

2. Indolines Arising from the Cyclization of Tryptamine

These are essentially the alkaloids of the Calabar bean, and in addition the oligomers from the Calycanthaceae and Rubiaceae (*Psychotria*) are of some interest.

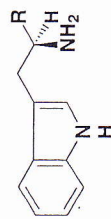
3. Ergoline Derivatives

They are highly specific to a few rare higher vegetables (Convolvulaceae) and to the Ascomycetes fungi. Although they are of fungal origin, they will be covered in the present book, because of their very high therapeutic interest.

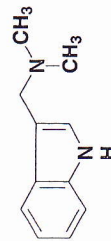
4. Monoterpenoid Indole Alkaloids

Monoterpenoid indole alkaloids are by far the largest group. They incorporate a C₁₀ (or C₉) monoterpenoid unit, and their distribution is limited to a small number of Angiosperm families, mainly the Apocynaceae, Rubiaceae, and Loganiaceae. Based on their biosynthesis, in this group of indole alkaloids we shall include the quinoline alkaloids of the cinchona: they are derived from the same precursor, namely strictosidine.

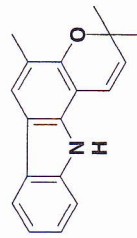
Because they have no applications (or interesting properties), the carbazoles of the Rutaceae, and the canthin-6-ones of the Rutaceae and Simaroubaceae will not be covered. Like the metabolites of phenylalanine and tyrosine, the mycotoxins formed from tryptophan will also be skipped (except for the ergolines: spirodesmin, paspalicine, and so forth).



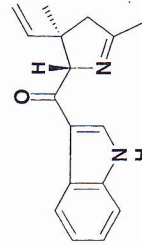
R = H: Tryptamine

R = CO₂H: Tryptophan

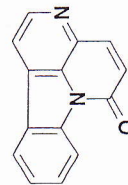
Gramine



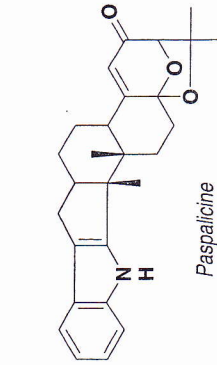
Gitrinimine



Borreline



Canthin-6-one



Paspalicine

Tryptamines, β-Carboline Alkaloids

“Drugs Containing Hallucinogenic Indole Alkaloids”

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1. GENERALITIES

Hallucinogens are substances capable of causing “substantial and transient modifications of perceptions, thought, and mood”, and are classified among psychoactive substances, a less restrictive term applicable to the hallucinogens but also to opium, alcohol, and solvents, and even to the psychoactive component of the action of the Solanaceae alkaloids.

Except for Indian hemp, whose properties are in fact markedly different, hallucinogenic plants owe their activity to nitrogen-containing substances. In most cases the structures responsible are indoles* (p. 970), indoalkylamines, or true alkaloids: tryptamines, carboline, and ergoline alkaloids; in a few rare cases, they are aryl-alkylamines (e.g., mescaline, see peyote) in which some authors see “virtual” indoles. In both cases, we shall note the obvious structural analogy with

Principal Hallucinogenic Drugs

Hallucinogenic drugs have been known since the dawn of time, and their use, rooted in the social life of all of the primitive civilizations, has been the source of mystico-religious practices and the basis of initiation rites. In cultures that consider disease to be the result of spiritual forces, they constitute a remedy, at least in the case of "mental" disorders: by establishing contact with the spirit which "possesses" the patient, the sorcerer (shaman or other) attempts to lure it out of the victim and to direct it to an object or animal instead; this is close to exorcism... In other cultures, hallucinogenic drugs act as a mediator between humans and gods, to reveal the existence of a "world of the spirits and an inner world within living creatures" beyond daily perception and appearance**. Sometimes this is a return to the origin of all things: as R.E. Schultes writes, "the user sees the gods of the tribe and relives the creation of the universe, of humans and animals [...] What is seen under the influence [of the drug] becomes the true reality". In some cases, hallucinogenic plants may have been used to support political power: is it not said that the Delphic oracle was inspired by inebriating fumes from plants?

2. AGARICACEAE (HALLUCINOGENIC, CENTRAL AMERICAN)

The *teonanacatl* used by the Aztecs of pre-Colombian America, and still used in some areas of Mexico, is not a well defined drug, but rather a group of mushrooms from the genera *Conocybe*, *Panaeolus*, *Psilocybe*, and *Stropharia*. Those most often used are *S. cubensis* Earle and *Psilocybe aztecorum* Heim. The cult of these mushrooms is probably ancient: how else can we interpret the existence of statuettes with human or animal faces, but shaped like mushrooms, found in Guatemala and dating from 1,000 B.C.? This cult was fought by the Spaniards, who saw in these mushrooms "dangerous and inebriating like wine" an obstacle to the diffusion of

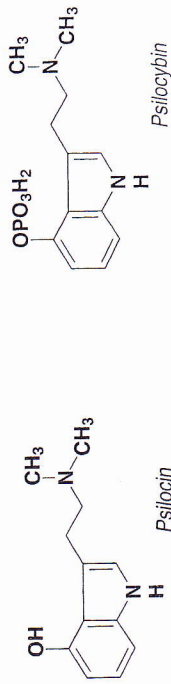
* Note, however, that the fly agaric [*Amanita muscaria* (L. ex Fr.) Hooker], traditionally used in Siberia by the shamans "to establish contact with the spirits" causes effects (auditory and visual hallucinations, transient excitation followed by stupor) which are not at all due to indoles. The toxicity of this mushroom, thought to be the Soma of the India of antiquity, is due not only to muscarine and its diastereomers, whose effects are linked to their affinity for the cholinergic receptors, but mostly to compounds of related structure: muscimol, ibotenic acid, and muscazone, which are GABA agonists (which is explained by the structural analogy with this amino acid). Sur A. *muscaria* see: Wasson, R.G. (1995).

Ethnomycology: Discoveries About *Amanita muscaria* Point to Fresh Perspectives, in

"Ethnobotany. Evolution of a Discipline", (Schultes, R.E. and von Reis, S., Eds.), p. 385-390, Chapman & Hall, London.

** Modern medicine has attempted, until it abandoned this approach, to use the "awakened dream" induced by hallucinogens for psychic exploration (oneiroanalysis, artificial

Christianity. The cult persisted underground, which made the identification of the species involved more difficult. It is now known that the active principles of these Agaricaceae are derivatives of tryptamine: psilocin and psilocybin.



Psilocin, which is phosphorylated 4-hydroxy-*N,N*-dimethyltryptamine, is active orally at doses ranging from 100 to 150 µg/kg. It causes few physical effects (mydriasis, muscle relaxation), but it induces substantial psychic effects: after an agitation, dizziness, and anxiety phase, hallucinations appear. These are visual hallucinations with shape distortion, color intensification, and distorted perception of time and space. The intensity of the effects depends on the personality of the subject and the environment.

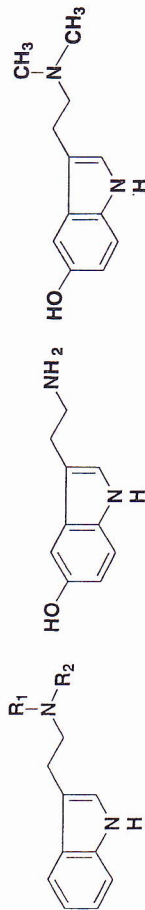
Several genera of mushrooms containing such amines are represented in temperate regions (*Psilocybe*, *Panaeolus*, *Copelandia*, *Gymnophilus*, *Inocybe*, *Pluteus*); however, it appears that their use to seek hallucinations is not very widespread. A few case reports of intoxication have been published in several European countries (including Austria, Denmark, Finland, France, Poland, and the United Kingdom). *Psilocybe semilanceata* (Fr.) Kumm. is among the species most often cited: it is occasionally consumed for its hallucinogenic properties, raw, cooked, or as an infusion. It is said that 20 to 30 carpophores are necessary to induce hallucinations, prolonged temporal distortion (4-8 hours), and potential synesthesia. In some patients, agitation, psychosis, and panic reactions can be observed. It is also said that 2 to 4 carpophores are sufficient to cause mild euphoria.

Similar uses are described in tropical areas. For example, in Asia, psychoactive mushrooms are used in certain Thai restaurants to cook "magic omelets" that are supposed to attract customers. Such mushrooms are also found in Hawaii, Australia, and New Zealand, among others.

3. MYRISTICACEAE (SOUTH AMERICAN)

These are trees with yellow flowers from the genus *Virola*, for example *V. elongata* (Benth.) Warb. (= *V. theiodora* Warb.), *V. calophylloidea* Markgraf, or *V. calophylla* (Spruce) Warb., whose trunk bark is prized among the tribes of the higher Orinoco basin. The method of preparation can vary greatly; often the powder is prepared from the bark soaked with the red resin which flows after the bark is peeled: the internal layers and the resin are scraped, dried over a fire, and pulverized; sometimes the bark is boiled and the resin collected and concentrated. Known under various names (*yakee*, *parica* [Colombia], *epéna*, *nyakwana* [Brazil],

Venezuela)], the drug is either reserved for medicine men or snuffed by all adult men, depending on the tribe. The drug contains derivatives of tryptamine, sometimes in considerable quantities—up to 11% in some specimens: examples include *N,N*-dimethyltryptamine and its 5-methoxylyated derivative, and traces of carboline. The mechanism of the effect *per os* is not well understood: other active constituents? Or inhibitors of amine degradation? The drug has a marked effect: intense agitation and excitability, followed by depression, and sometimes loss of consciousness.



Tryptamine, *N*-mono- and
N,N-dimethyltryptamine

Serotonin

Bufotenine

4. MIMOSACEAE (SOUTH AMERICAN)

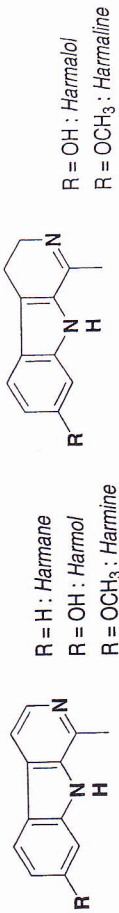
It is also in the Orinoco basin that this drug is found: known as *yopo* or *niopo*, it consists of the seeds of *Anadenanthera peregrina* (L.) Speg. (*Piptadenia peregrina* [L.] Benth.). *N,N*-Dimethyltryptamine, its *N*-methylated derivative, and its 5-hydroxylated derivatives (bufotenine) constitute the active principles of the “beans”, in which methoxylated carboline alkaloids have also been characterized. The seeds are roasted, crushed, mixed with alkaline ashes, and inhaled through bamboo tubes or hollow bird bones. As with *epéna*, a loss of motor coordination is observed, and fairly often, the subject perceives objects as larger than they are (macropsia). Another species, *A. colubrina* (Vell.) Benth., was used in the same fashion in southern Amazonia and is believed to still be in use in northern Argentina.

5. MALPIGHIACEAE (SOUTH AMERICAN)

This family of lignified tropical plants includes two hallucinogenic species known under the local names of *ayahuasca* (Ecuador, Peru) and *caapi* (Brazil). The bark of these vines with small pink flowers is used in the northwest Amazon region: it is shaved and macerated in cold water, or, in some areas, chewed directly.

Botanically, several species constitute *ayahuasca*. The mixture is based on *Banisteriopsis caapi* (Spruce ex Griseb.) C. V. Morton, whose bark can be used alone if need be. The concentration of total alkaloids in the drug is 0.5% on average, and the alkaloids that have been identified are β -carboline derivatives: harmine, tetrahydroharmine, harmaline, and harmol, among others. The bark is often mixed with other Malpighiaceae (*Diplopterys cabrerana* [Cuatrec.] Gates), or with plants from other families: Rubiaceae (*Psychotria viridis* Ruiz & Pavón), Solanaceae (*Brunfelsia grandiflora* D. Don). The beverage is thought to contain 500-800 mg of carbolines

and 40-80 mg of *N,N*-dimethyltryptamine (from the *Diplopterys* and *Psychotria*). Some authors explain the fact that the tryptamines are active orally by invoking the MAO inhibiting activity of the carbolines. Reputed as “telepathic”, this drug was used during religious ceremonies to gain the knowledge of the “true reality”. Its use has survived here and there, including in urban environments, as a panacea and also to allow healers to determine the cause of the malady, to treat psychosomatic ailments, or to gain knowledge of what plants to use to treat the patient. There is also some use in the context of religious syncretism.



R = H : Harmaline
R = OH : Harmol
R = OCH₃ : Harmine

R = OH : Harmalol
R = OCH₃ : Harmaline

6. ZYGOPHYLLACEAE: Harmel (Syrian Rue), *Peganum harmala* L.

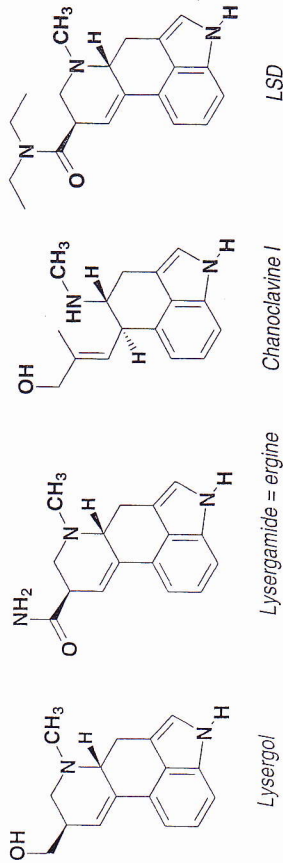
This herbaceous plant with very divided leaves grows from the north of the African continent to northern India and Manchuria. Its seeds contain 3-4% alkaloids identical to those of *ayahuasca*: harmine, harmol, harmaline, and related derivatives. The drug is reputed to be a CNS stimulant, and in some areas of western Asia, it is known that throwing the seeds into a fire releases psychoactive vapors.

7. CONVOLVULACEAE

Although the active principles of various Convolvulaceae are not tryptamines, we shall describe them here, in view of their hallucinogenic properties, which are comparable to those of the drugs listed above.

The species of interest—the sacred Mexican convolvulus—are comparable to the sacred mushrooms from the point of view of historical importance. Initially described under their Aztec names *otoliqui* and *tilitizin*, the plants used during religious, medical, and magic ceremonies have been identified as *Turbina corymbosa* (L.) Raf. (*otoliqui*, *coaxihuitl*) and *Ipomoea tricolor* Cav. (= *I. violacea* auct.), *tilitizin*). They continue to be used in certain regions of Mexico to predict the future and to diagnose and cure diseases.

The active substances in the seeds of these convolvulus arise, like the previous ones, from the metabolism of tryptophan, *via* tryptamine: ergine, lysergol, and various clavines (elymoclavine, chanoclavine) are alkaloids also described in some Ascomycetes whose hallucinogenic properties have long been known (see ergot). The concentrations of total alkaloids are generally low (*T. corymbosa*: 0.012%, *I. violacea*: 0.06%). The pharmacological properties of these compounds are well known, and they have been studied extensively in the case of one synthetic derivative, lysergic acid diethylamide or LSD 25 (*Lysergsäurediethylamid*, see the



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Calabar Bean Alkaloids

- **CALABAR BEAN,**
Physostigma venenosum Balf., Fabaceae

The seed of this vine was formerly official. It is a source of physostigmine, a cholinesterase inhibitor (also known as eserine). Recently, it was established that this alkaloid can also be obtained by fermentation: it is produced, with a yield that can reach 0.88 g/L, by a *Streptomyces* (*S. griseofuscus* NRRL 5324).

The Plant, the Drug. This climbing vine whose trifoliolate leaves are reminiscent of a creeping bean grows wild along the rivers of the Gulf of Guinea (Nigeria, Cameroon, Gabon). The seed is 2-3 cm long and 12-15 mm wide, and has a shiny brown tegument. It is odorless, tasteless, very hard, and marked on its convex side with a lighter groove which is 2-3 mm wide.

Chemical Composition. The seeds contain alkaloids (0.2-0.3%), chiefly represented by (-)-physostigmine (= eserine), occurring alongside norphysostigmine, eseramine, physovenine, geneserine, and unidentified substances. Physostigmine is unstable and is rapidly oxidized when exposed to air and light. In solution, its urethane group is rapidly hydrolyzed: it is converted to eseroline. In the presence of ammonia, a blue phenoxazone is formed.

