanceolate-linear, greyish lobes. The forks are irregular. The lobes have smooth margins, are 3–5 cm (1.2–2.0 in) long and 1–5 mm (0.04–0.20 in) broad, and end in points.

Flowers

It blooms with solitary flowers opposite to the leaves on the apical parts of branches. It flowers between March and October in India, between April and October in Pakistan, between May and June in China, between March and April in Palestine, and between May and July in Morocco. The flowers are white or yellowish white, and are about 2–3 cm in diameter. Greenish veins are visible in the petals. They have a threadlike, 1.2 cm long pedicel. The flowers have five (10-)12–15(−20)mm long, linear, pointy-ended, glabrous sepals, often divided into lobes, although sometimes entire and only divided at the end. There are five petals which are oblong-elliptic, obovate to oblong in shape, (10-)14–15(−20)mm long, (5-)6–8(−9)mm broad, and ending with an obtuse apex. The flowers are hermaphroditic, having both male and female organs. The flowers usually have 15 stamens (rarely fewer); these have a 4-5mm long filament with an enlarged base. The dorsifixed, 6mm long anthers are longer than the filaments. The ovary is superior, and has 3 locules and ends in an 8-10mm long style, the ending 6mm of which are triangular or 3-keeled in cross-section. The ovary is surrounded by a nectary which is glabrous and has five lobes in a regular pattern.

The fruit is a dry, round seed capsule which measures about 6–10(−15) mm in diameter.

Peganum harmala is native to a wide area stretching from Morocco in north Africa and Spain and Italy in Europe, north to Serbia, Romania (possibly), Dagestan and Kazakhstan, south to Mauritania (possibly), Yemen, Saudi Arabia, Kuwait and Pakistan, and east to western Mongolia, northern China and possibly Bangladesh.

All parts of the plant contain alkaloids - derivatives of quinazoline and indole. During the budding phase the alkaloids of the quinazoline group accumulate in the amount of 1.5 - 3%, mainly peganin (vasicin) and vasicinon. During the flowering and fruiting phase, the dominant alkaloids are derivatives of the indole group - garmin, garmallin etc. Since different alkaloid groups accumulate in different phases, it is necessary to observe the prescribed harvesting time in order to obtain quality raw material. In addition to alkaloids, tannins, saponins, organic acids, and up to 14% fatty oil in the seeds were found in the above-ground parts.

According to UFS 42 - 879 - 79 the content of the sum of alkaloids should be not less than 1.5%.

Usage. The alkaloids of the quinazoline group of the herb Garmala spp. are used to produce Desoxypeganine hydrochloride.It promotes the restoration of neuromuscular conduction, increases the tone of the smooth muscles. Used in lesions of the peripheral nervous system, in the treatment of the consequences of impaired cerebral circulation. **Contraindications** - gastric and duodenal ulcer, bronchial asthma and hypertension.

Medicinal plants and raw materials containing quinolone derivatives

Medicinal raw material: Cinchona bark-
Cinchona cortex
Producing plants: Cinchona pubescens Vahl
C. ledgeriana (Moens ex Trimen)
Family: Rubiaceae

History. The natives of South America do not appear to have been acquainted with the medicinal properties of cinchona bark, the bitter taste of which inspired them with fear. Although Peru was discovered in 1513, the bark was first used for the cure of fevers about 1630. The name 'Cinchona' is said to be derived from a Countess of Chinchon, wife of a viceroy of Peru who it was long believed was cured in 1638 from a fever by the use of the bark. According to recent study of the Count's diary, it appears that the Countess never suffered from malaria or other fever during her stay in Peru, and although the Count himself did so, there is no record of his having been treated with cinchona bark. The remedy, which became known as 'Pulvo de la Condesa', acquired a considerable reputation and was known in Spain in 1639. The further distribution of the bark was largely due to the Jesuit priests, and the drug became known as Jesuit's Powder or Peruvian Powder. It first appeared in the *London Pharmacopoeia* in 1677 under the name of 'Cortex Peruanus'.

The bark was originally obtained by felling the wild trees, which were exterminated in many districts. Ruiz (1792) and Royle (1839) suggested the cultivation of cinchonas in other parts of the world. Weddell germinated seeds in Paris in 1848, and the plants were introduced into Algiers in the following year but without much success. A further attempt by the Dutch was made in 1854, seeds and plants being obtained from Peru by Hasskarl and introduced into Java. An English expedition under Markham in 1860 led to the introduction of *C. succirubra* (the most hardy species), *C. calisaya*, and *C. micrantha* into India. Seeds of *C. ledgeriana* were obtained in Bolivia by Charles Ledger in 1865 and were bought by the Dutch for their Javanese plantations. A fascinating book covering Ledger's exploits is *The Life of Charles Ledger* (*1818–1905*) by G. Grammicia, Macmillan Press, London, 1988. World War II and subsequent fighting in Malaya and Vietnam increased the demand for cinchona and stimulated cultivation in Africa and Central and South America.

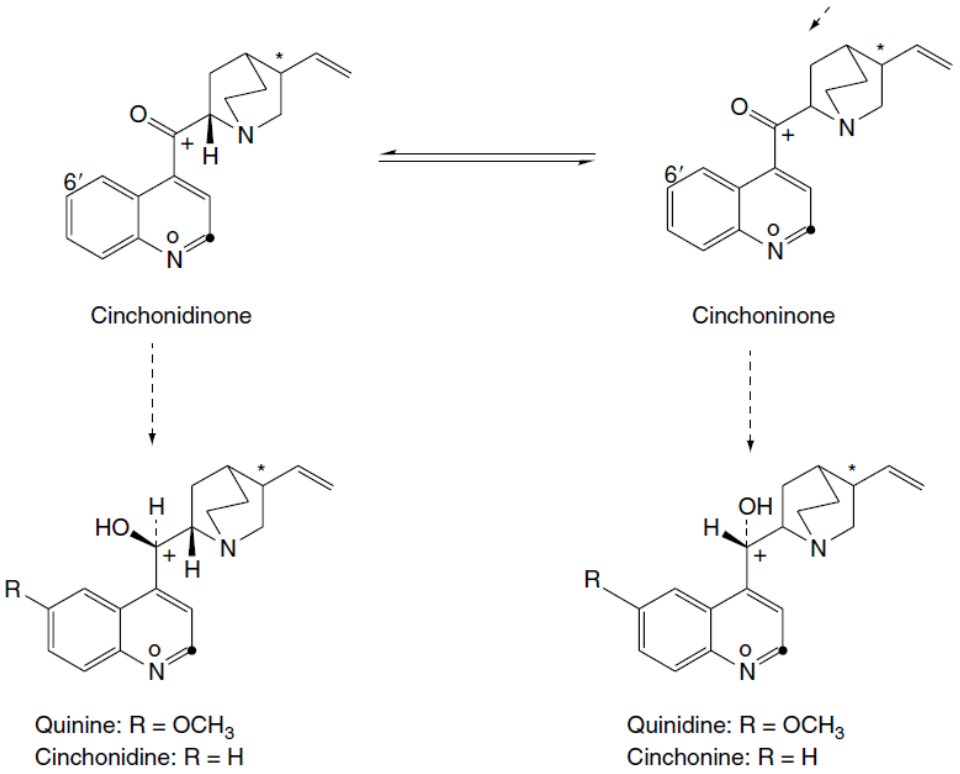
General characters

1. *Stem-bark*. The commercial ‘druggist’s’ quills are up to 30 cm long and usually 2–6 mm thick. Bark for manufacturing purposes is frequently in small curved pieces. The outer surface frequently bears moss or lichen. The cork may or may not be longitudinally wrinkled, and usually bears longitudinal and transverse cracks, which vary in frequency and distinctness in the different varieties. The inner surface is striated and varies in colour from yellowish-brown to deep reddish-brown. The fracture is short in the outer part but somewhat fibrous in the inner part. Odour, slight; taste, bitter and astringent.

2. *Root-bark*. Root-bark occurs in channelled, often twisted pieces about 2–7 cm long. Both surfaces are of similar colour, the outer, however, being somewhat scaly, while the inner surface is striated.

Special characters. In view of the number of hybrids which are cultivated, the distinction of the various commercial cinchona barks is a matter of some difficulty. In Table 26.7 the notes on four important species have been made as concise as possible to facilitate comparison.

Constituents. Cinchona bark contains quinoline alkaloids. The principal alkaloids are the stereoisomers quinine and quinidine and their respective 6′-demethoxy derivatives, cinchonidine and cinchonine. The quinine series has the configuration 8*S*, 9*R* and the quinidine 8*R*, 9*S* ; other alkaloids of lesser importance have been isolated. Some of these (e.g. quinicine and cinchonicine) are amorphous. The amount of alkaloids present and the ratios between them vary considerably in the different species and hybrids, also according to the environment of the tree and the age and method of collection of the bark.



The alkaloids appear to be present in the parenchymatous tissues of the bark in combination with quinic acid and cinchotannic acid. Quinic acid is present to the extent of 5–8%. Cinchotannic acid is a phlobatannin and a considerable amount of its decomposition product, ‘cinchona red’, is also found in the bark. Other constituents are quinovin (up to 2%), which is a glycoside yielding on hydrolysis quinovaic acid and quinovose (isorhodeose).

Anthraquinones, which as a group of compounds are associated with the family Rubiaceae (see Table 21.3), are not normally found in quantity in the bark of cinchona as indicated by the isolation of norsolorinic acid, a tetrahydroxyanthraquinone, in 0.0008% yield from the bark of C. ledgeriana. However, they are produced in cell cultures of the plant and by infection of the bark with Phytophthora cinnamomi.

Uses. Galenicals of cinchona have long been used as bitter tonics and stomachics. On account of the astringent action, a decoction and acid infusion are sometimes used as gargles. Before World War II, quinine was the drug of choice for the treatment of malaria but became largely superseded by the advent of synthetic antimalarials developed during that period. It has, however, remained of importance in Third World countries and has re-emerged as suitable for the treatment of *Plasmodium falciparum* infections (falciparum malaria) in the many areas where the organism is now resistant to chloroquine and other antimalarials. Quinidine is employed for the prophylaxis of cardiac arrhythmias and for the treatment of atrial fibrillation; it also has antimalarial properties and like quinine is effective against chloroquine-resistant organisms.

Medicinal plants and raw materials containing isoquinoline derivatives.

Medicinal raw material: Opium (Raw Opium)
Producing plants: Papaver somniferum L.
Family: Papaveraceae

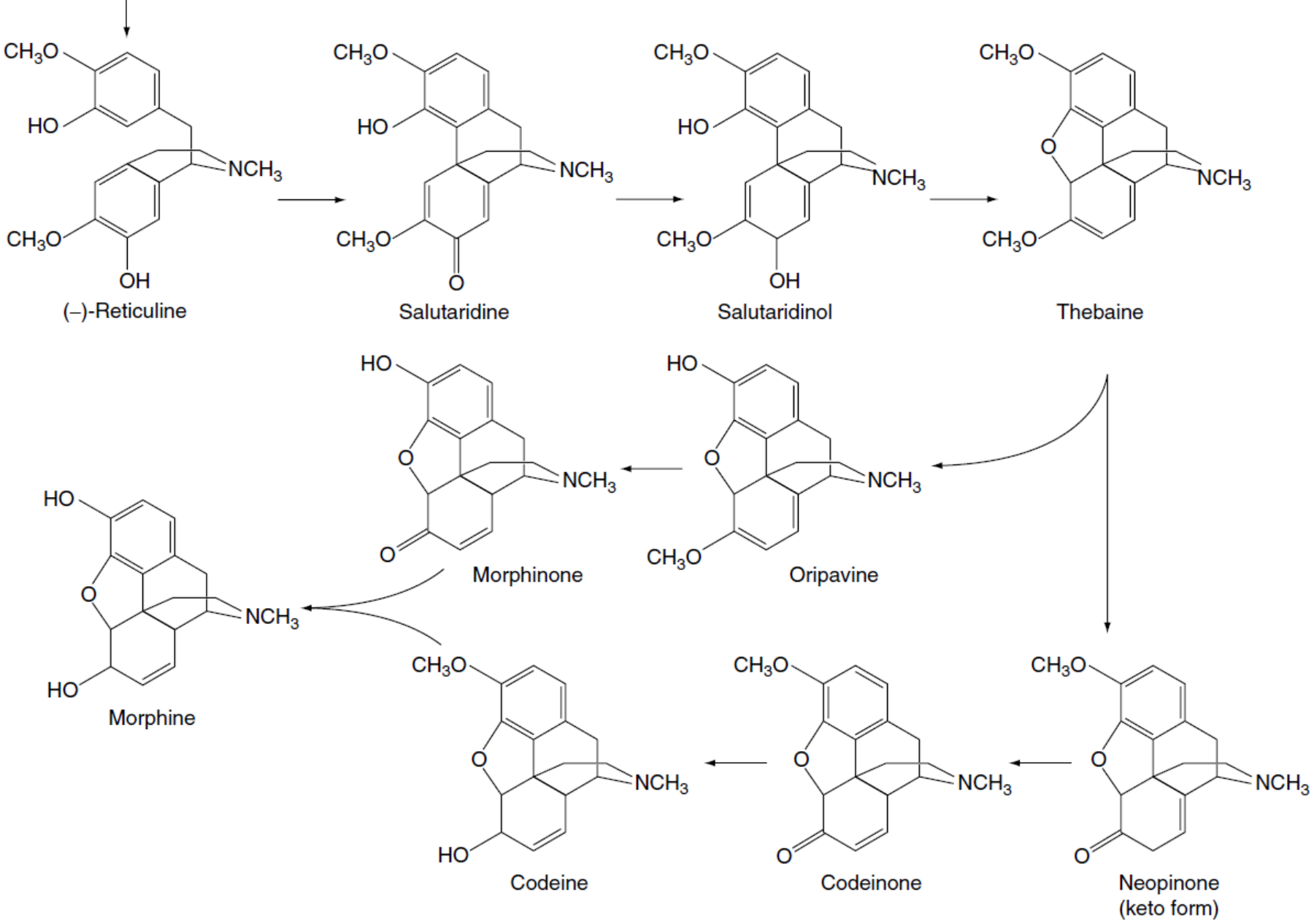
The opium poppy, *Papaver somniferum* L., is an annual herb about 50–150 cm in height. The stem and leaves are glaucous. The latter are about 10 cm in length, entire, sessile and amplexicaul. The margin is dentate but varies somewhat in the different varieties. The flowers, which are borne on a slightly hairy peduncle, are solitary, nodding in the bud, and have caducous sepals. The unilocular ovary contains numerous ovules attached to parietal placentas. It bears at its apex a flat disc formed by the union of the radiating stigmas. The capsule opens by means of small valves, which are equal in number to the carpels and situated immediately below the stellate stigma.

Poppy capsules contain, when ripe, 0.18–0.28% of morphine. Poppy seeds contain only very small quantities of narcotine, papaverine and thebaine in addition to morphine and codeine.

Opium (*Raw Opium*) is the latex obtained by incision from the unripe capsules of *Papaver somniferum* (Papaveraceae) and dried partly by spontaneous evaporation and partly by artificial heat. It is worked into irregularly shaped masses and is known in commerce as Indian opium. Indian opium is specifically stated because this is a legally available source of the drug. However, a number of countries e.g. Turkey, former USSR and Yugoslavia and Australia (Tasmania) grow considerable quantities of the opium poppy for alkaloid extraction and seed production. For strategic purposes, a relatively small crop is raised in southern England. Much illegal opium is produced in S.E. Asia.

History. Opium was well known to the ancients. Dioskurides, about ad 77, distinguishes between the latex of the capsules, *opos*, and an extract of the whole plant, *mekonion*. The use of opium spread from Asia Minor to Persia, where opium eating became popular, and from there to India and China. However, it was not until the second half of the eighteenth century that opium smoking began to be extensively practised in China and the Far East.

Asia Minor has from very early times been an important source of opium production. In Macedonia cultivation was started as recently as 1865. Persian opium was imported into England from about 1870 to 1955. Opium was cultivated in India during the Middle Ages, and the monopoly of the Mogul Government was taken over first by the East India Company and then by the British Government. Formerly, Indian opiums, being prepared mainly for smoking, were little esteemed for pharmaceutical purposes. However, that now imported is of good quality and constitutes the principal British source for the manufacture of alkaloids.


(–)-Reticuline
Salutaridine
Salutaridinol
Thebaine
Morphinone
Oripavine
Morphine
Codeine
Codeinone
Neopinone
(keto form)

Uses. The alkaloids present in opium in greatest proportion decrease in narcotic properties in the order morphine, codeine, noscopine. Opium and morphine are widely used to relieve pain and are particularly valuable as hypnotics, as, unlike many other hypnotics, they act mainly on the sensory nerve cells of the cerebrum. Codeine is a milder sedative than morphine and is useful for allaying coughing. Both morphine and codeine decrease metabolism, and the latter, particularly before the introduction of insulin, was used for the treatment of diabetes. Opium, while closely resembling morphine, exerts its action more slowly and is therefore preferable in many cases (e.g. in the treatment of diarrhoea). Opium is also used as a diaphoretic.
The habitual use of codeine may, in some individuals, produce constipation.

Medicinal plants and raw materials containing indole derivatives.

Ergot and Ergot Alkaloids

Medicinal raw material: Ergot sclerotia **-**Secale Cereale
Producing plants: Ergot of Rye **-** Claviceps purpurea Tulasne
Family: Clavicipitaceae

Ergot (*Ergot of Rye*) is the dried sclerotium of a fungus, *Claviceps purpurea* Tulasne (Clavicipitaceae), arising in the ovary of the rye, *Secale cereale*. Controlled field cultivation on rye is the main source of the crude drug. The most important producers are Czechoslovakia, Hungary, Switzerland and former Yugoslavia. With modern farming the supply of 'natural' ergot is decreasing and fields of rye are devoted to its cultivation.

Different selected strains of *C. purpurea* are used for the production of the alkaloids ergotamine, ergocristine, or ergocornine and ergokryptine.

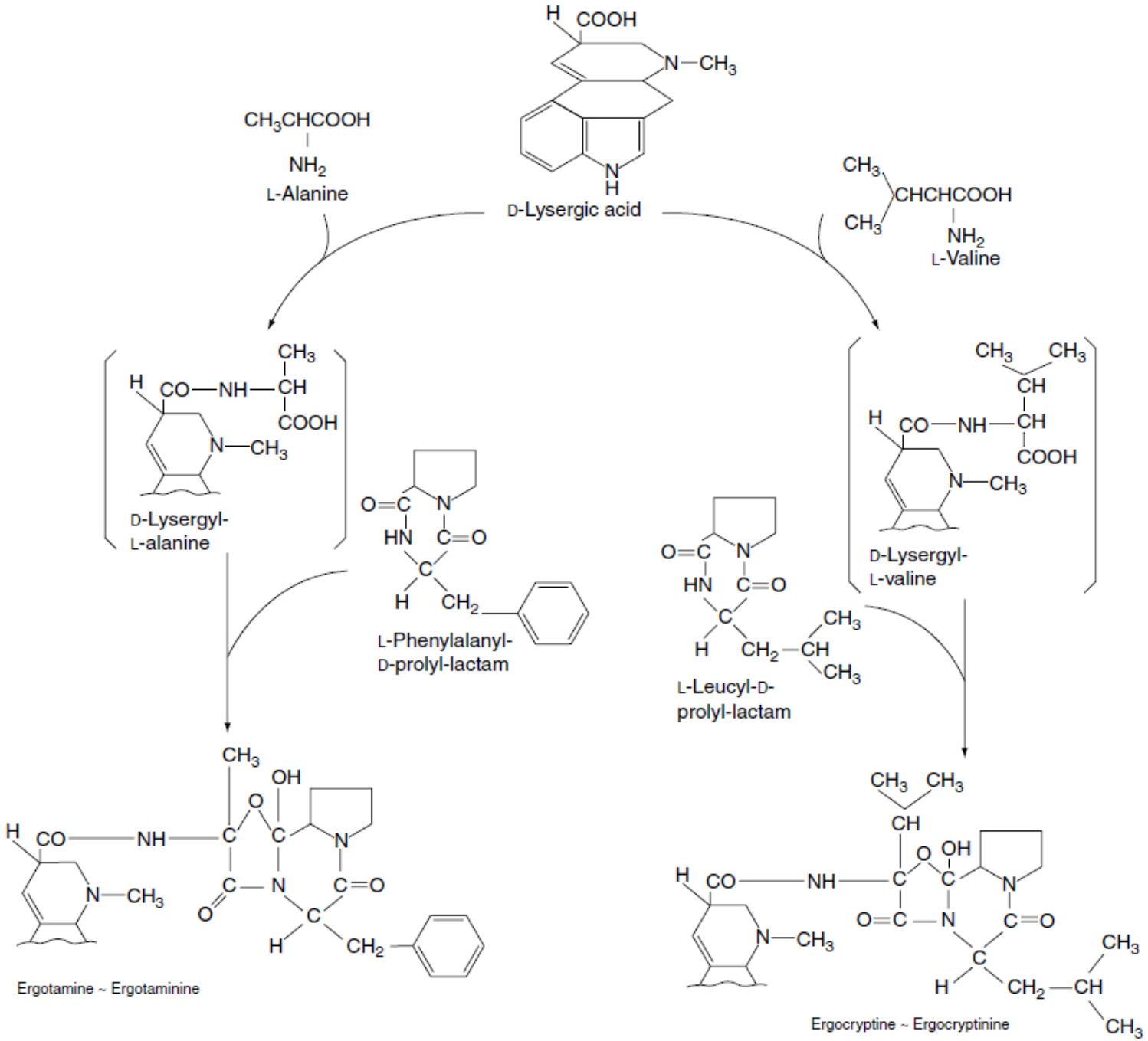
Life history and collection. The fungus *C. purpurea* and other species such as *C. microcephala* Wallr., *C. nigricans* Tul. and *C. paspali* produce ergots on many members of the Gramineae (including the genera *Triticum*, *Avena*, *Festuca*, *Poa*, *Lolium*, *Molinia* and *Nardus*) and Cyperaceae (including the genera *Scirpus* and *Ampelodesma*). Many of these ergots appear to be extremely toxic and to produce typical ergotism.
For the life-cycle and illustrations of the fungus, see earlier editions.

Macroscopical characters. The drug consists almost entirely of sclerotia, the amount of other organic matter being generally limited to not more than 1%. Each sclerotium is about 1.0–4 cm long and 2–7 mm broad; fusiform in shape and usually slightly curved. The outer surface, which is of a dark, violet-black colour, is often longitudinally furrowed and may bear small transverse cracks. Ergot breaks with a short fracture and shows within the thin, dark outer layer a whitish or pinkish-white central zone of pseudoparenchyma in which darker lines radiating from the centre may be visible. Ergot has a characteristic odour and an unpleasant taste.

Powdered ergot when treated with sodium hydroxide solution develops a strong odour of trimethylamine. In filtered ultraviolet light it has a strong reddish colour by means of which its presence in flour may be detected.

Constituents. The ergot alkaloids (ergolines) can be divided into two classes: (1) the clavine-type alkaloids, which are derivatives of 6,8-imethylergoline and have been extensively studied in cultures of the mycelium of the ergot fungus; and (2) the lysergic acid derivatives, which are peptide alkaloids. It is the latter class that contains the pharmacologically active alkaloids that characterize the ergot sclerotium (ergot).

Each active alkaloid occurs with an inactive isomer involving isolysergic acid; the inactive isomers are not formed initially in the sclerotium but tend to accumulate as a result of unsuitable processing and poor or long storage. These alkaloids have been studied over many years and were not easy to characterize. Thus 'ergotoxine', which since its isolation in 1906 (by Barger and Carr and independently by Kraft) had been accepted as a pure substance, and in the form of ergotoxine ethanosulphonate was formerly used as a standard, was shown to be a mixture of the three alkaloids ergocristine, ergocornine and ergocryptine. Six pairs of alkaloids predominate in the sclerotium and fall into either the water-soluble ergometrine (or ergonovine) group or the water-insoluble ergotamine and 'ergotoxine' groups.


D-Lysergic acid
L-Alanine
L-Valine
D-Lysergyl-L-alanine
D-Lysergyl-L-valine
L-Phenylalanyl-D-prolyl-lactam
L-Leucyl-D-prolyl-lactam
Ergotamine ~ Ergotaminine
Ergocryptine ~ Ergocryptinine

Among the less important constituents of ergot may be mentioned histamine, tyramine and other amines and amino acids; acetylcholine; colouring matters; sterols (ergosterol and fungisterol); and about 30% fat. The cell walls are chitinous.

Storage. Ergot is particularly liable to attack by insects, moulds and bacteria. After collection it should be thoroughly dried, kept entire, and stored in a cool, dry place. If powdered and not immediately defatted, the activity decreases, but if defatted and carefully stored in an air-tight container, it will remain active for a long period. However, as indicated above, under certain conditions, loss of activity arises by the conversion of the pharmacologically important alkaloids to inactive isomers. Any sample of ergot which shows worm holes or a considerable amount of insect debris will almost certainly deteriorate further on storage.

Uses. Although whole ergot preparations were traditionally used in labour to assist delivery and to reduce post-partum haemorrhage, ergot itself has been largely replaced in the pharmacopoeias by the isolated alkaloids. Only ergometrine produces an oxytocic (literally ‘quick delivery’) effect, ergotoxine and ergotamine having quite a different action. Ergometrine is soluble in water or in dilute alcohol. It is often known, particularly in the USA, as ergonovine. Ergotamine and the semisynthetic dihydroergotamine salts are employed as specific analgesics for the treatment
of migraine. Lysergic acid diethylamide (LSD-25), prepared by partial synthesis from lysergic acid, is a potent specific psychotomimetic.

Thank You For Your Attention