Hallucinogenic Plants

Various chemical substances are known to be the active hallucinogenic principles in many plants.

Norman R. Farnsworth

The so-called hallucinogenic drugs, many of which are widely used today, all seem to have in common the power to induce visual or other hallucinations and to divorce the subject from reality. The hallucinogens have a long history. Virtually all of them are derived from plants (*1*). Ancient man knew many of these plants, and, because of their effects, ascribed magical or mystical relevance to them, using them as sacraments in religious rites. In more recent times the hallucinogens (*2*) have been used by individuals who believe that they promote spiritual growth, enhance perception, stimulate personal development, and open up reality.

It is not known with certainty just how many plants have been used for hallucinogenic purposes, or even how many of those alleged to induce hallucinations actually do so (see *3*). Most of our definitive chemical knowledge of hallucinogenic plants has evolved only during the past decade or so. Three important factors have been responsible for this. First, valid botanical authentication of many hallucinogenic plants has been accomplished only during this period. Prior to this, chemical reports on these plants were, to say the least, chaotic. Second, the isolation and identification of active principles has been enhanced by the introduction of modern research techniques which require only small amounts of plant material. Finally, there has been an acute need for the active principles present in hallucinogenic plants, either as potentially useful drugs in the treatment of mental disease or as new tools for the pharmacologist in his attempts to shed some light on the biochemical causes of mental illness. These needs have accelerated the research, in which workers from many disciplines have participated: botanists, ethnobotanists, ethnologists, chemists, pharmacognosists, pharmacologists, psychologists, and others.

The hallucinogenic plants can be divided conveniently into two groups according to whether their activity is due to nonnitrogenous or nitrogenous principles, when this is known. The two representatives of the nonnitrogenous group discussed here are marihuana (*Cannabis sativa*), which contains several dibenz-α-pyrans (Fig. 1), and nutmeg (*Myristica fragrans*), which contains phenylpropenes (Fig. 1). The representatives of the nitrogenous group discussed here can be divided into the following subgroups: (i) β-phenethylamines [peyote (*Lophophora williamsii*, family Cactaceae)]; (ii) simple indoles (*Piptadenia* and *Mimosa*, family Leguminosae; *Virola*, family Myristicaceae); (iii) "teonanacatyl" (*Psilocybe*, *Conocybe*, and *Stropharia* species, family Agaricaceae); (iv) β-carbolines (*Peganum harmala*, family Zygophyllaceae); (v) isoquinuclides (*Tabernanthe iboga*, family Apocynaceae); (vi) ergolines [the morning glories (*Rivea corymbosa* and *Ipomoea* species, family Convolvulaceae)]; (vii) tropanes (*Methysticodendron amesianum* and *Datura* species, family Solanaceae); and (viii) the isoxazoles [fly agaric (*Amanita muscaria*, family Agaricaceae) (Fig. 1)].

In addition to the plants from these two major groups, selected members of a group of plants which are known to be hallucinogenic but in which the active principles are unknown are discussed.

Plants Having Nonnitrogenous Active Principles

Marihuana. Marihuana has been presenting a perplexing problem to various cultures and societies of the world for centuries. The controversy arising in recent times as to whether the use of marihuana is "good" or "bad" should remind us of some of the phrases used by different generations in other lands to describe the plant or, rather, its effects. In the pre-Christian era, the Chinese often referred to marihuana as the "Liberator of Sin," whereas, in a later period, these same people named the plant "Delight Giver." Hindus have long termed it "The Heavenly Guide" and the "Soother of Grief."

The nature of the descriptive phrases has, undoubtedly, depended on whether a society was interested in using the plant or interested in preventing its use. Giving valid scientific evidence against marihuana has always been difficult, for a number of reasons. A brief description of the plant, its growth characteristics, and its chemical constituents should show the reason for many of these difficulties.

The plant *Cannabis sativa* L. (family *Cannabinaceae*), the source of marihuana, is a tall, annual weed, sometimes reaching a height of 15 feet (4½ meters). It will grow in almost any waste or fertile area. It is important to note that this weed is dioecious—that is, it has male and female plants. The male (staminate) plant usually grows taller than the female (pistillate) plant. The staminate flowers are axillary and borne in panicles, whereas the axillary pistillate flowers are long catkins. Differentiation of the male and female plants is important because the chemical compounds responsible for the euphoric effect of marihuana are found primarily in a sticky resin that covers the female flowers and adjacent leaves. Of importance in identifying both the male and female plants are the leaves, which are large and palmately compound, each having five to seven linear-lanceolate leaflets, with serrate (toothed or notched) leaf margins. Although the literature invariably refers to the resin covering the female flower parts as the only portion of the plant containing the euphoric principles, very few data are available to support this statement. It is altogether possible that other parts of the female plant—and the male plant as well—may also contain active substances. Detailed phytochemical studies of all parts of both male and female plants, collected in different areas of the world, seem to be in order.

The seed, seed oil, seed oil cake, and

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fiber (hemp) from *Cannabis sativa* L. are all important and useful economic products; other parts of the plant, those that contain the euphoric principles, constitute a legal as well as a social problem.

Although the layman may not always use the proper terminology in speaking of marihuana or its derivatives, the meaning of certain words associated with this drug is quite clear. "Hashish" and "charas" are the unadulterated resin from the flowering tops of cultivated female *C. sativa* plants. "Bhang" is prepared from uncultivated female plants; the tops are cut from these plants, and a decoction in water or milk is made. The decoction is either drunk or dried and smoked. "Ganja" is prepared by harvesting the tops from very carefully selected cultivated female plants. This preparation is taken in the same way that bhang is. Ganja is superior to bhang but inferior to hashish. "Majun" is ganja that has been incorporated into sweetmeats.

Most of these terms are seldom encountered in the United States, with the exception of "hashish," a term that is generally used incorrectly, since most of the *Cannabis sativa* used in this country is in the form of dried flowering tops of the plants (probably a mixture of male and female plants in most cases). This mixture is admixed with considerable leaf material and ordinarily goes more correctly under the names of marihuana, pot, or grass. Cigarettes containing marihuana are referred to as "reefers," "mooters," "muggles," "greeters," or "gates." A large quantity of marihuana that finds its way into the United States is smuggled across the border from Mexico and is often referred to as "Acapulco Gold" by its users.

A number of chemical compounds have been isolated from the resin of *Cannabis sativa (4–6)*. Among these are cannabinol, cannabidiol, cannabidiolic acid, tetrahydrocannabinol-carboxylic acid, cannabigerol, cannabichromene, and a mixture of stereoisomers known collectively as tetrahydrocannabinols. Some of the tetrahydrocannabinol mixtures examined show considerable variation in their pharmacologic activity, but most exhibit euphoric activity of varying degrees. Recently it was established (*7*) that Δ^1-tetrahydrocannabinol is, in fact, the major active euphoric principle in *C. sativa* resin. These compounds and their close relationship are shown in Fig. 2.

Like the tetrahydrocannabinols, cannabichromene is said to have euphoric activity (*5*). Cannabinol and cannabidiol are inactive. Cannabigerol and cannabidiolic acid are sedative principles, and cannabidiolic acid is a potent antimicrobial agent (*4*).

The variation in the chemical composition and biological activity of *Cannabis sativa* results primarily from the fact that some of the constituents are unstable and change form. It has been explained that, on aging, cannabidiolic acid (inactive) is gradually converted to cannabidiol (inactive), then to tetrahydrocannabinols (active), and finally to cannabinol (inactive) (*8*). These biological conversions proceed at a more rapid rate in tropical areas than in more temperate zones. As a result, samples of varying age give rise to different biological effects in humans. Of course, other factors, ecological and geographical, are also important, since the active constituents are presumably mainly contained in the resin, and plants growing in hot climates produce a great deal more resin than plants growing in the temperate zones (*8*).

One of the chief problems confronting legislators with regard to marihuana has been the conflict of opinion on the exact physical and mental effects of the active principles from this plant. This uncertainty has been due to lack of valid, controlled, scientific experiments. Many of the available biological data, which are indeed scanty, have been obtained from experiments made with crude plant preparations having unknown chemical constituents. Even in

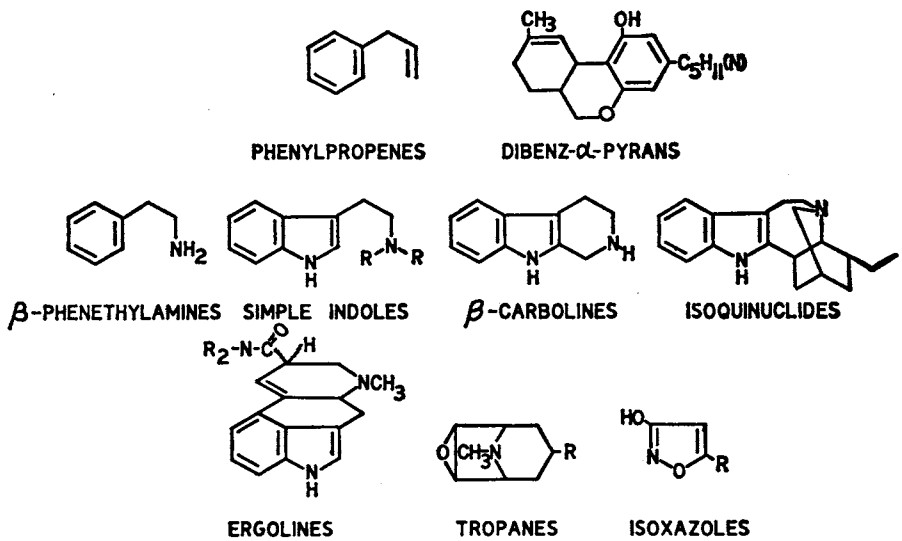


Fig. 1. Chemical structures of various types of hallucinogens.

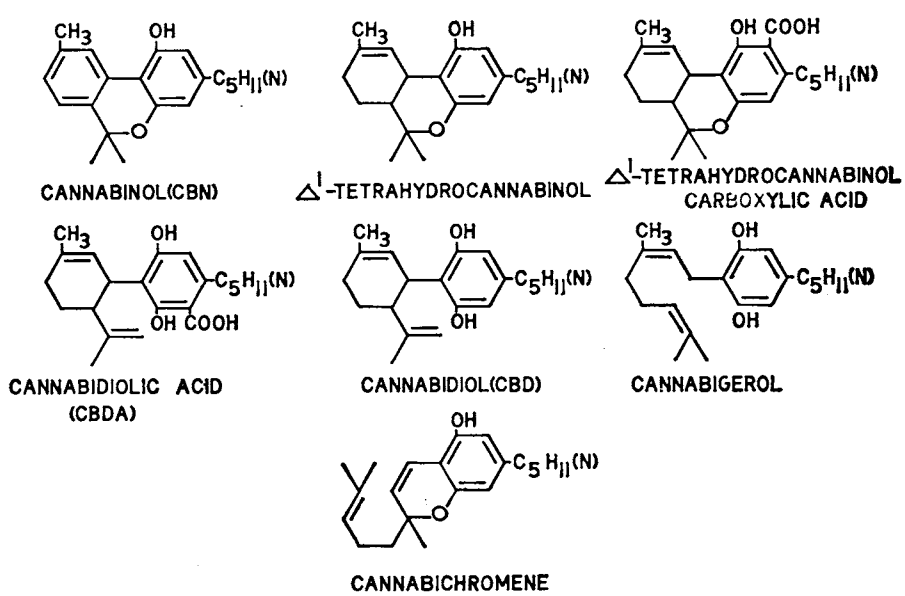


Fig. 2. Structures of major constituents of hashish.

Table 1. β-Phenethylamines in certain South American hallucinatory snuffs (*17*).

Species	Plant part	β-Phenethylamine content						
		MMT	5-MeO-MMT	DMT	DMT *N*-oxide	5-MeO-DMT	5-OH-DMT	5-OH-DMT-*N*-oxide
Piptadenia peregrina Benth.	Seed	−	−	+	+	+	+	+
Piptadenia peregrina Benth.	Bark	+	+	+	−	+	−	−
Piptadenia macrocarpa Benth.	Seed	−	+	+	+	−	+	+
Piptadenia excelsa (Gris.) Lillo	Seed	−	−	+	−	−	+	+
Piptadenia colubrina Benth.	Seed	−	−	−	−	−	+	−
Mimosa hostilis Benth.	Root	−	−	+	−	−	−	−
Virola calophylla Warburg	Bark	+	−	+	−	+	−	−

experiments made with so-called tetrahydrocannabinol, the experimental material was, in reality, probably a mixture of stereoisomers having different degrees of biological activity. Thus, it has proved almost impossible to correlate published data on effects of marihuana.

Recently, Rafael Mechoulan and Yehiel Gaoni, of the Hebrew University in Israel, announced that they had succeeded in synthesizing pure Δ^1-tetrahydrocannabinol in large-scale laboratory experiments (*9*). This, then, should be considered a major breakthrough in our understanding of marihuana, since a single pure entity is now available for studying the biological effects.

Nutmeg. The nutmeg of commerce consists of the dried seed of *Myristica fragrans* (family Myristicaceae), produced from trees grown in either the East Indies or the West Indies. Weil, who has studied the nutmeg problem extensively, has arrived at the following conclusions with regard to its use as a psychotomimetic drug. Nutmeg, administered orally in doses larger than one teaspoonful, can produce hallucinations after a delay of 2 to 5 or more hours. The reactions to nutmeg vary from none, in some individuals, to those typical of lysergic acid diethylamide (LSD). These symptoms frequently include distortion of time and space perception, and feelings of unreality. Visual hallucinations are infrequent. Concomitant side effects such as malaise, headache, dry mouth, tachycardia, and dizziness are frequent (*10, 11*).

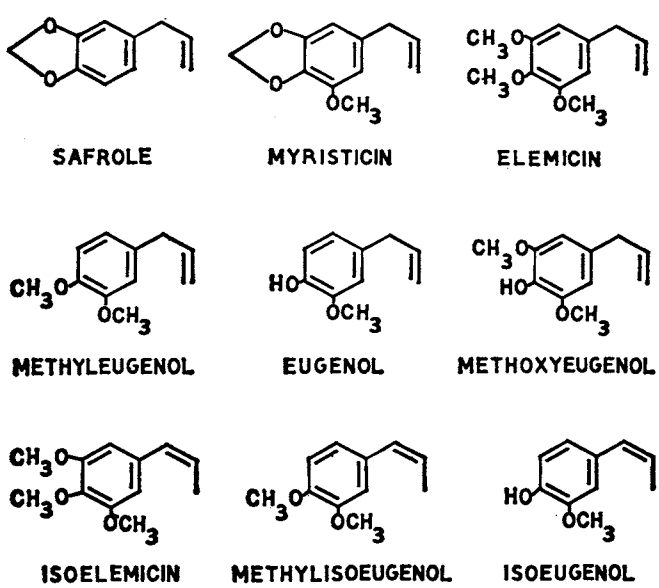
It seems clear that the active psychotomimetic substances of nutmeg are present in the volatile oil fraction of the seeds (*11*). This volatile oil contains fatty acids, terpenes, and aromatics (*12*). Analyses reported by several investigators (*12*) offer real evidence of chemical variability (both qualitative and quantitative) of nutmeg-oil samples.

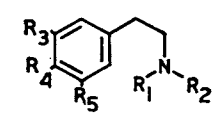
Safrole, myristicin, and elemicin are most frequently judged to be the active agents in nutmeg. If this judgment is correct, there is reason to believe that differences in the psychotomimetic effect of various lots of nutmeg are due to variations in the content of one or more of these three substances. A recent comparison involving the analysis of eight lots of nutmeg oil from various sources showed that the safrole content varied from 0.53 to 3.42 percent; the myristicin content, from 3.86 to 12.78 percent; and the elemicin content, from 0.02 to 2.36 percent (*12*). However, in all samples analyzed, these three compounds always accounted for from 84 to 95 percent of the total aromatic fraction of the volatile oil (*12*). The structures of known components of the aromatic fraction of nutmeg oil are given in Fig. 3.

To date, no psychopharmacologic investigations on pure safrole or on elemicin have been reported. The reports available show that early studies on myristicin were made with a product obtained by distillation from oil of nutmeg, and it is known that elemicin-free myristicin cannot be obtained in this manner. Thus, unless the oil of nutmeg was relatively free of elemicin, this latter compound may have been responsible for at least some of the psychotomimetic responses observed in these tests. In any event, elemicin may be a major contributor of activity, but this substance is not available in pure form for testing.

Safrole is probably not an active psychotropic substance; sassafras oil has a safrole content of some 80 percent, and this oil has never had a reputation of being a psychotomimetic substance.

Myristicin has been tested in humans at a dose equivalent to twice the dose which would be obtained through administration of 20 grams of typical nutmeg. The symptoms suggested psycho-





R-1	R-2	R-3	R-4	R-5	ALKALOID
H	H	H	OH	H	TYRAMINE
H	CH_3	H	OH	H	N-METHYLTYRAMINE
CH_3	CH_3	H	OH	H	HORDENINE
H	H	OCH_3	OCH_3	OCH_3	MESCALINE
H	CH_3	OCH_3	OCH_3	OCH_3	N-METHYLMESCALINE
H	AC	OCH_3	OCH_3	OCH_3	N-ACETYLMESCALINE
	$(CH_3)_3^+$	H	OH	H	CANDICINE

Fig. 3 (left). Structures of certain constituents of nutmeg oil. Fig. 4 (above). Structure of β-phenethylamine alkaloids from peyote.

tropic effects only in six of ten subjects (*12*). Thus it appears, from the absence of marked effects, that myristicin is not the major contributor of psychotomimetic activity in nutmeg.

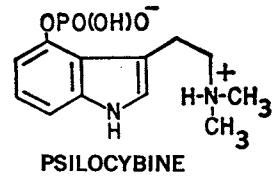
Plants Having Nitrogenous Active Principles

Peyote. Peyote, or mescal button, is derived from the cactus *Lophophora williamsii* (*Anhalonium lewinii*) and has been used for hallucinatory purposes for centuries (*13*). It is most commonly used in the southwestern part of the United States, but in recent years its use has spread throughout this country. In 1918, the Native American Church was formed, and part of its ceremonial rites involve the use of peyote. This church, which now has an estimated membership of some 225,000, preaches family responsibility, brotherly love, and abstinence from alcohol. Recently the courts ruled that peyote could be legally used as part of its ritual, thus making it a simple matter for persons to use this plant without fear of legal complications.

Although some 15 β-phenethylamine and simple isoquinoline alkaloids (Fig. 4) have been isolated from *Lophophora williamsii* (*14*), it is well established that the major hallucinogenic principle is mescaline.

The psychotomimetic effects of mescaline are induced with doses of 0.3 to 0.5 gram. After ingestion, mescaline first induces nausea, tremor, and perspiration. Then, in 1 to 2 hours, these unpleasant effects subside and a dreamlike intoxicating phase follows in which the user has vivid kaleidoscopic visions before falling into a deep sleep (*14, 15*).

South American snuffs. A number of *Piptadenia* and *Mimosa* species (family Leguminosae) and *Virola* species (family Myristicaceae) have been used in South America by Indians to induce psychotomimetic effects (*16*). The plant material is prepared as a snuff and is blown into the nasal cavity in any one of several ways. Although some chemical work has been done on these snuffs, in much of it plant material that was not properly identified was used. Recently several studies on botanically authenticated materials have been made, and the major chemical compounds responsible for the psychotomimetic effects of these snuffs, or compounds related to the active principles, have been identified as a



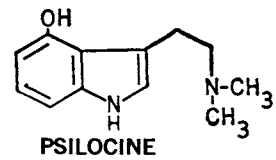


Fig. 5. Hallucinogenic principles of *Psilocybe mexicana.*

series of substituted β-phenethylamines: *N,N*-dimethyltryptamine (DMT), *N*-monomethyltryptamine (MMT), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), 5-methoxy-*N*-monomethyltryptamine (5-MeO-MMT), 5-hydroxy-*N,N*-dimethyltryptamine (bufotenine) (5-OH-DMT), *N,N*-dimethyltryptamine-*N*-oxide (DMT-*N*-oxide), and 5-hydroxy-*N,N*-dimethyltryptamine-*N*-oxide (5-OH-DMT-*N*-oxide). For a comparison of the different substituted tryptamines in certain South American snuffs, see Table 1 (*17*).

It is assumed that the active tryptamines reach the brain by way of absorption from the vascular nasal mucosa into the bloodstream, or that they act directly on the brain without having been transported through the general circulation (*17*). Although not all of the tryptamines known to be present in these snuffs have been pharmacologically investigated, it is reasonably certain that 5-OH-DMT does not account for the psychotomimetic action (*17*). DMT and 5-MeO-DMT, on the other hand, have been shown to be potent psychotomimetic agents (*17*). This difference has been explained as reflecting a low lipid solubility of 5-OH-DMT, as compared with a high lipid solubility for DMT and 5-MeO-DMT. Because of the higher lipid solubility, DMT and 5-MeO-DMT more readily penetrate the nervous system and exert their effects (*17*).

Table 2. Alkaloids in the seeds of *Rivea corymbosa* and *Ipomoea violacea* (*27*).

Alkaloid	Alkaloid content (%)	
	Rivea corymbosa	*Ipomoea violacea*
d-Lysergic acid amide (ergine)	0.0065	0.035
d-Isolysergic acid amide (isoergine)	.0020	.005
Chanoclavine	.0005	.005
Elymoclavine	.0005	.005
Lysergol	.0005	
Ergometrine (ergonovine)		.005

It is truly amazing that the South American Indians found that these plant materials were effective hallucinogens only when they were used as snuff; the tryptamines are not active when the material is ingested orally.

Hallucinogenic mushrooms. The mushroom-worshipping Indians of Mexico have long used "teonanacatl" ("Flesh of the Gods") as a sacrament in Aztec religious rites, and the fungi have indeed been shown to elicit psychotomimetic effects (*1, 18*). The sacred mushrooms are of several different genera: *Psilocybe, Conocybe,* and *Stropharia* (*1*).

The most important of the psychotropic mushrooms is *Psilocybe mexicana,* which was chemically analyzed by Hofmann and his co-workers (*19*) and found to contain the 4-hydroxydimethyltryptamines psilocybine and psilocine (Fig. 5), which are the active principles (*1, 20*). Psilocybine is the first example of a phosphorus-containing indole found in nature and, unlike most other substituted tryptamines, elicits psychotomimetic effects when taken orally.

Peganum harmala. The seeds of *P. harmala* (family Zygophyllaceae) have been used as a spice and as an intoxicant, and psychotropic effects have been attributed to them in India (*21*).

In addition to the major β-carboline base harmine, the seeds of this plant contain harmaline, harmalol, and harman (Fig. 6). Harmine and harmaline have both been shown to elicit hallucinogenic effects in humans when administered orally at doses above 4 milligrams per kilogram (*21*). Of interest is the recent discovery that 6-methoxytetrahydroharman is a natural hormone of the pineal body (*21*), and that it is closely related to the harmala bases (Fig. 6).

It has been shown that harmaline is more hallucinogenic than mescaline is (*21*) and that tetrahydroharmine is three times less active than harmaline. Synthetic 6-methoxyharmalan is active at oral doses of 1.5 milligrams per kilogram; 6-methoxytetrahydroharman from the pineal body is also a hallucinogen at these doses (*21*).

Banisteropsis species. Natives of the upper Rio Negro of Brazil and adjacent parts of Colombia, as well as Indians in

Table 3. Major hallucinogenic plants and their active principles.

Plant	Family	Active principle(s)
Cannabis sativa	Cannabinaceae	Δ^1-Tetrahydrocannabinol
Lophophora williamsii	Cactaceae	Mescaline
Piptadenia species	Leguminosae	Substituted tryptamines
Mimosa species	Leguminosae	Substituted tryptamines
Virola species	Myristicaceae	Substituted tryptamines
Banistereopsis species	Malpighiaceae	Harmaline, harmine
Peganum harmala	Zygophyllaceae	Harmaline, harmine
Tabernanthe iboga	Apocynaceae	Ibogaine
Ipomoea violacea	Convolvulaceae	*d*-Lysergic acid amide *d*-Isolysergic acid amide
Rivea corymbosa	Convolvulaceae	*d*-Lysergic acid amide *d*-Isolysergic acid amide
Datura species	Solanaceae	Scopolamine
Methysticodendron amesianum	Solanaceae	Scopolamine
Amanita muscaria	Agaricaceae	Pantherine, ibotenic acid
Psilocybe mexicana	Agaricaceae	Psilocybine

Amazonian Peru and Bolivia, use narcotic beverages known as "ayahuasca," "caapi," and "yaje" for purposes of prophecy and divination and to prepare the male adolescent for the painful rites of initiation into manhood (*1*, *20*). These three beverages are prepared from any one of several species of *Banisteriopsis* (*B. caapi, B. inebrians, B. rusbyana*) (family Malpighiaceae), either alone, together, or mixed with other plants (*1*, *20*).

It is generally agreed that the psychotomimetic principles in these *Banisteriopsis* species are β-carboline alkaloids, represented by harmine, harmaline, and (+)-tetrahydroharmine (Fig. 6) (*22*); exhaustive chemical studies on *Banisteriopsis* species are lacking, and a closer look might well yield additional hallucinogens.

Iboga. Natives of certain sections of Africa chew the root of *Tabernanthe iboga*; an intoxication follows that is characterized by excitement, mental confusion, and possibly hallucinations (*23*). The major alkaloid responsible for these activities is the 5-methoxyindole ibogaine (*23*).

Ibogaine has recently been placed in the same category as LSD by the U.S. Food and Drug Administration, since it has been shown to be a true hallucinogen (*21*).

Morning glories. The seeds of the morning glory *Ipomoea violacea* L., known as "badoh negra," and of *Rivea corymbosa* (L.) Hall. f., known as "ololiuqui," have been used since Aztec times in the uplands of southern Oaxaca for divinatory and hallucinogenic purposes (*24*, *25*). It has been firmly established that the active psychotomimetic agents in these seeds are ergoline (lysergic acid) derivatives, closely related to LSD (*24*, *25*). The natives of Mexico are known to have used smaller quantities of *I. violacea* than of *R. corymbosa* to produce hallucinogenic effects (*25*, *26*); Hofmann has pointed out that seeds from *I. violacea* contain larger quantities of the active ergoline principles than seeds of *R. corymbosa* do, and has thus demonstrated that there was a good reason for this practice. He subsequently was able to isolate, in pure form, several indole alkaloids from the seeds of these two plants (*27*). Interestingly enough, the major active constituent of each proved to be *d*-lysergic acid amide (ergine); a second important alkaloid was *d*-isolysergic acid amide (isoergine). In addition, the alkaloids chanoclavine and elymoclavine were isolated from each of the two species, but these had no psychotomimetic effects. Ergometrine (ergonovine), a well-known uterotonic and hemostatic alkaloid found in ergot, was isolated from *I. violacea* but not from *R. corymbosa*. On the other hand, lysergol was found in *R. corymbosa* but not in *I. violacea*. The structural relationships and the similarities of these active compounds from *Ipomoea* and *Rivea* to the synthetic and highly active LSD may be seen in Fig. 7. The alkaloid content of these seeds is given in Table 2.

Seeds from other convolvulaceous plants have been shown to contain ergoline derivatives; to date, the following have been detected: ergine, isoergine, ergosine, ergosinine, chanoclavine, elymoclavine, lysergol, ergometrine, ergometrinine, agroclavine, penniclavine, and lysergic acid-α-hydroxyethylamide (*25*, *28*).

When it was first announced that some common morning glory seeds contained these active alkaloids, seed sup-

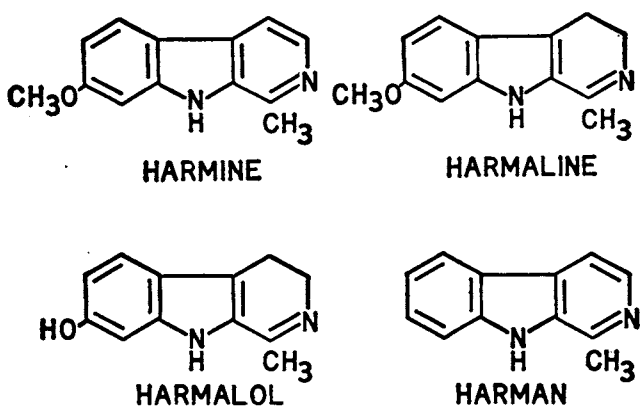


Fig. 6 (above). Major β-carboline alkaloids of *Peganum harmala*.

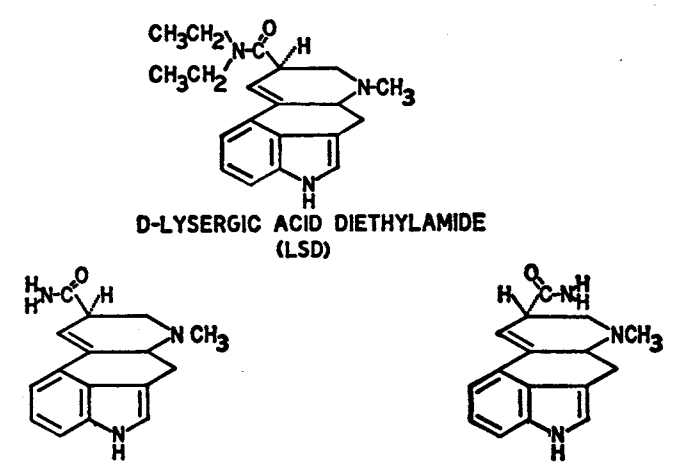
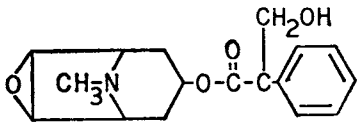


Fig. 7 (right). Hallucinogenic ergoline derivatives from *Rivea* and *Ipomoea* and their relationship to LSD.



SCOPOLAMINE

Fig. 8. Scopolamine, the hallucinogenic agent from solanaceous plants.

pliers soon reported a depletion of their stocks, and a serious public health problem arose from misuse of the seeds. In addition to the expected psychic phenomena, serious physical effects and deaths resulted (*25*, *29*). Some reports have indicated that ingestion of *Ipomoea violacea* seeds produced no effects. The reason, in most cases, was that the seeds were not pulverized before ingestion; the hard impervious seed coats allow them to pass through the alimentary tract intact, and the active alkaloids are not absorbed (*25*).

At present there is no specific legislation prohibiting the sale of morning glory seeds, and they continue to be used for psychotomimetic purposes. In England a proposal to ban the sale of these seeds is under consideration (*30*). Enforcement of such a ban would appear to be impossible.

Solanaceous plants. The seeds of the common jimsonweed (*Datura stramonium*) and of other *Datura* species have been used to produce psychotomimetic effects (*1*, *31*). Almost all *Datura* species contain tropane alkaloids, usually atropine, hyoscyamine, and scopolamine (Fig. 8). The hallucinogenic effects of scopolamine are well known (*32*, p. 544).

The leaves and stems of the South American plant *Methysticodendron amesianum* have been used by Indians in their witchcraft rites (*1*). Scopolamine constitutes over 80 percent of the alkaloid content of this plant (*33*). The natives consider *M. amesianum* to be more potent than the related *Datura* species, which they also use in their ceremonies to produce frenzy and narcosis. Undoubtedly it is more potent, since the scopolamine-atropine ratio is higher in *Methysticodendron* than in *Datura* (*33*). Even at therapeutic doses scopolamine may produce excitement, hallucinations, and delirium, whereas, in the case of atropine, doses bordering on the toxic are generally required before hallucinations and central nervous system effects are experienced (*32*, p. 544).

Amanita muscaria. Amanita muscaria Fr. (fly agaric) has an interesting history in Eurasian culture as a psychotomimetic agent (*34*). Ingestion of the mushroom produces psychotomimetic effects after about 15 to 20 minutes. Initially sleep is induced, of about 2 hours' duration. At times, the subject has colored visions. Some subjects have enjoyed a feeling of elation that lasted for 3 to 4 hours after they awakened from a sound sleep. Often these individuals perform extraordinary physical feats during this period, with great enjoyment (*34*).

The hallucinogenic properties of fly agaric pass into the urine and, for this reason, reportedly during times when *Amanita muscaria* was not available in abundance, the urine from an individual who had consumed the mushroom was drunk to produce the psychotomimetic effects (*34*).

To date, the following substances

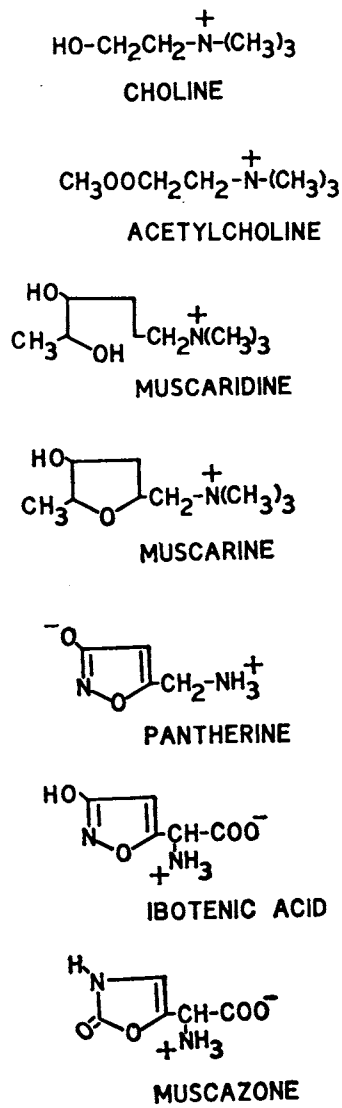
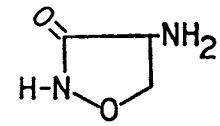


Fig. 9. Chemical compounds from fly agaric.



OXAMYCIN

Fig. 10. Oxamycin, an antibiotic closely related to the hallucinogenic isoxazoles.

have been reported as isolated from or detected in *Amanita muscaria;* muscarine, acetylcholine, choline, ibotenic acid (prämuscimol), pantherine (muscimole, agarin), muscazone, muscaridine, bufotenine, atropine, scopolamine, and hyoscyamine (*35*) (Fig. 9). Recent studies, however, have revealed that perhaps earlier reports of the presence of tropane alkaloids (tropine, scopolamine, hyoscyamine) in the fungus were due to misinterpretation of chromatographic data (*36*). Further, the report of the isolation of bufotenine from *A. muscaria* has been shown to be incorrect. In all probability the error resulted from the fact that the *A. muscaria* examined was contaminated with *A. citrina* or *A. porphyria* (*36*), both of which contain bufotenine.

Ibotenic acid is the zwitterion of α-amine-α-[hydroxyisoxazoylyl-(5)]-acetic acid monohydrate (see Fig. 9) and is considered to be the major psychotropic constituent of *Amanita muscaria* (*35*). Pantherine, also an active principle, is the enolbetaine of 5-aminomethyl-3-hydroxy-isoxazole (Fig. 9) and is easily formed from ibotenic acid by decarboxylation and loss of water (*35*) (Fig. 9). The pharmacologically less active muscazone (Fig. 9) is thought to be formed from ibotenic acid (*35*). Thus, one would expect to find varying ratios of ibotenic acid and muscazone in *A. muscaria,* which could well account for the variations in the biological effects induced by eating this fungus that have been reported in the literature (*35*). The chemistry of *A. muscaria* constituents has recently been reviewed (*37*).

The antibiotic oxamycin (D-4-amino-3-isoxazolidone) (Fig. 10) is structurally related to the active isoxazoles present in *Amanita muscaria;* in humans, side effects of this useful drug involve the central nervous system and include mental confusion, acute psychotic episodes, convulsions, and other abnormal behavioral states (*32*, p. 1326). Therefore, it is to be expected that the isoxazoles of *A. muscaria,* when ingested, will have similar effects.

Hallucinogenic Plants Not Yet Investigated

In the southern Mexican state of Oaxaca, Mazatec Indians utilize the leaves of *Salvia divinorum* (family Labiatae), known as "pipilzintzintle," in divination and as a hallucinogen (*24, 38, 39*). Wasson, after drinking the juice expressed by hand from 68 leaves of this plant, experienced dancing colors in elaborate three-dimensional designs (*39*). No chemical substances that would explain these effects have been isolated from *S. divinorum,* and preliminary attempts, by Hofmann, to isolate the active principles (or principle) have been unsuccessful, due to their apparent instability (*23*).

Natives living in the central part of the Brazilian Amazon prepare a psychotomimetic snuff from the fruit of *Olmedioperebea sclerophylla* Ducke (family Moraceae) (*40*). Nothing is known of the active principles of this plant.

More than 144 hymns of the *Rigveda,* the oldest holy scripture of the Aryan settlers of the Indus basin, glorify a divine plant and an intoxicating beverage prepared from it, both of which are known as "soma." Scientists have not been able to trace the identity of this plant with any degree of certainty. The plants which have been suggested, but which are discounted on specific points, are *Sarcostemma viminale, Periploca aphylla, Rheum* sp., *Ephedra* sp., *Peganum harmala,* and *Amanita muscaria* (*1, 23*). Wasson has been investigating this problem for several years and still has not reached a definite conclusion as to the identity of the elusive and mysterious soma.

Remarks

The chemical principles responsible for the effects elicited by the major hallucinogenic plants are summarized in Table 3. It is interesting to note that the genera of Table 3 are distributed in ten different plant families, and that the chemical substances responsible for the hallucinogenic effects are different for eight of the ten families. Or, put another way, when different genera of species of a particular plant family contain true psychotogens, these substances are always chemically similar, if not identical. This is a remarkable finding; chemotaxonomic relationships are not always so clear-cut.

We are not certain at present of the active psychotomimetic principle of *Myristica fragrans,* but it appears to be either elemicin or myristicin. Several other minor psychotomimetic plants (for example, *Salvia divinorum* and *Olmedioperebea sclerophylla*) remain a mystery, whereas we do not even know the botanical identity of soma. A number of additional hallucinogenic plants are alleged to exist, but in some cases there is a need for verifying the effects, whereas in others the plants are not botanically authenticated.

Our present state of knowledge concerning the identity of the active psychotomimetic principles of the well-known hallucinogenic plants is now relatively well established. However, much remains to be discovered regarding the biological effects of these substances, with respect to their action not only on the mind but on various biochemical systems of the body, and on the total organism. Continued interdisciplinary research should provide the answers to those questions that remain concerning these plants and their active principles, and should uncover new hallucinatory substances used in primitive cultures.

References and Notes

1. Although the most common hallucinogen is probably lysergic acid diethylamide (LSD), this is a purely synthetic chemical compound, which is not known to occur in nature, and therefore has not been included in this discussion.
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