8

Alkaloids

Alkaloids are extremely difficult to define because they do not represent a homogeneous group of compounds from either the chemical, biochemical, or physiologic viewpoint. Consequently, except for the fact that they are all organic nitrogenous compounds with a limited distribution in nature, reservations must be appended to any general definition. Plants have been a rich source of alkaloids, but some are found in animals, fungi, and bacteria; practically all have been reproduced in the laboratory by chemical synthesis. Most, but not all, possess basic properties, owing to the presence of an amino nitrogen, and many, especially those pertinent to pharmacy and medicine, possess marked physiologic activity. In spite of the difficulties attending a precise definition, the term alkaloid is extremely useful and is commonly applied to basic nitrogenous compounds of plant origin that are physiologically active.

In the plant kingdom, the alkaloids appear to have a restricted distribution in certain families and genera. This observation is based on the incomplete investigations of plants up to the present time; considerable research must be accomplished before definite statements concerning the occurrence of alkaloids can be made. Among the angiosperms, the Leguminosae, Papaveraceae, Ranunculaceae, Rubiaceae, Solanaceae, and Berberidaceae are outstanding alkaloid-yielding plants. The Labiatae and Rosaceae are almost free of alkaloids; the gymnosperms only rarely contain them (Taxaceae). Although it has been claimed that the monocotyledons do not generally produce alkaloids, investigations indicate that the Amaryllidaceae and Liliaceae are 2 of the most promising families (of a list of 11) in which to search for alkaloid-yielding plants.

Specific alkaloids of complex structures are ordinarily confined to specific plant families (hyoscyamine in Solanaceae, colchicine in Liliaceae). Nicotine, which is found in a number of widely scattered plant families, is not an exception to this rule because of the biosynthetic simplicity of its structure. However, the occurrence of ergot alkaloids in the fungus *Claviceps purpurea* and certain *Ipomoea* species (Convolvulaceae) is a definite exception and may be attributed to either parallel or convergent evolution of certain complex biochemical pathways. Alkaloids may occur in various parts of the plant: in seeds (physostigma, areca), in fruits (conium), in leaves (belladonna, coca), in underground stems (sanguinaria), in roots (belladonna root), in rhizomes and roots (ipecac, hydrastis), and in barks (cinchona). They are also found in the fungi (ergot, *Amanita citrina*).

The names of the alkaloids are obtained in various ways: (1) from the generic name of the plant yielding them (hydrastine, atropine), (2) from the specific name of the

plant yielding them (cocaine, belladonnine), (3) from the common name of the drug yielding them (ergotamine), (4) from their physiologic activity (emetine, morphine), and (5) occasionally from the discoverer (pelletierine).

Sometimes a prefix or suffix is added to the name of a principal alkaloid to designate another alkaloid from the same source (quinine, quinidine, hydroquinine). By agreement, chemical rules designate that the names of all alkaloids should end in "ine."

Alkaloids usually contain one nitrogen atom, although some, like ergotamine, may contain up to 5. The nitrogen may exist as a primary amine (RNH_2), as a secondary amine (R_2NH), or as a tertiary amine (R_3N).

Because the nitrogen atom bears an unshared pair of electrons, such compounds are basic and resemble ammonia's chemical properties. The degree of basicity varies greatly, depending on the structure of the molecule and the presence and location of other functional groups. Like ammonia, the alkaloids are converted into their salts by aqueous mineral acids, and when the salt of an alkaloid is treated with hydroxide ion, nitrogen gives up a hydrogen ion and the free amine is liberated. Quaternary ammonium compounds [$R_4N^+X^-$], such as tubocurarine chloride or berberine chloride, have 4 organic groups covalently bonded to nitrogen, and the positive charge of this ion is balanced by some negative ion. The quaternary ammonium ion, having no proton to give up, is not affected by hydroxide ion; consequently, quaternary ammonium compounds have chemical properties quite different from those of the amines.

In spite of the difficulty in precisely characterizing alkaloids by definition, they do have in common a surprising number of physical and chemical properties. For the most part, the alkaloids are insoluble or sparingly so in water, but the salts formed on reaction with acids are usually freely soluble. The free alkaloids are usually soluble in ether, chloroform, or other relatively nonpolar, immiscible solvents in which, however, the alkaloidal salts are insoluble. This permits a ready means for the isolation and purification of the alkaloids as well as for their quantitative estimation. Most of the alkaloids are crystalline solids, although a few are amorphous. An additional few, coniine, nicotine, and sparteine, which lack oxygen in their molecules, are liquids. Alkaloidal salts are crystalline, and their crystal form and habit are often a useful means of rapid microscopic identification.

Alkaloids are usually classified according to the nature of the basic chemical structures from which they derive. A number of these structures are shown in Figure 8–1. Arecoline, lobeline, and nicotine are derivatives of **pyridine** and **piperidine;** atropine, hyoscyamine, and hyoscine are derived from **tropane**, a condensation product of pyrrolidine and piperidine; the cinchona alkaloids, quinine, quinidine, cinchonine, and cinchonidine, contain **quinoline** as the principal nucleus; hydrastine, (+)-tubocurarine, emetine, and the opium alkaloids are characterized by the **isoquinoline** nucleus. Other types include ergonovine, reserpine, and strychnine, which derive from the **indole** ring; pilocarpine, which has the **imidazole** ring; caffeine and theobromine, which are **purine** bases, and protoveratrine, which contains a **steroidal** structure.

The alkaloids, like other amines, form double salts with compounds of mercury, gold, platinum, and other heavy metals. These double salts are usually obtained as precipitates, and many of them are microcrystallographically characteristic. The common alkaloidal reagents include Wagner's (iodine in potassium iodide), Mayer's (potassium mercuric iodide), Dragendorff's (potassium bismuth iodide), and many others. The alkaloids usually possess a bitter taste.

Much has been written about the pos-

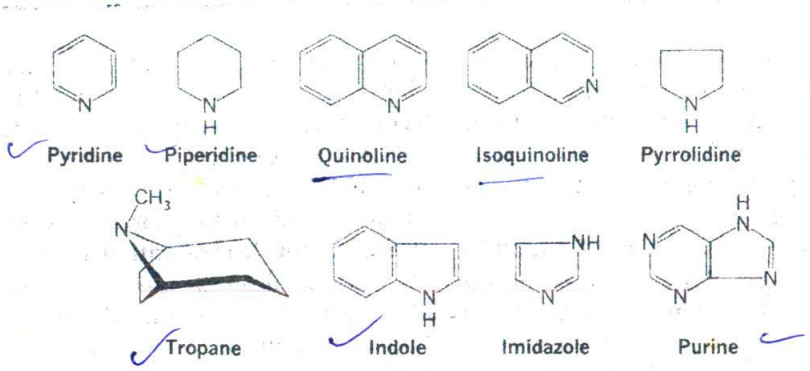


Fig. 8–1. Important nitrogen-containing ring structures present in alkaloidal drugs.

sible function of alkaloids in plants and about the reaons why they occur there. Some of the possibilities that have been discussed include their functions as (1) poisonous agents protecting the plant against insects and herbivores, (2) end products of detoxification reactions representing a metabolic locking-up of compounds otherwise harmful to the plant, (3) regulatory growth factors, or (4) reserve substances capable of supplying nitrogen or other elements necessary to the plant's economy.

Although certain exceptions exist because of the diverse nature of alkaloids, the evidence for any result of alkaloid formation useful to the existence of the plant is slight. Perhaps the best example of such a result is found in the wild plants of certain arid regions, where overgrazing by domestic animals has taken place for centuries. An extremely high percentage of such plants contains alkaloids that, because of their bitter taste or toxic properties, apparently confer survival value on the species producing them. Plants lacking such distasteful substances were long ago exterminated. However, to avoid being teleologic, we must emphasize that protection, like the other postulated functions, is a consequence of, not a reason for, alkaloid formation.

Perhaps alkaloids should be viewed as products of metabolic experimentation that reflect the intermediary evolutionary stages now attained by plants. Alkaloid formation is probably best regarded as a metabolic act involving longer or shorter reaction sequences that begin with substances normal and essential in plant metabolism and end with compounds not necessarily serving such a purpose. Because the process is genetically controlled, an alkaloid-producing plant is merely a plant in which this additional metabolic reaction has evolved through mutation of one or more genes. Proof that such changes occur irrespective of the utility of ultimate products is given by the thousands of pigments, tannins, polysaccharides, glycosides, volatile oils, and resins to which no essential role in plant metabolism can be ascribed.

Like many of these other secondary constituents, the alkaloids may be thought of as resulting from a "metabolic error," which will probably be eliminated when plants approach a stage of ultimate adaptation and eliminate all redundant features and processes. They are thus a kind of waste product retained within the organism that produces them. It must be emphasized that, unlike many such substances with which we are familiar, the alkaloids are structurally complex end products of energy-requiring reaction sequences.

The pharmacologic action of alkaloids varies widely: some (morphine, codeine) are analgesics and narcotics whereas others (strychnine, brucine) are central stimulants. Some (atropine) are mydriatics whereas others (physostigmine, pilocarpine) are miotics. Some (ephedrine) cause

a rise in blood pressure, but others (reserpine) produce a fall in excessive hypertension. In fact, the alkaloids are capable of extensive physiologic activity.

Various schemes for the classification of alkaloids have been suggested. The following plan is based on the ring structure or nucleus of the chief alkaloid group in the plant drug: (1) pyridine-piperidine combined, (2) tropane, (3) quinoline, (4) isoquinoline, (5) indole, (6) imidazole, (7) steroid, (8) alkaloidal amine, and (9) purine.

The biosynthesis of many alkaloidal structures can be rationalized through simple chemical reactions that involve amino acids. The amino acids that most often serve as alkaloidal precursors include phenylalanine, tyrosine, tryptophan, histidine, anthranilic acid, lysine, and ornithine. Some of the general reactions that are of particular importance include the decarboxylation and transamination of the amino acids to yield a corresponding amine or aldehyde. These can react to form a Schiff base which, in turn, can react with a carbanion in a Mannich-type condensation. These general reactions are illustrated in Figure 8–2. Specific examples of alkaloid biosynthesis are discussed under the various structural groups of alkaloids.

PYRIDINE-PIPERIDINE ALKALOIDS

Upon reduction, the tertiary base, pyridine, is converted into the secondary base, piperidine. These 2 nuclei form the basis of this group, which is sometimes divided into 3 subgroups: (1) derivatives of piperidine, including lobeline from lobelia; (2) derivatives of nicotinic acid, including arecoline from areca; and (3) derivatives of both pyridine and pyrrolidine, including nicotine from tobacco. The important alkaloidal drugs and their alkaloids that are classified in this group are areca, arecoline hydrobromide, lobelia, lobeline, and nicotine.

Biosynthesis of Pyridine-Piperidine Alkaloids

Nicotine. More than 65 years ago, the Swiss chemist Trier proposed that nicotine was biosynthesized from nicotinic acid and proline. If proline is considered a representative of the ornithine-proline-glutamic acid group, this remarkable hypothesis may be considered correct. However, numerous experiments conducted principally during the last 2 decades still have not clarified completely all of the reactions involved in the production of nicotine in *Nicotiana* species. The biosynthetic pathways leading to this compound are summarized in Figure 8–3.

Tracer studies have shown that ornithine is incorporated into nicotine by tobacco plants. This incorporation results in a symmetric labeling pattern of nicotine. Putrescine, *N*-methylputrescine, and *N*-methylaminobutanal are all incorporated, and the key intermediate is thought to be the *N*-methylpyrrolinium ion which, through electrophilic aromatic substitution, attaches to C-3 of the pyridine ring of nicotinic acid. Nicotinic acid is formed in higher plants and certain microorganisms via

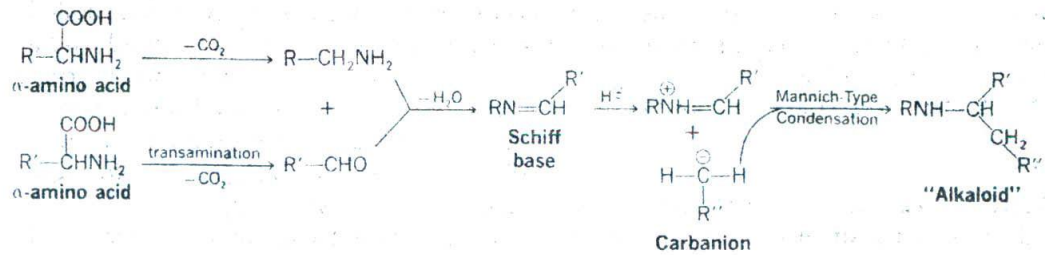


Fig. 8–2. General reactions in alkaloid biosynthesis.

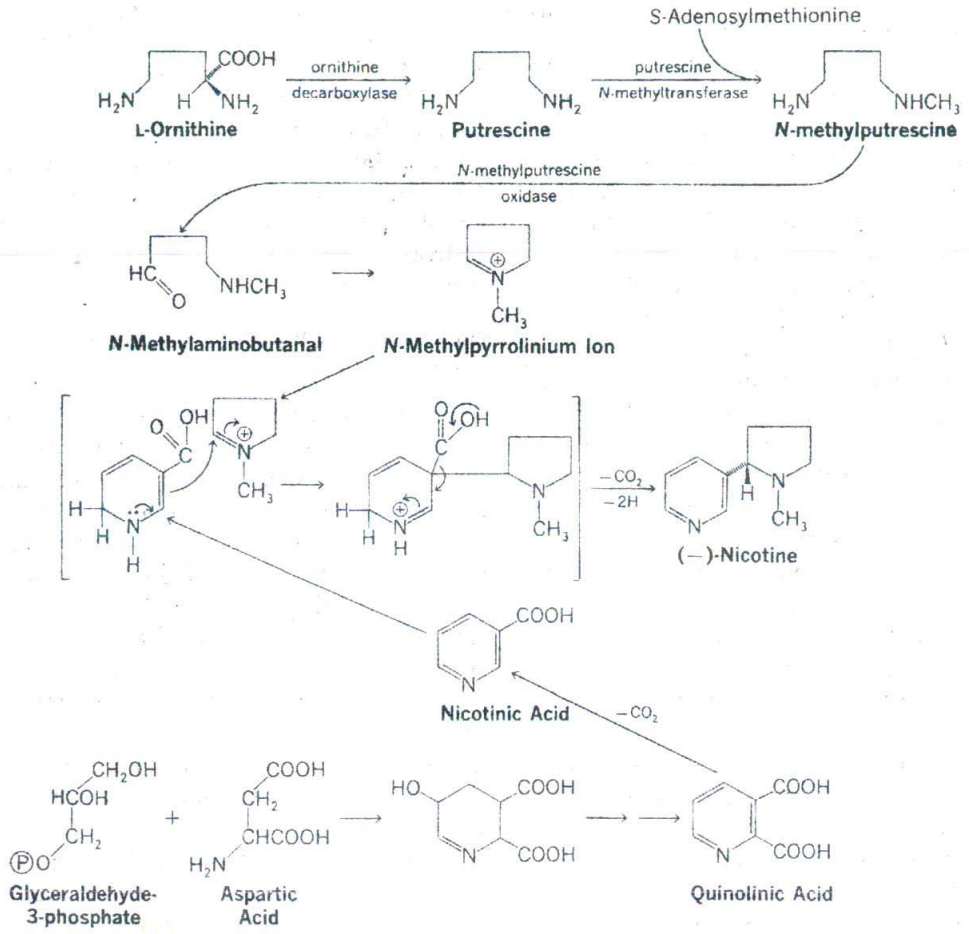


Fig. 8–3. Biosynthesis of nicotine.

quinolinic acid by the condensation of glyceraldehyde-3-phosphate and aspartic acid.

Nicotine is primarily a product of root metabolism, but the formation of small amounts, as well as subsequent reactions such as the demethylation of nicotine, can occur in the leaves of plants.

USE. Nicotine is bound to an ion exchange resin in a chewing gum base as a temporary aid to the cigarette smoker seeking to give up smoking.

PRESCRIPTION PRODUCT. Nicorette®.

Areca

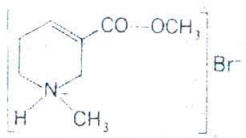
Areca, areca nut, or betel nut is the dried, ripe seed of *Areca catechu* Linné (Fam. Palmae). *Areca* is the Spanish and Portuguese term for the betel nut. *Catechu* is the East Indian name for an astringent extract or juice. *Areca catechu* is a beautiful tall palm extensively cultivated in India, southeastern Asia, the East Indies, and to some extent East Africa. The fruit is a nut that contains a single seed with a thin seed coat and a large ruminate endosperm. The seeds are removed from the fruits, boiled in water containing lime, and dried. India is a major producer of areca, but its production is mostly consumed domestically. The United States imports the drug from Sri Lanka. Sri Lanka also exports to India when areca is in short supply.

Areca is mixed with lime, the leaves of *Piper betle* Linné, and occasionally gambir.

The mixture is used as a stimulant masticatory in India and the East Indies. In India, the mixture is known as "punsupari." Betel chewing has been practiced since early times. The natives chew fresh betel nuts; dried betel nuts are used for pharmaceutic purposes. The value of areca as a taenicide apparently has been known in the East for a long time but was not known to western civilization until 1863.

Areca contains several alkaloids that are reduced pyridine derivatives. Among them are arecoline (arecaidine methyl ester), arecaidine (*N*-methyl guvacine), guvacine (tetrahydronicotinic acid), and guvacoline (guvacine methyl ester). The total alkaloid content can reach 0.45%. Arecoline, the most abundant and physiologically most active alkaloid, is a liquid occurring to the extent of about 0.2%. Areca also contains tannin (about 15%), lipids, volatile oils, and gum.

USE AND DOSE. Areca is classified as an anthelmintic in veterinary practice and is employed as a vermicide and taenifuge. The usual dose in dogs is 2 to 4 g; in sheep, 4 to 8 g, based on the weight of the animal.



Arecoline Hydrobromide

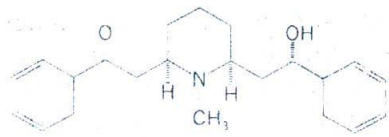
Lobelia

Lobelia or Indian tobacco consists of the dried leaves and tops of *Lobelia inflata* Linné (Fam. Lobeliaceae). *Lobelia* was named in honor of Matthias de L'Obel, a Flemish botanist (1538 to 1616); *inflata* refers to the fruit, which is hollow and distended. The plant is an annual herb indigenous to the eastern and central United States and to Canada.

Commercial supplies come from collecting stations in North Carolina, Virginia, and Tennessee. It should be collected after a portion of the capsules has become inflated; then it should be carefully dried and preserved. Lobelia was employed by the Indians, when necessity required, as a substitute for tobacco. Its emetic properties were first observed in 1785, and the drug was introduced into medicine in 1807.

The drug contains 14 alkaloids, of which lobeline is the major and most important, a pungent volatile oil, resin, lipids, and gum.

Lobeline, (−)-lobeline, or *alpha* lobeline (to distinguish it from a mixture of the lobelia alkaloids formerly designated as lobeline) occurs as colorless crystals that are slightly soluble in water but readily soluble in hot alcohol.



(−)-Lobeline

USES AND DOSE. Lobeline produces similar, but weaker, pharmacologic effects to those of nicotine on the peripheral circulation, neuromuscular junctions, and the central nervous system. For this reason, a 2.0-mg dose of lobeline sulfate is incorporated in tablets or lozenges that are intended to aid in breaking the tobacco habit (smoking deterrents). The majority of controlled studies show that lobeline has only a placebo effect on decreasing the physical craving for cigarettes.

NONPRESCRIPTION PRODUCT. Bantron®.

TROPANE ALKALOIDS

Tropane is a dicyclic compound formed by the condensation of a pyrrolidine precursor (ornithine) with 3 acetate-derived carbon atoms. Both pyrrolidine and piperidine ring systems can be discerned in the molecule.

The 3-hydroxy derivative of tropane is known as tropine. Its esterification with (−)-tropic acid yields hyoscyamine (tropine tropate), which may be racemized to form atropine.

Biosynthesis of Tropane Alkaloids

Because of the commercial importance of hyoscyamine and scopolamine, investigation of their biosynthesis has been extensive, especially in *Datura* species. Feeding studies with labeled ornithine have revealed that this amino acid is incorporated stereospecifically to form the pyrrolidine ring of tropine. The remaining 3 carbon atoms are derived from acetate and thus complete the piperidine moiety. Methylation results via transmethylation from *S*-adenosylmethionine to complete the tropine nucleus.

Phenylalanine is the precursor of tropic acid. Tracer studies have shown that the side chain of the amino acid undergoes a novel type of intramolecular rearrangement during the conversion. Esterification of tropic acid with tropine produces hyoscyamine. These reactions are summarized in Figure 8–4.

The important drugs and alkaloids in this group are belladonna leaf, hyoscyamus, stramonium, atropine, hyoscyamine, scopolamine, coca, and cocaine.

Belladonna

Belladonna leaf, belladonna herb, or deadly nightshade leaf consists of the dried leaf and flowering or fruiting top of *Atropa belladonna* Linné or of its variety *acuminata* Royle ex Lindley (Fam. Solanaceae) (Fig. 8–5). Belladonna leaf yields not less than 0.35% of alkaloids.

Atropa is from *Atropos*, meaning inflexible, the name of the Greek Fate who cuts the thread of life, and probably alludes to the poisonous character of the drug. Belladonna is from the Italian *bella*, meaning beautiful, and *donna*, meaning lady. (The juice of the berry, when placed in the eyes, causes dilation of the pupils, thus giving a striking appearance.)

The plant is a perennial herb that grows to a meter in height. It is indigenous to central and southern Europe and to Asia Minor and is cultivated in sunny locations in England, Germany, India, and the United States. At present, the chief source of supply is the Balkans.

Belladonna was probably known to the ancients, but the first authentic notice appeared in 1504. The poisonous character of the plant has been known for many years, particularly in its indigenous localities. It was the subject of many treatises during the 18th century. Its mydriatic properties were first recorded in 1802, but its analgesic properties were not recognized until 1860. The leaves were used earlier than the root, whose use did not occur until about 1860.

The stems are cut about halfway down when the fruits begin to form and the alkaloids are most abundant. After rains or irrigation, the plant produces a second crop of leaves and flowers, which are gathered in the fall. Most of the herb crop is dried or partially dried and extracted with acidified water to obtain the alkaloids. A fine grade of leaf is obtained by hand picking the leaves and drying them rapidly at rather low temperatures and in the shade.

The leaf yields alkaloids in concentrations ranging up to more than 1%. About three fourths of the isolated alkaloid mixture is (−)-hyoscyamine; the remainder is atropine. The latter compound exists, at most, only in traces in fresh plant material. Atropine is formed by racemization during the extraction process. Small but varying amounts of other bases are found in the root but not in the leaf. These include apoatropine, belladonnine, cuscohygrine, and scopolamine.

The yield of alkaloids averages as follows: roots, 0.6%; stems, 0.05%; leaves, 0.4%; unripe berries, 0.19%; ripe berries, 0.21%; seeds, 0.33%.

USES AND DOSE. Belladonna acts as a parasympathetic depressant, which accounts for its use as a spasmolytic agent. The drug is used as adjunctive therapy in the treatment of peptic ulcer; functional digestive disorders, including spastic, mucous, and ulcerative colitis; and diarrhea, diverticulitis, and pancreatitis. It possesses

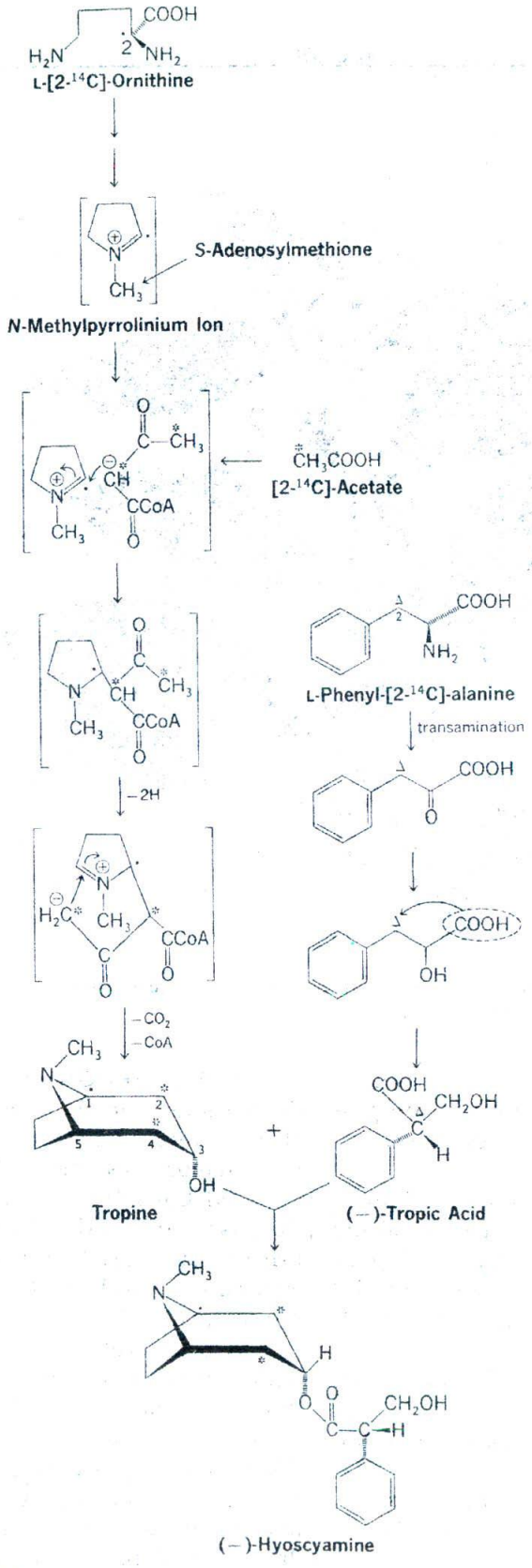


Fig. 8–4. Biosynthesis of hyoscyamine.

Fig. 8–5. *Atropa belladonna* showing the alternate, petiolate, ovate, entire leaves, in the axils of which are the solitary fruits or flowers with large, leafy bracts.

anticholinergic properties and is used to control excess motor activity of the gastrointestinal tract and spasm of the urinary tract.

Belladonna leaf is commonly administered in the form of the tincture (30 mg alkaloids/100 ml) or the extract (1.25 g alkaloids/100 g). The usual dose is 0.6 to 1.0 ml of the tincture or 15 mg of the extract, 3 or 4 times a day.

PRESCRIPTION PRODUCTS. Belladonna alkaloids: Bellafoline®. Belladonna extract: Belap SE®. Among the preparations containing mixtures of the belladonna alkaloids in combination with barbiturates or other ingredients are Belladenal®, Bellergal®, Butibel®, and Donnatal®.

NONPRESCRIPTION PRODUCTS. Belladonna is used in the following cold and allergy preparations that have drying effects on mucus secretions: Allerprop®, Protac Cold Capsules®, Hista-Vadrin T.D.®, Ru-Tuss®. In antidiarrheal preparations belladonna is used in combination with either opium alkaloids, kaolin, and/or pectin; see page 217.

Practically no alkaloids are isolated from belladonna on a commercial scale, although a total alkaloid fraction of belladonna is available. One must ascertain that this product represents the true, total alkaloids of belladonna rather than an admixture of alkaloids of other solanaceous drugs. Belladonna, hyoscyamus, and stra-

monium are seldom used in any form other than as the powdered extract, fluidextract, or tincture.

Most of the alkaloids are derived from Egyptian henbane (*Hyoscyamus muticus* Linné). Another important source is *Duboisia*, particularly *Duboisia myoporoides* R. Brown and *D. leichardtii* F. Moeller. The relative percentages of scopolamine and hyoscyamine occurring in *Duboisia* depend on the species used, the area in which the plants are collected, and the season of the year. After *Duboisia* was developed as a source of solanaceous alkaloids (during World War II), T. Smith and H. Smith of Edinburgh, Scotland, developed a purely synthetic process for the formation of atropine starting with tropine. Although this process was successful, it was not economical; at present, atropine and the related alkaloids are still produced from *Duboisia* (see page 199) and from *Hyoscyamus muticus* (see page 197).

Solanaceous Alkaloids

The principal alkaloids of this group are (−)-hyoscyamine; atropine [(±)-hyoscyamine]; scopolamine (also known as hyoscine); and the anhydride of atropine (apoatropine) and its stereoisomer, belladonnine. These are tropine derivatives and esters.

Atropine and scopolamine are competitive with acetylcholine at the postganglionic synapse (muscarinic site) of the parasympathetic nervous system. Clinically useful effects obtained from blocking the muscarinic activity of acetylcholine are an antispasmodic effect used principally to relieve spasms of the bowel in the treatment of spastic colitis, gastroenteritis, and peptic ulcer; an antisecretory effect used to reduce respiratory secretions in anesthesia (antisialogogue), gastric secretions in peptic ulcer therapy, and nasal and sinus secretions in common cold and allergy medications; and a mydriatic and cycloplegic effect used to prevent adhesions between the iris and lens of the eye in cases of iritis.

Atropine is an antidote in cases of poisoning caused by cholinesterase inhibitors such as physostigmine and organophosphate insecticides.

Scopolamine has a depressant activity on the central nervous system and is used to treat motion sickness. It is also employed for preanesthetic sedation and for obstetric amnesia in conjunction with analgesics, and to calm delirium.

Toxicity symptoms that can occur during the therapeutic use of atropine, scopolamine, and belladonna tincture are skin rash, skin flushing, mouth dryness, difficulty in urination, eye pain, blurred vision, and light sensitivity. The patient should also be advised that such antacids as alumina gels may interfere with absorption of these drugs when taken simultaneously.

Hyoscyamine is the tropine ester of (−)-tropic acid and is readily hydrolyzed by boiling in dilute acids or alkalies to form these compounds (see Fig. 8–4).

The carbon atom α to the carboxyl group of tropic acid is asymmetric and accounts for the natural occurrence of the optical isomer. When (−)-hyoscyamine is extracted from the plants in which it occurs, it usually is racemized during the process and thus converted into the (±)-compound, which is atropine. The piperidine ring system of tropine can exist in 2 principal conformations. The chair form has the lowest energy requirement. In addition, 2 stereoisomeric forms can exist because of the rigidity imparted to the molecule through the ethane chain across positions 1 and 5. Pharmacologically, the most active isomer results when the esteratic group is substituted axial at position 3, as in the case of (−)-hyoscyamine and atropine.

Hyoscyamine sulfate is the sulfate of an alkaloid usually obtained from species of *Hyoscyamus* Linné or other genera of Solanaceae. **It is extremely poisonous.** Hyoscyamine sulfate occurs as white, odorless crystals or as a crystalline powder; it is deliquescent and is affected by light.

USE AND DOSE. Hyoscyamine sulfate is

an anticholinergic. It is used to aid in the control of gastric secretion, visceral spasm, hypermotility in spastic colitis, pylorospasm, and associated abdominal cramps. In parkinsonism it is used to reduce rigidity and tremors and to control associated sialorrhea and hyperhidrosis. The usual dose, oral or sublingual, is 125 to 250 μg, 3 or 4 times a day. The parenteral dose is 250 to 500 μg given subcutaneously, intramuscularly, or intravenously, 3 or 4 times a day, as needed.

PRESCRIPTION PRODUCTS. Levsin®, Anaspaz®, Levamine®, Cystospaz®.

Atropine is an alkaloid obtained from botanical sources (from *Atropa belladonna* Linné, from species of *Datura* Linné, and from *Hyoscyamus* Linné [Fam. Solanaceae]) or produced synthetically. **It is extremely poisonous.** Synthetic production of atropine is more costly than extraction from natural sources and cannot compete in price. Formerly, *Hyoscyamus muticus* represented the chief natural source; however, atropine is now also obtained from species of *Duboisia* (see page 199). It pre-exists in the solanaceous plants only in traces and is formed from hyoscyamine during the process of extraction.

Atropine occurs as colorless, needlelike crystals or as a white, crystalline powder; it is optically inactive but usually contains some levorotatory hyoscyamine, the limit of which produces an angular rotation not to exceed −0.70°.

Atropine sulfate occurs as colorless crystals or as a white, crystalline powder. **It is extremely poisonous.** It effloresces in dry air, is slowly affected by light, and is an anticholinergic.

USE AND DOSE. Atropine sulfate is an anticholinergic. Used in surgery as an antisialogogue to control bronchial, nasal, pharyngeal, and salivary secretions, it is usually injected intramuscularly prior to induction of anesthesia. During surgery, the drug is given intravenously when reduction in pulse range and cessation of cardiac action are attributable to increased vagal activity. It is also useful in pylorospasm and other spastic conditions of the gastrointestinal tract and for ureteral and biliary colic when administered concomitantly with morphine. The usual dose, tablets, is 300 to 600 μg, 3 or 4 times a day; injection, 400 to 600 μg, 4 to 6 times a day, and as an antidote to cholinesterase inhibitors, intravenously, 2 to 4 mg initially, followed by 2 mg intramuscularly, repeated every 5 to 10 minutes until muscarinic symptoms disappear or signs of atropine toxicity appear; topically to the conjunctiva, 0.1 ml of a 0.5 to 4% solution, 3 times a day.

Scopolamine or hyoscine is an alkaloid that is particularly abundant in *Datura fastuosa* var. *alba* and in *D. metel*. It is an ester that, upon hydrolysis, yields tropic acid and scopoline, a base resembling tropine.

It occurs as an almost colorless, syrupy liquid from its chloroformic solution and as colorless crystals from its ether solution. It is levorotatory.

Scopolamine hydrobromide or hyoscine hydrobromide occurs as colorless or white crystals or as a white, granular powder that is odorless and slightly efflorescent in dry air. **It is extremely poisonous.**

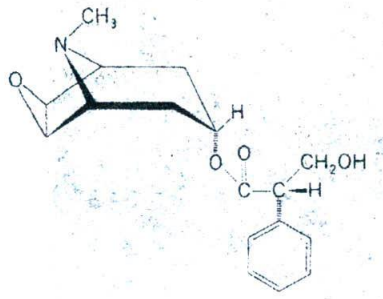
USE AND DOSE. Scopolamine hydrobromide is classified as an anticholinergic.

At usual therapeutic doses, scopolamine is a central nervous system depressant, whereas atropine is a stimulant. For this reason, scopolamine hydrobromide is used for preanesthetic sedation and for obstetric amnesia in conjunction with analgesics; it is also employed for calming delirium. It is administered subcutaneously or intramuscularly in a single dose of 320 to 650 μg.

In addition to its systemic anticholinergic effects, scopolamine is effective in the prevention of nausea and vomiting associated with motion sickness. It is applied as the free base in a transdermal system behind the ear at least 4 hours before the antiemetic effect is required. The scopolamine is gradually released from an adhesive matrix of mineral oil and polyisobutylene. A

continuous controlled release of scopolamine flows from the drug reservoir through a rate-controlling membrane to maintain a constant plasma level for 3 days.

PRESCRIPTION PRODUCT. Transderm-Scop®.



(−)-Scopolamine

Hyoscyamus

Hyoscyamus or henbane is the dried leaf, with or without the stem and flowering or fruiting top, of *Hyoscyamus niger* Linné (Fam. Solanaceae) and contains not less than 0.04% of the alkaloids of hyoscyamus. *Hyoscyamus* is the ancient Greek and Latin name formed from 2 Greek words, meaning hog and bean. The plant is poisonous to swine.

The plant is an annual or biennial herb (Fig. 8–6) indigenous to Europe, western Asia, and northern Africa and is cultivated in the Soviet Union, the Balkans, Belgium, England, and Germany, and, to some extent, the United States and Canada. The biennial form is most generally cultivated in England; the annual form is cultivated on the Continent. The leaves should be gathered when the plant is in full flower and should be carefully dried immediately. Dioscorides mentioned the plant, and under the name of henbane, it has been employed in European domestic medicine from the remotest times. It is mentioned in Anglo-Saxon works on medicine written in the 11th century and in the *Arabian Nights*. After the Middle Ages the drug fell into disuse but was reintroduced into European medicine about 1760, largely through the efforts of Störck.

The alkaloids, hyoscyamine and scopolamine, 0.05 to 0.15%, of which three fourths is hyoscyamine, are the active principles.

USE. Hyoscyamus is a parasympatholytic, but the crude drug is rarely employed in medicine today.

Egyptian henbane, the dried leaves and flowering tops of *Hyoscyamus muticus*, yields about 1.5% of total alkaloid, consisting largely of hyoscyamine. The plant is indigenous to and cultivated in Egypt. It is also cultivated in irrigated soils of southern California. The drug is used, perhaps entirely, for the extraction of its alkaloids.

Stramonium

Stramonium, jimson weed, or Jamestown weed consists of the dried leaf and flowering or fruiting tops with branches of *Datura stramonium* Linné or of its variety *tatula* (Linné) Torrey (Fam. Solanaceae). It yields not less than 0.25% of alkaloids. The name *Datura* is derived from the Sanskrit, *dhattura* and from the Arabic *tatura* or *tatula*, the native name; *stramonium* is from the French *stramoine*, meaning stinkweed. The plant is an annual herb that attains the height of about 2 meters. It is indigenous to the region of the Caspian Sea, naturalized in waste places in Europe and North America, and cultivated in central Europe and South America. The leaves and tops (Fig. 8–7) are collected when the plant is in flower and are carefully dried and preserved. A few years ago, most of the commercial supply was obtained from plants cultivated in Argentina. At present, Europe is again supplying reasonable quantities of the drug. The purple stramonium (*Datura stramonium* var. *tatula*), which is naturalized in the United States from tropical America, is similar to *D. stramonium*, but the stems and flowers are purplish. The active constituents in the 2 plants are alike. Stramonium was grown in England in about the 16th century from seeds obtained from Constantinople. The early settlers

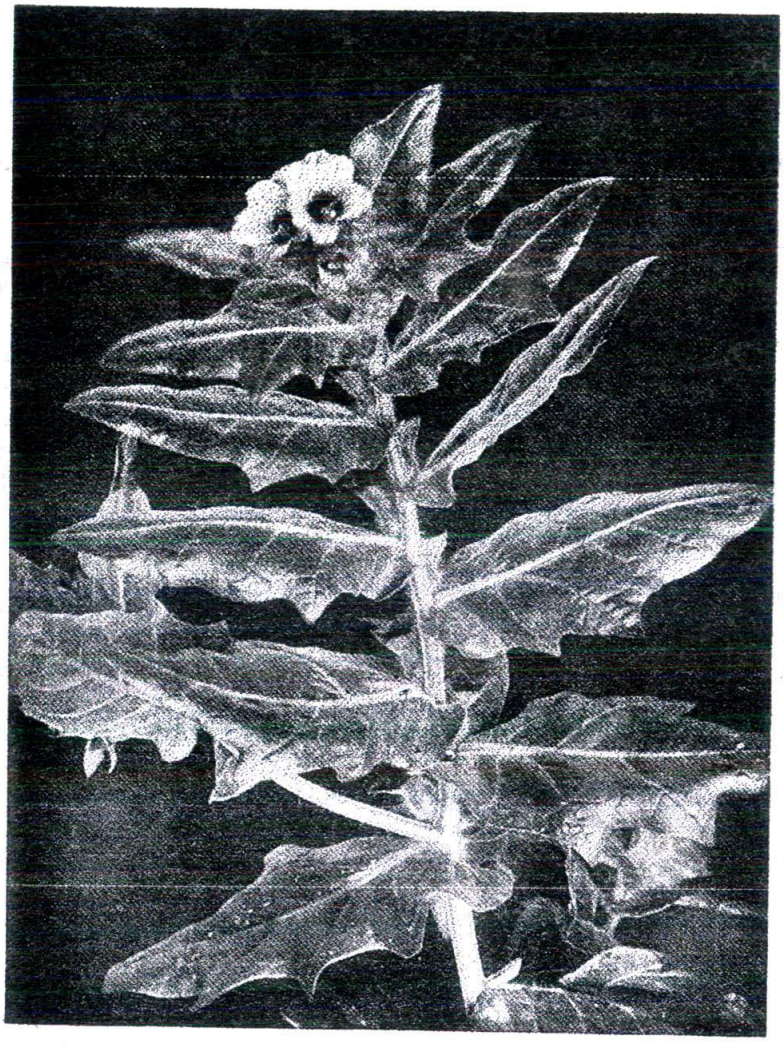


Fig. 8–6. Flowering branch of *Hyoscyamus niger* var. *agrestis* K. showing sessile, acutely lobed leaves and two of the funnel-form flowers.

near Jamestown, Virginia, used it as a "pot herb" with fatal results, thus establishing its common name of Jamestown weed, which was subsequently modified in some areas to jimson weed. It can serve as a source of atropine.

The drug contains hyoscyamine and scopolamine, the former more abundantly.

USE. Stramonium is an anticholinergic and has an action like that of belladonna.

Powdered stramonium is an ingredient in preparations that are intended to burn. The resultant vapor is inhaled for the relief of asthma. These so-called asthma powders were widely sold on an over-the-counter basis until thrillseekers began to ingest them in order to become intoxicated. In 1968, the Food and Drug Administration placed stramonium-containing asthma powders in the prescription-drug category.

Stramonium seed is the ripe seed of *D. stramonium*. The ripening capsules are gathered and dried until the seeds shake out. The seeds are reniform, flattened, 3 to 4 mm in length, bluish black, and minutely reticulate.

Fig. 8–7. *Datura stramonium* leaves, flower, and fruit.

Stramonium seed contains about 0.4% of alkaloids, principally hyoscyamine with a small proportion of scopolamine and traces of atropine.

Stramonium is generally regarded as a noxious weed and has frequently caused poisoning in children when seeds were ingested. The chief toxic symptoms are those of atropine poisoning: dilated pupils, impaired vision, dryness of the skin and secretions, extreme thirst, hallucinations, and loss of consciousness. Although newspaper items often describe the circumstances, such cases are also reported in the medical literature. Because the plant is rather widespread, pharmacists may be asked to help in identifying the plant and in applying emergency measures pending arrival of a physician.

Other Solanaceous Drugs

Withania is the dried root of *Withania somnifera* Dunal (Fam. Solanaceae), a plant that grows within a broad range from southern Europe to India, and in Africa. It is cultivated in India, where it has been employed as a sedative since antiquity.

Studies have shown that withania, which is closely related botanically to belladonna and hyoscyamus, contains about a dozen biochemically heterogeneous alkaloids. Tropine and pseudotropine are accompanied by hygrine (pyrrolidine derivative), isopelletierine (piperidine derivative), cuscohygrine (2 pyrrolidine moieties), anaferine (2 piperidine moieties), and anahygrine (1 pyrrolidine moiety and 1 piperidine moiety). The principle responsible for the sedative action of the drug has not yet been determined, but the study of the alkaloids of this drug has advanced our knowledge of the chemical-taxonomic relationships of solanaceous plants.

Duboisia consists of the dried leaves of

Duboisia myoporoides R. Brown (Fam. Solanaceae), a large shrub indigenous to Australia. The drug contains (−)-hyoscyamine, scopolamine, and a number of related alkaloids, in addition to small amounts of nicotine and nornicotine. Duboisia currently is a chief source of atropine, the racemic mixture of the isomers of hyoscyamine, which is formed during the extraction process. The leaves of *D. leichardtii* F. von Mueller, of Australia, also contain a relatively large percentage of similar alkaloids.

Pituri or Australian tobacco is the leaf of *D. hopwoodii* F. von Mueller and is used in Australia like tobacco. It contains nicotine and nornicotine.

Mandragora or European mandrake is the root of *Mandragora officinarum* Linné and contains hyoscyamine, scopolamine, and mandragorine. This drug and its method of collection are the subjects of many superstitions and forklore tales. It should not be confused with the resin-containing American mandrake (podophyllum); see page 141.

Cocaine

Coca or coca leaves have been described as the dried leaves of *Erythroxylum coca* Lamarck, known commercially as Huanuco coca, or of *E. truxillense* Rusby, known commercially as Truxillo coca (Fam. Erythroxylaceae). The plants are shrubs or small trees that attain a height of about 2 meters and are indigenous to certain areas of South America. They have been cultivated there for centuries but were later introduced as crops on the islands of Java and Ceylon. *Erythroxylum* is from 2 Greek words meaning red and wood, alluding to the color of the plants; *coca* is the Spanish name for the tree; and *truxillense* is from Truxillo, a coastal city in Peru.

Modern studies have revealed that many of the old concepts regarding this drug were inaccurate. It is now generally recognized that all of these plants characterized by relatively high concentrations of ecgonine bases belong to one polymorphic species, *Erythroxylum coca* Lamarck. Three varieties yielding the commercial drug may be distinguished:

1. var. *coca* (= *E. coca* Lamarck *sensu stricto*), yields Huanuco (Bolivian) coca. The leaves of commerce are large, dark green, and coriaceous with an acute or obtuse apex.
2. var. *spruceanum* Bruck (= *E. truxillense* Rusby) yields Truxillo (Peruvian) coca. In commerce, these leaves are smaller, narrower, thinner, and lighter green than those of the var. *coca*.
3. var. *novogranatense* (Morris) Hieron yields a type of Truxillo coca from Colombia. It rarely occurs in commerce but may be distinguished from the previous varieties by its obtuse to emarginate apex.

Most of the present-day supply of the drug is obtained from cultivated plants grown at an altitude of 500 to 2000 meters in Peru and Boliva. According to estimates, Bolivia and Peru each produces about 50,000 metric tons of leaves a year. About 25% of the harvest is consumed by the indigenous population who chew the coca leaves. Approximately 2% is exported in legitimate commerce for the manufacture of pharmaceutic cocaine, with nearly 250,000 kg of coca leaves being imported into the United States from Peru annually. About 75,000 metric tons of leaves remain available for the production of illicit substances.

In the processing of the leaves to cocaine, the farmers themselves often engage in the first steps by turning the leaves into coca paste which is easier to transport to a cocaine processing laboratory. More than 100 kg of dried leaves are needed to make a single kilogram of paste. The leaves are collected from twigs that are cut off in the spring, pruned again in June, and pruned for a third time in the fall. The dried, crushed leaves are mixed with water and

calcium carbonate or lime to produce an alkaline reaction. The mixture is crushed, kerosene or gasoline is added, and the mixture is stirred. After the leaf pulp is discarded, the kerosene is mixed with acidified water, and the aqueous layer is separated and made alkaline with ammonia or baking soda, which precipitates a thick, aromatic paste containing not only cocaine but also several other alkaloids. The smoking of coca paste has become a drug abuse problem in Peru, Bolivia, Colombia, and Ecuador.

Cocaine was first isolated in 1860, but until 1884, coca was considered only as an inferior substitute for tea. In that year, Koller discovered its local anesthetic properties.

Coca leaves contain 3 basic types of alkaloids: derivatives of ecgonine (cocaine, cinnamylcocaine, α- and β-truxilline), tropine (tropacocaine, valerine), and hygrine (hygroline, cuscohygrine). Only the ecgonine derivatives are commercially important. The composition of the alkaloid mixture in the leaf varies qualitatively and quantitatively according to the variety of the plant and, to some extent, to the stage of development of the leaves when collected.

Huanuco coca contains 0.5 to 1% of ester alkaloids, derivatives of tropine and ecgonine, of which cocaine constitutes the major part. Cuscohygrine is the principal nonester alkaloid in the leaf.

Truxillo coca has a somewhat lower content of ester alkaloids, but a much higher percentage (up to 75%) of this quantity is cocaine.

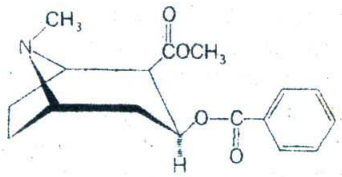
Coca leaves were highly valued by the natives long before the Spanish conquest; the shrub was known as "The Divine Plant of the Incas." Monardes published an extensive article on the drug in 1569. The natives chew the leaf, either as such or mixed with lime (Fig. 8–8) and are thus able to travel great distances without experiencing fatigue and without any but the most meager food rations.

At present, coca chewing is an integral part of the native culture pattern in many isolated highland areas of Colombia and in most of the mountainous sections of Peru, Bolivia, and the northwestern part of Argentina. Its use has spread from these areas to the lowlands and is prevalent in most parts of the northwestern Amazon valley in Colombia and Peru.

Much has been written about the effect this habit has on its practitioners. Dr. R.E. Schultes, the well-known ethnobotanist at Harvard University, expressed the following opinion:

"What is very commonly overlooked or even purposely ignored in many governmental and sociologic circles is the fact that coca as chewed by the native is not of necessity physically, socially, and morally dangerous. It has nothing in common with cocaine addiction, and coca chewing does not lead to addiction. . . . Unwise legal prohibitions in certain Andean areas aimed at extirpation of the coca custom have invariably driven the Indian, deprived in his inhospitable cold altitudes of the euphoric coca, to the dangerously poisonous local distilled drinks with an attendant rapid rise in crime."

Cocaine is an alkaloid obtained from the leaves of *Erythroxylum coca* and its varieties. As explained subsequently, much of the alkaloid is actually prepared by semisynthesis from plant-derived ecgonine.



(−)-Cocaine

Cocaine is the methyl ester of benzoylecgonine. When hydrolyzed, it splits into ecgonine, benzoic acid, and methyl alcohol. Cinnamylcocaine splits into ecgonine, methyl alcohol, and cinnamic acid, whereas α- and β-truxilline split into ecgonine, methyl alcohol, and α- and β-trux-

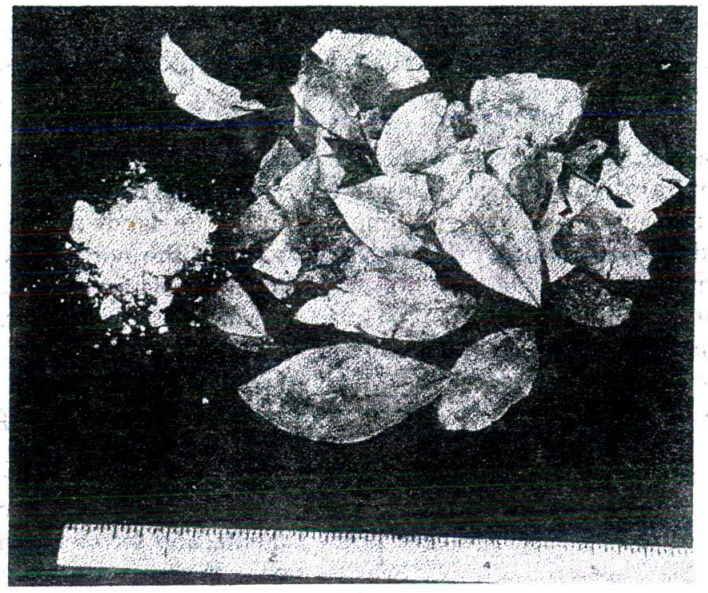


Fig. 8–8. Dried coca leaves *(Erythroxylum coca)* and lime with which they are chewed by Peruvian natives. (Photo courtesy of Dr. Julia F. Morton, Director, Morton Collectanea, University of Miami.)

illic acids. (The truxillic acids are isomeric dicinnamic acids.)

The production of cocaine is ordinarily conducted on a large scale by a number of methods that are similar but not identical. Many of the important steps are protected by patents. Ordinarily, the total bases are extracted, the ester alkaloids are converted to (−)-ecgonine by acid hydrolysis, and cocaine is synthesized from it by esterification first with methanol and then with benzoic acid. When this procedure is utilized, only the total content of ecgonine derivatives in the leaf is commercially significant.

Cocaine has multiple central and peripheral nervous system actions. Over most of its effective dose range, it is a psychomotor stimulant with a strong abuse potential. The action responsible for the rewarding property, and hence the abuse liability, is through a prolongation of dopamine in the synapse by blocking the dopamine reuptake mechanism. When drug access is unlimited, cocaine has the ability to dominate behavior, reducing other behaviors such as eating and sleeping. It has one of the highest reinforcing potentials of any drug as measured by breaking point studies and is the drug which animals with unlimited access are most likely to select repeatedly in preference to food and water, to the point of death.

Cocaine hydrochloride is the hydrochloride of the alkaloid cocaine. It occurs as colorless crystals or as a white, crystalline powder.

USE. Cocaine hydrochloride is a local anesthetic. It is applied topically to mucous membrane as a 1 to 4% solution.

Cocaine hydrochloride is an ingredient in Brompton's cocktail, which is widely used to control severe pain associated with terminal cancer. Because of its CNS stimulant properties, cocaine counteracts the narcotic-induced sedation and respiratory depression associated with the narcotic analgesic ingredient (morphine or methadone) used in the cocktail. It also potentiates the analgesic effect.

The United States, in the 1980s, is in the middle of a cocaine abuse epidemic in many major urban areas. Government officials estimate that 75 tons of cocaine come into the United States illicitly every year.

Cocaine and cocaine hydrochloride, as agents of abuse, are generally inhaled or sniffed and are rapidly absorbed across the pharyngeal mucosa, resulting in cerebral stimulation and euphoria. In addition, they are injected intravenously and subcutaneously, and cocaine free-base is smoked. Inhalation of the vapors of alkaloidal cocaine, known as "free-basing," has become a popular practice because of the rapidity of onset and the intensity of the euphoric experience. The reason for converting cocaine hydrochloride to the free amine is that the latter substance volatilizes at about 98°C whereas the salt volatilizes at 195°C, a temperature at which some of the cocaine is decomposed. Since the cocaine is absorbed by pulmonary capillaries and moves from the lungs to the left side of the heart and then directly to the brain, the effects are perceptible in 7 to 10 seconds. Repeated use results in psychic dependence and tolerance; therefore, cocaine is classified as a Schedule II drug under the Controlled Substances Act.

Cocaine served as the model for a large number of synthetic local anesthetics that have been produced to increase the stability and reduce the toxicity of the natural product. Some of them are vasodilators and are often employed in conjunction with epinephrine. Such compounds are considered in detail in the standard textbooks of medicinal chemistry.

QUINOLINE ALKALOIDS

Alkaloids containing quinoline as their basic nucleus include those obtained from cinchona (quinine, quinidine, cinchonine, and cinchonidine).

Cinchona and its alkaloids are the only members of this group that are therapeutically important at present. Cinchonine, which is isomeric with cinchonidine, is the parent alkaloid of the quinine series. Quinine and its isomer, quinidine, represent 6-methoxycinchonine.

Biosynthesis of Quinoline Alkaloids

Alkaloid Precursors. Tryptophan is a precursor of quinine in cinchona. Because quinine is the first secondary compound derived from this amino acid to be considered, it is convenient to review the biosynthesis of tryptophan here.

The biosynthetic pathway leading to tryptophan in higher plants is unknown; however, it has been elucidated in microorganisms using auxotrophic mutants of *Escherichia coli* and *Enterobacter aerogenes* that required tryptophan for growth. In the pathway, shikimic acid, through a series of phosphorylated intermediates, yields chorismic acid, which is an important branch-point intermediate. One branch leads to prephenic acid and the aromatic amino acids, phenylalanine and tyrosine (see page 112). The other leads to anthranilic acid and then to tryptophan. Chorismic acid is converted to anthranilic acid by aromatization and transfer of the amide nitrogen of glutamine. The anthranilic acid then reacts with 5-phosphoribosyl-1-pyrophosphate to form, via an intermediate, 1(*o*-carboxyphenylamino)-1-deoxyribulose 5-phosphate, which undergoes ring closure to produce indole-3-glycerol phosphate. The final step in the reaction sequence involves replacement of the glycerol phosphate side chain with serine, thereby yielding tryptophan (Fig. 8–9).

Quinoline Derivatives. Studies with labeled geraniol and tryptophan-2-^{14}C indicate that quinine is metabolically derived from the monoterpenoid-tryptophan pathway that leads to the *Corynanthe*-type indole alkaloids (see page 219). The most distinctive feature of quinine biosynthesis appears to be cleavage of the benzopyrrole ring of the tryptophan moiety and rearrangement to form the quinuclidine nucleus and then the quinoline nucleus. Details of the biosynthetic processes are lacking, but a presumed biogenetic origin involving strictosidine and corynantheal as intermediates

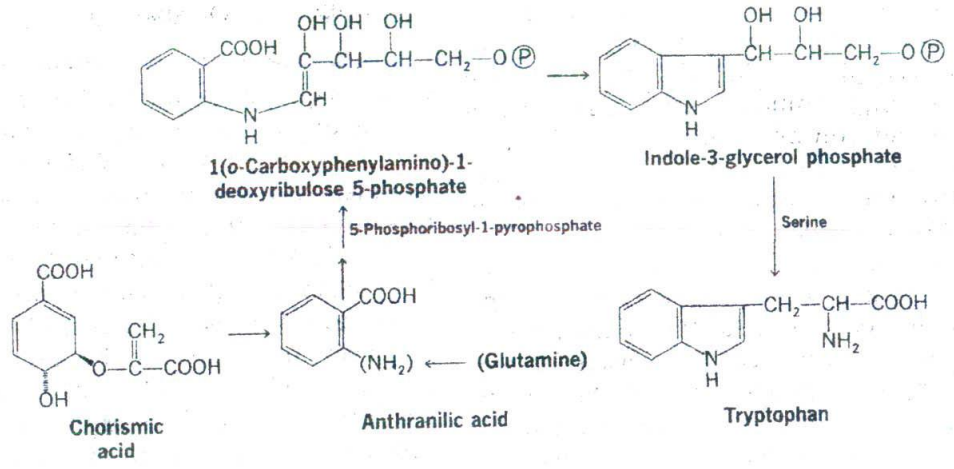


Fig. 8–9. Pathway of tryptophan biosynthesis.

is illustrated in Figure 8–10. Both of these compounds are precursors.

Cinchona

Cinchona, cinchona bark, or Peruvian bark is the dried bark of the stem or of the root of *Cinchona succirubra* Pavon et Klotzsch (Fig. 8–11), or its hybrids, known in commerce as red cinchona; or of *C. ledgeriana* (Howard) Moens et Trimen, *C. calisaya* Weddell, or hybrids of these with other species of *Cinchona*, known in commerce as calisaya bark or yellow cinchona (Fam. Rubiaceae).

Cinchona was named in honor of the Countess of Chinchon, wife of the Viceroy of Peru; *succirubra* is Latin and means red juice; *calisaya* is the Spanish and Indian name in Peru for the bark of a tree; *ledgeriana* is named in honor of Charles Ledger who introduced *Cinchona* into the East Indies. The plants are trees indigenous to the Andes of Ecuador and Peru. They grow at an elevation of 1000 to 3000 meters and are cultivated in Indonesia and India. There are over 36 known species and hybrids of *Cinchona*.

Just before World War II, Java (Indonesia) supplied over 90% of the world consumption of this important drug. When the Japanese cut off this supply from the world, several synthetic antimalarials (chloroquine, quinacrine, and primacrine) were developed to replace cinchona. Cultivation of cinchona trees was also undertaken in several countries in Central and South America (where it originally occurred). Alkaloid production from these trees during the early months of World War II was a deciding factor in preventing further advances by the Japanese in the Pacific area. Extraction techniques were improved in such a manner as to utilize all of the important alkaloids in any type of cinchona bark that could be obtained from any source.

The Dutch have now resumed the manufacture of cinchona alkaloids using bark obtained from Indonesia. A certain amount of alkaloids is produced in Germany; owing to economic factors, practically none is produced in the United States.

Cultivation gives the opportunity to select seeds from plants producing high-quality bark and to hybridize one choice strain with another. Thus, hybrids of *Cinchona ledgeriana-Cinchona calisaya* produce a higher yield of alkaloids than do either of the parent species. Selected seeds planted in seed beds develop into young plants that can be transplanted within 2 years. The stems tend to grow tall, the lower branches tend to die and drop off, and the tree crowns grow closely, thus shading the

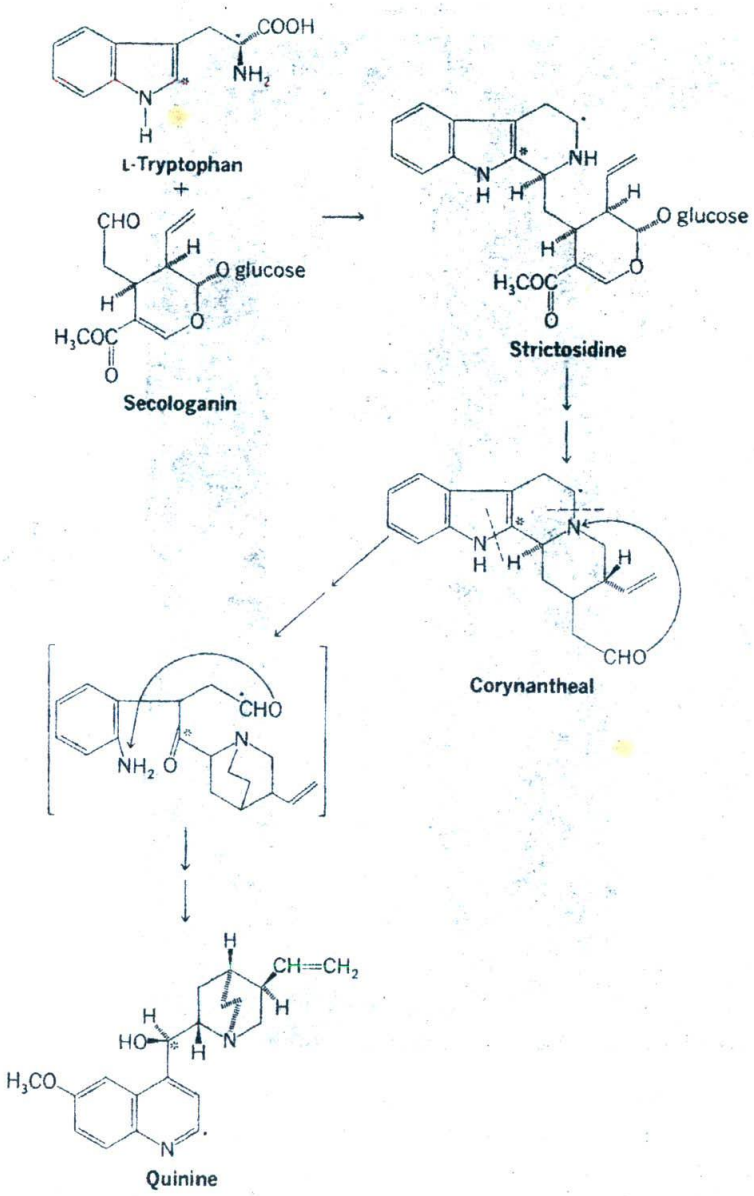


Fig. 8–10. Probable biosynthetic origin of quinine.

trunks. Shade is favorable to the production of quinine. Trees that are 6 to 9 years old possess the maximum amount of alkaloids in the bark. They can easily be uprooted with tractors, and the fresh bark of both trunk and roots can then be removed by hand. When young bark is dried, it may have an alkaloidal content 3 times as great as that in bark from an old tree. A considerable amount of cinchona bark enters into the manufacture of vermouth and certain bitter liqueurs.

A number of fantastic tales have been told about the origin of the medicinal use of cinchona. One of these states that an Indian in Peru was overcome with fever and was forced to drink stagnant water from a pond into which several cinchona

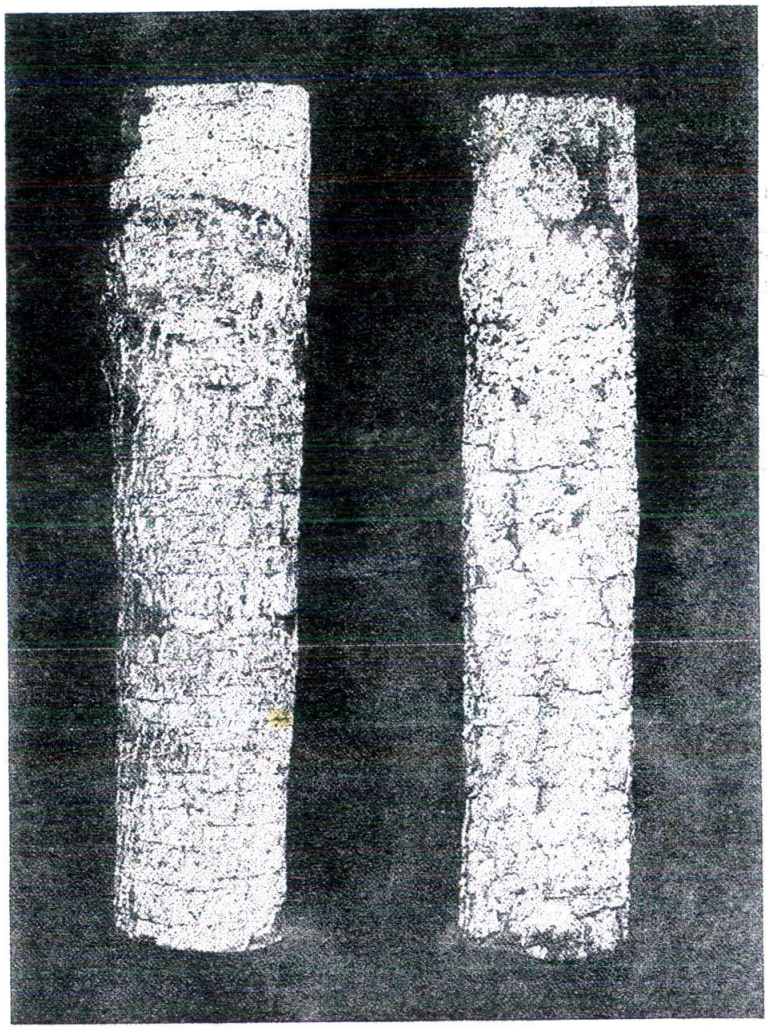


Fig. 8–11. Typical specimens of *Cinchona succirubra* bark from Indonesia.

trees had fallen. Enough alkaloids had been extracted by the prolonged maceration that, within hours of drinking the solution, the Indian's fever had abated and he eventually recovered.

A Jesuit missionary learned of the use of the drug from the Indians. He taught others, among them Canizares, the corregidor of Loxa. Canizares sent the bark to Juan de Vega, who at that time was treating the Countess Ana de Osorio, wife of the Count of Chinchon and Viceroy of Peru, for tertian fever. The Countess recovered and shortly thereafter introduced the bark into Europe. The use of cinchona was further spread through the efforts of the Jesuit Order. For the next half century or more Europe seethed with a controversy over cinchona. The drug was both widely condemned and widely praised. Early names for the drug were Countess bark, Jesuit's bark, and Peruvian bark. It is interesting to note that Linnaeus, when naming the genus, desired to honor the Countess but omitted the second letter in the name Chinchon. This error has continued to the present day. The tree yielding cinchona bark was unknown until 1737. In 1854, the Dutch began its introduction into Java, and in 1860, the English introduced it into India.

The alkaloids are chiefly formed in the

parenchymal cells of the middle layers of the bark. Cinchona contains some 25 closely related alkaloids, the most important of which are quinine, quinidine, cinchonine, and cinchonidine, and the average yield is 6 to 7%, of which from one half to two thirds is quinine in the yellow barks. In the red barks, cinchonidine exists in greater proportion; specimen pieces have yielded as high as 18% of total alkaloids. Another constituent of cinchona is cinchotannic acid, from 2 to 4%, which decomposes into the nearly insoluble cinchona red, occurring in red barks to the extent of 10%. The red color in cinchona bark is caused by an oxidase similar to the oxidase that causes fruits to darken when cut. If the fresh bark is heated in boiling water for 30 minutes and then dried, it does not become red.

In commerce, cinchona bark is priced on the basis of its total alkaloid content and frequently on its quinine content.

USES AND DOSE. Cinchona and its alkaloids have been used in the treatment of malaria fever for many years. Quinine continues to be used for malaria in many parts of the world, but in the United States this alkaloid is utilized primarily in the preparation of effervescent tonic water. Quinidine is now the principal cinchona alkaloid employed therapeutically.

Overdoses of cinchona products result in temporary loss of hearing and in impaired sight. Ringing in the ears is a symptom of toxicity. When these symptoms are produced as the result of continuous use of cinchona or of quinine, the condition has been called **cinchonism.** Cinchona was formerly given in doses of 1 g.

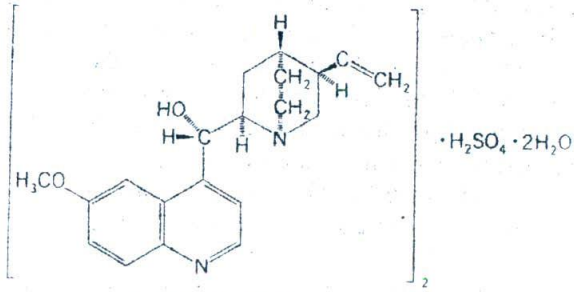
Cuprea bark is obtained from *Remijia purdieana* Triana and *R. pedunculata* Flückiger (Fam. Rubiaceae), of central and southern Colombia. It has a copper-red color, is hard, compact, and heavy, and contains numerous transversely elongated stone cells and 2 to 6% of alkaloids, of which one third may be quinine. Cuprea bark is a commercial source of quinidine.

Cinchona Alkaloids

Quinidine is a stereoisomer of quinine and is present in cinchona barks to the extent of 0.25 to 1.25%. It depresses myocardial excitability, conduction velocity, and, to a lesser extent, contractility.

Quinidine sulfate is the sulfate of an alkaloid obtained from various species of *Cinchona* and their hybrids and from *Remijia pedunculata,* or prepared from quinine. It occurs as fine, needlelike, white crystals that frequently cohere in masses. It is odorless, has a bitter taste, and darkens when exposed to light. It is readily soluble in water, alcohol, methanol, and chloroform.

USE AND DOSE. Quinidine is used to treat various cardiac arrhythmias such as premature atrial, AV junctional, and ventricular contractions; atrial and ventricular tachycardia; atrial flutter; and atrial fibrillation. When administered orally, the peak serum levels are slightly lower with the gluconate and polygalacturonate salt than with the sulfate salt. The usual oral dose for all available salts is 10 to 20 mg/kg/day in 4 to 6 divided doses in order to obtain the average therapeutic serum levels of 3 to 6 μg/ml. Toxic reactions occur at levels above 8 μg/ml. The patient should be instructed to notify the physician if skin rash, fever, unusual bleeding or bruising, ringing in the ears, or visual disturbance occurs.



Quinidine Sulfate

PRESCRIPTION PRODUCTS. Cin-Quin®, Quinidex®, and Quinora®.

Quinidine gluconate occurs as a white

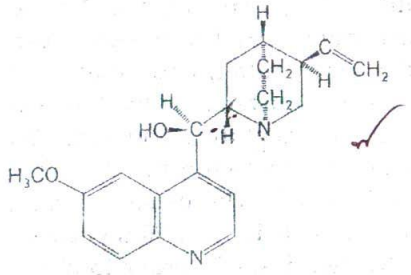
powder that is odorless and has a bitter taste. It is available in sustained release tablets.

PRESCRIPTION PRODUCTS. Quinaglute®, Duraquin®.

Quinidine polygalacturonate affords controlled and more uniform absorption through the intestinal mucosa than does quinidine sulfate. In addition, it produces a lower incidence of gastrointestinal irritation.

PRESCRIPTION PRODUCT. Cardioquin®.

Quinine is the diastereoisomer of quinidine. It occurs as white, odorless, bulky, bitter crystals or as a crystalline powder. It darkens when exposed to light and effloresces in dry air. It is freely soluble in alcohol, ether, and chloroform but slightly soluble in water.



Quinine

Quinine sulfate is the sulfate of an alkaloid obtained from the bark of *Cinchona* species. It occurs as white, odorless, bitter, fine, needlelike crystals that are usually lusterless. It becomes brownish when exposed to light. It is not readily soluble in water, alcohol, chloroform, or ether.

The drug is an antimalarial and once was the only agent available to treat this disease, which afflicts millions of people worldwide. Quinine's antimalarial action is believed to be the intercalation of the quinoline moiety into the DNA of the *Plasmodium* parasite, thereby reducing the effectiveness of DNA to act as a template. Intercalating agents such as quinine are rigid planar polycyclic molecules that insert between the adjacent stacked base pairs of the double helix of DNA. This results in DNA that has increased length, and because of a greater electrostatic interaction between the intercalated molecule and the two DNA strands, there is an inhibition of the strand separation that is required for replication and transcription of the genetic code. It suppresses but does not cure vivax malaria and was once almost abandoned in this country in favor of chloroquine or other newer, synthetic antimalarials. Recently, it has regained considerable importance in the treatment of chloroquine-resistant falciparum malaria in combination with pyrimethamine and sulfadiazine or tetracycline. The usual dose is 650 mg every 8 hours for 10 to 14 days. The patient should be instructed to notify the physician if ringing in the ears or visual disturbance occurs. Quinine has a skeletal muscle relaxant effect, increasing the refractory period by direct action on the muscle fiber, decreasing the excitability of the motor end-plate by a curariform action, and affecting the distribution of calcium within the muscle fiber. Therefore, it is used for the prevention and treatment of nocturnal recumbency leg cramps in a dose of 260 to 300 mg at bedtime. Daily doses of 0.2 to 0.4 g as a tonic or as an analgesic in the treatment of colds were used extensively in the past.

Over 1.65 million avoirdupois ounces of quinine and over 1.2 million ounces of quinidine are imported annually into the United States.

PRESCRIPTION AND NONPRESCRIPTION PRODUCTS. Quinamm®, Quinite®, Strema®, Quine®.

ISOQUINOLINE ALKALOIDS

The isoquinoline structure occurs in a considerable number of alkaloids in widely separated plant families.

Although the more important opium alkaloids (morphine, codeine, thebaine) exhibit a phenanthrene nucleus, the majority of its alkaloids have the isoquinoline ring structure. These phenanthrene alkaloids are derived biosynthetically from benzyli-

soquinoline intermediates. For this reason, opium is included in this group. Sanguinaria, another member of the Papaveraceae, also contains isoquinoline alkaloids.

The important drugs and their alkaloids in this group are ipecac, emetine, hydrastis, hydrastine, sanguinaria, curare, tubocurarine, berberine, and opium and its alkaloids.

Biosynthesis of Isoquinoline Alkaloids

Although the isoquinoline alkaloids possess relatively complex structures, the basic biosynthetic reactions that account for their formation in plants are relatively simple. These compounds result from the condensation of a phenylethylamine derivative with a phenylacetaldehyde derivative. Both of these moieties are derived from phenylalanine or tyrosine. Administration of tyrosine-2-^{14}C to *Papaver somniferum* resulted in the formation of papaverine labeled in corresponding positions. Norlaudanosoline is an intermediate in this reaction (Fig. 8–12).

Morphine is also formed from 2 molecules of tyrosine, and its biosynthesis is related to the biosynthesis of papaverine. Norlaudanosoline serves as a key intermediate. This medicinally important alkaloid is derived from a benzylisoquinoline metabolite. The biosynthesis of morphine and related alkaloids has been studied extensively, and these experiments provide some of the most complete and detailed observations available for any secondary plant constituent. The biosynthetic pathway leading to morphine is shown in Figure 8–12. A key feature of this pathway is the enzymatically controlled methylation pattern that gives rise to (−)-reticuline, thus facilitating formation of the dienone, salutaridine, which is the first intermediate with a phenanthrene nucleus. Another interesting aspect of this pathway is the biosynthetic relationship of thebaine, codeine, and morphine; stepwise demethylation of the therapeutically unimportant thebaine leads first to the relatively mild analgesic codeine and then to the potent narcotic morphine.

P. somniferum has a highly evolved and useful secondary metabolism that culminates, at least from the therapeutic viewpoint, in morphine. *P. bracteatum* Lindley, a thebaine-producing poppy, appears to lack any significant demethylation capability; this feature is not only useful for biosynthetic studies but has recently become commercially significant. Because thebaine can be converted to codeine semisynthetically, a source of the latter alkaloid is assured without concomitant production of morphine, which is more subject to abuse by drug addicts. These 2 species emphasize the subtle metabolic difference that frequently separates useful plants from those of only scientific interest.

Presumably, morphine and other opium alkaloids are formed primarily in various cells of the poppy plant and are excreted into the laticiferous ducts. However, isolated latex is capable of alkaloid biosynthesis in the presence of suitable precursors and cofactors. The latex is also capable of metabolic destruction of morphine, and diurnal variations in alkaloid composition of the latex have been recorded. These observations, which establish a metabolic function for the latex, are fundamentally significant and undoubtedly contribute to the normal variability in alkaloid composition of crude opium samples.

Ipecac

Ipecac consists of the dried rhizome and roots of *Cephaelis ipecacuanha* (Brotero) A. Richard, known in commerce as Rio or Brazilian ipecac, or of *Cephaelis acuminata* Karsten, known in commerce as Cartagena, Nicaragua, or Panama ipecac (Fam. Rubiaceae). Ipecac yields not less than 2% of the ether-soluble alkaloids of ipecac.

Cephaelis is from 2 Greek words, meaning head and to collect or roll up, and refers to the inflorescence; *ipecacuanha* is Portuguese from the Brazilian Indian *ipekaaguene*, meaning a creeping plant that

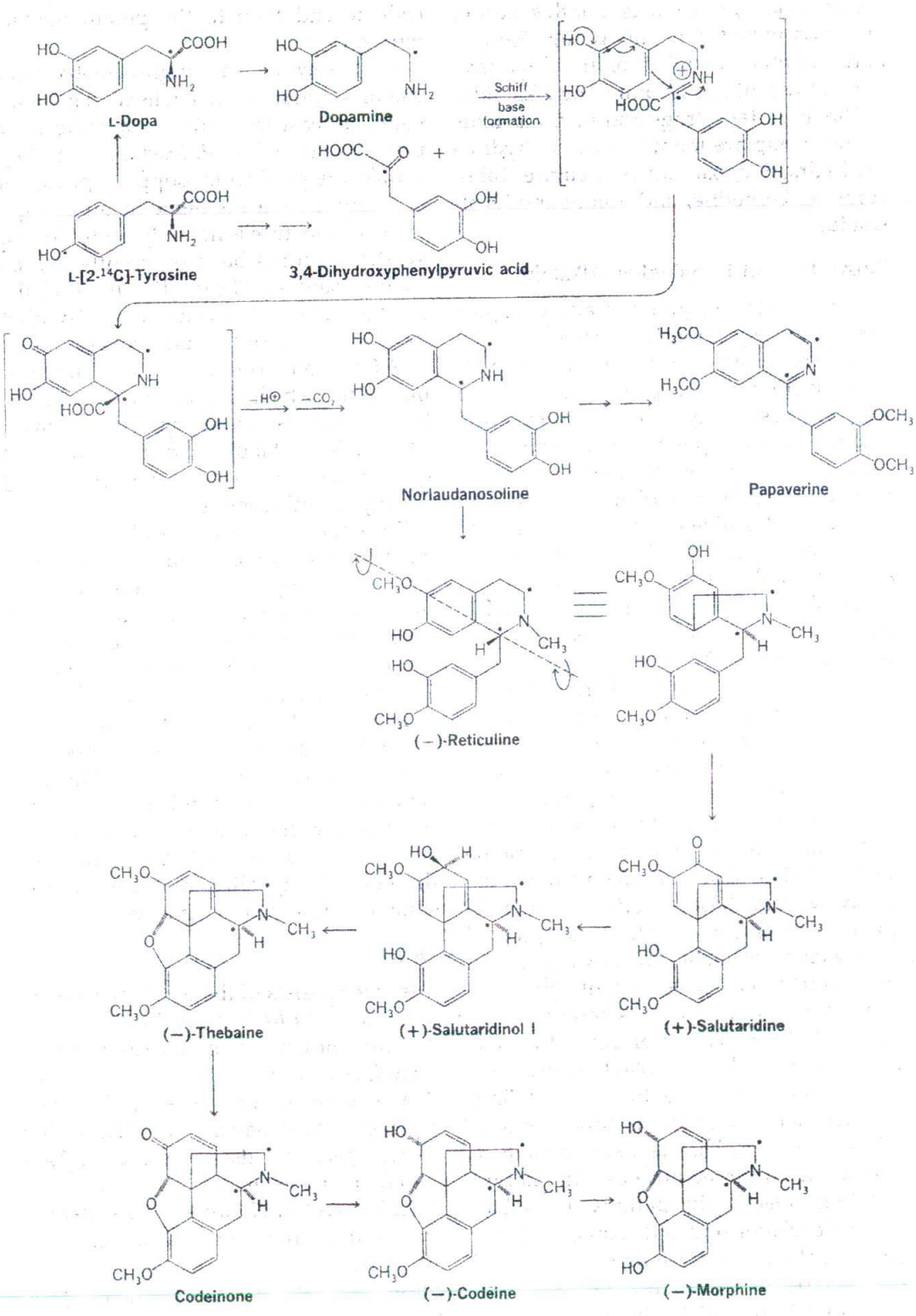


Fig. 8–12. Biosynthesis of papaverine and morphine.

causes vomiting; *acuminata* refers to the acute apex of the leaf.

The plants are low, straggling shrubs, with slender rhizomes bearing annulated wiry roots. *C. ipecacuanha* is indigenous to Brazil, which furnishes most of the present supply. It has been cultivated to a limited extent in Malaysia and in India. The drug is gathered during the dry season and dried rapidly in the sun for 2 to 3 days. *C. acuminata* is indigenous to the northern portions of Colombia and extends into Panama and Nicaragua; it is exported from Cartagena and Savanilla. Apparently, ipecac was used by the South American Indians. The drug was first mentioned by a Jesuit friar in 1601. It was introduced into Europe by Le Gras in 1672 and by 1690 was well-known in medicine.

Ipecac contains 5 alkaloids (2 to 2.5%). The 3 principal alkaloids are emetine, cephaeline, and psychotrine, contained chiefly in the bark which makes up about 90% of the drug. About 40% of starch is present.

In Rio (Brazilian) ipecac, the total alkaloid content reaches slightly over 2%, about one-third cephaeline and two-thirds emetine. At the present time, the plants are becoming rather scarce despite the laws of most South American countries that require a portion of the root to be planted when collections are made. Roots that are collected are usually immature, and the total alkaloid content barely reaches the minimum percentage.

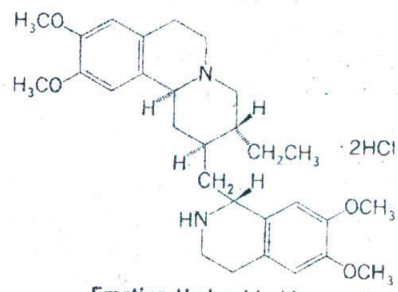
In Cartagena (Colombia) ipecac and in Panama ipecac, the total alkaloid content reaches 2.2%. The rhizomes and roots from Nicaragua and Costa Rica yield more than 2.5% of total alkaloids. In these 4 varieties, the ratio of emetine to cephaeline is somewhat constant and is composed of about one-third emetine to two-thirds cephaeline.

USES AND DOSE. Ipecac, in the form of a syrup, is used in the treatment of drug overdose and in certain poisonings. It produces emesis through a local irritant effect on the gastrointestinal mucosa and a central medullary effect by stimulation of the chemoreceptor trigger zone. The usual dose in adults and children older than one year of age is 15 ml, followed by one to 2 glasses of water and may be repeated once in 20 minutes if emesis does not occur. The syrup should be recovered by gastric lavage if emesis does not occur after the second dose. Ipecac syrup should not be confused with ipecac fluidextract, which is 14 times stronger. Ipecac mixed with opium (as Dover's powder) acts as a diaphoretic. Ipecac syrup is included in poison antidote kits because of its emetic properties (see page 439).

Emetine or methylcephaeline is an alkaloid obtained from ipecac or prepared synthetically by methylation of cephaeline. It was discovered by Pelletier and Magendie in 1817.

Emetine hydrochloride is a hydrated hydrochloride of emetine. It occurs as a white, odorless, crystalline powder that becomes yellowish when exposed to light. It is freely soluble in water and alcohol.

USES AND DOSE. Emetine hydrochloride is an antiamebic and acts primarily in the intestinal wall and the liver. It inhibits polypeptide chain elongation, thereby blocking protein synthesis. The usual dose is, intramuscularly or subcutaneously, 1 mg per kg of body weight, but not exceeding 65 mg daily, for not more than 5 days. The drug is not administered orally because it produces nausea and vomiting. Emetine hydrochloride has been used extensively as an antiprotozoan, particularly in the treatment of amebic dysentery, pyorrhea alveolaris, and other amebic diseases. It possesses expectorant and emetic properties.



Emetine Hydrochloride

PRESCRIPTION AND NONPRESCRIPTION PRODUCTS. A number of expectorant mixtures include ipecac in their formulas: Cetro-Cirose®, Ipsatol DM®, Cerose DM®, and Quelidrine®.

Hydrastis

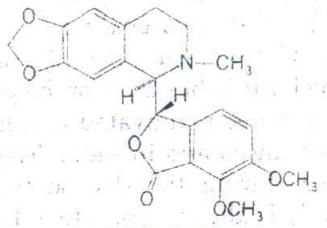
Hydrastis or goldenseal consists of the dried rhizome and roots of *Hydrastis canadensis* Linné (Fam. Ranunculaceae).

Hydrastis is Greek and means to accomplish or act with water; the specific name refers to the habitat. The plant is a perennial herb with a short horizontal rhizome that bears numerous long, slender roots. Internally, the rhizome and roots show a golden yellow color. Goldenseal was plentiful in the forests of the eastern United States and Canada; in recent years, it has become almost extinct because of ruthless collection. Its market price is relatively high and presently approximates $16 per lb. Goldenseal has been cultivated in Oregon, Washington, North Carolina, Tennessee, Michigan, Wisconsin, and other localities; most of the commercial supply now comes from Arkansas and from the Blue Ridge Mountain area. The plants, propagated from rhizome buds, require 3 to 4 years to produce marketable drug. It is gathered in autumn, the terminal buds are replanted, and the drug is carefully dried. Hydrastis was known to the Cherokee Indians, who used it as a dye and an internal remedy. These Indians introduced its use to the early American settlers.

Three alkaloids have been isolated from hydrastis: hydrastine, berberine, and canadine. Of these, hydrastine (1.5 to 4%) is the most important. Hydrastis yields not less than 2.5% of the anhydrous ether-soluble alkaloids of hydrastis.

USE. The hydrastis alkaloids, hydrastine and berberine, are used as astringents in inflammation of the mucous membranes.

Hydrastine is readily soluble in chloroform, alcohol, and ether but almost insoluble in water. It crystallizes in prisms, melting at 131 to 132° C.



(−)-β-Hydrastine

Hydrastine hydrochloride occurs as a white or creamy white powder that is odorless, bitter, and hydroscopic.

Berberine is readily soluble in water but almost insoluble in ether. The salts of berberine form bright yellow crystals.

Sanguinaria

Sanguinaria or bloodroot is the dried rhizome of *Sanguinaria canadensis* Linné (Fam. Papaveraceae). The generic name is from *sanguinarius*, meaning bloody, and refers to the color of the juice; *canadensis* refers to the plant habitat in Canada. The plant is a low perennial herb (Fig. 8–13) with a horizontal branching rhizome that bears slender roots and contains an orange-red latex. The rhizomes are dug during the early summer, deprived of their roots, and carefully dried. The plant grows in the rich open woodlands in North America east of the Mississippi. Most of the collection takes place in the eastern states. Bloodroot was used by the Indians to stain their faces and was also used as an acrid emetic. Its use in homemade cough remedies seems to have been adopted by the early settlers.

Sanguinaria contains alkaloids of the protopine series, including sanguinarine (about 1%), chelerythrine, protopine, and allocryptopine. These alkaloids are colorless but tend to form colored salts. Sanguinarine yields reddish salts with nitric or sulfuric acids; yellowish salts are formed with chelerythrine.

All alkaloids of sanguinaria are found in other members of the Papaveraceae and, like berberine and hydrastine, are isoquin-

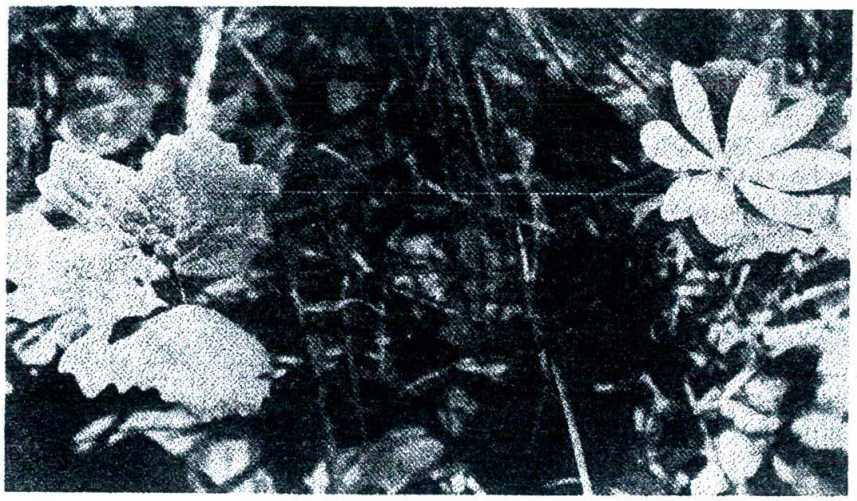


Fig. 8–13. *Sanguinaria canadensis* showing (left) seed pod and characteristic leaf and (right) showy white flower.

oline derivatives. Species of the families Ranunculaceae, Berberidaceae, Menispermaceae, and Papaveraceae contain alkaloids of this type.

Sanguinaria of good quality contains not more than 5% of the roots of the plant. Shriveled rhizomes that are gray and free from starch should be rejected.

USES AND DOSE. Sanguinaria has stimulating expectorant and emetic properties. The usual dose is 125 mg.

PRESCRIPTION PRODUCT. Prunicodeine®.

Tubocurarine Chloride

Curare or South American arrow poison is a crude dried extract from the bark and stems of *Strychnos castelnaei* Weddell, *S. toxifera* Bentham, *S. crevauxii* G. Planchon (Fam. Loganiaceae) and from *Chondodendron tomentosum* Ruiz et Pavon (Fam. Menispermaceae). The term "curare" is derived from *woorari* or *urari*, Indian words for poison. Curare varies in composition among the Indian tribes. Each tribe modifies the formula in accordance with tribal custom.

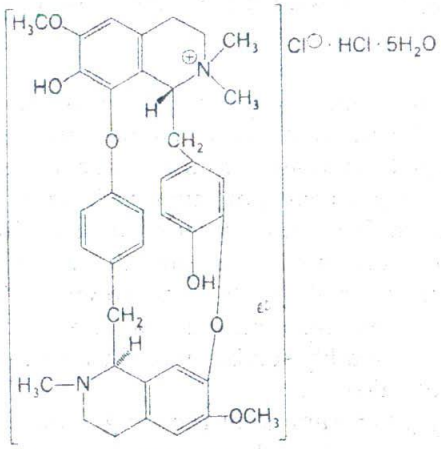
The young bark is scraped off the plants, mixed with other substances, and boiled in water and strained or extracted by crude percolation with water. It is evaporated to a paste over a fire or in the sun. The earliest available preparations were named according to the containers in which the drug was packaged: **calabash** (gourd), **tube** (bamboo), or **pot** (clay pot) **curare.** Curare is obtained from the Orinoco basin, the upper Amazon regions, and the eastern Ecuadorian plateau. It is a brownish or black, shiny, resinoid mass with a bitter taste. It is readily soluble in cold water and in dilute alcohol.

Any given sample of the drug contains at least several of a large possible number of alkaloids and quaternary compounds, but the specific composition varies according to the identity of the plant material from which it was prepared. (+)-Tubocurarine, the most important constituent, is a quaternary compound that contains a *bis*-benzylisoquinoline structure. The crude extract exhibits a paralyzing effect on voluntary muscle (curariform effect) by blocking nerve impulses to skeletal muscles at the myoneural junction. It also produces a toxic action on blood vessels as well as a histaminelike effect.

Curare was brought to England by Sir Walter Raleigh in 1595, but it has only recently come into prominence in medical circles. Claude Bernard, Kolliker, Langley, and other investigators studied the effect

of curare on mechanisms of neuromuscular activity; however, its heterogeneous nature, its variability, and its uncertain supply limited its use in therapeutics.

Tubocurarine chloride or (+)-tubocurarine chloride is a white or yellowish white to grayish white, odorless, crystalline powder. It is derived from tube curare and was first isolated by Boehm in 1898 and later by King in 1947. King obtained it from *Chondodendron tomentosum* and confirmed the structure as a quaternary ammonium compound. It is soluble in water and in alcohol but is insoluble in acetone, chloroform, and ether.



(+)-Tubocurarine chloride

Tubocurarine chloride is standardized by the "head-drop" crossover test in rabbits in which groups of animals for testing and for control are used on alternate days (crossover). The standard "head-drop" dose is the least amount of the drug capable of producing muscle relaxation so that the head of the animal drops in a characteristic manner.

USES AND DOSE. Tubocurarine chloride is employed as a skeletal muscle relaxant to secure muscle relaxation in surgical procedures without deep anesthesia. It is also used to control convulsions of strychnine poisoning and of tetanus; it is an adjunct to shock therapy in neuropsychiatry and a diagnostic aid in myasthenia gravis. Usual initial dose, intramuscularly or intravenously, is 200 to 400 μg per kg of body weight, not exceeding 27 mg, then 40 to 200 μg per kg, repeated as necessary.

PRESCRIPTION PRODUCT. Metubine Iodide® is a modified tubocurarine product.

Opium

Opium or gum opium is the air-dried milky exudate obtained by incising the unripe capsules of *Papaver somniferum* Linné or its variety *album* DeCandolle (Fam. Papaveraceae). The term *opium* is from the Greek *opion*, meaning poppy juice; *Papaver* is the Latin name for the poppy; *somniferum* is Latin and means to produce sleep.

The opium poppy is an annual herb with large, showy, solitary flowers that vary in color from white to pink or purple. The color of its seeds is also variable, ranging from blue-black or gray to yellow-white or rose-brown. Plants that produce the lighter-colored seeds have been classified as variety *album*, but this designation is not employed in modern taxonomic writings. Because of its long history as a cultivated plant, numerous varieties of *P. somniferum* exist, and their taxonomy is extremely complicated.

The plant was first cultivated somewhere in the northeastern corner of the Mediterranean region, where opium was first produced. Opium was then introduced into India (the date is uncertain). Some scholars credit the introduction to Alexander the Great (327 B.C.), others to the Arabs who invaded the Province of Sind in the 8th century. The first recorded cultivation of the opium poppy in India dates from the 15th century, and cultivation began in Macedonia and Persia (Iran) about the middle of the 19th century. The opium poppy is grown commercially now in many countries throughout the world, but production is concentrated in a zone that extends from the Turkish Anatolian Plain to the northern border of Laos. The discovery of the medicinal qualities of opium is lost in antiquity. Theophrastus (3rd century B.C.) mentioned it, and Dios-

corides (77 A.D.) distinguished between the juice of the poppy and an extract of the entire plant. In 1806, Sertürner first isolated the alkaloid morphine from opium.

CULTIVATION, COLLECTION, AND COMMERCE. The cultivation of the opium poppy is controlled internationally by the International Narcotics Control Board of the United Nations. At the present time, the only country with a major involvement in the licit production of opium is India, with an estimated production of approximately 750 metric tons (750,000 kg) of opium for 1985.

The opium poppy, however, is widely cultivated for the purpose of harvesting poppy seed, the straw being obtained as a by-product and used as a raw material in the production of morphine. The morphine is extracted from poppy straw, prepared by cutting and drying the entire overground plant at a suitable stage of development. The major producers of poppy straw are Turkey, the Soviet Union, Roumania, Australia, France, and Spain. Turkey, formerly a major producer of both licit and illicit opium, has made it illegal to produce opium and permits poppy cultivation exclusively for the production of poppy straw and seeds. Most of the opium destined for the illicit trade originates in remote border areas of Burma, Thailand, and Laos, commonly referred to as the "Golden Triangle," and in India, Pakistan, Afghanistan, and Mexico.

For the production of opium in northern India, the poppy seeds are sown in winter in well-cultivated soil. In the spring, when the plants have attained a height of 15 cm, the fields are cultivated, and the plants are thinned to stand about 60 cm apart. The poppy blossoms in April or May, and the capsules mature in May or June. Each plant bears from 5 to 8 capsules (see Fig. 8–14).

The ripening capsules, about 4 cm in diameter, change from bluish green to yellowish in color. This time is critical for latex collection. The capsules are incised with a knife, which is usually 3-bladed, and the incision is made around the circumference of the capsule. The latex tubes open into one another; therefore, it is not necessary to incise them all. Great skill, however, is required so that the endocarp is not cut. When the endocarp is broken, the latex flows into the interior of the capsule and is lost. The latex, which is at first white, rapidly coagulates and turns brown to blackish. In Rajasthan, each capsule is incised 4 or 5 separate times, and it is claimed that the third lancing produces the highest yield of latex. The morning after each lancing, the congealed opium is scraped off with an iron scoop or knife before the heat makes it stick too tightly. Thus each capsule may be handled 10 times. When sufficient latex is collected, it is kneaded into balls that are wrapped in poppy leaves and dried in the shade. Additional processing of the raw opium takes place at government collection centers. Rectangular pans containing about 35 kg of opium sit in the sun, and every 30 minutes or so each pan is stirred with wooden paddles. Eight to 20 days of stirring, depending on the sun, reduces the moisture content from 30% to 10%. When sufficiently dry, it is formed into 5-kg cakes. Externally, opium is pale olive-brown or olive-gray. It is more or less plastic when fresh and becomes hard and brittle or tough when kept. Internally, it is coarsely granular or nearly smooth, reddish brown, frequently interspersed with lighter areas, and somewhat lustrous. Its odor is characteristic and its taste is bitter and characteristic.

Indian opium is produced in the states of Madhya Pradesh, Rajasthan, and Uttar Pradesh. At present it is the only licit source of opium. The 5-kg cakes are shipped in polyethylene bags. Indian opium yields about 10% of anhydrous morphine.

Approximately 200,000 kg of opium, with a market value in excess of $5 million, are imported into the United States annually.

More than 30 different alkaloids have

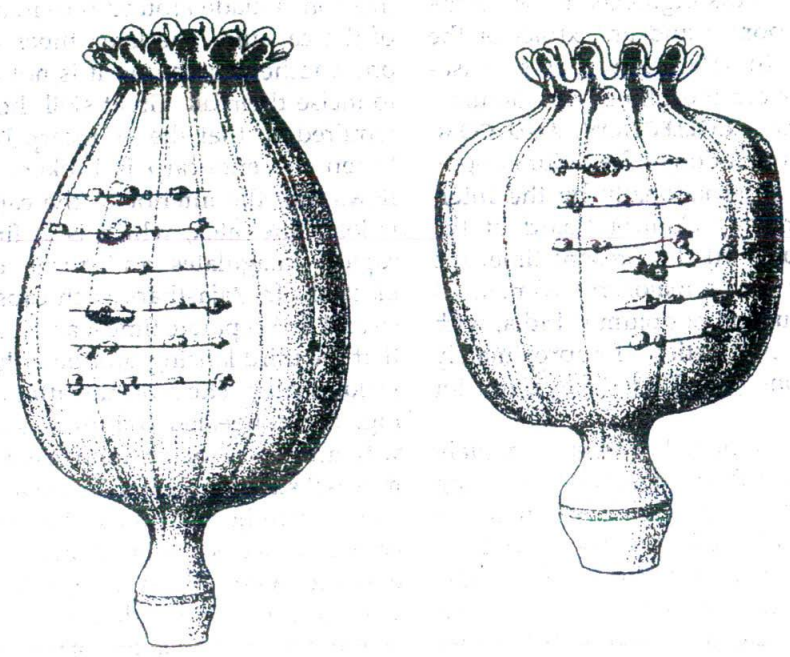


Fig. 8–14. Poppy capsules showing the milky juice exuding from transverse incisions and forming irregular globular masses on the surface. The hardened milky juice forms opium.

been obtained from opium and its extracts, some of which are alteration products of the alkaloids occurring naturally in the drug. The most important of these are **morphine,** which exists to the extent of 4 to 21%; **codeine,** 0.8 to 2.5%; **noscapine** (formerly **narcotine**), 4 to 8%; **papaverine,** 0.5 to 2.5%; and **thebaine,** 0.5 to 2%. Other alkaloids include narceine, protopine, laudanine, codamine, cryptopine, lanthopine, and meconidine.

Opium also contains from 3 to 5% of meconic acid, which exists free or in combination with morphine, codeine, and other alkaloids. It forms rhombic prisms that are soluble in water and alcohol and give a red color in solutions of ferric chloride. The color is not altered when diluted hydrochloric acid is added. Because meconic acid is found only in opium, this test may be used for the detection of opium. The total ash yield of opium is from 4 to 8%, with about 0.55% of acid-insoluble ash.

Opium in its normal, air-dried condition yields not less than 9.5% of anhydrous morphine.

USES AND DOSE. Opium is a pharmaceutic necessity for powdered opium. It acts chiefly on the central nervous system; its action first stimulates and then depresses nerve response. It serves as an analgesic, a hypnotic, and a narcotic and checks excessive peristalsis and contracts the pupil of the eye. A dose of 60 mg was formerly listed for opium and powdered opium.

ADULTERANTS. Fragments of the capsules, the pulp of figs and other fruits, tragacanth, beeswax, powdered cumin seed, starch, and such inorganic substances as clay, sand, stone, lead piping, and lead bullets have been found in opium.

Powdered opium yields not less than 10% and not more than 10.5% of anhydrous morphine. Powdered opium of a higher percentage morphine may be reduced to the official standard by admixture with powdered opium of a lower percentage or with any of the diluents, except starch, permitted for powdered extracts.

The diluents may be colored with caramel to simulate the color of the drug.

Powdered opium is used in making Dover's powder and camphorated opium tincture and is combined with other agents in antidiarrheal preparations.

PRESCRIPTION PRODUCTS. Diabismul®, KBP/O®.

Paregoric or camphorated opium tincture is classed as an antiperistaltic. The usual dose of paregoric is 5 to 10 ml, 1 to 4 times a day, and it may be mixed before taking with a small amount of water to form a milky solution. It is used in combination with belladonna alkaloids, kaolin, pectin, and/or other ingredients for the symptomatic treatment of diarrhea. Many of these preparations are Schedule V drugs under the Controlled Substances Act.

NONPRESCRIPTION PRODUCTS. Parepectolin®, Parelixir®, Donnagel-PG®.

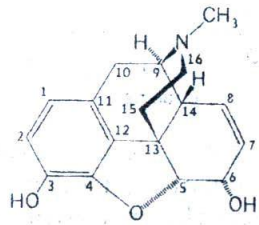
Laudanum, opium tincture, or deodorized opium tincture was formerly used similarly to paregoric. Its dose is 0.6 ml, 4 times a day.

Poppy seed or maw seed is the dried seed of *Papaver somniferum* variety *nigrum* DeCandolle. The seeds are bluish black or yellowish white, reniform, from 0.5 to 1 mm in diameter, and reticulate. They have a yellowish hilum scar, a white oily endosperm, and a curved embryo. Their taste is slight and oily. Poppy seeds are used in baking (poppy seed rolls). They contain about 50% of a fixed oil **(poppy seed oil)**, which is used in some parenteral formulations, by artists as a drying oil, and also for food and salad dressings. **Poppy seed oil cake** is used as a cattle food. Poppy seed contains no significant quantity of alkaloids.

Alkaloids of Opium

Morphine is the most important of the opium alkaloids. Morphine and the related alkaloids are phenanthrene derivatives. The molecule contains a phenolic and an alcoholic hydroxyl group.

The alkaloid and its salts occur as white silky crystals, sometimes in cubic masses, or as a fine crystalline powder. It is stable in air, odorless, and bitter-tasting.



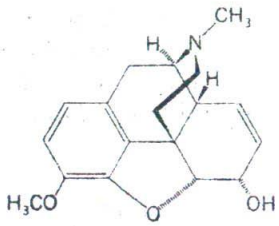
Morphine

Morphine and its salts are classed as narcotic analgesics; they are strongly hypnotic and narcotic. Their use tends to induce nausea, vomiting, constipation, and habit formation. The usual dose of morphine sulfate, parenterally, is 10 mg, 6 times a day, as necessary.

Centrally acting analgesics, in most cases, have certain structural features in common. They are: (1) a central carbon atom with no hydrogen substitution (quaternary), (2) a phenyl group or isostere attached to this carbon atom, (3) a tertiary nitrogen atom, and (4) a 2-carbon bridge separating the tertiary nitrogen atom and the central carbon atom.

Morphine and the related opium alkaloids that have analgesic activity possess these structural features. In the case of morphine, the central carbon atom is C-13; the phenyl ring attached to C-13 is composed of carbon atoms 1 to 4 and 11 and 12; and the tertiary nitrogen atom is linked via a 2-carbon bridge (C-15, C-16) to the central carbon atom.

Codeine is the most widely used opium alkaloid. It may be either obtained from opium (0.2 to 0.7%) or prepared from morphine by methylation or from thebaine by appropriate reduction and demethylation. Codeine is methylmorphine in which the methyl group replaces the hydrogen of the phenolic hydroxyl group. Codeine and its salts occur as fine needles or as white crystalline powders that effloresce in air.



Codeine

Codeine and its salts are narcotic analgesics and antitussives; they are used as sedatives, especially in allaying coughs. Although its action is similar to that of morphine, codeine is considerably less toxic and involves much less danger of habit formation. The usual dose of codeine, codeine phosphate, and codeine sulfate is: analgesic, 15 to 60 mg every 4 hours as needed; antitussive, 10 to 20 mg every 4 to 6 hours as needed.

Diacetylmorphine or heroin is formed by the acetylation of morphine; the hydrogen atoms of both the phenolic and alcoholic hydroxyl groups are replaced by acetyl groups. Heroin's action is similar but more pronounced than that of morphine. Because of its potency and the danger of habit formation, its manufacture in the United States is forbidden by law, and its use in medicine has been discontinued.

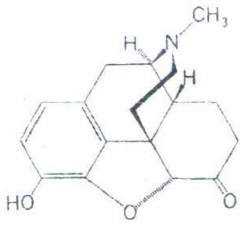
Apomorphine hydrochloride is formed when morphine is treated with hydrochloric acid in a sealed tube, and one molecule of water is lost. The compound decomposes readily and must be rejected if an emerald green color is produced when it is shaken with distilled water (1 to 100).

Apomorphine is an emetic and is particularly valuable in cases of poisoning because it may be administered subcutaneously. The usual dose, subcutaneously, is 100 μg per kg of body weight (maximum, 6 mg).

Papaverine occurs naturally in opium to the extent of about 1%, but it may also be produced synthetically. **Papaverine hydrochloride** occurs as white crystals or as a white crystalline powder. It is odorless but has a slightly bitter taste.

Papaverine hydrochloride is a smooth muscle relaxant. The usual dose, orally, is 150 mg; intramuscularly, 30 mg. Papaverine hydrochloride is represented by Pavabid® and Pavadyl®. It is also used as an antitussive in combination with codeine sulfate (Copavin®). The dose of each is 15 mg.

Hydromorphone hydrochloride or dihydromorphinone hydrochloride differs from morphine hydrochloride because one of the hydroxyl groups of morphine is replaced by a ketone group, and the adjacent double bond is removed. It is prepared by reducing morphine in hydrochloric acid solution with hydrogen in the presence of a catalyst.



Hydromorphone

The drug is a powerful narcotic analgesic and tends to strongly depress the respiratory mechanism. Its dosage is smaller than that of morphine, it causes nausea and constipation less frequently than does morphine, and perhaps it is less habit-forming. The usual dose, orally and subcutaneously, is 2 mg every 4 hours, as needed. Dihydromorphinone hydrochloride is represented by the product Dilaudid® Hydrochloride. It is the chief ingredient in Dilaudid cough syrup as an antitussive.

Hydrocodone bitartrate or dihydrocodeinone bitartrate bears the same relation to codeine as dihydromorphinone does to morphine—a ketone group replaces one of the hydroxyl groups and the adjacent double bond is saturated. It is classed as an antitussive and is an excellent aid in treating a troublesome cough. The usual dose is 5 to 10 mg, 3 to 4 times a day, as necessary. Dihydrocodeinone bitartrate is rep-

resented by the products Hycodan® and Tussend®.

Noscapine (commonly called **narcotine**) exists in opium as a free base (1.3 to 10%). It possesses no narcotic properties and is therefore sometimes called anarcotine. To eliminate misunderstanding and wrong connotation, the name noscapine is employed in pharmaceutic literature, but narcotine remains the common chemical designation of this alkaloid.

Noscapine is an antitussive. The usual dose is 15 mg, up to 4 times a day. It is available in syrup and chewable tablets in the nonprescription preparations Conar® and Actol®.

A long-standing prescription product composed of the hydrochlorides of the alkaloids of opium in the same proportion in which they occur in the natural product is Pantopon®. This drug has been freed from inert or irritating gums, waxes, and resins, and it may be administered parenterally, either subcutaneously or intramuscularly, in a dose of 5 to 20 mg every 4 to 5 hours.

The term **"opioid"** has been devised to refer to the synthetic morphinelike compounds. Many of these substances offer the same narcotic and pain-relieving properties as morphine, but they are not as habit-forming. Others possess the cough-relieving activity of codeine but are not addictive.

INDOLE ALKALOIDS

A number of important alkaloids possess an indole ring as part of their structure. Strychnine and brucine (dimethoxystrychnine) from nux vomica and physostigmine from physostigma belong to this group. However, strychnine and brucine also contain a quinoline nucleus, and some authors classify them in the quinoline group.

The important drugs and their alkaloids of the indole group are rauwolfia, reserpine, catharanthus (vinca), vinblastine, vincristine, nux vomica, strychnine, brucine, physostigma, physostigmine, ergot, ergotamine, and ergonovine.

Biosynthesis of Indole Alkaloids

Many of the therapeutically useful indole alkaloids are rather complex multicyclic molecules. Incorporation of a tryptamine moiety into this type of alkaloid was established at a fairly early stage in the study of alkaloid biosynthesis. The origin of the balance of the molecules proved more elusive. However, it is now established that the nontryptophan portions of the molecules are derived from monoterpenoid precursors. Three general monoterpenoid skeletons give rise to most of the complex indole alkaloids; these skeletons are designated as the *Aspidosperma*, *Corynanthe*, and *Iboga* types, taking the names of genera that are rich in alkaloids with the respective monoterpenoid nuclei (Fig. 8–15).

The reactive form of the terpene presumably involves an aldehyde group, and the loss of one carbon atom during the biosynthetic process to give a C_9 unit appears to be fairly common. Most of the details on the sequence of biosynthetic reactions and various rearrangements remain to be clarified. It is suspected that the *Corynanthe* type of monoterpenoid moiety is metabolically the most primitive. Studies on the formation of therapeutically unimportant monomeric alkaloids in *Catharanthus roseus* have demonstrated that the glucoside, secologanin, provides the terpenoid unit. Evidence suggests that secologanin reacts initially with tryptamine to form strictosidine (see Fig. 8–10) and that the glycosidic linkage is cleaved during subsequent metabolic steps.

The *Rauvolfia* alkaloids, ajmaline, reserpine, and serpentine, are derived from a *Corynanthe*-type monoterpenoid precursor. They can be used to illustrate some of the multicyclic structures that arise during tertiary cyclization and rearrangement steps in biosynthesis (Fig. 8–16)

Ergot Alkaloids. The alkaloids of ergot are

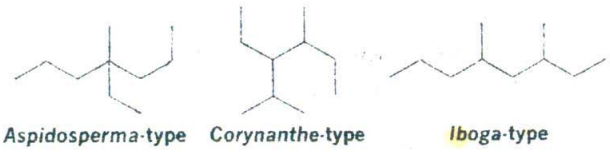


Fig. 8–15. Carbon skeletons of the general types of monoterpenoid precursors of indole alkaloids.

also derived from a combination of tryptophan and acetate metabolism. Studies with various physiologic strains of *Claviceps* species, including some significant stereospecific experiments, have clarified many of the key steps leading to the biosynthesis of the lysergic acid nucleus. Dimethylallyl pyrophosphate condenses at the 4-position of tryptophan as an initial step in the pathway (Fig. 8–17). Recent evidence indicates that the next intermediate arises from the *N*-methylation of dimethylallyltryptophan to give N_a-methyldimethylallyltryptophan. The next anticipated step would be decarboxylation, with a subsequent formation of chanoclavine-I. The number of intermediates and enzymatic conversions in these events is still unknown. Concerning the biosynthetic mechanism of alkaloid formation, there is evidence that 2 *cis-trans* isomerizations in the isoprenoid moiety take place in the course of forming the tetracyclic ring system. If the *trans* methyl group of dimethylallylpyrophosphate is radioactively labeled, the *cis* methyl group of chanoclavine-I will be labeled indicating one *cis-trans* isomerization, and the *trans* methyl group

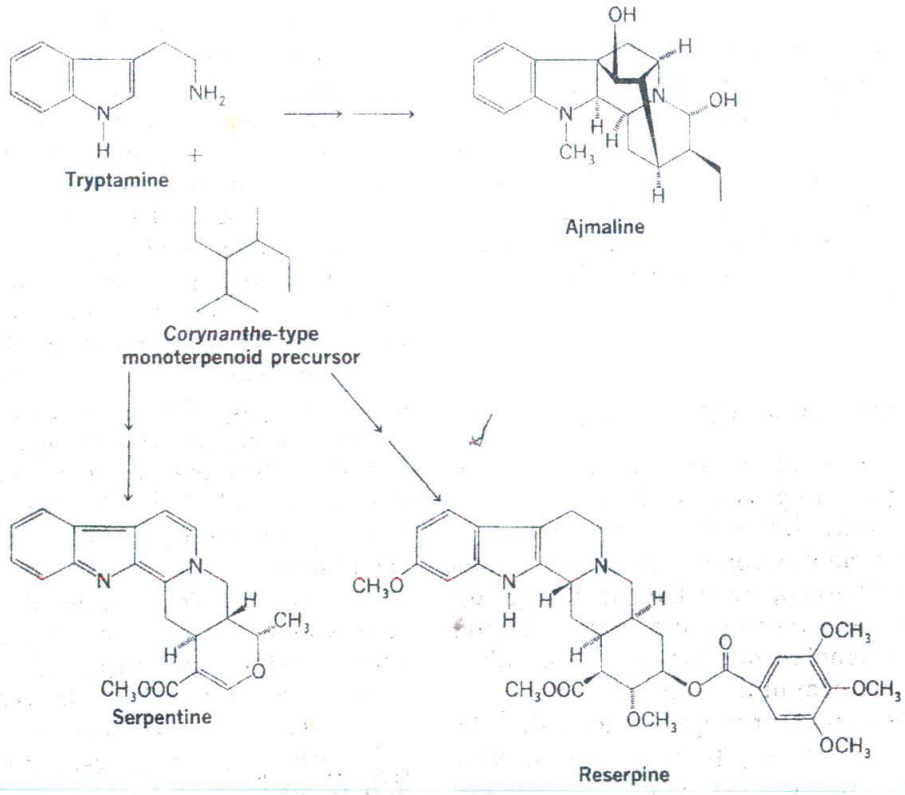


Fig. 8–16. Biosynthesis of *Rauvolfia* alkaloids.

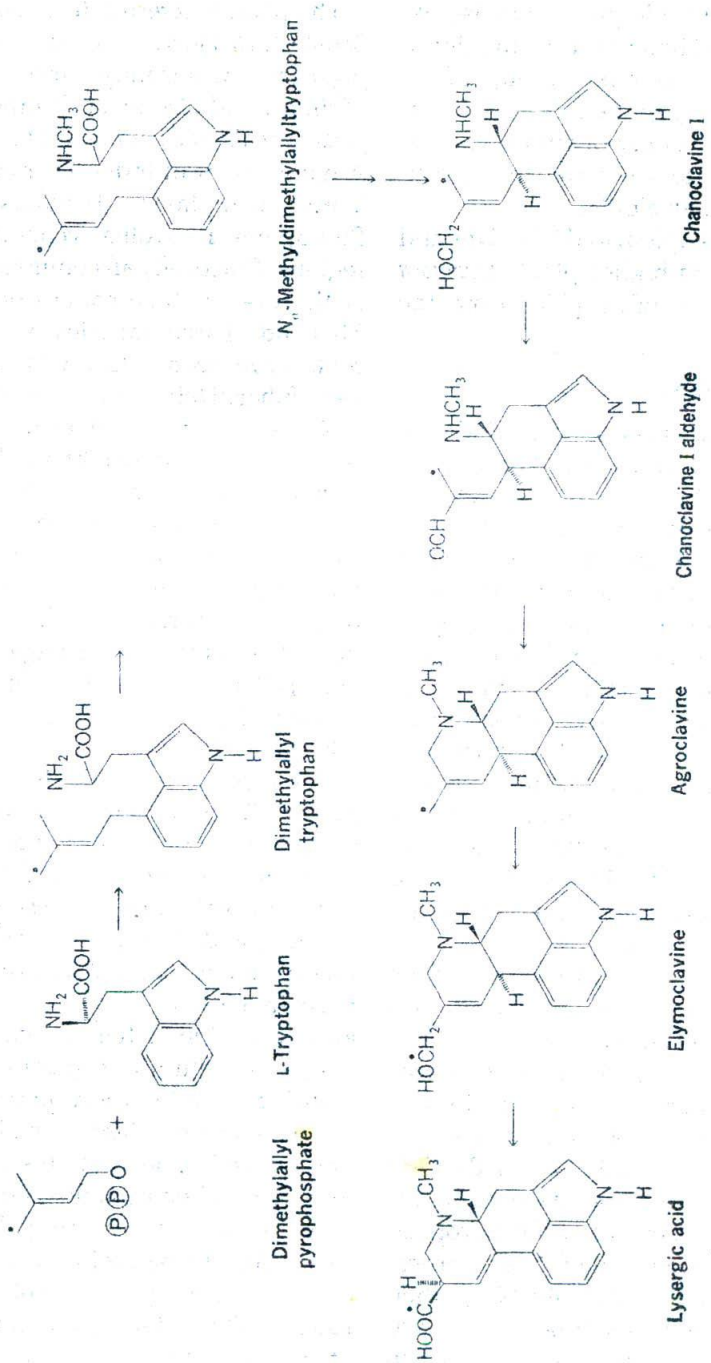


Fig. 8–17. Biosynthesis of lysergic acid.

of the isoprenoid moiety of agroclavine will be labeled indicating a second isomerization. Agroclavine undergoes stepwise oxidation to elymoclavine and eventually to lysergic acid. The carboxyl group of lysergic acid forms a peptide linkage with an amino group of a variety of amino acids or peptide residues to yield the therapeutically useful ergot alkaloids.

Synthesis of lysergic acid derivatives and clavine alkaloids in higher plants (*Ipomoea* species) apparently takes place from the same precursors.

Rauwolfia Serpentina

Rauwolfia serpentina is the dried root of *Rauvolfia serpentina* (Linné) Bentham ex Kurz (Fam. Apocynaceae). Sometimes fragments of rhizome and aerial stem bases are attached (Fig. 8–18). When assayed as directed, it contains not less than 0.15% of reserpine-rescinnamine group alkaloids, calculated as reserpine. The genus name was selected in honor of Dr. Leonhard Rauwolf, a noted 16th century German botanist, physician, and explorer; *serpentina* refers to the long, tapering, snakelike roots of the plant. It must be emphasized that the name of the drug and the name of the genus of plants from which it derives are spelled differently. For technical reasons, the genus must be spelled with a *v* instead of a *w*. The plant *Rauvolfia serpentina* is thus the correct botanic origin of the drug rauwolfia serpentina (rauwolfia).

For centuries *Rauvolfia serpentina* was used by the medicine men of India to treat a variety of maladies, ranging from snakebite to insanity. In 1563, Garcia de Orta mentioned the plant and its uses in his book on the drugs of India, but European physicians were skeptical of its properties. Consequently, it was not until 1952, when Müller succeeded in isolating the alkaloid, reserpine, that this plant was conceded to be valuable. In the form of the powdered root, the alkaloidal extract, and purified alkaloids, rauwolfia serpentina has become an exceedingly important therapeutic aid in the treatment and control of hypertension.

The plant is referred to as *sarpagandha* in Sanskrit, *chota-chand* or *chandrika* in Hindi, *pagla-ka-dawa* (insanity cure) in the dialect of Bihar, and also by such other names as *patala-gandhi*, *dhanburua*, and *covanamilpori*. A native plant of India, Burma, Sri Lanka, Vietnam, Malaysia, Indonesia, and the Philippines, rauwolfia occurs in hot, moist regions. Practically all commercial supplies at the present time come from India and Thailand. Three varieties of *R. serpentina* roots have been sold on the Indian markets: Bihar, Dehra Dun, and Assam.

R. serpentina is an erect shrub that reaches 1 meter in height and has cylindric stems. These stems bear pale bark and exhibit a light-colored viscous latex when ruptured. It has leaves that may be simple and opposite or, more commonly, arranged in whorls of 3 to 5. The white or pale rose flowers are arranged in terminal and axillary cymes. The fruit is a single, 2-lobed drupe that turns purplish black when mature.

Three series of alkaloids have been reported: (1) weakly basic indole alkaloids, (2) indoline alkaloids of intermediate basicity, and (3) strong anhydronium bases. The principal alkaloids, reserpine, rescinnamine, and deserpidine, are tertiary indole alkaloids that have a carbocyclic structure in ring E. Other tertiary indole alkaloids exhibit a heterocyclic structure in ring E: δ-yohimbine (identical with ajmalicine, tetrahydroserpentine, and raubasine) and reserpiline. Ajmaline, isoajmaline, rauwolfinine, and others are listed as tertiary indoline alkaloids; however, these bases do not have a tranquilizing action. Serpentine, serpentinine, and alstonine are classed as strongly basic anhydronium alkaloids. The latter type is not considered of practical therapeutic importance. From the 25 or more species of *Rauvolfia* investigated, at least 50 alkaloids have been reported.

Rauwolfia alkaloids probably exert their

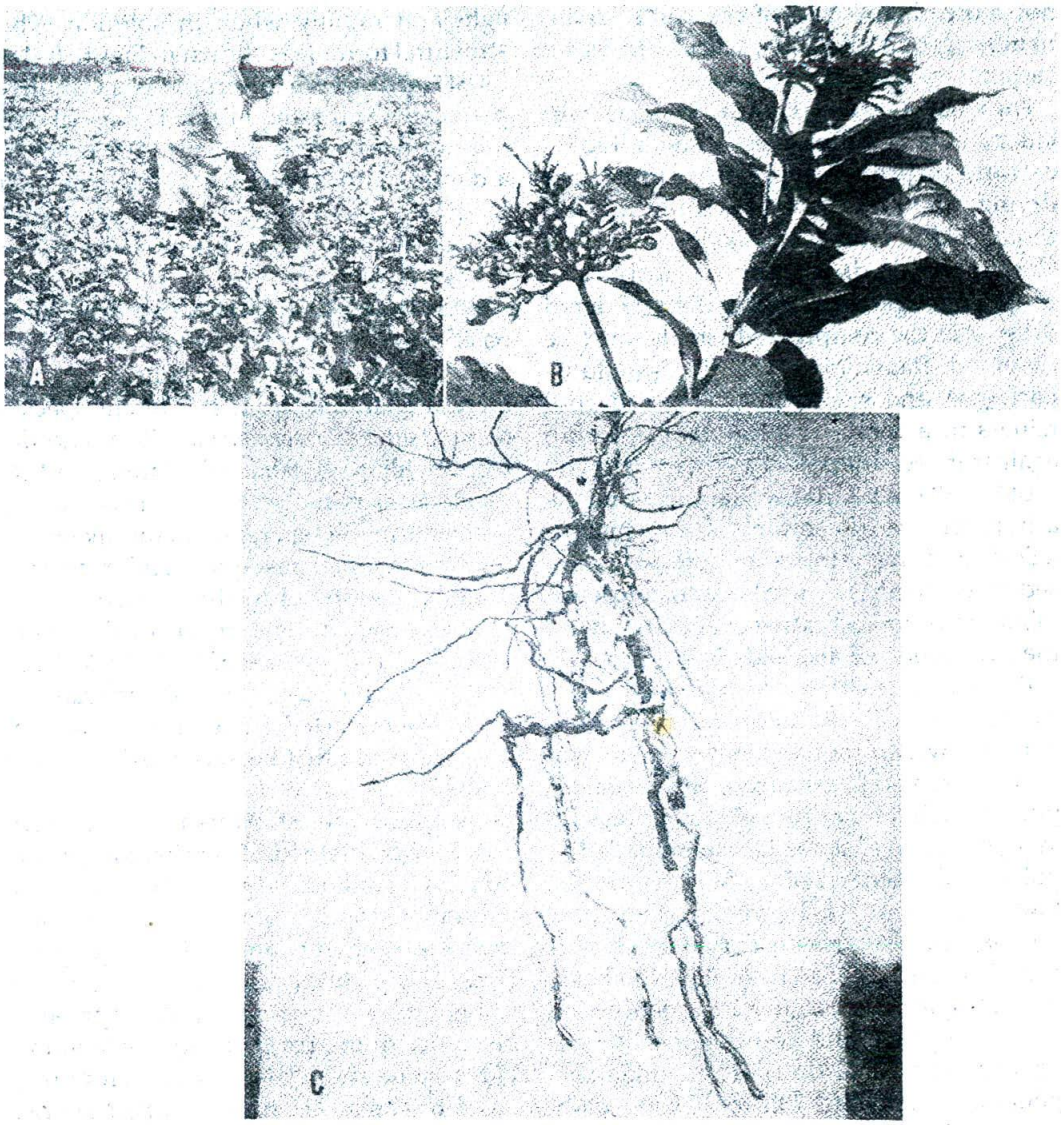


Fig. 8–18. *Rauvolfia serpentina: A,* field of cultivated plants; *B,* branch with flowers and fruits; *C,* typical root system of a 2-year-old plant. (Photo courtesy of Dr. P.K. Dutta, Regional Research Laboratory, Jammu & Kashmir, India.)

hypotensive effects by depletion of norepinephrine through inhibition of catecholamine storage in postganglionic adrenergic nerve endings. However, their sedative and tranquilizing properties are thought to be related to depletion of amines in the central nervous system.

Powdered rauwolfia serpentina is *R. serpentina* root reduced to a fine or very fine powder that is adjusted, if necessary, to conform to the official requirements for reserpine-rescinnamine group alkaloids by admixture with lactose or starch or with a powdered rauwolfia serpentina containing a higher or lower content of these alkaloids. It contains not less than 0.15% and

not more than 0.20% of reserpine-rescinnamine group alkaloids, calculated as reserpine.

PACKAGING AND STORAGE. Seasonal variation, genetic differences, geographic location, improper handling, improper drying, and other factors account for percentage differences in alkaloid amount. Certain alkaloids hydrolyze easily, and proper storage of the roots, the powdered drug, and the compressed tablets must be observed. Rauwolfia serpentina should be packaged and stored in well-closed containers in a cool, dry place that is secure against insect attack.

USES AND DOSE. Rauwolfia serpentina is a hypotensive. (Reserpine is the chief alkaloid and has strong hypotensive and sedative activity.) A total alkaloidal determination is not indicative of activity unless the proportion of alkaloids is known.

Because at least 50 alkaloids have been isolated, it is easy to understand the claim that the whole root exhibits a medicinal action that is different from that of reserpine. A definite lowering of blood pressure in hypertensive states, a slowing of the pulse, and a general sense of euphoria follow administration. In mild anxiety conditions, the drug has a transquilizing effect. (The alkaloid has been described as a phenotropic drug because it influences the function of the mind and the affective behavior). The usual dose of rauwolfia serpentina is, initially, 200 to 400 mg daily given in 2 divided doses for 1 to 3 weeks; maintenance, 50 to 300 mg daily.

PRESCRIPTION PRODUCTS. Powdered whole root in tablet form is represented by Raudixin®, Rauval®, Wolfina®, and others.

Alseroxylon fraction is a basic powdered alkaloidal extract of rauwolfia serpentina and is claimed to possess a lack of toxicity over long-range administration. It is given in doses of 2 mg, twice daily.

PRESCRIPTION PRODUCT. Rauwiloid®.

Reserpine is a white or pale buff to slightly yellow, odorless, crystalline powder that darkens slowly when exposed to light and rapidly when in solution. The structural formula is shown in Figure 8–16.

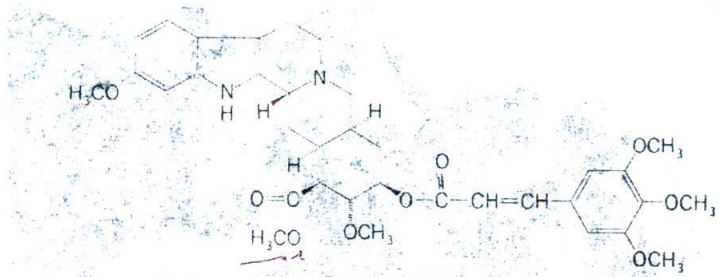
USES AND DOSE. Reserpine is an antihypertensive and tranquilizer. The usual oral dose of reserpine is, initially, 500 μg once a day for 1 to 2 weeks; maintenance, 100 to 250 μg once a day. The patient should be advised to notify his physician if a change in mood occurs.

PRESCRIPTION PRODUCTS. Sandril®, Serpasil®, and other products.

Reserpine has been obtained in commercial quantities from 4 different species of *Rauvolfia; R. serpentina, R. micrantha* Hooker filius, *R. tetraphylla* Linné, and *R. vomitoria* Afzelius. Several of these present problems in the separation of the alkaloids. In *R. serpentina,* reserpine and rescinnamine both respond to the extraction procedures, and the end result of the assay procedure is a mixture of both. In *R. tetraphylla,* reserpine and deserpidine (raunormine) are extracted together; in *R. vomitoria,* reserpine must be separated from the resins.

Laboratory investigators in France have developed a method of synthesizing reserpine on a commercial scale. However, the natural alkaloid is much less expensive than the synthetic, and, with large quantities of *R. vomitoria* available from the Congo, the commercial supplies appear to be sufficient to provide adequate amounts of reserpine and related alkaloids for many years to come. In addition, other species of plants are being studied to ascertain their alkaloidal composition. Because the family Apocynaceae consists of many additional species, it is probable that untapped sources of reserpine and other valuable alkaloids may be discovered by pharmacognosists and plant chemists.

Rescinnamine is an alkaloid that occurs in several species of *Rauvolfia.* Its appearance, properties, and solubility are somewhat similar to those of reserpine. Chemically, it is the methyl reserpate ester of 3,4,5-trimethoxy cinnamic acid; its structural formula is shown on the next page.



Rescinnamine

USE AND DOSE. The usual antihypertensive dose of rescinnamine is, initially, 500 μg, 2 times a day and increase dosage gradually, if necessary; maintenance is 250 to 500 μg daily. Higher doses should be used cautiously because serious mental depression may be increased considerably.

PRESCRIPTION PRODUCT. Moderil®.

Deserpidine (canescine, recanescine) is an alkaloid obtained from the root of *Rauvolfia canescens* L. Chemically, it is 11-desmethoxyreserpine. It is a wide-range tranquilizer and antihypertensive and is relatively free from the incidence and severity of the side effects that accompany other forms of rauwolfia therapy. It is usually administered orally in doses of 250 μg daily for mild essential hypertension and 500 μg daily for psychiatric disorders.

PRESCRIPTION PRODUCT. Harmonyl®.

Authorities are not in complete agreement as to the relative efficacy or safety of rauwolfia therapy as achieved by administration of the powdered whole root, a total alkaloidal extract, a partial alkaloidal extract, mixture of the alkaloids, or certain individual alkaloids. In general, 100 mg daily of the standardized alkaloidal extract, or 500 μg to 1 mg of reserpine daily, is an adequate dosage.

In mild or moderate hypertension, rauwolfia or its derivatives may be the sole therapy, but in more severe hypertension, rauwolfia acts synergistically with more potent hypotensive agents. Products are available that utilize combinations of rauwolfia or reserpine with thiazide diuretics and/or other antihypertensive agents.

PRESCRIPTION PRODUCTS. Diupres®, Serpasil-Esidrix®, Hydropres®, Salutensin®, Rauzide®, Rautrax-N®, Ser-Ap-Es® and Serpasil-Apresoline®.

ALLIED PLANTS. Roots of *Rauvolfia canescens* L. (which are used in India similarly to *R. serpentina*), *R. densiflora*, *R. micrantha*, *R. perakensis*, and 2 additional unidentified species of *Rauvolfia* are frequently found as adulterants. The genuine *R. serpentina* roots may be differentiated from roots of the other species by the absence of sclerenchyma tissue in the cortex and secondary phloem and by the shorter and nonfibrous fracture of its thicker pieces. Restrictions formerly placed on exports of *R. serpentina* roots from India have resulted in the use of other species, particularly for the extraction of reserpine. Root of *R. tetraphylla* Linné obtained from plants growing in Mexico and Guatemala is a source of the alkaloid.

Catharanthus

Catharanthus or vinca is the dried whole plant of *Catharanthus roseus* G. Don (Fam. Apocynaceae), formerly designated *Vinca rosea* Linné. The plant is an erect, everblooming pubescent herb or subshrub that is woody at the base and stands 40 to 80 cm high. It probably originated in Madagascar but is now cosmopolitan in the tropics and is widely cultivated as an ornamental. The flowers are normally violet, rose, or white; ocellate forms are found in cultivated varieties. Botanically, it is closely related to *Vinca minor* Linné, the common periwinkel (Fig. 8–19).

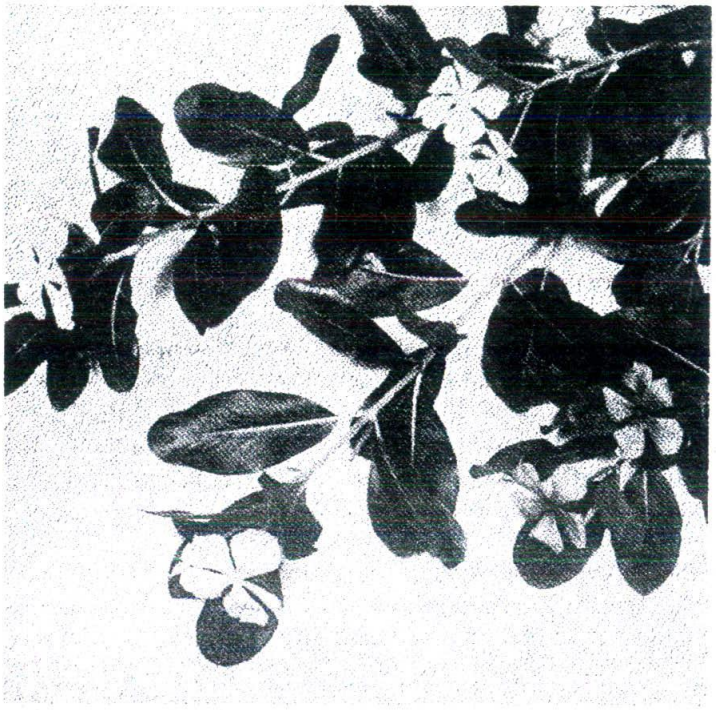


Fig. 8–19. Periwinkle (*Catharanthus roseus*, also known as *Vinca rosea*) showing both white-flowered and pink-flowered varieties. This plant grows abundantly in southern Florida. (Photo courtesy of Dr. Julia F. Morton, Director, Morton Collectanea, University of Miami.)

During the course of a modern scientific investigation prompted by the folklore reputation of this plant as an oral hypoglycemic agent, the ability of certain fractions to produce peripheral granulocytopenia and bone marrow depression in rats was observed by the Canadian group of Noble, Beer, and Cutts. Continued study led to the isolation of an alkaloid, vinblastine, which produced severe leukopenia in rats.

Recognizing the anticancer potential of this plant, G. H. Svoboda and coworkers at Eli Lilly and Company isolated an extremely large number of alkaloids from the plant. Of these, 4 dimeric indole-indoline compounds, vinblastine, vinleurosine, vinrosidine, and vincristine, possess demonstrable oncolytic activity. An extremely confusing situation regarding the nomenclature of these alkaloids exists in the scientific literature. The names just mentioned are the United States Adopted Drug Names but are not the names assigned by the original discoverers who, by tradition, are accorded the privilege of selecting the scientific name for a new chemical compound of complex structure. Equivalent names of these alkaloids are:

U.S. Adopted Drug Names	*Scientific Names*
Vinblastine	= Vincaleukoblastine (VLB)
Vinleurosine	= Leurosine
Vinrosidine	= Leurosidine
Vincristine	= Leurocristine (LC)

Because the active alkaloids exist in the crude drug in relatively small amounts, enormous quantities of the latter are required for commercial production. Nearly 500 kg of catharanthus are utilized to produce 1 g of vincristine. To satisfy the demand, the plant is collected from both nat-

ural and cultivated sources in Madagascar, Australia, South Africa, South America, the West Indies, Europe, India, and the southern United States.

Catharanthus Alkaloids

More than 70 different alkaloids have been isolated from catharanthus. They are generally indole and dihydroindole derivatives, some of which occur in other members of the Apocynaceae. These include ajmalicine, tetrahydroalstonine, serpentine, and lochnerine. The alkaloids with antineoplastic activity belong to a new class of dimeric indole-dihydroindole derivatives. Two of them are available at present as prescription drugs.

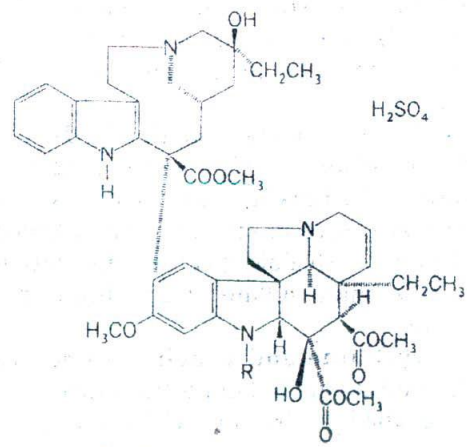
The most characteristic effect of these drugs is the arrest of cell division at metaphase, in a manner resembling the effect of colchicine (see page 243). Both vinblastine and vincristine bind tightly to tubulin and interfere with the functioning of the microtubule system, which is a component of the mitotic spindle. Recent findings indicate that the alkaloids actually inhibit the polymerization of tubulin into microtubules.

Vinblastine sulfate is the salt of an alkaloid extracted from catharanthus. It is unstable and is available in sealed ampoules, which should be stored in a refrigerator to ensure extended stability. The alkaloid is being used experimentally for the treatment of a wide variety of neoplasms and is recommended for generalized Hodgkin's disease, lymphocytic lymphoma, histiocytic lymphoma, mycosis fungoides, advanced testicular carcinoma, Kaposi's sarcoma, and choriocarcinoma and breast cancer unresponsive to other therapies. Vinblastine is effective as a single agent but is usually administered with other antineoplastic agents in combination therapy for an enhanced therapeutic effect without additive toxicity. It is administered intravenously in doses regulated by the patient's age, body surface, and white-blood-cell count. The usual dose given intravenously, is a single dose of 3.7 mg/m² of body surface for an adult and 2.5 mg/m² for a child, once weekly. Each succeeding dose is increased by increments of 1.8 mg/m² for adults and 1.25 mg/m² for a child once a week, until a maximum dose is reached, as determined by a white-blood-cell count.

PRESCRIPTION PRODUCT. Velban®.

Vincristine sulfate is also obtained from catharanthus. The structure of this alkaloid is quite similar to that of vinblastine, differing only in the substitution of an *N*-formyl group for the *N*-methyl group of vinblastine. Despite the structural similarities, there are differences in the antitumor spectra of the 2 compounds, and no cross-resistance has been observed. Because vincristine sulfate is unstable, refrigerated storage in sealed ampoules is essential. It is recommended for the treatment of acute leukemia and in combination therapy in Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, rhabdomyosarcoma, neuroblastoma, and Wilms' tumor.

The dose must be calculated and administered cautiously since overdose may be fatal. It is administered intravenously at weekly intervals in doses of 1.4 mg/m² for adults and 2 mg/m² for children.



R=CH_3 **Vinblastine Sulfate**
R=CHO **Vincristine Sulfate**

PRESCRIPTION PRODUCT. Oncovin®.

Vindesine (Eldisine®), a semisynthetic

derivative of vinblastine, was released in 1984 for use in patients who have become resistant to vincristine and vinblastine.

Nux Vomica

Nux vomica is the dried, ripe seed of *Strychnos nux-vomica* Linné (Fam. Loganiaceae). *Strychnos* is the Greek name for a number of poisonous plants; *nux-vomica* is from 2 Latin words and means a nut that causes vomiting.

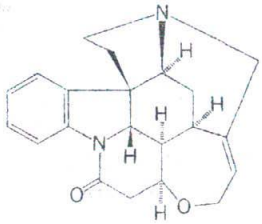
The plant is a small tree, about 12 meters tall, that is native to the East Indies and is also found in the forests of Sri Lanka, on the Malabar Coast, and in northern Australia. The fruit is a berry with from 3 to 5 seeds (Fig. 8–20) that are freed from the bitter pulp by washing before exportation. Most of the commercial supply comes from Cambodia and Sri Lanka. The drug was introduced into Europe about the 16th century, although it was used mainly for poisoning animals. Its use in medicine began about 1640. The natives of India apparently had no knowledge of its medicinal value.

Nux vomica contains alkaloids, 1.5 to 5%, consisting chiefly of **strychnine** and **brucine,** the former comprising from one third to one half of the total amount. Studies have shown that these alkaloids occur in the large, thick-walled cells of the endosperm, but strychnine is concentrated in the cells near the center of the seed and brucine in the outer cells near the epidermis.

USE. Nux vomica and the seeds of the closely related *Strychnos ignatii* Bergius **(ignatia** or **St. Ignatius bean)** serve as a commercial source of strychnine and brucine. The former alkaloid is commonly marketed as strychnine sulfate or strychnine phosphate.

Strychnine and brucine (dimethoxystrychnine) are obtained from nux vomica or ignatia by extraction with dilute sulfuric acid. The solution is concentrated. The alkaloids are precipitated with lime, separated by means of solvent, and purified by recrystallization. Brucine is far more soluble in water and in alcohol than is strychnine; however, strychnine sulfate is somewhat more soluble in these 2 solvents than is brucine sulfate.

Strychnine is interesting pharmacologically and is a valuable tool in physiologic and neuroanatomic research. It is extremely toxic, functioning as a central stimulant. The alkaloid produces excitation of all parts of the central nervous system and blocks inhibitory spinal impulses at the postsynaptic level. This leads to an exaggeration in reflexes, with resulting tonic convulsions. Fatal poisoning in human beings ordinarily results from doses of 60 to 90 mg. The drug is seldom employed in modern medical practice but is utilized as a vermin killer. Brucine, which is less toxic than strychnine, is used commercially as an alcohol denaturant.



Strychnine

Physostigmine

Physostigma, Calabar bean, or ordeal bean is the dried, ripe seed of *Physostigma venenosum* Balfour (Fam. Leguminosae) yielding not less than 0.15% of the alkaloids of physostigma.

The name *Physostigma* is Greek and means an inflated or bladderlike stigma (Fig. 8–21); *venenosum* is Latin and means full of poison. The plant is a perennial, woody climber that grows on the banks of streams in West Africa, particularly in the vicinity of the Gulf of Guinea. In 1846, Daniell described the use of the seed, known as *esere* by the natives of old Calabar, to prove the innocence or guilt of persons accused of crime.

Calabar bean contains several alkaloids, physostigmine (eserine), eseramine,

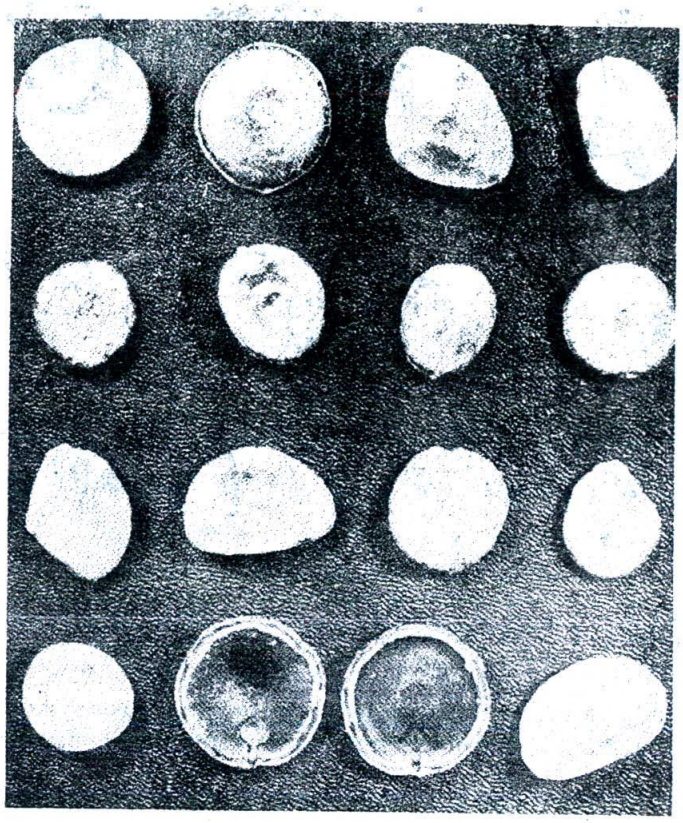


Fig. 8–20. Nux Vomica: orbicular, compressed, concavo-convex, sometimes irregularly bent, margin acute or rounded, 10 to 30 mm in diameter, 3 to 5 mm in thickness; externally grayish yellow or grayish green, covered with appressed hairs giving the seed a satiny luster, sometimes with adhering dark brown fragments of the fruit pulp; hilum, near the center of one side and a more or less distinct ridge resembling a raphe extending from it to the micropyle; very hard when dry, tough when damp; internally whitish, horny; endosperm in two more or less regular concavo-convex halves; embryo small, situated near the micropyle, and with two heart-shaped cotyledons; inodorous; taste intensely and persistently bitter. The two halves of the seed at the middle of the bottom row show the two cotyledons and the caulicle of the embryo lying against the endosperm.

geneserine, and physovenine. Physostigmine is the major alkaloid and is present in the cotyledons to the extent of 0.04 to 0.3%.

Physostigmine or eserine is an alkaloid usually obtained from the dried, ripe seed of *P. venenosum*. It occurs as a white, odorless, microcrystalline powder that may acquire a red tint when exposed to heat, light, air, or contact with traces of metals. Therefore, physostigmine should be preserved in tight, light-resistant containers in quantities not exceeding 1 g.

USE. Physostigmine is a reversible inhibitor of the cholinesterases and thus enhances the effects of endogenous acetylcholine. In the eye, increase in cholinergic activity leads to miosis, contraction of the ciliary muscle, and a decrease in intraocular pressure caused by an increased outflow of the aqueous humor. Physostigmine is employed in ophthalmology to treat glaucoma.

Physostigmine salicylate or eserine salicylate is the salicylate of the alkaloid, physostigmine. It is a white powder that also acquires a red tint when exposed to the conditions described under physostig-

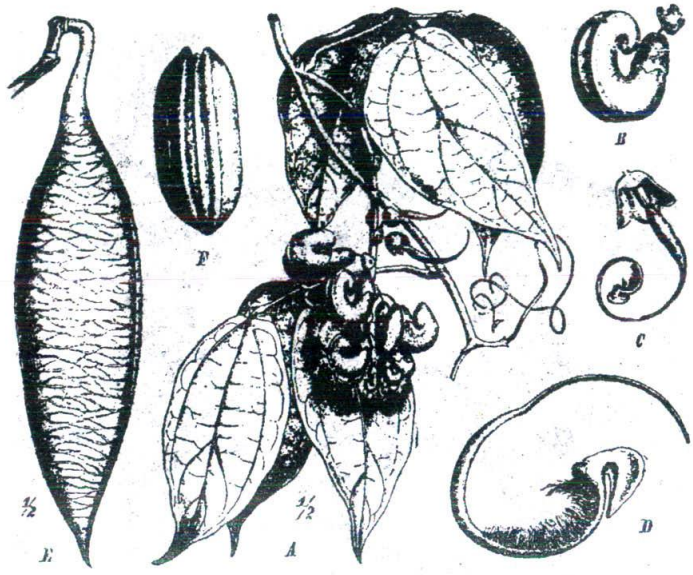
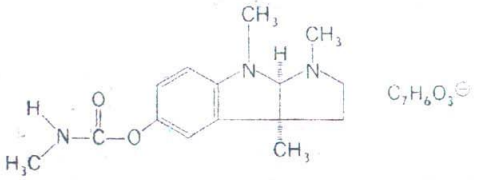


Fig. 8–21. *Physostigma venenosum*: *A*, flowering branch; *B*, a single flower; *C*, flower showing ovary and part of the calyx; *D*, enlarged view of style and stigma; *E*, legume; *F*, seed. (After Bentley and Trimen.)

mine. It also should be preserved in tight, light-resistant containers in quantities not exceeding 1 g.



Physostigmine Salicylate

USES AND DOSE. Physostigmine salicylate is a cholinergic (ophthalmic) and is administered topically, 0.1 ml of a 0.25 to 0.5% solution, to the conjunctiva 1 to 4 times a day. Because it prolongs and exaggerates the effect of acetylcholine, physostigmine salicylate is given by injection as an antidote in poisonings caused by anticholinergic agents.

PRESCRIPTION PRODUCTS. For ophthalmic use, Isopto Eserine®; for poisoning antidote, Antilirium®.

Physostigmine sulfate or eserine sulfate is the sulfate of the alkaloid, physostigmine. This white, microcrystalline powder is deliquescent in moist air and acquires the red tint previously described. Storage requirements are the same as for physostigmine and physostigmine salicylate. It is a cholinergic (ophthalmic) used in the form of a 0.25% ointment that is applied topically to the conjunctiva up to 3 times a day.

Ergot

Ergot, rye ergot, or secale cornutum was formerly defined in the official compendia as the dried sclerotium of *Claviceps purpurea* (Fries) Tulasne (Fam. Clavicipitaceae) developed on plants of rye, *Secale cereale* Linné (Fam. Gramineae). Ergot was required to yield not less than 0.15% of the total alkaloids of ergot calculated as ergotoxine and water-soluble alkaloids equivalent to not less than 0.01% of ergonovine.

The generic name, *Claviceps*, refers to the clublike character of the sclerotium; *purpurea* refers to its purple color. Because these sclerotia are long and somewhat pointed, the common name of **spurred rye** has been applied to the drug.

Because galenic preparations of the crude drug are seldom employed in pharmacy in this country, ergot has been omit-

ted from the official compendia. Nevertheless, its alkaloids continue to enjoy widespread use as extremely important medicinal agents. It therefore appears worthwhile to redefine, in light of modern knowledge, the source of these active compounds.

At present, ergot alkaloids are obtained on a commercial scale from both parasitic and saprophytic sources. The former is the dried sclerotium of *C. purpurea* developed on rye plants. Some alkaloids are also obtained from the fermentation broth in which the mycelium of selected strains of *Claviceps paspali* Stevens & Hall has been grown saprophytically in submerged culture.

The qualitative and quantitative composition of the alkaloids obtained from either source is influenced by a number of factors, but especially by the identity of the strain (chemical race) of organism involved. At present, both peptide alkaloids and nonpeptide (water-soluble) alkaloids are obtained from parasitically developed ergot sclerotia. Only the latter type is produced commercially in saprophytic culture. However, lysergic acid produced by fermentation is converted on a commercial scale to the peptide alkaloid, ergotamine, by chemical semisynthesis.

In the absence of official standards, the word, **ergot**, may be used in a variety of ways to describe either one or more species of *Claviceps*, the mycelium produced by these species in saprophytic culture, or the resting body (sclerotium) of the fungus produced parasitically on rye plants. When the crude drug ergot is referred to in this book, it designates the latter product.

Some knowledge of the rather complex life cycle of the ergot fungus is required to understand the different methods of production of the alkaloids. In nature, the organism is parasitic. In the spring, one of its spores comes into contact with the ovary of a grass, frequently rye, where it germinates, forming hyphal strands that penetrate into the host tissue. The hyphae eventually form a mass of tissue known as a **mycelium**, which supplants the ovary. Some of the hyphal strands produce asexual spores, known as conidiospores, which become suspended in a viscous, sugary liquid, known as honeydew. Honeydew is secreted by the mycelium. Insects are attracted to this honeydew and carry it and the spores to other host plants, where the process is repeated. This stage of development of the organism is termed the asexual or **sphacelial stage.**

In the second stage of development, the mycelium eventually replaces the entire ovary, then gradually hardens, becomes dark purple, and forms a resting body, known as a **sclerotium** (Fig. 8–22). The sclerotium, in turn, normally falls to the ground, overwinters, and, in the spring, produces sexual spores or ascospores that repeat the entire cycle. This second phase of development of the organism is referred to as the sexual or **ascigerous stage.**

When ergot spores are germinated in a suitable nutrient medium in the laboratory (saprophytic growth), hyphae are formed. The hyphae produce mycelium and conidiospores, but no further development occurs. Because the medicinally useful alkaloids are normally produced only during the latter stages of parasitic sclerotial development, the difficulties in producing them in saprophytic mycelial culture are apparent.

Before the introduction of modern agricultural practices, the fungus periodically invaded rye fields in Russia and in other European countries, and the ergot sclerotia were harvested with the rye grains. Rye flour made from the contaminated rye grains was subsequently made into rye bread and ingested. Thus, the fungus was responsible for severe outbreaks of a disease, both in humans and in cattle, which is today known as ergotism. Two distinct types are recognized. One, common in parts of France, was characterized by the appearance of gangrene in the extremities. The gangrene was caused by the restricted

Fig. 8–22. Ergot sclerotia developed in heads of the rye plant.

blood flow resulting from the vasoconstrictor action of the ergot alkaloids. The second type, which frequently occurred east of the Rhine in Germany, was characterized by convulsions. Although the factors responsible for the different types of ergotism have not been completely clarified, it is believed that the convulsive variety is associated with a dietary deficiency of vitamin A. Before the causative agent was known, gangrenous ergotism was often referred to as "St. Anthony's fire." As early as 1582, the drug was known to promote uterine contractions.

Originally, the main sources of supply for ergot were Spain, Russia, and the Balkan countries; however, Russia (the Soviet Union) and the Balkans export little ergot today. Because of the currency exchange, much of the Spanish ergot is exported through Portugal. Currently, ergot is cultivated in Czechoslovakia, Germany, Hungary, and Switzerland. Entire fields of rye are utilized for this purpose. Prior to fertilization, the flowers of the plants are artificially inoculated with conidiospores of *Claviceps purpurea*. Different types of inoculative apparatus are employed. A small (15 cm × 15 cm), hand-operated puncture board studded with eyed or grooved

needles that are dipped into a spore suspension before application to the rye inflorescence is the simplest device but requires an adequate supply of inexpensive labor. The same principle is utilized in motor-driven machines with needle-studded inoculating rollers that are mounted on the front of tractors and are capable of inoculating 5 to 7 acres of rye per day.

Cultured conidiospores are utilized for the inoculum. Much effort has been devoted to the isolation, development, and selection of the best strains of *C. purpurea* for field cultivation. Strains capable of producing about 0.35% of selected alkaloids, principally ergotamine, are now employed.

Approximately 6 weeks after inoculation, the mature sclerotia are harvested. They may be picked by hand or collected by machines developed especially for this purpose in Hungary and Germany. Sclerotia not collected in these ways can be harvested with the grain and separated after threshing by sieving, by specific gravity, or by electrostatic attraction processes. Ergot must be dried immediately after collection and stored properly to prevent deterioration.

The yield of ergot varies considerably, but if the weather has been reasonably favorable and the cultivation has been done well, the yield amounts to 30 to 100 kg or more per acre. If performed by hand, labor involved in collecting and harvesting the ergot amounts to at least 6 hours per kg. This may be reduced appreciably by mechanization, but a substantial investment in machinery is then required. These factors, coupled with the present low price and limited market for the crude drug, have discouraged the field cultivation of ergot in the United States. Although ergot is not cultivated on a commercial scale in this country, the electrostatic attraction process is utilized to separate the naturally occurring drug from quantities of grain. The small domestic supply thus obtained is not uniform in quality or quantity.

Successful saprophytic production of ergot alkaloids dates from the monumental work, first published in 1948, of Matazo Abe of the Takeda Pharmaceutical Industries in Japan. The principal alkaloids produced by Abe's strains and by other strains of the fungus subsequently isolated by A. Stoll and his colleagues at the Sandoz Company in Switzerland were found to be new ergoline derivatives. These compounds, although closely related, proved not to be derivatives of lysergic acid and were designated as clavine alkaloids (see Fig. 8–17). Although their discovery furnished great impetus to the scientific investigation of ergot alkaloid production in saprophytic culture, the clavine alkaloids proved disappointing from the pharmacologic and, consequently, from the commercial viewpoint.

Large-scale production of lysergic acid derivatives in submerged culture was finally achieved in 1960 by A. Tonolo, E. B. Chain, and coworkers of the Istituto Superiore de Sanita in Italy. These investigators utilized an artificially virulented strain of *C. paspali* Stevens & Hall, which produced several simple lysergic acid derivatives, especially (+)-lysergic acid methylcarbinolamide, in stirred fermenters containing a suitable medium. Yields reaching up to 6 mg per ml of nutrient medium have been obtained in 7 to 10 days. A United States patent covering this process was assigned by the investigators to Societa Farmaceutici Italia. The alkaloids obtained can be converted to lysergic acid, which is utilized for the semisynthesis of ergonovine and ergotamine.

CONSTITUENTS. Ergot contains or produces a large number of alkaloids, the most important of which are ergonovine, ergotamine, and a mixture of ergocristine, ergokryptine, and ergocornine that has been marketed for many years under the name, ergotoxine. The alkaloids are often separated into 2 groups based on their solubility in water. Ergonovine is the principal component of the water-soluble fraction.

Ergotamine and the ergotoxine group are water-insoluble and are often referred to as peptide alkaloids. Significant semisynthetic alkaloids include methylergonovine, dihydroergotamine, Hydergine®, methysergide, and LSD.

The medicinally useful alkaloids, either natural or semisynthetic, are all derivatives of (+)-lysergic acid. Because that compound is readily converted to its isomer, (+)-isolysergic acid, the corresponding isolysergic acid derivatives often accompany the (+)-lysergic acid alkaloids in the plant material or are produced during the course of extraction. Isolysergic acid derivatives are practically physiologically inert. They are named by inserting an additional syllable, -in, in the name of the corresponding lysergic acid derivatives, e.g., ergotamine-ergotaminine.

In addition to its characteristic alkaloids, ergot contains a large number of other constituents, including several pigments, a fixed oil (up to 35%), and steroids (ergosterol). Two compounds that contribute to the physiologic activity of the crude drug are histamine and tyramine.

STANDARDS AND ASSAY. Ergot contains not more than 8% of moisture. The use of a cartridge of a nonliquefying, inert, dehydrating agent to maintain low humidity in the container of ergot is desirable. Ergot is assayed for its alkaloid content by colorimetric procedures involving the use of *p*-dimethylaminobenzaldehyde.

USE. Ergot is used as a source of ergot alkaloids. In the past, galenic preparations were used for their oxytocic properties.

Ergot Alkaloids

Ergonovine maleate or ergometrine maleate occurs as a white or faintly yellow, odorless, microcrystalline powder. It is affected by light and is readily soluble in water but less soluble in alcohol.

The alkaloid was discovered almost simultaneously in 1935 by 5 independent research groups, and it was assigned 4 different names. To resolve the conflict, a fifth name, ergonovine, was officially adopted in the United States. That title has not been accepted elsewhere. Ergometrine is used in practically all other countries, except Switzerland, where ergobasine is preferred. Establishment of a clear-cut priority is difficult but, based on the first isolation of a pure compound, it probably should be awarded to ergobasine. Even in the United States, the accepted chemical name of the isolysergic acid isomer of ergonovine is ergometrinine.

Because of its ready solubility in water, this alkaloid has marked advantages over the other ergot alkaloids (Fig. 8–23). The oxytocic effect of the drug, either orally, subcutaneously, or intramuscularly, is sometimes noted within 5 minutes after giving the dose, and its effect is more marked than that of either ergotoxine or ergotamine. However, the vasoconstrictor action is much less marked.

USE AND DOSE. Ergonovine maleate is an oxytocic and produces much faster stimulation of the uterine muscles than do other ergot alkaloids. The gravid uterus is very sensitive to this effect, and small doses of alkaloid can be given immediately postpartum to increase the frequency and amplitude of uterine contractions as well as to increase the basal tone of the uterine smooth muscle, resulting in a decrease in blood loss from the postpartum uterus. It exerts its effects by acting as a partial agonist or antagonist at α-adrenergic, dopaminergic, and serotonergic receptors. The usual dose is, orally, 200 to 400 μg, 2 to 4 times a day; intramuscularly or intravenously, 200 μg, repeated after 2 to 4 hours if necessary.

PRESCRIPTION PRODUCT. Ergotrate Maleate®.

Methylergonovine maleate is a semisynthetic homolog of ergonovine prepared from lysergic acid and 2-aminobutanol. It occurs as a white to pinkish tan, microcrystalline powder.

USE AND DOSE. Methylergonovine maleate is an oxytocic reputed to be slightly

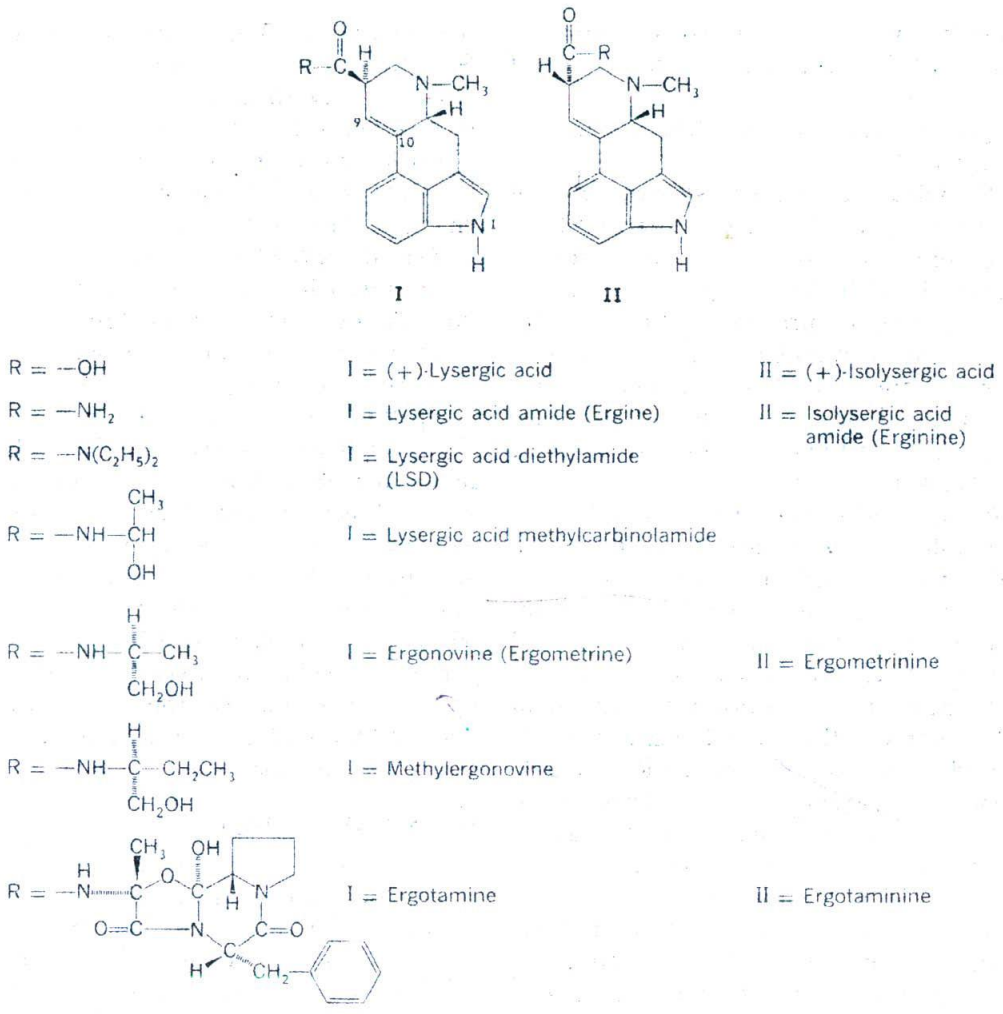


Fig. 8–23. Structural relationships of ergot alkaloids.

more active and longer acting than ergonovine. The usual dose is the same as that for ergonovine.

PRESCRIPTION PRODUCT. Methergine®.

Ergotamine tartrate occurs as colorless crystals or as a white, crystalline powder, sparingly soluble in water or in alcohol. Ergotamine possesses oxytocic properties, but it is not employed for that effect. It is categorized as a specific analgesic in treatment of migraine. Ergotamine reduces extracranial blood flow and decreases the amplitude of pulsations in the cranial arteries that have been associated with migraine. It may inhibit receptor uptake of norepinephrine at sympathetic nerve endings, increasing the vasoconstrictive action. The usual dose is, sublingually, 2 mg, then 2 mg every 30 minutes, if necessary, to a total of 6 mg per 24 h; do not exceed 10 mg per week. The patient should be advised to initiate therapy at onset of the attack and to lie down in a quiet and darkened room for 2 hours after taking the medication.

PRESCRIPTION PRODUCTS. Ergomar®, Ergostat®, Medihaler Ergotamine®.

Ergotamine tartrate is used with caffeine for the treatment of migraine headache.

Both act as cerebral vasoconstrictors; caffeine is believed to enhance the action of ergotamine.

PRESCRIPTION PRODUCTS. Cafergot®, Wigraine®.

Dihydroergotamine mesylate is the salt of a semisynthetic alkaloid prepared from ergotamine by hydrogenation of the Δ^9 double bond in the lysergic acid nucleus. Dihydroergotamine is employed in the treatment of migraine because it is more effective and better tolerated than the parent alkaloid. The usual dose is, parenterally, 1 mg, and may be repeated at 1-hour intervals up to 3 mg.

PRESCRIPTION PRODUCT. D.H.E. 45®.

Ergotoxine was formerly employed as a reference standard in the form of ergotoxine ethanesulfonate, which was discontinued because it was a variable mixture of 3 closely related alkaloids, ergocristine, ergokryptine, and ergocornine. A mixture of equal parts of these component alkaloids is hydrogenated to eliminate the Δ^9 double bond of the lysergic acid nucleus and to yield an equivalent mixture of dihydroergocristine, dihydroergokryptine, and dihydroergocornine. The methanesulfonates of this mixture, known as **ergoloid mesylates,** are marketed for the treatment of selected symptoms in elderly patients. They produce vasorelaxation, increased cerebral blood flow, lowering of systemic blood pressure, and bradycardia. The usual dose is, orally or sublingually, 1 mg 3 times a day.

PRESCRIPTION PRODUCTS. Hydergine®, Hydroloid-G®.

Methysergide maleate is the salt of methylergonovine that has an additional methyl group attached to the nitrogen at position 1 of the lysergic acid nucleus. It is prepared by semisynthesis from lysergic acid. Methysergide is a serotonin antagonist employed in the prophylaxis of vascular headache. The usual dose is, orally, 4 to 8 mg daily in divided doses. Time of continuous administration should not exceed 6 months, and there must be a drug-free interval of 3 to 4 weeks after each 6-month course of treatment.

The patient should be advised to take medication with meals and to notify the physician if cold, numb, or painful hands, leg cramps, abdominal or chest pain, or change in skin color occurs.

PRESCRIPTION PRODUCT. Sansert®.

Lysergic acid diethylamide or LSD does not occur in nature but is prepared by semisynthesis. The compound has a 2-fold action, producing a predominant central sympathetic stimulation that parallels a slight depression. Discovered by A. Hofmann in 1943 during the course of experiments directed toward the synthesis of analeptics, it is the most active and most specific psychotomimetic agent known. The effective oral dose in humans is 30 to 50 μg. LSD is of considerable interest and value in experimental psychiatry. Because of widespread misuse, the drug is available, at this writing, only to qualified scientific investigators.

Drugs Related to Ergot

The active principles of **ololiuqui,** an ancient Aztec hallucinogenic drug still used in Mexico for magicoreligious purposes, have been identified as ergot alkaloids. Seeds of ololiuqui, *Rivea corymbosa* (Linné) Hallier filius (Fam. Convolvulaceae), as well as certain closely related *Ipomoea* species (commonly known as morning glories) and *Argyreia* species, contain up to about 0.05% of total alkaloids. (+)-Lysergic acid amide (ergine), the principal psychotomimetic compound in these species, is accompanied by (+)-isolysergic acid (erginine), ergonovine, (+)-lysergic acid methylcarbinolamide, and certain clavine alkaloids.

Many of these morning glories are widely cultivated ornamentals. The ready availability of their seeds has led to misuse by thrill-seeking teenagers and adults who ingest the seeds to experience hallucinations. Needless to say, the practice is dangerous because of the extreme potency of the active principles.

Occurrence of the biosynthetically complex ergot alkaloids in both fungi and higher plants is unusual and of considerable chemotaxonomic interest. Aside from *Claviceps* species and the members of the Convolvulaceae, ergot alkaloids have been reported only in a few other fungi—*Aspergillus fumigatus* Fres., *Penicillium chermesinum* Biourge, *Penicillium roquefortii* Thom, *Rhizopus arrhizus* Fischer and *Sphacelia typhina*. Only clavine alkaloids were detected in these latter species.

IMIDAZOLE ALKALOIDS

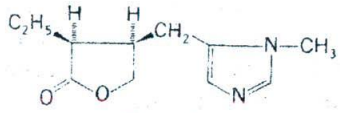
The imidazole (glyoxaline) ring is the principal nucleus in pilocarpine from pilocarpus. Pilocarpine is a monoacidic tertiary base containing a lactone group as well as the imidazole nucleus. Obvious structural similarities suggest that this alkaloid probably is formed from histidine or a metabolic equivalent, but experimental confirmation of such a biosynthetic origin is lacking.

Pilocarpus and pilocarpine are the important drugs of this group.

Pilocarpine

Pilocarpus or jaborandi consists of the leaflets of *Pilocarpus jaborandi* Holmes (Pernambuco jaborandi), of *P. microphyllus* Stapf (Maranham jaborandi), or of *P. pinnatifolius* Lamaire (Paraguay jaborandi) (Fam. Rutaceae). The plants are shrubs indigenous to Brazil.

All of the commercial kinds of pilocarpus, when freshly dried, yield from 0.5 to 1% of the alkaloid pilocarpine. Isopilocarpine, pilocarpidine, and pilosine are also present in some of the species. Even under ideal storage conditions, the leaves lose at least half of their alkaloidal content in 1 year through deterioration. Leaves that are 2 years old are practically worthless.



Pilocarpine

Pilocarpine is the lactone of pilocarpic acid, an acid with a glyoxaline nucleus. It is an oily, syrupy liquid, though its salts crystallize easily. It may be obtained by treating the powdered leaves with sodium carbonate, extracting with benzene, and then shaking the benzene extract with dilute hydrochloric or nitric acid. The aqueous solution is then made alkaline and shaken with chloroform; the chloroform solution is then shaken with acid, and the alkaloidal salt is allowed to crystallize.

Pilocarpine directly stimulates the muscarinic receptors in the eye, causing constriction of the pupil and contraction of the ciliary muscle. In narrow-angle glaucoma, miosis opens the anterior chamber angle to improve the outflow of aqueous humor. In chronic open-angle glaucoma, the increase in outflow is independent of the miotic effect. Contraction of the ciliary muscle enhances the outflow of aqueous humor via indirect effects on the trabecular system.

Pilocarpine hydrochloride is the hydrochloride of an alkaloid obtained from the dried leaflets of *Pilocarpus jaborandi* or of *P. microphyllus*. It is hygroscopic.

Pilocarpine nitrate is the nitrate of the alkaloid. It is stable in air but is affected by light.

Pilocarpine hydrochloride occurs as colorless, translucent, odorless, faintly bitter crystals; pilocarpine nitrate occurs as shiny, white crystals.

USE AND DOSE. Both pilocarpine hydrochloride and pilocarpine nitrate are cholinergic (ophthalmic) drugs used in the treatment of glaucoma. They are applied topically, 0.05 to 0.1 ml of a 0.25 to 10% solution of pilocarpine hydrochloride or of a 0.5 to 6% solution of pilocarpine nitrate to the conjunctiva, 1 to 6 times a day. The patient should be advised to wash hands immediately after application. Pilocarpine

is also available in an ocular therapeutic system that provides continuous release over one week following placement in the conjunctival cul-de-sac.

PRESCRIPTION PRODUCTS. Pilocarpine hydrochloride is an ingredient in Pilocel®, Adsorbocarpine®, Pilocar®, Almocarpine®, Ocusert Pilo®, and Isopto Carpine®.

STEROIDAL ALKALOIDS

The steroidal alkaloids are characterized by the cyclopentanophenanthrene nucleus. They apparently are either formed from cholesterol, or they and cholesterol have a common precursor. The results of preliminary tracer experiments are consistent with this idea.

The important drugs and their alkaloids of this group are veratrum viride and veratrum album.

Veratrum Viride

Veratrum viride, American or green hellebore, consists of the dried rhizome and roots of *Veratrum viride* Aiton (Fam. Liliaceae) (Fig. 8–24).

Veratrum is from the Latin *vere,* meaning truly, and *ater,* meaning black. *Viride* is Latin and means green. The plant grows in wet meadows in the mountainous section of New England and the eastern United States, North Carolina, Tennessee, and northern Georgia. Most of the commercial drug is collected in New York State and eastern Canada. The rhizomes are dug, cleaned, cut longitudinally, and dried. The drug was known to the Indians,

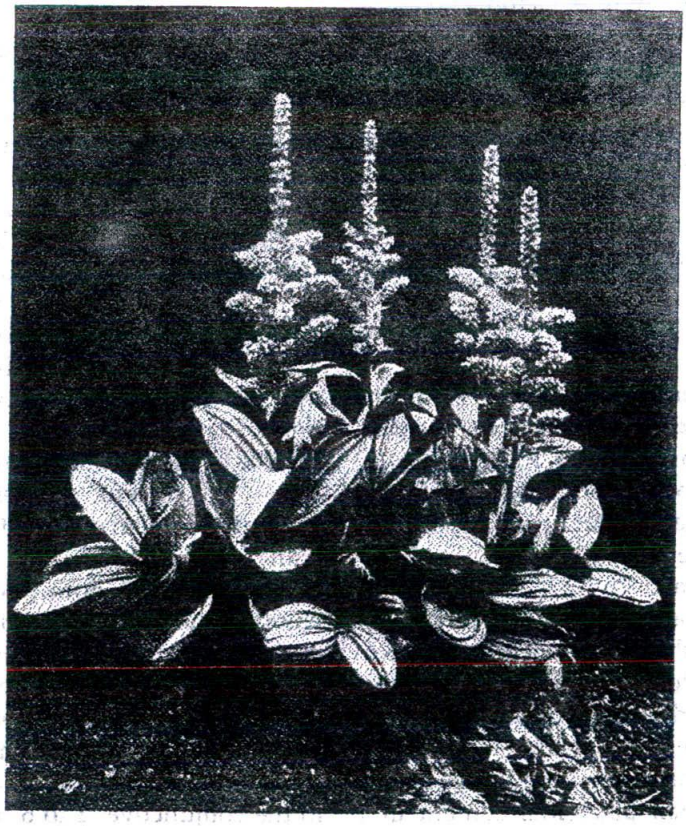


Fig. 8–24. Plants of *Veratrum viride* growing in the Royal Botanic Society's Gardens (London) and showing the parallel-veined leaves with entire margin and the large terminal panicles of flowers.

who probably introduced its use to the early settlers.

Veratrum viride contains a large number of alkaloids customarily classified in 3 groups on the basis of their chemical constitution. Group I, consisting of esters of the steroidal bases (alkamines) with organic acids, includes cevadine, germidine, germitrine, neogermitrine, neoprotoveratrine, protoveratrine, and veratridine. Group II includes pseudojervine and veratrosine, which are glucosides of the alkamines. The alkamines themselves—germine, jervine, rubijervine, and veratramine—compose group III. The ester alkaloids, germidine and germitrine, are probably the most important therapeutically. The complexity and relative instability of these constituents account for the problems encountered in the biologic standardization of this drug.

USES. Veratrum viride possesses hypotensive, cardiac-depressant, and sedative properties. It has been used in the treatment of hypertension. Small doses principally affect blood pressure without notably changing respiratory or cardiac rate. The drug has its most uniform effects in small doses.

Veratrum viride, in the form of the tincture, was used for many years by American physicians as a cardiac depressant. This form of medication was abandoned when a study of the alkaloids demonstrated their hypotensive properties.

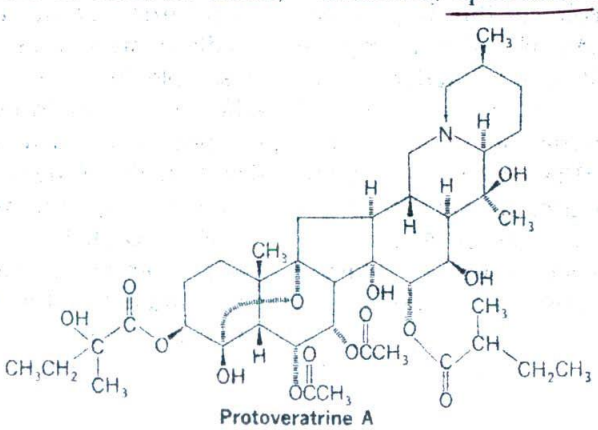
White hellebore or European hellebore is the dried rhizome of *Veratrum album*, Linné (Fam. Lilaceae). It is similar to *V. viride* but is indigenous to central and southern Europe. White hellebore is similar in appearance and structure to green hellebore, but the external color is much lighter.

The drug contains a complex mixture of ester alkaloids, glycoalkaloids, and alkamines similar, and in some cases identical, to those occurring in veratrum viride. Two ester alkaloids, protoveratrine A and protoveratrine B, are the most active. On hydrolysis, both yield protoverine, acetic acid, methylbutyric acid, and methylhydroxybutyric acid (in protoveratrine A) or methyldihydroxybutyric acid (in protoveratrine B).

USES. White hellebore possesses hypotensive properties, but the crude drug is not used therapeutically. Both white and green hellebores are also employed as insecticides.

ALKALOIDAL AMINES

The alkaloids in this group do not contain heterocyclic nitrogen atoms. Many are simple derivatives of phenylethylamine and, as such, are derived from the common amino acids, phenylalanine or tyrosine. Some of the alkaloids in this category whose biosynthesis has been studied utilizing labeled precursors include hordenine in barley *(Hordeum vulgare)*, mescaline in the peyote cactus *(Lophophora williamsii)*, ephedrine in *Ephedra distachya*,



Protoveratrine A

cathinone in the khat plant *(Catha edulis)*, and colchicine in the autumn crocus *(Colchicum autumnale)*.

Ring A and carbon atoms 5, 6, and 7 of colchicine derive from the phenylalanine-cinnamic acid pathway in *Colchicum* species (Fig. 8–25). Tyrosine cannot replace phenylalanine as a precursor for this part of the molecule. Radioactivity from tyrosine-3-^{14}C is incorporated into the C-12 position of the tropolone ring. Many of the details of the biosynthetic pathway are unknown; a phenethylisoquinoline intermediate is suspected, and androcymbine also occurs in *Colchicum*. Labeled acetate is readily incorporated into the acetyl group of the molecule, presumably during a terminal phase of biosynthesis.

Other alkaloidal amines are tryptamine derivatives and, as such, are biosynthesized from tryptophan. Examples include gramine in *Hordeum vulgare*, psilocybin in the Mexican hallucinogenic mushroom, *Psilocybe semperviva*, and serotonin and bufotenine in a number of plant and animal species.

The drugs and their alkaloids classified as alkaloidal amines are ephedra, ephedrine, colchicum seed, colchicum corm, colchicine, khat, and peyote.

Ephedrine

Ephedra or ma huang is the entire plant or the overground portion of *Ephedra sinica* Stapf (Fam. Gnetaceae). In Chinese characters, "ma" means astringent and "huang" means yellow, probably referring to the taste and color of the drug. It has been used as a medicine in China for more than 5000 years. Its use in modern medicine began in 1923 with the discovery of the valuable properties of ephedrine. The plant is found near the seacoast in southern China, and this source formerly supplied most of the American market. At the present time, northwestern India and Pakistan represent the areas from which ephedra is obtained.

The plant is a low, dioecious, practically lealfless shrub that grows 60 to 90 cm high. The stem is green, slender, erect, small ribbed and channeled. It is 1.5 mm in diameter and usually terminates in a sharp point. At the nodes, which are 4 to 6 cm apart, the leaves appear as whitish, triangular, scarious sheaths. Small blossoms appear in the summer.

Ephedrine or (−)-*erythro*-α-[1-(methylamino)ethyl]benzyl alcohol is an alkaloid produced commercially either by the extraction of plant material (*Ephedra* spp.) or by a chemical procedure involving a reductive condensation between L-1-phenyl-1-acetylcarbinol and methylamine (Fig. 8–26). This yields L-ephedrine essentially free from the D-isomer. The carbinol precursor used in the reaction is produced biosynthetically by the fermentative action of brewer's yeast on benzaldehyde.

Studies indicate that the reaction involves the dismutation of pyruvic acid to lactic acid and acetyl-CoA which, in turn, condenses with benzaldehyde to yield L-1-phenyl-1-acetylcarbinol.

An undesirable by-product of the fermentation process is benzyl alcohol, which is produced as a result of competition for the benzaldehyde by the carbinol synthesizing system and another enzyme, alcohol dehydrogenase. Addition of structural analogs of nicotinamide to the fermentation medium appreciably reduces benzyl alcohol production. These probably function by competing with NAD for its enzyme site because $NADH_2$ is required as the H^+ donor in the reductive reaction.

Ephedrine occurs as white, rosette or needle crystals, or as an unctuous mass. It is soluble in water, alcohol, chloroform, ether, and in liquid petrolatum. The latter solution is turbid if the ephedrine is not dry. Ephedrine melts between 33 and 40° C, depending on its water content.

USES AND DOSE. Ephedrine is a potent sympathomimetic that stimulates alpha, $beta_1$, and $beta_2$ adrenergic receptors. It excites the sympathetic nervous system, causes vasoconstriction and cardiac stim-

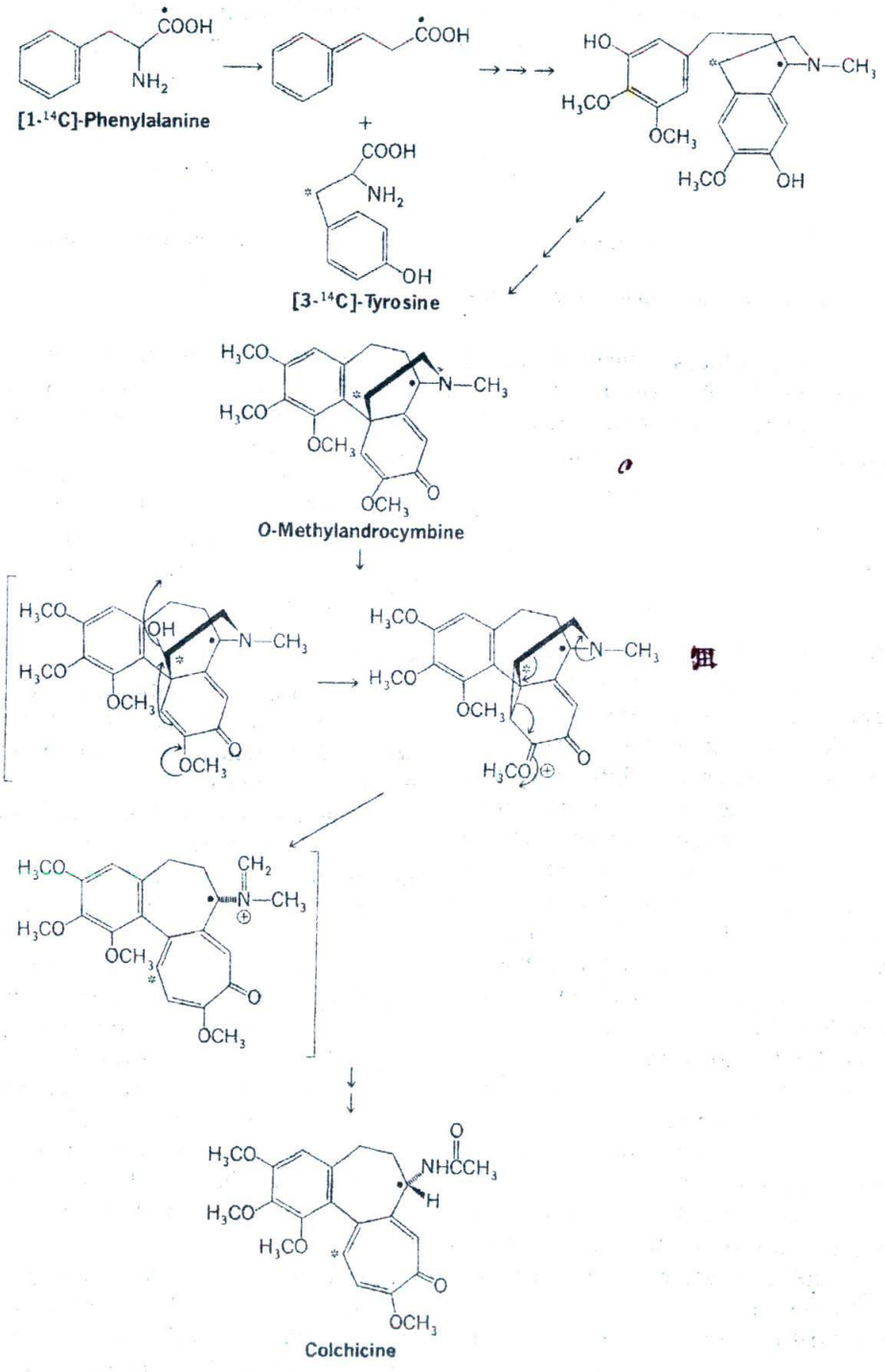


Fig. 8–25. Biosynthetic incorporation of phenylalanine and tyrosine into colchicine.

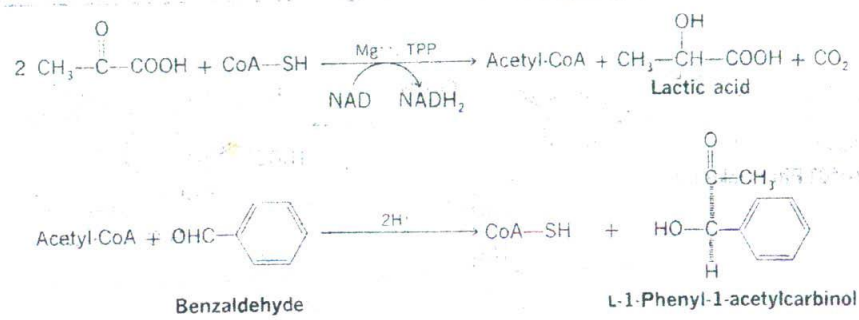
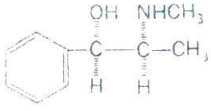


Fig. 8–26. Biosynthesis of L-1-phenyl-1-acetylcarbinol.

ulation, and produces effects similar to those of epinephrine. It produces a rather lasting rise in blood pressure, causes mydriasis, and diminishes hyperemia.



(−)-Ephedrine

Ephedrine sulfate is the sulfate of the alkaloid obtained from the natural sources or prepared synthetically. It occurs as fine, white, odorless crystals or as a powder and darkens when exposed to light. Ephedrine sulfate is used to combat hypotensive states and for allergic disorders, such as bronchial asthma, as well as for local treatment of nasal congestion. The usual dose is, orally or parenterally, 25 to 50 mg, 6 to 8 times a day, as necessary. For external use, intranasally, 0.1 to 0.15 ml of a 1 to 3% solution, 2 or 3 times a day.

Ephedrine hydrochloride also occurs as fine, white, odorless crystals or as a powder and is affected by light.

It has the same pharmacologic properties as ephedrine and is used as a sympathomimetic. The usual dose is 25 to 50 mg, every 3 to 4 hours. Both of these salts are readily soluble in water and in hot alcohol but not in ether.

PRESCRIPTION PRODUCTS. Ephedrine salts are ingredients in the following products: Dainite KI®, Quadrinal®, Tedral®, Bronkotabs®, Bronkaid®, and many others.

ALLIED PLANTS. In addition to *Ephedra sinica* (the source of ma huang) and *E. equisetina* Bunge (the chief source of the extracted alkaloid), *E. distachya* Linné also yields ephedrine. These plants grow in northern China, India, and Spain in sandy and clay soil. Attempts to grow the plants in the United States, particularly in the Dakotas, were successful but not economically feasible.

Colchicine

Colchicum seed is the dried, ripe seed of *Colchicum autumnale* Linné (Fam. Liliaceae). **Colchicum corm** is the dried corm of the same species.

The genus name is from Colchis on the Black Sea, where the plant flourishes; *autumnale* refers to the season when the plant blooms. The plant is cultivated in England, central and southern Europe, and northern Africa, where it grows in moist meadows. It is also cultivated as an ornamental in the United States. Two to six flowers with long perianth tubes develop from the corm buds in the fall (hence, the name **autumn crocus**). The seed is collected in July and August and the corm in the spring before leaf development. Italy and Yugoslavia produce most of the supply of the seed and the corm.

Dioscorides mentions a *Colchicum*. The Arabs recommended the use of the corm for gout in medieval times, but the drug was abandoned because of its toxicity. It again came into use in Europe about the middle of the 17th century.

Colchicum contains the alkaloid colchi-

cine, up to 0.8% in the seed and 0.6% in the corm.

USE. Colchicum is a source of colchicine.

Colchicine is an alkaloid obtained from various species of *Colchicum*, usually *Colchicum autumnale*. It has also been found in other genera of the lily family. Colchicine has one amido nitrogen atom. The compound lacks pronounced basicity and does not form a well-defined series of salts as do other alkaloids. Nevertheless, it is precipitated by many alkaloid reagents and is conventionally considered an alkaloid. (See Fig. 8–25 for the structural formula.)

Colchicine occurs as pale yellow, amorphous scales or powder that gradually turns darker when exposed to light. It is soluble in water and ether and is freely soluble in alcohol and chloroform.

The exact mechanism of action of colchicine in the treatment of gout is not known. It does inhibit leukocyte migration and reduces lactic acid production by leukocytes which results in a decreased deposition of uric acid. In addition, there is a reduction in phagocytosis which decreases the inflammatory response.

USE AND DOSE. Colchicine is used as a suppressant for gout. The usual prophylactic dose is, orally, 500 to 650 μg, 1 to 3 times a day; intravenously, 500 μg to 1 mg, 1 or 2 times a day.

PRESCRIPTION PRODUCTS. Colchicine is combined with probenecid in the following: ColBenemid®, Colabid®, and Proben-C®.

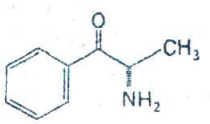
The use of colchicine to double chromosomes has opened a large field in plant genetics. Any numeric change in chromosome number entails a mutation that becomes evident in a number of the characteristics of the experimental plant. New varieties of plants of economic and pharmacognostic value may result from further research. The interrelationship between the action of colchicine and mitosis is being investigated in animals; preliminary experiments show that injections of colchicine can affect the dispersal of tumors; thus, it has been employed experimentally in the treatment of various neoplastic diseases.

Other Alkaloidal Amine Drugs

Khat or Abyssinian tea consists of the fresh leaves of *Catha edulis* Forskal (Fam. Celastraceae). The plant is a small tree or shrub native to tropical East Africa. It is cultivated extensively in the Ethiopian highlands near Harar and to a lesser extent in other parts of East Africa, in South Africa, and in Yemen. Fresh leaves are regularly transported by air to areas distant from the centers of cultivation.

The leaves are chewed habitually by many people in East Africa and the Arabian countries to alleviate the sensations of hunger and fatigue. Authorities disagree as to the safety of the practice. The Expert Committee on Addiction-Producing Drugs of the World Health Organization does not classify khat as a drug that produces habituation or addiction, but the French government considers it a narcotic. Regardless, khat-chewing is a theologically accepted and lawful custom in Arabian and African countries today.

Khat contains a potent phenylalkylamine alkaloid called (−)-cathinone. It has pharmacologic properties analogous to those of (+)-amphetamine and is of similar potency with a similar mechanism of action, namely, the induction of catecholamine release from storage sites. The young, fresh leaves that come from the tips of the branches contain the optimum amount of cathinone. In older leaves, it is converted to the weakly active compounds (+)-norpseudoephedrine (80%) and (−)-norephedrine (20%). This conversion also occurs rapidly during the drying of young leaves.



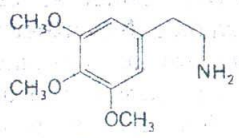
(−)-Cathinone

Fig. 8–27. *Lophophora williamsii:* top view of flowering plant. (Photo courtesy of Dr. J.L. McLaughlin, Department of Medicinal Chemistry and Pharmacognosy, Purdue University.)

Peyote or mescal buttons consist of the dried tops of *Lophophora williamsii* (Lemaire) Coulter (Fam. Cactaceae), growing in northern Mexico and the southwestern United States (Fig. 8–27). The main axis of the plant lies beneath the ground, and from it arise a number of aerial shoots that are button-shaped or disklike and reach 20 to 50 mm in diameter. In the center of each disk are a tuft of hairs and usually one or more pink flowers.

This plant has been associated with Indian ceremonies for many years. It disturbs normal mental function and causes concomitant hallucinations and euphoria. Ingestion of mescal buttons results in mydriasis accompanied by unusual and bizarre color perception. Flashing lights and vivid configurations characterize the visions at first; later, the colors become dim and the subjects become drowsy; eventually, sleep is produced.

The drug contains several alkaloids, including mescaline (the most active of the peyote constituents), anhalanine, anhalamine, and anhalidine. Mescaline (3,4,5,-trimethoxy-β-phenylethylamine) also occurs in other cacti, e.g., *Trichocereus* species, or it may be produced synthetically.



Mescaline

Mescaline is regarded as the first of a series of hallucinogens or psychotomimetics. Others are psilocybin (obtained from the mushroom *Psilocybe mexicana* Heim) and lysergic acid diethylamide (LSD). All of these drugs have proved valuable in experimental psychiatry.

PURINE BASES

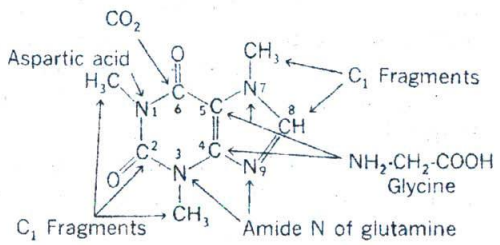
The purines are derivatives of a heterocyclic nucleus consisting of the 6-membered pyrimidine ring fused to the 5-membered imidazole ring. Purine itself does not occur in nature, but numerous derivatives are biologically significant. The pharmaceutically important bases of this group are all methylated derivatives of 2,6-dioxypurine (xanthine). Caffeine is 1,3,7-trimethylxanthine, theophylline is 1,3-dimethylxanthine, and theobromine is 3,7-dimethylxanthine (see page 247).

The methylxanthines competitively inhibit phosphodiesterase, which results in an increase of cyclic adenosine monophosphate with a subsequent release of endogenous epinephrine. This results in a direct relaxation of the smooth muscles of the bronchi and pulmonary blood vessels, a stimulation of the central nervous system, an induction of diuresis, an increase in gastric acid secretion, an inhibition of uterine

contractions, and a weak positive chronotropic and inotropic effect on the heart.

Caffeine is synthesized from the same precursors in *Coffea arbacia* as are the purine bases in all other biologic systems that have been investigated. Carbon atoms 2 and 8 derive either from formate or from any compound that can give rise to an active 1-carbon fragment (serine, glycine, formaldehyde, and methanol). These same compounds, as well as methionine, are active precursors of the *N*-methyl groups of the molecule. Carbon atom 6 is derived from carbon dioxide, and carbons 4 and 5, together with the nitrogen at 7, are derived from glycine. The nitrogen atom at position 1 derives from aspartic acid, but those in positions 3 and 9 originate from the amide nitrogen of glutamine.

The drugs of this group are coffee, caffeine, guarana, kola, maté, tea, theophylline, cocoa, and theobromine.



Caffeine

Caffeine-Containing Drugs

Kola, cola, or kolanuts is the dried cotyledon of *Cola nitida* (Ventenat) Schott et Endlicher, or of other species of *Cola* (Fam. Sterculiaceae). It yields not less than 1% of anhydrous caffeine. Kolanut is important because of its caffeine content and its flavor. Its principal use in the United States is in the manufacture of nonalcoholic beverages. In the tropical countries where it grows, the fresh nut is chewed as a stimulant, similar to the betel nut (see page 190), *C. nitida* is a large tree indigenous to West Africa between Sierra Leone and the Congo. It is also cultivated in East Africa, Sri Lanka, Indonesia, Brazil, and the West Indies, particularly in Jamaica. The commercial supplies come chiefly from cultivated plants that grow in West Africa and in the West Indies.

Kola nuts in Jamaica are harvested twice a year when the pods ripen (May and June and again in October and November). The chocolate-colored pods, which range from 5 to 10 cm in length, are shaken from the tree and gathered immediately. The seeds are removed from the pods, and the outer coat is cut off, exposing the bare cotyledons. These cotyledons are then carefully graded because only sound cotyledons do not deteriorate quickly. Fresh kolanuts tend to mold and spoil rather easily; they must be transported to the markets quickly for local consumption. Kolanuts prepared for shipment to the United States are split in half, dried in the sun, and shipped in bags.

Kolanuts contain caffeine, up to 3.5%, and theobromine, less than 1%. In the fresh nuts, these purine derivatives are bound to the tannin, kolacatechin. During the drying process, the complex is split, yielding free caffeine and theobromine and converting the colorless kolacatechin to the red-brown kola red.

USE. Kola possesses the central stimulating action of caffeine. It is an ingredient in several carbonated beverages.

Coffee bean or coffee seed is the dried, ripe seed of *Coffea arabica* Linné or *C. liberica* Hiern (Fam. Rubiacae), deprived of most of the seed coat.

Roasted coffee is coffee roasted until it acquires a dark brown color and develops the characteristic aroma.

The plants are small evergreen trees or shrubs with lanceolate, acuminate, entire, slightly coriaceous, dark green, short petiolate leaves, which are partly united with the short interpetiolar stipules at the base. The name *Coffea* is from the Turkish *qahveh* or the Arabic *qahuah*, the name of a beverage. The coffee plant is indigenous to Ethiopia and other parts of eastern Africa

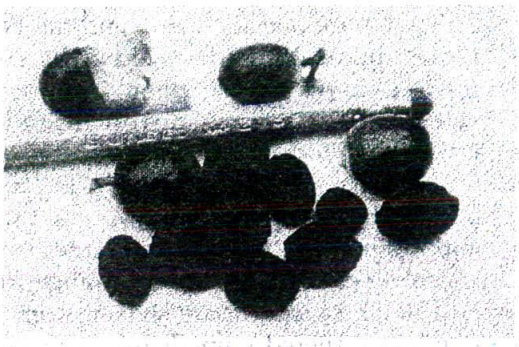


Fig. 8–28. Roasted coffee beans occupy the foreground. Behind them are fresh coffee fruits, one of which has been opened to show the 2 contained seeds or beans. (Photo courtesy of Dr. Jerry L. McLaughlin.)

and is widely cultivated in tropical countries, notably in Indonesia, Sri Lanka, and Central and South America, particularly Brazil. More than 600,000 tons are produced annually in the latter country. The yield from one tree is between 0.5 and 5 kg.

The fruit is a small spheroidal or ellipsoidal drupe with 2 locules, each containing one seed or coffee bean (Fig. 8–28). There are 2 methods of freeing the seeds from the parchmentlike endocarp: (1) the fruits are allowed to dry and are then broken, and (2) the wet method in which the sarcocarp is removed by means of a machine, and the 2 seeds with the parchmentlike endocarp are allowed to dry in such a manner as to undergo a fermentation; after drying, the endocarp is removed. The green seeds are sent into commerce and roasted.

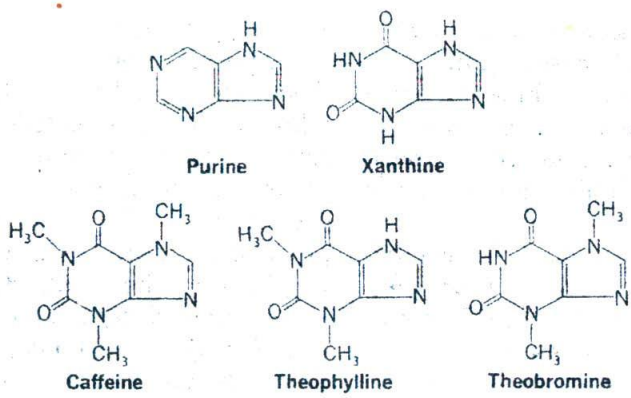
Coffee seeds contain from 1 to 2% of caffeine; about 0.25% of trigonelline (*N*-methylbetaine of nicotinic acid); from 3 to 5% of tannin; about 15% of glucose and dextrin; 10 to 13% of a fatty oil consisting chiefly of olein and palmitin; and 10 to 13% of proteins. They yield 4 to 7% of total ash, nearly all of which is acid-soluble.

When the coffee is roasted, the seeds swell, change in color to dark brown, and develop the characteristic odor and flavor. The aroma is caused by an oil known as caffeol, consisting of about 50% furfurol with traces of valerianic acid, phenol, and pyridine. It is produced during the roasting process. At the same time, the caffeine is freed from its combination with chlorogenic acid with which it exists in the unroasted seed. The caffeine may be partially sublimed during this roasting process; much of the caffeine of commerce is collected in condensers attached to coffee roasters.

The action of coffee depends principally on the caffeine, which acts on the central nervous system, the kidneys, the muscles, and the heart. However, chlorogenic acid and caffeol are also physiologically active, and some of the unpleasant side effects connected with coffee consumption, at least in certain persons, have been attributed to these compounds. The usual cup of brewed coffee contains about 100 to 150 mg of caffeine and a cup of instant coffee contains about 85 to 100 mg of caffeine. For comparative purposes of caffeine content, a cup of tea contains 60 to 75 mg; of cocoa, 5 to 40 mg; and 12 oz of cola drink, 40 to 60 mg. The estimated maximum daily dose of caffeine is 1.5 g. Although coffee is mainly a dietetic, it is also a stimulant and a diuretic. It is of value in the treatment of poisoning by certain central nervous system depressants.

Decaffeinized coffee is prepared by extracting most of the caffeine from the coffee bean, yet retaining the pleasant characteristic aroma of coffee. Such preparations normally contain up to 0.08% of caffeine. Decaffeinized coffee has an extensive American market and brings a higher price than the ordinary roasted coffee.

Guarana is a dried paste composed chiefly of the crushed seed of *Paullinia cupana* Kunth (Fam. Sapindaceae). The plant is a climbing shrub native to Brazil and Uruguay. The seeds are collected by the Indians and roasted over fires for about half a day; the kernels are ground with water to a pasty mass in crude stone mor-



tars and molded into cylindric sticks that are dried in the sun or over fires.

Guarana enters into the preparation of a stimulating beverage that is used like tea and coffee by the people of Brazil. Guarana was introduced into France from South America in 1817, and caffeine (2.5 to 5%) was discovered as its principal constituent in 1840. The drug also contains 25% of tannin (cathechutannic acid).

In recent times, guarana has been extensively promoted as a stimulating drug. Its action is caused by the caffeine present, but it also possesses astringent properties.

Maté or Paraguay tea consists of the leaves of *Ilex paraguariensis* St. Hil. (Fam. Aquifoliaceae). Maté contains caffeine (up to 2%) and tannin. It is used in large doses as a laxative or purgative; it also has diaphoretic and diuretic properties. It is employed in South America in the preparation of a tealike beverage.

Caffeine

Caffeine or 1,3,7-trimethylxanthine occurs in coffee, tea, cacao, guarana, kola, and maté. Although caffeine can be produced sythetically, it is usually prepared from tea, tea dust, or tea sweepings, or recovered from coffee roasters. Caffeine is anhydrous or contains one molecule of water of hydration.

Caffeine occurs as a white powder or as white, glistening needles matted together in fleecy masses. It has a bitter taste. Caffeine may be sublimed without decomposition when heated.

The solubility of caffeine in water is markedly increased by the presence of citric acid, benzoates, salicylates, and bromides; medicinal compounds of this class are citrated caffeine and caffeine and sodium benzoate. The latter is most suitable for intramuscular injection as an analeptic in the treatment of poisoning, as a stimulant in acute circulatory failure, and as a diuretic.

USE AND DOSE. Caffeine and its related compounds are central nervous system stimulants. The usual dose of caffeine is 200 mg; of citrated caffeine, 300 mg; of caffeine and sodium benzoate injection, parenterally, 500 mg.

PRESCRIPTION PRODUCTS. Caffeine is an ingredient in a number of products, including: Trigesic®, Excedrin®, Anacin®, Fiorinal®, Cafergot®, and Wigraine®. In all of these drugs, it is combined with other therapeutic agents.

Theophylline

Thea or tea consists of the prepared leaves and leaf buds of *Camellia sinensis* (Linné) O. Kuntze (Fam. Theaceae), a shrub or tree with alternate, evergreen leaves. The tea tree is indigenous to eastern Asia and is now extensively cultivated in China, Japan, India, and Indonesia. The

generic name is Greek and means goddess; *sinensis* refers to its Chinese origin.

Green tea is prepared in China and Japan by rapidly drying the freshly picked leaves in copper pans over a mild artificial heat. The leaves are often rolled in the palm of the hand as they dry.

Black tea is prepared in Sri Lanka and India by heaping the fresh leaves until fermentation has begun. They are then rapidly dried artificially with heat.

Tea occurs as more or less crumpled, bright green or blackish green masses. Its odor is agreeable and aromatic; its taste is pleasantly astringent and bitter.

Tea contains 1 to 4% of caffeine (theine) and small amounts of adenine, theobromine, theophylline, and xanthine; about 15% of gallotannic acid; and about 0.75% of a yellow volatile oil that is solid at ordinary temperatures and has a strongly aromatic odor and taste.

The stimulating action of tea is essentially that of the contained caffeine; its astringent properties are owing to the tannin content. Tea leaf waste and tea dust represent important sources for the extraction of caffeine.

Theophylline or 1,3-dimethylxanthine is isomeric with theobromine and was first isolated from tea in 1885. It is prepared synthetically from caffeine or by other means. Theophylline occurs as a white, odorless, bitter crystalline powder that is soluble in about 120 parts of water. It is rendered more soluble when combined with basic compounds. Aminophylline or theophylline ethylenediamine, theophylline monoethanolamine, choline theophyllinate, and theophylline sodium glycinate are commonly employed in medicine.

USES AND DOSE. Theophylline and related compounds are utilized principally as smooth muscle relaxants for the symptomatic relief or prevention of bronchial asthma and for the treatment of reversible bronchospasm associated with chronic bronchitis and emphysema. In addition, theophylline possesses diuretic properties. The usual dose of theophylline is, orally, the equivalent of 2.4 mg of anhydrous theophylline per kg of body weight every 6 hours initially, adjusted as necessary to control symptoms with a usual optimal dosage of 4.8 mg per kg of body weight every 6 hours. The usual dose of aminophylline is, orally, 3 mg per kg of body weight every 6 hours adjusted as necessary to an optimal dosage of 6 mg per kg every 6 hours and, intravenously, 250 to 500 mg every 6 hours.

Aminophylline is also a valuable diuretic. It exhibits dilating action on the pulmonary vessels in relieving asthma and can lower venous pressure in certain cases of heart failure.

PRESCRIPTION PRODUCTS. Theophylline: Bronkodyl®, Theophyl®, Theospan®, Theolair®, Accurbron®, Sustaire®; aminophylline: Somophyllin®, Phyllocontin®; theophylline sodium glycinate: Glynazan®, Synophylate®; choline theophyllinate: Choledyl®. Tedral® and Bronkotabs® contain theophylline in combination.

Theobromine

Theobromine or 3,7-dimethylxanthine is a compound prepared from the dried, ripe seed of *Theobroma cacao* Linné (Fam. Sterculiaceae), or is made synthetically. It occurs as a white, crystalline powder with a bitter taste and sublimes at about 260° C.

The base is slightly soluble in cold water or in alcohol but is readily soluble when mixed with salts that form basic solutions, such as calcium salicylate, sodium acetate, or sodium salicylate.

USES AND DOSE. Theobromine is a diuretic and a smooth muscle relaxant. It has little stimulant action on the central nervous system and hence is preferred over caffeine in treatment of cardiac edema and of angina pectoris. The usual dose is 200 mg, 3 times daily.

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