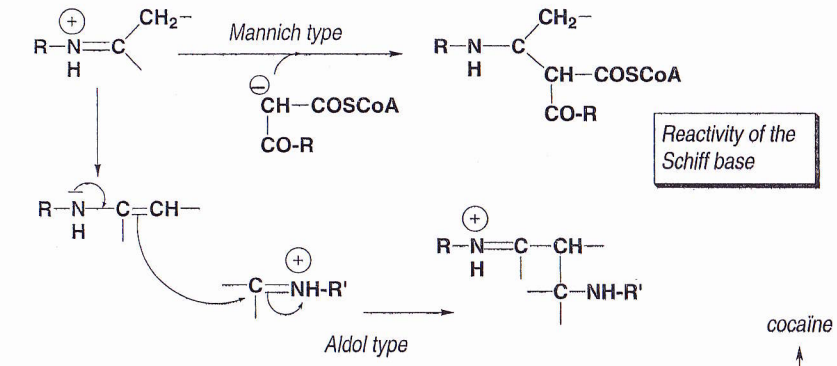
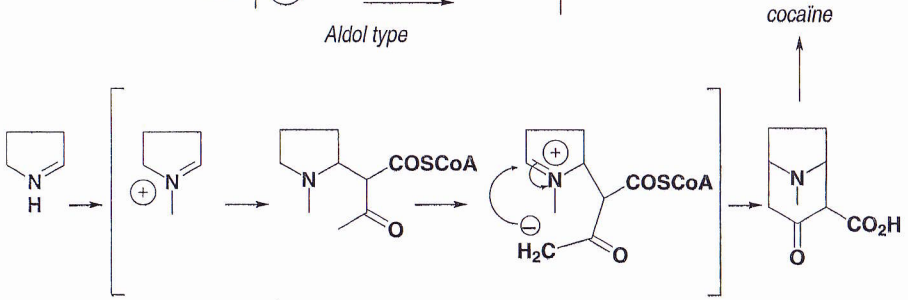
Subsequently, the mechanisms that are likely to lead to the more complex structures can be envisioned through simple chemical reactions (formation of Schiff bases, Mannich condensation, aldol condensation). The *N*-methyl groups that are often found are generally provided by *S*-adenosylmethionine.


Mannich type
Reactivity of the Schiff base
Aldol type



The pharmacological and therapeutic interest of the alkaloids derived from ornithine and lysine is very uneven. Some are currently used in therapy (atropine, scopolamine), while others are now of limited use (sparteine) or only of historical interest (lobeline, arecoline). Many ought to be known only because of their toxicity: pyrrolizidine alkaloids from Boraginaceae and Asteraceae that are often gifted with medicinal virtues, quinolizidine alkaloids of Fabaceae that are common in our environment because of their ornamental character, not forgetting nicotine in tobacco. A small number have an interesting potential, for example, some indolizidines (castanospermine) which are efficacious against retroviruses, or huperzine, which has been tested in the context of Alzheimer's disease.

Thus, we shall limit our coverage to these few examples, and we shall follow a chemical classification. The figure on page 803 gathers the most common alkaloid structural types that are related to ornithine and lysine.

Tropane Alkaloids

Tropane alkaloids have in common a nitrogen-containing bicyclic structural element, namely azabicyclo[3,2,1]octane: they are 8-methyl-8-azabicyclo[3,2,1]octanes.

Approximately 200 alkaloids are known in this group, and they are distributed in a small number of Angiosperm families: Solanaceae (they are found in about twenty genera, e.g., *Anthocercis*, *Atropa*, *Brugmansia*, *Datura*, *Mandragora*, *Physalis*,

Schizanthus, *Scopolia*, *Solandra*, *Withania*), Erythroxylaceae (*Erythroxylum*), Proteaceae (*Bellendena, Darlingia, Knightia* [pyranotropanes]), Convolvulaceae (*Convolvulus*, *Calystegia* [aromatic esters of tropanol and calystegines]) and, more sporadically, in some isolated genera: *Bruguiera* (Rhizophoraceae), *Phyllanthus, Peripentadenia* (Euphorbiaceae), *Cochlearia* (Brassicaceae), and *Heisteria* (Olacaceae).

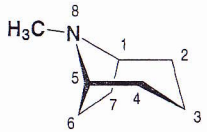
From a pharmacological point of view, (–)-hyoscyamine and its racemate, (±)-atropine, are substances of considerable interest: they have parasympatholytic properties, and they are also the starting point from which synthetic organic chemistry created, among others, most of the anticholinergics. Similarly, cocaine was at the origin of the synthetic local anesthetics.

1. STRUCTURE OF TROPANE ALKALOIDS

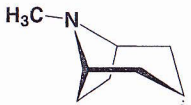
With only a few exceptions (particularly the pyrano- and dihydropyranotropanes of the Proteaceae and the calystegines [see p. 831]), tropane alkaloids are esters of tropane alcohols and of acids of various structures, either aliphatic or aromatic.

A. Tropanols

These alcohols fall into two series depending on the orientation of the hydroxyl group at C-3. Derivatives of tropan-3α-ol * (e.g., tropanol) are by far the most common, and those of tropan-3β-ol are essentially specific to the Erythroxylaceae. In the absence of other substituents, the tropanols are optically inactive: they are *meso* compounds and the two bridgehead carbons have opposite chirality. The tropanols are often hydroxylated at C-6 or C-7 or both, and sometimes 6,7-epoxidized. Almost all of the alkaloids of the Erythroxylaceae are esters of ecgonine, which is tropan-3β-ol substituted at C-2 and in the β configuration by a carboxyl group.

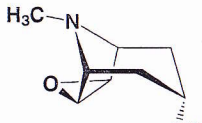


Tropane



Tropanol (3α-hydroxytropane)

Pseudo-tropanol (3β-hydroxytropane)



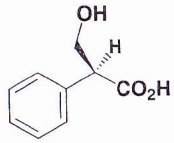
Scopanol

Ecgonine

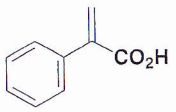
* Currently the tendency is to generalize the use of the *endo/exo* nomenclature for these compounds: 3-*endo*-ol (e.g. tropanol) and 3-*exo*-ol (e.g. ψ-tropanol).

B. Acids

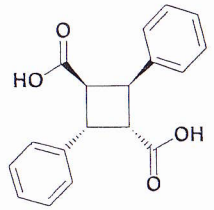
The acids may be aliphatic (acetic, butyric, isovaleric, 2-methylbutyric, 2*E*,2-methyl-2-butenoic acid, commonly known as tiglic acid, angelic acid) or aromatic. In the latter case, the acid may be specific like (*S*)-(–)-tropic acid, or may be more widely distributed in the plant kingdom like benzoic, phenylacetic, cinnamic acid, and their derivatives. The acids are rarely heterocyclic.



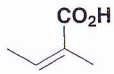
Tropic acid



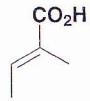
Apotropic acid (atropic acid)



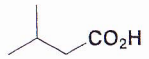
α-Truxillic acid



Angelic acid



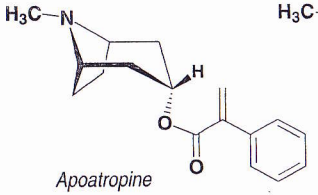
Tiglic acid



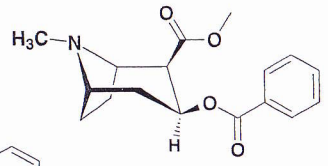
Isovaleric acid

C. Alkaloids

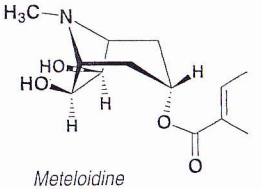
The most representative structures are shown in the figure below and in the figure on page 808. Either configuration (axial and equatorial) is possible for the *N*-methyl group, but, in most of the alkaloids of interest, it is the equatorial position which largely predominates at equilibrium (although the nature of the solvent may be a



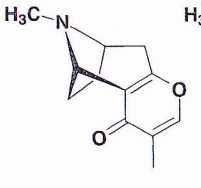
Apoatropine



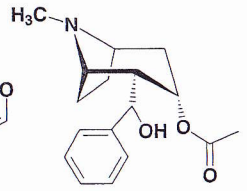
Cocaine



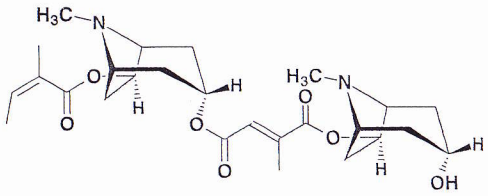
Meteloidine



Bellendine



Knightinol

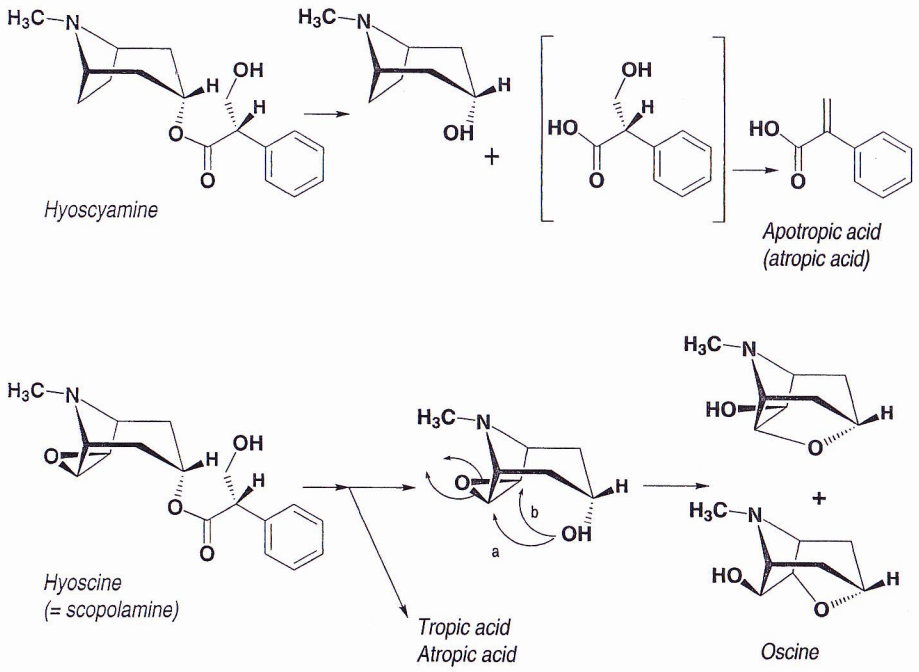


Schizanthine D

determining factor). A small number of alkaloids, improperly referred to as dimers, are tropane diesters of dicarboxylic acids (truxillines, belladonine, schizanthine D). In some exceptional cases, tropane alkaloids have a pyrone-type structure (e.g., bellendine in the Proteaceae).

Such ester alkaloids are particularly fragile. Thus, (–)-hyoscyamine is rapidly converted, in acidic as well as basic conditions, to tropanol and (–)-tropic acid, and the latter is transformed by intramolecular dehydration, into apotropic (atropic) acid, which is optically inactive. In the case of scopolamine (also known as hyoscine), acidic or alkaline hydrolysis leads to (–)- and (±)-tropic acid and to oscine. The latter is a compound which is optically inactive, but which can be resolved as a benzoate. Under the mild conditions of an enzymatic hydrolysis, the product is scopolanol, which is unstable and readily converted to oscine. Under the same conditions, cocaine is hydrolyzed to ecgonine, methanol, and benzoic acid; partial hydrolysis leads to benzoylecgonine.

Optically active alkaloids such as (–)-hyoscyamine are readily racemized through enolization: a simple reflux in chloroform is enough to transform it into (±)-atropine. Although atropine has often been described—and in many different plants—it is fair to wonder if it is really, in all of the known cases, a natural product or an artefact.



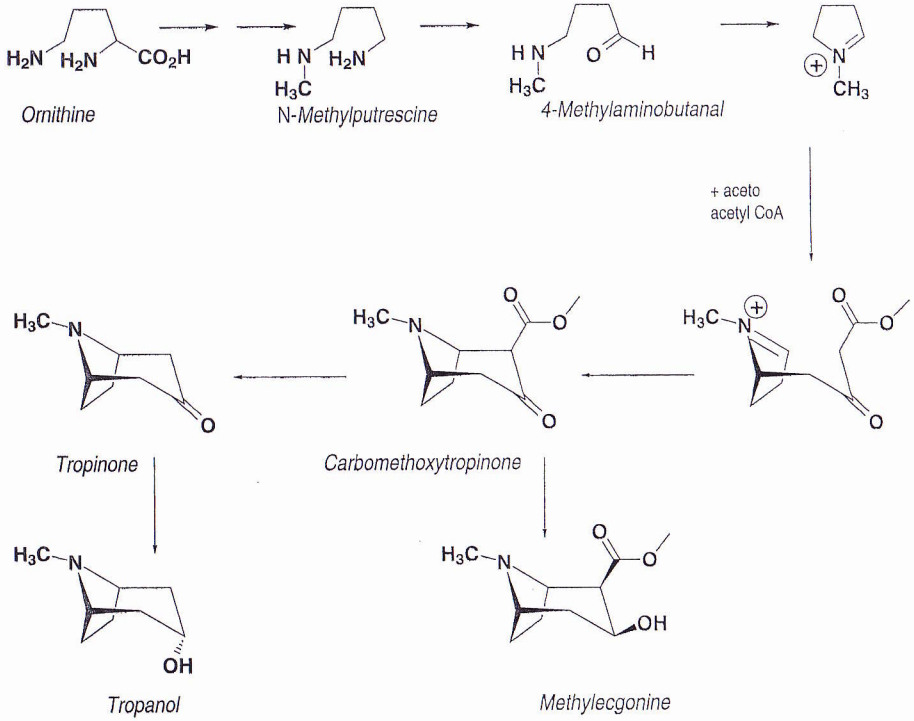
2. BIOSYNTHETIC ORIGIN

Several precursors are involved in the elaboration of tropane alkaloids:

- phenylalanine is at the origin of the C_6-C_1 and C_6-C_3 aromatic acids as well as of tropic acid;
- isoleucine is the precursor of C_5 aliphatic acids such as tiglic acid or 2-methyl-butanoic acid;
- ornithine is at the origin of the pyrrolidine ring of the tropane nucleus;
- acetate (in the form of acetoacetyl coenzyme A or malonyl coenzyme A) contributes the additional carbon atoms needed to build the piperidine ring of the tropane nucleus.

Formation of the tropane nucleus

Ornithine, the precursor of the tropane nucleus, is rapidly decarboxylated to putrescine, which is then methylated. Putrescine can also be formed from arginine, by decarboxylation followed by the transformation of the guanidine system into amidine and final hydrolysis of *N*-carbamoyl-putrescine. The oxidative deamination of *N*-methylputrescine leads to 4-methylaminobutanal, which is subsequently cyclized (Schiff base formation) to the *N*-methyl-Δ^1-pyrrolinium cation.

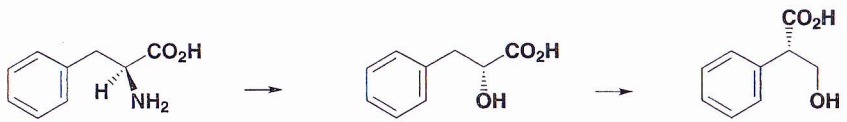


Biosynthetic origin of tropane structures (principle)

The incorporation of the amino acid is not symmetrical. Indeed, the incorporation of 5-^{14}C-ornithine leads, in *Datura stramonium*, to 1-^{14}C-hyoscyamine only. This asymmetry is not, however, a general rule: in the case of *Erythroxylum coca*, the radioactivity is evenly distributed between C-1 and C-5 of the tropane moiety of cocaine; the same was observed with the hyoscyamine produced by *Hyoscyamus albus* and with the scopolamine biosynthesized by *Duboisia leichardtii*. Asymmetrical incorporations are due to the fact that the decarboxylation of ornithine and the methylation of putrescine involve a "bound" form of putrescine (if instead, putrescine does not remain bound to the decarboxylase, the *N*-methylation proceeds symmetrically).

The key step in the biosynthesis of the tropane nucleus has been studied in the Solanaceae and Erythroxylaceae, and is the nucleophilic attack by the C-2 of acetoacetyl coenzyme A on the *N*-methyl-Δ^1-pyrrolinium. The β-ketoester is incorporated in cocaine as well as hyoscyamine or cuscohygrine, whereas hygrine, long considered to be a precursor of hyoscyamine, is incorporated only to a small extent under the same conditions. An intramolecular Mannich reaction then leads to carbomethoxytropanone. In the case of cocaine, the carbomethoxytropanone is reduced stereospecifically to methylecgonine. In the case of hyoscyamine, it is decarboxylated to tropanone, which is then reduced to tropanol. The oxidations at C-6 and C-7 take place after the esterification of the secondary alcohol at C-3; the epoxidation at C-6, C-7 (e.g., scopolamine) involves a 6β-hydroxylated intermediate and the direct attack of the C-6 hydroxyl group on C-7.

Origin of tropic acid. The precursor of tropic acid is (*S*)-phenylalanine. Labeling experiments first revealed an intramolecular migration of the carboxyl group from C-2 to C-3, then that (*R*)-phenyllactic acid is also a precursor, which led to postulating—and verifying—the role of littorine in the biosynthesis of tropic esters (littorine is the (*R*)-phenyllactate of tropanol). The carboxyl group migration is accompanied by a double inversion of configuration.



(S)-Phenylalanine *(R)-Phenyllactic acid* *(S)-Tropic acid*

Characterization of Alkaloids Containing a Tropane Nucleus

Alkaloids that are esters of tropic acid are easy to characterize by the Vitali-Morin reaction: after treating with fuming nitric acid and redissolving the residue with acetone, a dark purple color develops in the presence of an ethanol solution of potassium hydroxide. This reaction can be used for colorimetric quantitation: its selectivity makes it possible to measure only tropic esters in a mixture of esters of tropanol (an alkaloid like littorine is practically unreactive).

Tropane alkaloids are easy to detect by TLC. HPLC gives good resolution (reverse phase and ion pair). GC can also be used, particularly to analyze coca leaves, and after extraction, to analyze products suspected of containing cocaine. In the case of the Solanaceae alkaloids, hyoscyamine and scopolamine are partially dehydrated to apo derivatives (apoatropine, aposcopolamine) on the chromatography columns. For purposes of quantitation, preliminary silylation prevents dehydration.

3. OFFICIAL SOLANACEAE CONTAINING TROPANE ALKALOIDS

Tropane alkaloids are common in the Solanaceae (e.g., *Anthocercis, Anthotroche, Crenidium, Cyphantera, Mandragora, Przewalskia, Simonanthus, Solandra*), but the number of species actually used in therapeutics is small. In Europe, they essentially amount to the deadly nightshade, thorn apple, and henbane, generally known as the "official parasympatholytic Solanaceae". The pharmaceutical industry uses various species of *Brugmansia, Datura, Hyoscyamus*, and *Duboisia* to produce atropine and scopolamine.

- **DEADLY NIGHTSHADE**, *Atropa belladonna* L., (Belladona),
  THORN APPLE, *Datura stramonium* L., (Stramonium, Jimson weed),
  HENBANE, *Hyoscyamus niger* L.

The 3rd edition of the European Pharmacopoeia gives identical definitions for the three drugs, which consist in each case of the leaf: "[belladonna, stramonium, hyoscyamus] leaf consists of the dried leaf or of the dried leaf, flowering tops and occasionally, fruit-bearing tops of [*A. belladona, D. stramonium, H. niger*]". In the case of stramonium, the definition specifies "... of *Datura stramonium* L. and its varieties". For each of the three drugs, the Pharmacopoeia indicates in addition the minimum concentration of total alkaloids expressed as hyoscyamine relative to the drug dried at 100-105°C as well as the approximate proportions of the chief alkaloids. These are toxic drugs, and they appear on the French *liste I* of poisonous substances.

The toxicity of these Solanaceae has been known for a very long time, and although stramonium was not introduced in Europe until the end of the sixteenth century, henbane (*H. albus* L. and *H. niger* L.) had been widely used in the practice of witchcraft characteristic of certain periods of the Middle Ages: tales of sabbath and of levitation suggest hallucinations due to tropane alkaloids*. In contrast, the introduction of these species in therapeutics took place rather late.

* At the same time in history, another Solanaceae, namely the mandrake, *Mandragora officinarum* L., had a reputation for having to do with the devil. Like henbane, this drug was used as a soporific and an anesthetic during surgery. The drug, in other words the root, contains about 0.4% alkaloids (atropine or hyoscyamine and scopolamine).

DATURA STRAMONIUM L.

The Plants. All three species are herbaceous plants with leaves normally alternate, simple, and without stipules. The flowers are pentamerous, regular or almost regular, and have a gamosepalous indeciduous calyx, stamens inserted on the tube of the corolla, and a gynoecium that only includes two carpels. The fruit is either a subglobulous bilocular berry (deadly nightshade), or a bilocular capsule with a cover that opens (thorn apple's pyxidium), or an incompletely tetralocular with multiple dehiscence (henbane).

- The **deadly nightshade** is a plant indigenous to western Europe, although rare in France. It is a perennial plant with a rhizome-like root, erect stems (1-1.5 m), and oval entire leaves, which grows in clearings in the woods and on piles of rubble, preferably on limestone. The leaves are alternate on the lower part of the stem, and in close pairs near the inflorescence; they are of uneven size and not opposite. The flowers are normally solitary, with a campanulate corolla with purplish-brown or brownish-yellow lobes. The fruit is the size of a cherry, shiny black, and surrounded at the base by an indeciduous and well-developed calyx.

- The **thorn apple** grows abundantly in Europe where it most likes neglected fields and country roadsides. This is a hardy annual species which reaches 0.8 to 1.2 m and has a rounded stem with oval acute leaves deeply divided in uneven pointy lobes. The flowers are solitary, large (8-10 cm long), have a calyx with five sepals pleated longitudinally, and a tubulous corolla, pleated, and white. The fruit is covered with tough thorns.

- **Henbane** can be annual or biennial depending on the variety. Originally from Asia, it prefers to grow on sandy soils: vacant lots, road shoulders, and piles of rubble all over Europe and North America. The stem is hairy and viscous, either simple (var. *annua*) or ramified (var. *biennis*), and bears leaves that are petiolate at the base (this is mostly true for the first-year rosette of the *biennis* variety), sessile or sheathing on the stem, with triangular lobes, very hairy, and pale green. The flowers, grouped into a short raceme at the base of a large bract, have a corolla with five lobes incompletely actinomorphic, and are grayish-yellow with purple or purplish-black veins. The pyxidium is surrounded by an indeciduous, enlarged, and hardened calyx with thorny teeth.

The Drugs. The leaves of these Solanaceae are often rolled, wrinkled, agglomerated, or broken in commercial samples and their identification can be difficult, hence the importance of the macroscopic characteristics. Partially rehydrating the drug (by soaking it in warm water and gently spreading it) facilitates the morphological examination.

1. Origin of the Drugs

The three official species are cultivated chiefly in the eastern European countries. Different breeds and varieties are cultivated (e.g., the varieties *inermis*

[Jacq.] Timm. and *tatula* [L.] Torr. of *Datura stramonium*, the biennial varieties of *H. niger*). The harvest normally occurs at the beginning of the floration, and the drying must be at low temperature; in the case of belladonna, another harvest at the end of the season is possible.

2. Morphology

• The **deadly nightshade** leaf has an elliptic blade, acuminate at the apex, and attenuate at the base (5-25 x 3-12 cm). The pubescence of the young leaves only remains near the veins in the older leaves. The secondary veins are at 60° and are anastomosed near the margin.

• The blade of the **thorn apple** leaf (8-25 x 7-15 cm) is acuminate and very often asymmetric at the base. It is lighter on the lower side and brittle. The secondary veins are prominent on the lower side and depressed on the upper side. The older leaf is practically glabrous, whereas the veins of the young leaves are tomentose. The secondary veins are at 45° and end at the apex of the blade.

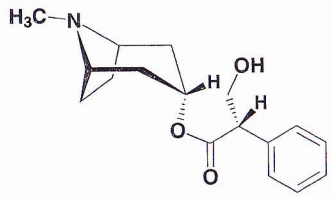
• The **henbane** leaf can be sessile, in which case it is cordate at the base, or on a short petiole, in which case it is acute. The blade (25 x 5-7 cm) is highly pubescent and viscous on both sides, especially near the midribs; its margin is irregular and divided in wide triangular lobes. The secondary veins form a wide angle with the midrib and run to the apex of the blade.

3. Microscopic Characteristics

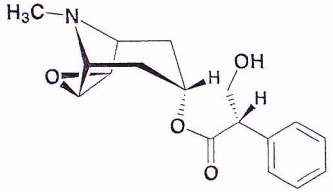
The analysis of the cut reveals epidermal cells with wavy walls and a smooth cuticle (official stramonium, henbane) or a striated cuticle (belladonna). Also examine the nature and localization of calcium oxalate, always abundant in these drugs: it is finely crystallized (microsphenoidal crystals), and it is visible in the cells of all of the parenchymas, especially under the palisade layer (belladonna) or, on the contrary, only in the vein (stramonium, henbane). Larger crystalline forms characterize official stramonium (essentially clusters from 10 to 30 µm) and henbane (vast majority of prisms from 5 to 20 µm). Stramonium may contain a few prisms and henbane may contain a few clusters, but these crystalline forms are exclusively localized under the palisade layer.

A final differentiating element—also of interest in the analysis of powders—is the morphology of the trichomes: multicellular, uniseriate, rare covering trichomes (belladonna); numerous conical covering trichomes, often broken and with a verrucose wall (official stramonium); very numerous glandular trichomes of several types, often fragmented, and numerous covering trichomes (henbane).

Chemical Composition. All three drugs are rich in minerals: 12-15% (belladonna), 15-18% (official stramonium), 18-20% (henbane). The belladonna leaf contains a small quantity of a coumarin, namely scopoletol; the other two drugs only contain traces. The foul odor of henbane is due to tetramethylputrescine.



(–)-Hyoscyamine



(–)-Hyoscine
[= (–)-Scopolamine]

• **Belladonna**. The concentration of the total alkaloids in the leaf* ranges from 0.3 to 0.6% (1% in cultivated clones?). Hyoscyamine is by far the chief constituent (90%) and occurs alongside small quantities of scopolamine (2%) and their dehydration products (apoatropine and aposcopolamine, 7% [?]).

• **Official Stramonium**. The concentration of the total alkaloids is between 0.2 and 0.5%, and at the time of the harvest, hyoscyamine and scopolamine represent two-thirds and one-third of the total alkaloids, respectively.

• **Henbane**. This is the species containing the least total alkaloids: 0.04-0.15%. Hyoscyamine is the chief constituent, and the percentage of scopolamine can be high (25% and more).

Assay. The identification is based, for all three drugs, on the microscopic examination of the powder and the characterization of the tropic esters by the Vitali-Morin reaction: extraction of the alkaloids in dilute sulfuric acid, back-extraction (Et_2O) after alkalinization (NH_4OH), solvent evaporation, nitration of the residue at high temperature (HNO_3), and color development in an acetone solution of the nitrated product in the presence of an ethanol solution of NaOH. A purple color develops.

The assay *per se* includes a search for foreign elements and an estimate of the ashes insoluble in hydrochloric acid:

• belladonna, stramonium: stems of diameter greater than 5 mm <3%; total ash <16% [belladonna] or <20% [stramonium]; ash insoluble in hydrochloric acid <4%;

• henbane: stems of diameter greater than 7 mm <2.5%; total ash <30%; ash insoluble in hydrochloric acid <12%.

* The root is where the alkaloids are synthesized and its concentration in total alkaloids is much higher (0.7-0.9%): hyoscyamine is by far the chief constituent (near 70%) and the level of apoatropine is high; many other alkaloids are present in small quantities (scopolamine, hydroxyhyoscyamine, tigloyloxytropane).

Also required is a TLC analysis of a methanol solution of the total alkaloids. The plates are visualized with potassium iodobismuthate, followed by sodium nitrite. Under these conditions, and according to the French Pharmacopoeia, the spots or bands corresponding to hyoscyamine turn from brown to reddish-brown, but not to bluish-gray, which is characteristic of atropine. The use of reference standard mixtures of known proportions allows a rough estimate of the proportions of the chief alkaloids in the drugs.

The quantitation method is classic: extraction (ethanol + diethyl ether in the presence of ammonia), dilution (diethyl ether), formation of salts (H_2SO_4), return to the bases (NH_4OH, $CHCl_3$), and quantitation of the total alkaloid residue by back-titration (acidimetry). The concentration of the total alkaloids, calculated as hyoscyamine, must be not less than 0.3% (belladonna), 0.25% (official stramonium), and 0.05% (henbane).

Pharmacological Activity. The activity of the alkaloids must be distinguished from that of the drugs, and the substantial toxicity of the drugs must be emphasized.

1. Pharmacological Activity of the Alkaloids

a. Atropine. Atropine and hyoscyamine have the same activity: they are parasympatholytics; hyoscyamine has a stronger activity than racemic atropine, but it is the latter that is commonly prepared and used. Atropine is an inhibitor of the muscarinic receptors of the peripheral organs innervated by the parasympathetic post-ganglionic fibers, and of the central nervous system. It acts by competitive and reversible inhibition of acetylcholine binding onto its receptors, and this antagonism leads, in the organs in question, to sympathomimetic-like effects.

- In the heart and after temporary bradycardia, atropine increases the heart rate by suppressing vagal inhibition.
- In the blood vessels, the effects on blood pressure are not marked (but with toxic doses, a vasodilation of cutaneous capillaries is observed, especially on the face).
- In the smooth fibers, atropine induces relaxation and motor inhibition: it decreases intestinal tone as well as the amplitude and frequency of peristaltic contractions, paralyzes the ureters, increases bladder pressure, decreases biliary duct tone, and blocks the bronchoconstricting effect of acetylcholine.
- Secretions are affected: saliva, sweat, gastric, pancreatic, bronchial, and lachrymal secretions are all decreased (toxic doses inhibit sweat production and cause high fever).
- In the eyes, the alkaloid induces a passive mydriasis, by paralysis of the sphincter pupillae. There is also a paralysis of the accommodation consecutive to the loss of ciliary muscle tone (the eye remains adjusted for distant vision) and an increase in intra-ocular pressure.

In addition to the effects on the autonomic nervous system, atropine has effects resulting from its interaction with central muscarinic receptors. Toxic doses cause

substantial excitation: agitation, disorientation, exaggerated reflexes, hallucinations, delirium, mental confusion, and insomnia; at low doses, the action is less clear, and tends to be depressant and sedative.

b. Scopolamine. The parasympatholytic activity of scopolamine is identical to that of atropine, but much less marked, especially on the myocardium. Its effects on the CNS are clear: sedative, depressant, hypnotic, with amnesia. It potentiates neuroleptics, improves parkinsonism, and is "incapacitating" at high doses.

2. Pharmacological Activity of the Drugs: Toxicity

Belladonna (fruits, roots, leaves), stramonium (seeds, leaves, roots), and *Brugmansia* (i.e., ornamental arborescent "daturas") are toxic. Belladonna fruits attract children and stramonium is sometimes prized for its "hallucinogenic" effects (the same is sometimes true of *Brugmansia*). The ingestion of these plants induces characteristic symptoms, just like drug overdosage: after a very brief delay, the face turns red, the mouth and mucosal membranes turn dry, and an intense thirst and muscular weakness develop. The heart rate increases substantially (120-150 beats/min), and mydriasis and hyperthermia are always observed. Hallucinations and delirium follow, accompanied by agitation, loss of motor coordination, sometimes convulsions; sleepiness or a coma is next. Recovery takes time (1-3 days). The altered mental status can drive the patient to random acts with threat to life. The patient must be monitored and maybe treated (e.g., charcoal, sedatives). Administration of physostigmine (a cholinesterase inhibitor, see p. 975) is justified in a few special cases.

Henbane intoxications are exceptional and not serious. The whole plant has little alkaloidal content and its repulsive odor deters inadvertent consumers.

Uses of the Drugs. The three official drugs are exclusively directed to the preparation of galenicals, since the industrial extraction of alkaloids is done from Solanaceae with higher concentrations of total alkaloids (see p. 822). All medicines based on Solanaceae containing tropane alkaloids can induce non-negligible adverse effects. Such medicines contain atropine, therefore they have the corresponding contraindications (see below: Uses of the Alkaloids. Atropine).

The following forms are listed in the European Pharmacopoeia (3rd Ed.):

- belladonna powder, titrated to contain 0.28 to 0.32% total alkaloids; French *liste I*, i.e., prescription drug which may not be renewed; usual doses: 0.05-0.1 g/day; maximum doses: 0.25 g/single dose, 0.5 g/day;
- official stramonium powder, titrated to contain 0.23 to 0.27% total alkaloids;
- henbane powder, titrated to contain 0.05 to 0.07% total alkaloids;

The following forms remain listed in the French Pharmacopoeia (10th Ed.):

- belladonna tincture, titrated to contain 0.027 to 0.033% total alkaloids; French *liste II*, i.e., prescription drug which may be renewed; usual doses: 0.5-2 g/day or 30 to 120 calibrated drops; maximum doses: 2.5 g/single dose, 5 g/day;

- belladonna extract, titrated to contain 2.3 to 2.7% total alkaloids (relative to an extract consisting of 90% dry residue); French *liste I*; usual doses: 0.015-0.03 g/day; maximum doses: 0.03 g/single dose, 0.1 g/day.
- henbane tincture, titrated to contain 0.009 to 0.011% total alkaloids;

Belladonna. The galenicals—tincture, powder, extract—are ingredients of various combinations, the number of which decreases over the years because of their unfavorable benefit-to-risk ratio, which causes most manufacturers to remove these galenicals from their products:

1. Most combinations are proposed for the symptomatic treatment of unproductive coughs, and sometimes for acute congestion of the throat and larynx. These forms (most often syrups) combine—and the rationale for some of these combinations is not always clear—belladonna with sodium benzoate, camphor, codethyline, ethylmorphine, eucalyptol, pholcodine, erysimum syrup, sulfoguaiacol, or else aconite, sundew, ipecac, or snakeroot tincture;

2. Other combinations are a short-term symptomatic treatment for constipation: in this case, belladonna is combined with buckthorn, cascara, and/or aloe. Its use in this type of formulation is justified by its spasmolytic activity, which attenuates the effects of anthraquinone glycosides on peristalsis. On the other hand, such mixtures have both the disadvantages of the anthraquinone laxatives (see p. 425), and the risk of side effects and drug interactions due to the tropane alkaloids;

3. In combination with henbane, belladonna is indicated for the symptomatic treatment of the pain associated with functional problems of the gastrointestinal and biliary tracts. Some feel that the potential untoward effects of such products outweigh the benefits expected from treating symptoms that generally subside spontaneously;

4. Belladonna continues to be included in (rare) antalgic or antineuralgic proprietary drugs.

Stramonium. Official stramonium has practically been abandoned: it is no longer found except in one syrup proposed for the symptomatic treatment of unproductive coughs. In the late 1980s, it was still used, without clear pharmacological justification, in cigarettes designed to relieve respiratory difficulties. The lack of therapeutic benefits of such forms and the potential for abuse (ingestion of infusions or decoctions), have led French authorities to require their withdrawal from the market (August 13, 1992) and to delete them from the French national formulary (September 10, 1992).

Henbane. Henbane is not used much more than stramonium. It is an ingredient of combinations, for example with buckthorn, aloe (stimulant laxative), belladonna

ATROPA BELLADONA L.

Uses of the Alkaloids

1. Atropine. Atropine sulfate (French *liste I*, i.e., prescription drug which may not be renewed) is available in France as an injectable solution (0.25-, 0.5-, or 1-mg ampules) and as an ophthalmic solution (0.3, 0.5, and 1%). The injectable form is administered by IM or slow IV injection.

The recommended dose for the parenteral route is, for adults, 0.25 to 0.5 mg/single dose; the maximum dose of 2 mg/day must not be exceeded. This drug should be administered to children only in exceptional cases, and the daily dose is 0.5 mg (>7 years old), 0.25 mg (between 1 and 7 years old), or from 62.5 to 125 µg depending on body weight (<1 year old). It is available in the United States (prescription drug) in tablets (0.4 mg), as an injectable solution (0.05-1 mg/mL), and as an ophthalmic solution (0.5-2%) or ophthalmic ointment (1%).

Therapeutic indications

• The indications for the *injectable solutions* of atropine sulfate are currently the following:

- A-V block or atrioventricular heart block;
- in case of myocardial infarction: for the prevention and treatment of A-V block and sinus bradycardia;
- in preanesthesia: to prevent symptoms caused by vagal stimulation (bradycardia upon induction);
- for the symptomatic treatment of acute pain due to functional problems of the gastrointestinal and biliary tracts;
- as an antispasmodic for ureteral colic and spasmodic anuria;
- as a specific antidote to treat anticholinesterase poisoning (by organophosphorus pesticides and carbamates) or by parasympathomimetic or cholinergic medications;
- to treat Parkinson's disease (if caused by neuroleptics and as an adjunct to levodopa).

• Atropine sulfate in *eye drops* has the following indications:

- to treat uveal inflammations: anterior uveitis (iritis, iridocyclitis) and posterior uveitis, uveal reactions secondary to injury or surgery;
- to induce cycloplegia for refraction examinations (required in children with strabismus) particularly in case of accomodative strabismus.

• Atropine is also used in some combinations, particularly with diphenoxylate for the symptomatic treatment of diarrhea.

Contraindications

The activity on the eye prohibits the use of atropine in the case of narrow (closed) angle glaucoma, in which the iris tissue comes in contact with the posterior surface of the cornea, thereby preventing the outflow of the aqueous humor. Other contraindications are a risk of urinary retention of urethro-prostatic origin,

gastroesophageal reflux, paralytic ileus, intestinal atony in the elderly, pylorospasm; ulcerated and hemorraghic rectocolitis; breast-feeding women.

Atropine must be used with caution in case of prostatic hyperplasia, as well as renal, hepatic, or coronary insufficiency, cardiac rhythm abnormalities, chronic bronchitis, or pregnancy. The side effects of atropine limit its use: dryness of the mouth, difficulties of accommodation (with eye drops), reddening of the face, constipation, and less frequently, tachycardia and palpitations, urinary retention, decrease in bronchial secretions, irritability and potential mental confusion (in the elderly). These side effects can be diminished or avoided by adjusting the posology.

2. Hyoscyamine. It is practically not used in France, and still used in the United States.

3. Scopolamine. Scopolamine hydrobromide (French *liste I*, i.e., prescription drug which may not be renewed; recommended dose for IM injection: 0.125-0.25 mg/day, maximum dose 0.25 mg/single dose, 0.5 mg/day; a prescription drug in the United States) has been used in the treatment of parkinsonism and of painful spasms. It can be used as a component of preanesthetic medication.

Currently * , the chief use of scopolamine is for the prevention of motion sickness. The delivery system is a skin patch to be applied behind the ear. It contains 1.5 mg scopolamine, which is released gradually through a membrane (0.5 mg in 72 hours). This form is contraindicated in case of narrow (closed) angle glaucoma, in the case of urinary retention of urethroprostatic origin, and in children under 12 years of age. Scopolamine can induce atropine-like side effects (dryness of the mouth, blurred vision) and potentially, drowsiness. The simultaneous absorption of alcoholic beverages is to be strictly avoided. Mental confusion is possible in the elderly.

4. SOLANACEAE THAT ARE INDUSTRIAL SOURCES OF TROPANE ALKALOIDS

• *Brugmansia sanguinea* (Ruiz & Pavón) D.Don
(= *Datura sanguinea* Ruíz & Pavón)

This tree-datura ** is a small tree characterized by large flowers (17-25 cm long) with a tubulous corolla, yellow and orangy with red veins. The tree is fairly frequently grown in the villages and cities of several countries of the Andes: Colombia, Ecuador, and Peru.

Reproduced by *in vitro* micropropagation of selected clones, this plant is cultivated in Ecuador in high altitude (3,000 m) areas. The leaves, which contain

* In France, the motion sickness medicine was taken off the market on February 1996 but marketed again in November 1998.

** Arborescent daturas are usually classified within the genus *Brugmansia* Pers., which is distinct from the genus *Datura* L.

about 0.8% total alkaloids, with scopolamine as by far the chief constituent, are harvested mechanically three times a year. The Ecuadorian production, which is all directed to scopolamine extraction, is estimated at 400 metric tons of dry leaves per year. Other arborescent daturas or their hybrids could also be used for extraction.

B. sanguinea, like other species (*Datura innoxia* Mill. from Mexico, *Brugmansia suaveolens* [Humb. & Bonpl. ex Willd.] Bercht & J. Presl., *Brugmansia arborea* [L.] Lagerh. from Amazonia and Colombia, among others) is traditionally used for its hallucinogenic properties.

• *Datura metel* L.

This is an annual species native to India and naturalized around the Mediterranean rim. The leaves contain approximately 0.5% total alkaloids with scopolamine as by far the chief constituent together with norscopolamine, hyoscyamine, and meteloidine. They can be used for the extraction of alkaloids.

• Egyptian Henbane, *Hyoscyamus muticus* L.

This perennial species, widespread from Egypt to Iran, is botanically very close to henbane; two subspecies are known, ssp. *muticus* and spp. *faleslez* (Coss.) Maire, and the latter one is infamous for its toxicity. Its leaves, which can be used for the extraction of alkaloids, contain more than 1% total alkaloids, with the hyoscyamine-atropine group dominating.

• Corkwood Tree, Piturі, *Duboisia myoporoides* R.Br., *D. leichardtii* F. Muell.

The corkwood trees are small trees with alternate and narrow leaves, with panicles of tubulate white flowers, and with black berries. Both species are Australian: *Duboisia myoporoides* is widespread on the eastern seaboard, whereas *D. leichardii* is localized around Brisbane. Both species, as well as their hybrids, are rich in alkaloids (up to 3%) and are cultivated. *D. myoporoides* comprises chemical breeds (with either scopolamine or hyoscyamine as the chief constituent; there are even chemotypes with nicotine) and it appears that the alkaloid profile fluctuates with the season, with hyoscyamine reaching a maximal concentration in the fall, and scopolamine reaching a maximal concentration in the spring. Both species are exploited for the extraction of alkaloids, which used to be carried out on site for a long time. Since the beginning of the 1980s, the leaves of *Duboisia* produced in Australia have been exported toward Europe, mainly to Germany, for extraction. Thus, in 1988-89, about 500 metric tons of leaves were exported.

Other Modes of Obtention of Tropane Alkaloids

Several synthetic approaches are possible, but they cannot compete with extraction. Much research has also been conducted on *in vitro* cell culture. To date, the low levels obtained do not allow one to envision industrial production. Note, however, that the culture of "hairy roots" in fermentors has true potential: those are particularly productive forms obtained by infection with *Agrobacter rhizogenes*.

Semisynthetic Anticholinergics

Their study is outside of the scope of pharmacognosy. Note however, the structure of the closest synthetic analogs, which can be prepared from naturally-occurring alkaloids, amine oxides, and quaternary ammonium salts (quaternarization slows down the passage across biological membranes, therefore the central effects are greatly decreased). For all of these products (oral forms), the contraindications, side effects, and warnings are similar to those of atropine.

- the hydrochloride of atropine *N*-oxide (oral and parenteral routes), indicated for the symptomatic treatment of the pain associated with functional disorders of the gastrointestinal and biliary tracts.

- the hydrobromide of scopolamine *N*-oxide (oral route), indicated in the treatment of Parkinson's disease and the postencephalitic parkinsonism;

- the bromide of *N*-isopropylatropine or ipratropium bromide (INN), used, among others for 1. the treatment of acute severe asthma and acute attacks of chronic bronchopneumopathy, and in combination with a β-2-sympathomimetic (use by trained hospital personnel only) and 2. the symptomatic treatment of seromucous rhinorrhea in case of vasomotor rhinitis without infection or allergy, and the treatment of asthma attacks.

- the bromide of *N*-ethylscopolamine or oxitropium bromide (INN), a bronchodilator indicated for the maintenance treatment of asthma, of the reversible bronchospasm of chronic obstructive bronchopneumopathy, and to treat asthma attacks.

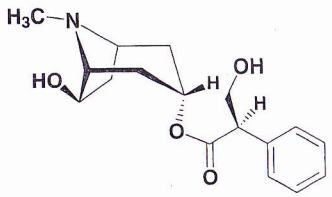
- Other quaternary ammonium salts with similar structure and properties are marketed outside of France (e.g., xenytropium bromide, atropine methylnitrate).

5. OTHER SOLANACEAE

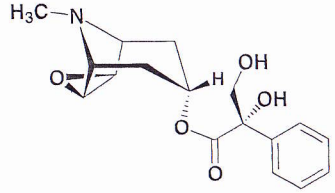
• *Anisodus tanguticus* (Maxim.) Pasch

This Chinese plant (*zang qie*) is an ingredient of traditional anesthetic preparations. Its roots contain alkaloids, namely anisadine and [illegible]

are structurally related to those of the official Solanaceae. Anisodamine [(–)-3α-tropoyloxy-6β-hydroxytropane], a CNS stimulant, an anticholinergic and an antispasmodic, is used to treat acute enteritis and septic shock (bacillary dysentery); by dilating the capillaries, it improves microcirculation. Anisodine [(–)-3α-(2'-hydroxytropoyloxy)-6β,7β-epoxytropane] is a CNS depressant, it is antagonized by physostigmine, and chiefly used to treat migraine headaches.



Anisodamine



Anisodine

6. ALKALOID-CONTAINING ERYTHROXYLACEAE: COCA

The use of coca in South America predates the Incan empire: it was nearly five thousand years ago that the natives of the Andes began cultivating, optimizing, and using coca for the production of its leaves. These are traditionally used as a masticatory to abolish hunger and fatigue. The Incas believed that it had a divine origin, and reserved it for religious ceremonies and privileged social classes. Today, coca leaves continue to be chewed by hundreds of thousands of people of the Andes; it is also a source of cocaine, an alkaloid without any therapeutic interest today, but whose traffic and illicit use keep growing endlessly *. Although the use of coca leaves by the Indians had been known in Europe since the beginning of the sixteenth century, there were no applications until cocaine was isolated in 1859. At that time, this alkaloid was used for its anesthetic properties, and considering its stimulating properties, it held promise for becoming a treatment for morphine addiction. The focus on cocaine was probably due in part to the monograph published by S. Freud in 1884, although he later lost interest in this alkaloid. The accumulation of data on its harmful effects led to limiting its use to anesthesiology, designing synthetic anesthetics (xylocaine, 1906), and implementing, at the beginning of the twentieth century, the first restrictive legislation. The most recent years have been marked by novel forms and modes of administration (coca paste, crack cocaine), and in several countries, by the rapid expansion of illicit use.

* In its 1995 report, the French *Observatoire géopolitique des drogues* estimated the 199[illegible] production of cocaine hydrochloride to be between 1,000 and 1,500 t (La Découverte Eds. 1995, Paris). In France, 1,060 persons were arrested for possession of cocaine in 199[illegible] (1.53% of all arrests), a figure which, according to the *Observatoire français des toxicomanies* (OFDT), is only the tip of the iceberg for a type of drug abuse that is still often reserved to closed upper class circles. The same year, the use of crack increased substantially [illegible]

The history of coca cannot be told, even briefly, without mentioning that in 1885, an American pharmacist by the name of J.S. Pemberton concocted a "French wine of coca, ideal tonic", an imitation of a preparation marketed in France since 1863 and internationally renowned, namely "*vin Mariani*". Soon, Pemberton modified his formula, replacing the alcohol with cola extract and the plain water with fizzy water: Coca-Cola® was born (A.G. Candler, 1892), and at the beginning of the twentieth century (1903) cocaine was removed from the original formula.

• Coca, *Erythoxylum* spp.

Until 1972 (9th Ed.), the French Pharmacopoeia had a monograph on the leaves "harvested after they fully mature, from *E. coca* [...] which occurs as several subspecies and varieties...".

The Plant, the Drug. Coca is a cultivated shrub, pruned to different heights depending on the geographical area (70-80 cm in the Yungas of Bolivia). The branches are reddish (hence the genus name *erutros - xulon*), and bear oval, entire, and shortly petiolate leaves. The flowers are pentamerous and yellowish-white. The fruit is a small red drupe. The leaf of the typical species has a slightly acuminate blade (2.5-7.5 x 1.5-4 cm), more or less prominently marked on the lower side by two curved lines, which delineate an oval area centered on the midrib. The taste is weakly bitter; the odor is weak in the fresh drug and becomes clearly aromatic in the dried drug. Chewing coca leaves causes a more or less rapid sensation of anesthesia of the tongue and mucosas. The microscopic examination shows, in the section and powder, an epidermis with a characteristic papillose cuticle.

The *Erythroxylum* cultivated to produce leaves rich in cocaine includes three taxa, which are morphologically very close—they are really three varieties—and which are linked to two species, namely *E. coca* and *E. novogranatense*.

• *E. coca* Lam. var. *coca* grows wild in the Peruvian and Bolivian Andes: this is the coca actually cultivated on the damp eastern side of the mountains, in the Cusco and Huanaco area in Peru, and in the Yungas and the Cochabamba area in Bolivia. The leaves are dark green; the blade is elliptic and wide; its midrib forms a prominent ridge on the upper side; the stipules are indeciduous; and the bark of the stem is verrucose. Another variety, var. *ipadu* Plowman, is cultivated in the low lands of the Amazon basin by seminomadic tribes: this form is thought to be a cultivar subject to vegetative propagation rather than an isolated taxon.

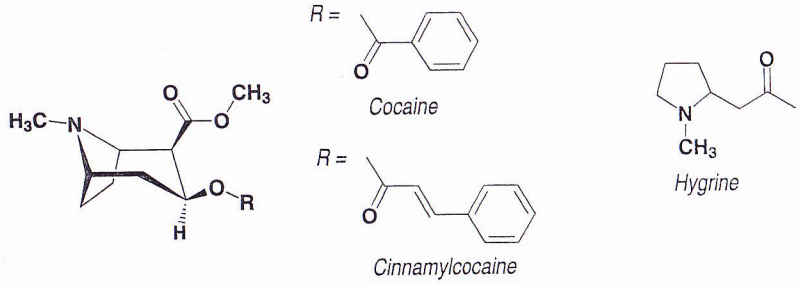
• *E. novogranatense* (Morris) Hieron var. *novogranatense*. This forest variety grows in Colombia and Venezuela. The leaves are a bright yellowish-green, the blade is elliptic and elongated, and the stipules disintegrate.

• *E. novogranatense* (Morris) Hieron var. *truxillense* (Rusby) Plowman. This variety is characteristic of the dry areas of the north of Peru and of Ecuador. The leaves have an elliptic, very narrow, and pale green blade; the stipules are marcescent or indeciduous. Like the previous variety, this one has smooth bark on the stems, more or less visible secondary veins on the blade, and the midrib ridge is flattened.

Reviewing the flavonoid composition and some hybridization experiments suggests that *E. novogranatense* var. *truxillense* is an intermediate between *E. coca* and *E. novogranatense* var. *novogranatense*, but that it is not a hybrid. The three taxa are thought to represent stages in evolution, which would have *E. coca* var. *coca* as their ancestor; the latter is the only form capable of reproducing without human intervention.

Chemical Composition. The drug contains variable quantities of an essential oil which includes methyl salicylate (this may have something to do with the fact that the *coqueiros* prefer one or the other coca cultivar), flavonoids, and tannins.

The alkaloid concentration ranges from 0.5 and 1.5% depending on the species, the variety, the geographical origin, and other factors. The chief alkaloid (30 to 50%) is an ester, volatile as a free base, namely cocaine (= methylbenzoylecgonine, see generalities). It occurs alongside other derivatives of ecgonine: cinnamylcocaine (= methylcinnamylecgonine), truxillines (esters of a dicinnamic acid), and several pyrrolidines (hygrine, cuscohygrine).



Tests. The 9th edition of the French Pharmacopoeia (1972) required a TLC analysis of a tincture (1/5) in 60% ethanol and a gravimetric quantitation of the "non-volatile" total alkaloids (>0.7%).

Pharmacological Properties. Cocaine is a local anesthetic. As a contact anesthetic, it blocks ion channels in neuronal membranes, and interrupts the propagation of action potentials corresponding to the sensory message. Cocaine is also a parasympathomimetic: it acts as an adrenergic stimulant by blocking the reuptake of dopamine and noradrenaline at the presynaptic neuron by binding to their transporters (but for some activities, some authors postulate that there is a decrease in parasympathetic inhibition).

This adrenergic stimulation causes hyperthermia, mydriasis, and vasconstriction of most of the blood vessels, which increases resistance and contributes to

ERYTHROXYLUM COCA Lam.

increasing blood pressure. The heart rate increases. Centrally, the stimulation results in a sensation of euphoria with intellectual stimulation, decreased inhibition, hyperactivity, and other effects sought by drug addicts.

The depletion which follows the reuptake blockade explains the short term depressant effect (psychic and physical asthenia, respiratory and vasomotor depression) and the rapid development of an intense psychic dependence which is reinforced by further abuse (at least with the IV and smoked forms). Cocaine does not induce physical dependence.

Uses. Neither coca leaf nor its galenicals are used any more, but the leaves are still used to extract cocaine. The hydrochloride (Fr. Ph., 10th Ed., controlled narcotic, maximum dose: 0.03 g/single dose - 0.6 g/day) is practically no longer used. For a long time it had been the active ingredient of the French mixture of Bonain or *mélange de Bonain* (an anesthetic used in ear, nose, and throat surgery [phenol, menthol, cocaine]). In the United States, cocaine is used in combinations (e.g., tetracaine, adrenaline, cocaine) for local anesthesia, for example to stitch small wounds.

Traditional Uses of the Coca Leaf. The use of the coca leaf as a masticatory is very ancient. Proved by statuettes found in archeological digs, this use predates the Inca domination by a very long time. Traditionally, the coca leaf is chewed, and added alkalis facilitate the release of cocaine*. The coca leaf is also used, in countries such as Bolivia, in infusion**; the common form is the tea bag which yields a strikingly aromatic infusion, consumed like coffee or tea (*mate de coca*).

Illicit Use of Cocaine

• Cocaine hydrochloride is generally "snorted" by the intranasal route, and less often used by IV injection. During IV use, the dysphoria which follows the brief euphoria is substantial, and leads some users to simultaneously consume heroin (speedball). Cocaine intake causes euphoria, intellectual stimulation, hyperactivity, a feeling of hyperlucidity, and an acceleration in the elaboration of ideas. Its activity resembles that of amphetamines, and also manifests itself by a decrease in fatigue, insomnia, anorexia, and increased talkativeness, but also by irritability, altered sensations and impaired judgement, physical exhaustion, and emotional depression. Cocaine use commonly causes severe headaches and sometimes causes convulsions;

* Chewing 20 g of coca (in other words 48 mg of cocaine) rapidly leads to a plasma concentration of alkaloid of 150 ng/mL. The substance is still present in the blood after seven hours. The experiment has been conducted with *ipadú*, which is a mixture of coca leaves and of ashes of *Cecropia* leaves. See: Holmstedt, B. *et al.* cited by Holmstedt, B. (1991). Historical Perspective and Future of Ethnopharmacology, *J. Ethnopharmacol.*, **32**, 7-24.

** Part of the cocaine goes into the infusion (Siegel, R.K., ElSohly, M.A., Plowman, T., Rury, P.M. and Jones, R.T. (1986). Cocaine in Herbal Tea, *JAMA*, **255**, 40).

delusions and hallucinations suggesting a serious paranoid psychosis are also described. Another effect is compulsive scratching (delusions of parasitosis), and difficulties with verbal expression and memorization are common. The most serious complications are cardiovascular: cocaine can cause a hypertensive emergency and myocardial ischemia degenerating—this is not uncommon—into an infarct. The hypertension can be at the origin of cerebral hemorrhage.

Massive overdose is characterized by coma, convulsions, and cardiac alterations. The risks are higher in alcohol users (who drink alcohol to mask the side effects of cocaine): the liver esterases transesterify cocaine into cocaethylene (benzoyl-ethylecgonine), which is particularly toxic.

• Coca paste, the initial product of the extraction of the leaves, contains from 40 to 70% cocaine (extraction with sulfuric acid, alkalinization with carbonate, dissolution of the free base in kerosene). First used in South America, this paste has spread outside of this continent and is probably the origin of "crack cocaine" use. The paste is smoked. Kerosene and other residual solvents impart their own toxicity to the preparation.

• Cocaine is also smoked (this is "freebasing"). Some use the pure base, extracted with diethyl ether after treatment with bicarbonate. Many others use "crack cocaine" which is the free base, obtained by treating the hydrochloride with bicarbonate ("rock" *). The free base is sometimes mixed with tobacco, cannabis, or other herbs. The smoked forms have intense effects with a rapid onset (rapid pulmonary absorption, very high plasma concentrations), but these effects do not last; the profound depression which follows drives the user to take the drug again, and dependence sets in very rapidly.

7. POLYHYDROXY*NOR*TROPANES

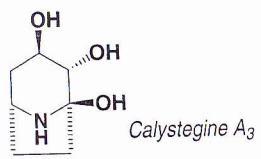
So far, polyhydroxy*nor*tropanes have been isolated from Solanaceae, Convolvulaceae, and Moraceae. Among them, the calystegines—characterized by a hydroxyl function at C-1**—can be tri-, tetra-, or pentahydroxylated (calystegines A, B, or C). In the Solanaceae, they have been isolated from the genera *Atropa*, *Datura*, *Duboisia*, *Scopolia,* and *Physalis,* as well as from edible fruits (calystegine B2: chili pepper, tomato, eggplant). They are highly water soluble alkaloids, therefore they are not extracted by the conventional methods and it is possible that they occur more widely than is suggested by the literature.

* It is the excess of this salt which produces cracking noises upon heating, hence the name "crack".

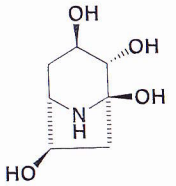
** In at least one case, it is replaced by an NH_2 (calystegine N_1). *Cf.* Asano, N., Kato, A., Yokoyama, Y., Miyauchi, M., Yamamoto, M., Kizu, H. et Matsui, K. (1996). Calystegin N_1, a Novel nortropane Alkaloid with a Bridgehead Amino Group from *Hyoscyamus niger*: Structure Determination and Glycosidase Inhibitory Activities. *Carbohydr. Res.*, **284**, 169-178.

Like the polyhydroxy-indolizidines, polyhydroxy*nor*tropanes inhibit various glycosidases (α- and β-glucosidases, α- and β-galactosidases, trehalase), and the selectivity and intensity of the inhibition depend on the structure of the alkaloid.

It is possible that the polyhydroxy*nor*tropanes are responsible for the neurological toxicity of certain *Solanum* known to cause cerebellar degeneracy in animals: the hydroxy-indolizidines of *Swainsona* induce identical symptoms. Along the same lines, polyhydroxy-pyrrolidines may be the agents truly responsible for the toxicity attributed to the (English) bluebell (*Hyacynthoides non-scripta* [L.] Rothm.).



Calystegine A_3



Calystegine B_1

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Coca – Cocaine

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