alkaloids in this group are characteristic of a certain number of families of the orders Magnoliales (according to Cronquist), Laurales, or Papaverales (Annonaceae, Magnoliaceae, Lauraceae, Monimiaceae, Papaveraceae, Fumariaceae). They also occur in several families of the Ranunculales (Berberidaceae, Menispermaceae, Ranunculaceae), and more sporadically in other families (Euphorbiaceae, Fabaceae).

3. Phenethylisoquinoline Alkaloids

As before, a second molecule of aromatic amino acid participates in the elaboration of a C_6C_2-N-C_3C_6 nucleus, but this time it is a phenylpropanoic acid (e.g., cinnamic acid). Homologous to the previous alkaloids—phenethylisoquinolines, bisphenethylisoquinolines, homoaporphines, homomorphinandienones, homoerythrinanes, dibenz[d,f]azecines—or rearranged to tropolones (e.g., *Colchicum* alkaloids), these compounds are fairly specific to the Liliaceae (*Androcymbium, Bulbocodium* [*Colchicum*], *Gloriosa, Kreysigia, Schelhammera*).

4. Alkaloids of the Amaryllidaceae

Again, two aromatic amino acids are required for the formation of the alkaloids, but one of the two loses one carbon atom to form a C_6C_2-N-C_1C_6 nucleus, which only occurs in members of this botanical family (e.g., *Clivia, Crinum, Galanthus, Haemanthus, Leucojum, Sprekelia, Sternbergia*).

5. Monoterpenoid Isoquinoline Alkaloids

These compounds incorporate a monoterpenoid unit, secologanin, according to a mechanism resembling the one which leads to monoterpenoid indole alkaloids; in fact, they occur in certain species of Rubiaceae, a family otherwise known to elaborate, from this seco-iridoid, a variety of alkaloidal structures (see the chapter on indole alkaloids).

The figure on the previous page summarizes the different pathways for the formation of alkaloids from phenylalanine and tyrosine.

Phenethylamines

1. INTRODUCTION

Phenethylamines occur in many plants. Some are species specific (ephedrine, mescaline, cathinone) and have marked pharmacological properties, others are common products of the metabolism of aromatic amino acids such as tyramine or phenylethylamine. Although the concentration of these decarboxylation products in edible or medicinal plants is too low to induce harmful effects, it is sometimes sufficient to play a role in the onset of an attack of migraine. The effects of these amines, particularly tyramine, can become serious in patients treated with MAO inhibitors: tyramine is no longer metabolized in the intestine and liver, and a risk of hypertensive crisis ensues. Therefore, it is necessary to monitor the consumption of certain drugs by these patients (e.g., broom flowers), as well as certain vegetables (avocado, cabbage, cucumber, spinach) and certain other foods (cheese).

2. PHENETHYLAMINE-CONTAINING DRUGS

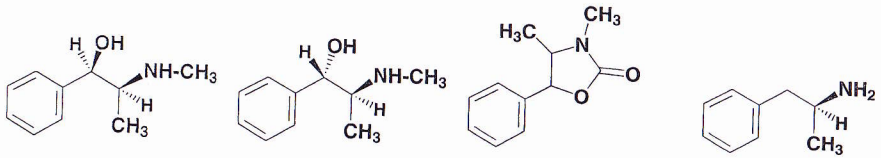
• EPHEDRAS, *Ephedra* spp., Ephedraceae

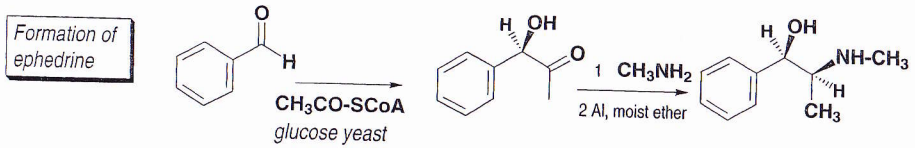
Although ephedrine is the topic of a monograph in the 3rd edition of the European Pharmacopoeia, ephedra has long disappeared from most pharmacopoeias: only synthetic ephedrine still finds some uses.

The Plants. Ephedras are dioecious subshrubs with the same habit as horsetails, with slender, angular, and striated branches, and with leaves reduced to membranous scales. The female flowers are reduced to the ovule and surrounded by bracts that are red and fleshy at maturity. The male flowers are grouped in yellowish catkins.

The species that contain substantial quantities of alkaloids are mostly Asian: *E. equisetina* Bunge and *E. sinica* Stapf. from China, *E. intermedia* Schrenk and C.A. Meyer, and *E. gerardiana* Wall ex Stapf. from India and Pakistan. About ten species are found in North America, for example Mormon tea, *E. nevadensis* S. Watson. Ephedras are seldom found in Europe (*E. major* Host., *E. procera* Fisch. & C.A. Meyer, *E. campylopoda* C.A. Meyer, or *E. distachya* L. [shrubby horsetail] of the Atlantic coast) and, except for *E. major*, most of these species, like the North American species, are thought to contain alkaloids at a negligible concentration or no alkaloids.

Chemical Composition. Flavonoids and proanthocyanidins have been identified in the drug, but nitrogen-containing substances—protoalkaloids—are the focus of attention. These are phenethylamine-type derivatives and their concentration, which varies as a function of the species, can exceed 2%. The chief constituent is almost always (–)-ephedrine, which represents from 40 to 90% of the total alkaloids. (–)-Ephedrine [= (1*R*,2*S*)-1-phenyl-2-methylaminopropan-1-ol] occurs alongside (+)-pseudoephedrine (which has the 1*S*,2*S* configuration) and the corresponding *nor* and *N*,*N*-dimethyl derivatives. All of the Asian ephedras contain alkaloids, but their





concentration varies depending on the species: *E. sinica* (1.3%), *E. equisetina* (2.2%), *E. monosperma* (2.8%), *E. intermedia* (1.1-1.6%). Ephedrine is the major compound in most species, except in *E. intermedia* where pseudoephedrine is dominant. The drug also contains traces of cyclic compounds: 5-phenyloxazolidines and ephedroxane (a 3,4-dimethyl-5-phenyloxazolidone). The stems also contain a small amount of an alkaloid derived from spermidine, namely orantine, whose structure is very closely related to that of the macrocycles described in the subterranean parts of some species in the genus.

The roots of several species contain an imidazole derivative (feruloyl histamine), alkaloidal macrocycles derived from spermine (ephedradines A-D), and dimeric flavonoids: bisflavanols (mahuannines) and flavano-flavonols.

Pharmacological Activity. Ephedrine is an indirect sympathomimetic. Structurally very close to adrenaline, it triggers the release of endogenous catecholamines from the post-ganglionic sympathetic fibers. It stimulates cardiac automaticity and has a positive inotropic activity; it accelerates respiration and increases its intensity; it is a bronchodilator and a stimulant of the brain stem respiration center; it decreases the contractility of the bladder. It is not metabolized much, can be used orally, and its duration of action is longer than that of adrenaline. It is well resorbed and highly lipophilic; it crosses the blood-brain barrier and, by releasing mediators centrally, has a stimulating psychic effect: stimulation of the attention and ability to concentrate, decrease in the sensation of fatigue and the need for sleep. High doses can cause headaches, anxiety, tremors, insomnia, and psychotic manifestations; redness of the face; nausea; tachycardia and precordial pain; sweating; urinary retention, and more.

Ephedroxane and (+)-pseudoephedrine are experimental anti-inflammatory agents.

Uses of ephedras. Ephedra is not listed in the annex of the 1998 French Explanatory Note on plant-based medicines. In France, its uses are very limited. In Germany, *E. sinica* can be used by the oral route, but only for a short time. It is believed that in Asia, the drug has been used for about 5 millenia. *Mahuang* consists of the stems of *E. sinica*, *E. intermedia*, and *E. equisetina*, and is official in the People's Republic of China where it is used as an antiasthmatic, diuretic, and sudorific. The Chinese Pharmacopoeia also describes *mahuanggen* (ephedra root), a drug reputed to be an antisudorific and used as such.

In the United States, ephedras and ephedrine have been presented for a few years as potential aids in weight loss, a claim based on a hypothetical stimulating action on the combustion of fats. Also in the U.S. and based on the sympathomimetic properties of ephedrine, some promote products more or less explicitly and in a wide variety of sales networks as "uppers" (e.g., "*herbal ecstasy*", "X*phoria*"). In addition, ephedrine can be converted chemically into methcathinone and metamphetamine, two illicit substances. Naturally, this has led several states in the U.S. to enact restrictive legislation. The proliferation of products based on *mahuang*

and/or ephedrine has caused an increase in the number of case reports of more or less serious side effects and in 1997, the FDA proposed detailed labeling requirements for ephedra-based dietary supplements: warnings against prolonged used and against combinations with products such as caffeine, limited claims, information on side effects, and so forth. The directions for using these dietary supplements must not lead the consumer to take more than 8 mg per unit dose and 24 mg/24 hours.

Production of Ephedrine. Although ephedrine can be extracted from ephedras, it is also easy to synthesize. The first step in the synthesis is a biological conversion of benzaldehyde to (*R*)-1-phenyl-1-hydroxy-2-propanone by a yeast (*Saccharomyces* sp.). The second step is a treatment with methylamine.

Uses of Ephedrine. Ephedrine hydrochloride has long been used to treat the acute attack of asthma. Its multiple activities, numerous contraindications (coronary insufficiency, arterial hypertension, closed angle glaucoma, hyperthyroidism), drug interactions (MAO inhibitors, tricyclic antidepressants), the required precautions (prostatic hypertrophy, cardiac insufficiency, diabetes), potential adverse effects (tachycardia, headaches, sweating, agitation, insomnia, anxiety), as well as the fact that the effects wear out if the doses are repeated in close time proximity (tachyphylaxis) have led to the virtual abandon of this compound as a bronchodilator and analeptic. However, it remains available in France for this indication, particularly in combinations (with theophylline, caffeine, and others).

Ephedrine was formerly used widely for its vasoconstrictive properties, as an ingredient of nasal sprays or nasal drops, for the antiseptic and vasoconstrictive treatment of the acute congestion of rhinitis, sinusitis, and rhinopharyngitis. These solutions, several of which are still available, must not be used in children under three years of age (risk of central excitation symptoms); they are also contraindicated in case of closed angle glaucoma and treatment with MAO inhibitors. Hypertensive and coronary patients ought to use the greatest caution. Limiting the use of these solutions to a short time is crucial, because they can induce iatrogenic rhinitis.

Ephedrine is also an ingredient of syrups and other formulations designed for the symptomatic treatment of non-productive coughs. Marginal uses include in preparations for the topical treatment of ear inflammations. Note that ephedrine is a banned stimulant in sports, so that its use may result in a positive doping control test.

Uses of Pseudoephedrine. Pseudoephedrine hydrochloride, alone or in combination (with chlorphenamine, ibuprofen, paracetamol, or triprolidine), is an ingredient of drugs designed for the symptomatic treatment of nasal congestion and rhinorrhea (coryza). These products are contraindicated in children and in patients taking MAO inhibitors. They must be avoided in pregnant or breast-feeding women. They must be used with caution in case of hypertension or urination difficulties. Pseudoephedrine has a low toxicity, but it can cause dryness of the mouth, insomnia, sweating, and anxiety. The onset of tachycardia requires discontinuing the treatment. Pseudoephedrine sulfate is used for similar indications.

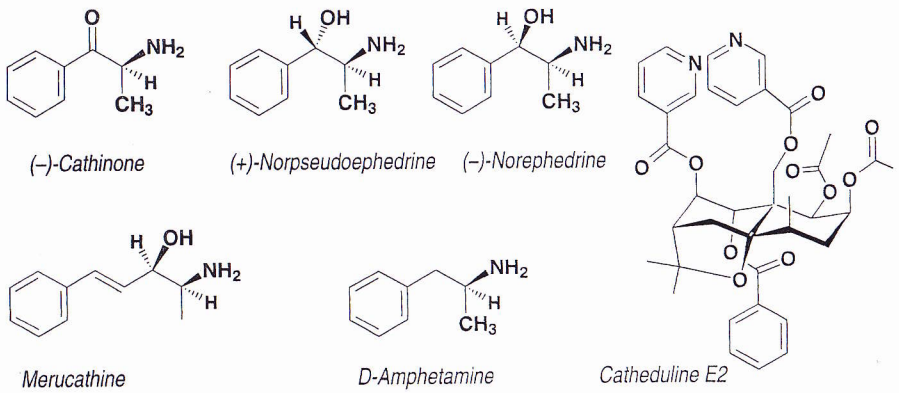
Pseudoephedrine, like its stereoisomer, is a banned stimulant in sport, so that its use may result in a positive doping control test.

Other Compounds. Combinations of the same type as above contain a synthetic analog of protoalkaloids: norephedrine (= phenypropanolamine).

• KHAT, *Catha edulis* Forsk., Celastraceae

Khat (or cath, chat, jat, tschatt, and so forth) is a shrub of modest size in aric areas (1-2 m), but it can reach 10 m in the tropics. The leaves are highly polymorphic and indeciduous. Also known as Abyssinian tea, it is native to the horn of Africa (but some think that it originated in Yemen). Commonly reproduced by vegetative propagation, it is cultivated in the south-east of the Arabian peninsula (Ta'izz, Yemen), in Somalia, Sudan, Ethiopia (Harrar), and as far as Kenya (Meru district) and Madagascar. The leaves are harvested from the tip of the branches in the morning and carefully wrapped (banana leaves, damp paper, plastic) for protection against drying and wilting.

Chemical Composition. Chemically, the leaf contains flavonoids, some essential oil, complex polyesters of polyhydroxylated dihydroagarofurans (cathedulines) and arylalkylamines (the khatamines), which are responsible for the activity of the drug. In the fresh and young leaves, the chief constituent is cathinone, in other words (*S*)-α-aminopropiophenone. In the dried drug and in older leaves, this (–)-cathinone has been converted to an 80-20 mixture of (*S*,*S*)-(+)-*nor*pseudoephedrine and (*R*,*S*)-(–)-*nor*ephedrine. Fresh drug from northern Kenya also contains the C_6-C homologs of these phenylpropylamines: (*R*,*S*)-(+)-merucathine, (*S*)-(+)-merucathinone, and (*S*,*S*)-(–)-pseudomerucathine. The phenylpropylamine content is maximal in the young shoots and appears to depend on the geographical origin: the cathinone level is reported to range from 9 to 330 mg/100 g depending on the harvest location. A range of variation just as wide has been observed for *nor*ephedrine and *nor*pseudoephedrine.



The cathedulines (K1, K2, K5,...E1-6) are complex molecules whose structure varies as a function of the geographical origin of the drug. Their molecular weight ranges, depending on the acids that esterify the polyhydroxylated sesquiterpene, from 600 to 1,200. Structurally, they are quite close to the constituents with alkaloid-like behavior that occur in spindle trees and in some species of *Maytenus*.

Pharmacological Activity - Toxicity. Pharmacologically, the activity of (–)-cathinone is qualitatively quite comparable to that of D-amphetamine: it causes anorexia, hyperthermia, respiratory stimulation, mydriasis, arrhythmia, and hypertension. This amine induces the release of catecholamines from storage. Its effects on the central nervous system depend in part on the subject's environment; they are characterized by a subjective and euphoric sensation of increased energy, well-being, self-confidence, mental acuity, and ease in thought formation. Objectively, slight euphoria can be observed in a talkative and sometimes hyperactive subject. Later on, undesired effects can appear: insomnia, nervousness, and nightmares. In very rare cases, khat can induce a toxic psychosis, probably by potentiating a prepsychotic condition. Depression is then observed, and even schizophreniform or paranoid symptoms.

Khat use induces a psychic dependence which is moderate, but common—the use becomes compulsive. In contrast, there is no physical dependence or tolerance (at least to the central effects) although a withdrawal syndrome can be observed in heavy abusers. The tannins that occur in the drug are thought to be in part at the origin of the constipation observed in regular users.

Use of Khat. The *fresh* leaves, sold within 24 hours of harvest, constitute a masticatory known for its stimulating properties. In some countries (Yemen), khat use is an ancient custom and it is practiced at social events, thereby strengthening social bonds. In other countries, khat is used mainly to seek the pharmacological effects of the alkaloids (to suppress the appetite and to combat fatigue). Traditionally, the leaves (50-200 g) are chewed one by one, kept in the mouth for a while, then most often spit out.

In the early 1990s, Brenneisen and El Sohly estimated the number of daily users of khat leaves to be between two and eight million (northeast Africa, Yemen). Khat use is officially forbidden in some countries (Saudi Arabia, Sudan, Somalia) and more or less tolerated in other countries. Tolerated in Yemen where the authorities ban alcohol, khat is thought to be consumed daily by 50% of adult men. Cultivated without restriction in Ethiopia, it makes a massive contribution to the national economy: it is widely consumed there, and it is also exported to Djibouti where 90% of men and 10% of women are thought to be regular or occasional users. In the past few years, khat has been exported by air to a limited extent to large western cities, essentially toward the emigrant communities.

The use of the drug has now exceeded the scope of social and cultural traditions. It is at the origin of serious socio-economic problems linked to the malnutrition that can result from khat chewing (and its public health consequences) and to

seeking behaviors (disintegration of the family, absenteeism), without forgetting its impact on agriculture (superior profitability compared to food crops).

Cathinone is on the list of substances whose production, marketing and use are prohibited (see: French decree of September 10, 1992 and prior texts, *J. O. Rép. fr.* September 20, 1992, p. 13 039 *sq.*).

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