Hallucinogenic Indole Compounds from Higher Plants[1]

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In recent years, there has been a revival of interest in the constituents of various species of plants and their uses for therapeutic purposes (12, 21). The literature is replete with examples of chemical and pharmacological studies of numerous plants based on their use in folklore medicine. Extensive literature and field studies of many plants by various ethnic groups have been made. In particular, interesting discoveries have been made of plant sources with some use as psychotherapeutic agents.

One of the more specific areas of investigation which has recently received attention, deals with those plants which contain hallucinogenic or psychotomimetic principles. The terms "psychotomimetic" and "hallucinogenic" are used to describe those agents which cause distortion of perception in man, occasionally accompanied by vivid colored illusions and sensations or hallucinations. (The psychotomimetics may be considered as a subdivision of the large class "psychotropic", which refers to all substances having some effect on the psyche.) Other names for these substances include psycholytics, psychodysleptics, phantastica, and psychedelics (36, 39, 62, 65, 66). None of these is entirely suitable in describing

TABLE 1. *Botanical sources of psychotomimetic substances* (39).

Source and common or native name	Active principles
Leguminosae	
Piptadenia peregrina Benth. (cohaba)	*N,N*-dimethyltryptamine, bufotenin
Piptadenia macrocarpa Benth.	(active doses: 0.05–0.07 g)
Malpighiaceae:	
Banisteriopsis spp. (caapi)	harmine, harmaline (active dose:
Tetrapterys spp. (yage, ayahuasca)	0.1–0.4 g)
Rutaceae:	
Peganum harmala L.	harmine, harmaline
Agaricaceae:	
Psilocybe spp. (teonanacatl)	psilocybin, psilocin (active dose:
Stropharia cubensis Earle	0.006–0.015 g)
Convolvulaceae:	
Rivea corymbosa (L.) Hallier f. (ololiuqui)	*d*-lysergic acid amide, *d*-isolysergic acid
Ipomoea violacea L. (badoh negro)	amide, elymoclavine and related compounds (active dose: 0.001–0.002 g)
Synthetic: LSD	*d*-lysergic acid diethylamide (LSD25) (active dose: 0.00002–0.00006 g)

the psychic effects produced by these agents, but the terms, "psychotomimetic" and "hallucinogenic" are among the most frequently used in the scientific literature.

With respect to narcotic[2] and/or hallucinogenic plants in general, several articles and reviews may be seen in the literature (12, 13, 18, 36, 39, 41, 64–66). Table 1 shows botanical sources of psychotomimetic plants. It can be seen from

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[2]The word narcotic is here used in the classic sense, meaning "to benumb," from the Greek, narkotikōs, derivative of narkē, meaning torpor. It should not be confused with the presently popular connotation which refers to substances which are "habit forming" or "addictive."

this table that some higher plants contain certain indole compounds as their active hallucinogenic principles. Consideration of these plants in detail is the major consideration of this paper.

PLANT FAMILIES CONTAINING PSYCHOTOMIMETIC INDOLES

LEGUMINOSAE

In this large, widely distributed pea or bean family there are several representatives which deserve scrutiny because they contain indoles with psychotomimetic properties. The legumes are already well known for yielding members which are of pharmaceutical importance. In the U.S.D.A. survey (83), alone, 525 plants in this family are listed which contain alkaloids. Of these, eleven members studied contained psychotomimetic indole alkaloids (table 2).

The genus which has received the greatest attention is *Piptadenia*. This genus contains about 45 species of shrubs or trees which are for the most part native to South and Central America. According to Altschul (1) they are strictly a New World genus. They are closely related to and are similar to the genera *Mimosa* and *Acacia*.

Because *Piptadenia* is a common source of narcotic snuffs used widely in aboriginal America (especially South America) and because certain hallucinogens have been isolated from it, Altschul (1, 78) undertook a taxonomic study of this genus. Based on evidence provided by certain botanical and morphological characters this author supports the upholding of the genus *Anadenanthera* which includes all species of the former section *Niopa* of *Piptadenia*. This may help to explain why certain of these now referred to the genus *Anadenanthera* contain a much larger concentration of bufotenine and related substances than those remaining in the *Piptadenia* complex (1). As seen in table 2, some of the Piptadenias even contain no alkaloids at all. Obviously, further work is needed to clarify this point.

There are several reports in the literature concerning the use of yopo or snuff from the *Piptadenia* species (62, 64–66). Generally, the seeds are used, and are powdered and mixed with quicklime. The material is administered much like tobacco snuff. Apparently this potentially dangerous habit continues today in Columbia and Venezuela, particularly in the Orinoco basin. Not only do the witch doctors partake of its use but also all other members of the tribes. Originally it was used to rid warriors of fear and pain of battle.

The intoxication by the snuff proceeds from convulsive movements, distortions of the face and body muscles through desire to dance until loss of coordination ensues, and finally ending in nightmarish deep sleep and stupor.

In the case of *Mimosa hostilis* Benth., a beverage called "wine of Jurema" is prepared from the seeds and is used by the Pancaru Indians of the interior of the State of Pernambuco, Brazil in their mystico-religious ceremonies (57, 64–66). *Lespedeza bicolor* var. *japonica* is apparently similarly used (19).

Varying results have been obtained in pharmacological tests on bufotenine and dimethyltryptamine. Bufotenine has, on one hand, been found to produce hallucinations (1–16 mg/kg iv) (19, 20, 39, 49, 50) and, on the other, no hallucinations (19, 39, 76). Bufotenine given in doses of 1–16 mg iv to healthy male convicts caused hallucinogenic activity, nystagmus, mydriasis, little cardiovascular effect, pulse rate varying about 12 beats per minute, and a unique purple hue on the face of the subject (19). Orally, up to 50 mg of bufotenin produced no psychic effect (39). Jacobsen (48) lists bufotenine as nonhallucinogenic. Dimethyltryptamine, according to various authors (19, 20, 39) has similar effects to bufotenin (ED 1 mg/kg im). Mental effects, including anxiety, perceptual distortions and hallucinations have been produced by doses of 50 to 70 mg iv or im. The onset of action was 15–30 minutes and the duration up to 1 or 2 hours.

With respect to 5-methoxy-*N*,*N*-dimethyltryptamine, 5-methoxy-*N*-methyl-

TABLE 2. *Representatives of the Leguminosae which contain hallucinogenic indoles.*

Genus, species, native names	Origin of material tested	Constitutents and plant part	References
Piptadenia peregrina Benth. or *Anadenanthera* var. *peregrina* (Cohoba, yopo in Orinoco basin of Columbia, Venezuela)	Las Mesas, Puerto Rico	A. Bufotenine (0.94% in seeds)	(62, 70)
	Puerto Rico	B. Bufotenine, bufotenine oxide, and *N,N*-dimethyltryptamine oxide in seeds (organic base content approximately 1.6%) and *N,N*-dimethyltryptamine in pods	(22, 62, 83)
	Santa Maria, Brazil	C. 5-methoxy-*N,N*-dimethyltryptamine, 5-methoxy-*N*-methyltryptamine and *N*-methyltryptamine in bark	(52)
Piptadenia macrocarpa Benth. (Huilca in Amazonian regions of Peru)	Florida	A. Same as B above except organic base content approximately 1.5–2.0%. Also 5-hydroxyindole base of unknown structure found in seeds	(22, 62, 83)
	Argentina	B. Bufotenine, *N,N*-dimethyltryptamine in seeds and seed pods. Also unidentified 5-hydroxyindole derivative in seeds. Bark yielded 0.1% 5-methoxy-*N*-menthyl tryptamine as crystalline oxalate, but no bases found in wood.	(45)
Piptadenia paniculata Benth.	Puerto Rico	Weak test for alkaloids in seeds and no test for alkaloids in pods	(22, 83)
Piptadenia colubrina or *Anadenthera colubrina* var. Cebil	Brazil	Bufotenine (2.1% in seeds)	(57)
Piptadenia communis Benth.	———	Bufotenine and related substances in lower concentration than 1 or 2 above	(1)
Piptadenia contorta Benth.	———	"	"
Piptadenia leptostachya Benth.	———	"	"
Piptadenia excelsa (Gris.) Lillo	Argentina	Bufotenine and bufotenine oxide in the seeds. *N,N*-dimethyltryptamine in seed pods	(45)
Piptadenia rigida (Benth.)	"	Negative test for alkaloids	"
Piptadenia paraguayensis (Benth.) Lindm.	"	"	"
Piptadenia viridiflora (Kunth.) Benth.	"	"	"
Piptadenia falcata	———	Bufotenine	(30)
Mimosa hostilis Benth. (Pancaru Indians of Pernambuco, Brazil prepare a beverage from this known as "wine of Jurema")	Brazil	*N,N*-dimethyltryptamine (0.57% found in roots) Nigerine identical with this compound (?). Seeds of plant used also	(57, 64, 66, 83)
Lespedeza bicolor Turcz. var. *japonica* Nakai	———	*N,N*-dimethyltryptamine	(19, 83)

tryptamine and *N*-methyltryptamine found in the bark of *Piptadenia peregrina* by Legler (52), no pharmacological data is available (see table 2).

In view of these divergent results with pure compounds it would seem that either the method of preparation or application by snuff alters in some way the psychic activity or more principles remain to be discovered. It may also be that the proportion or mixture of these principles in the crude snuff has a different psysiological effect than any of the single pure principles.

Although direct biogenetic studies on these legumes have apparently not been carried out (2, 51) it would seem reasonable to assume that the indole nucleus is derived in part from tryptophan or its decarboxylation product tryptamine. Obviously, studies here are indicated to confirm this.

A cursory examination of the family (83) reveals that several of the related *Acacia* species contain phenethylamine and tryptamine alkaloids. More species of *Anadenanthera*, *Piptadenia*, *Mimosa*, and *Lespedeza* should be examined for indole alkaloids to determine the extent of distribution of these compounds in the family.

MALPIGHIACEAE

In this family, the most widely used species are members of the genus, *Banisteriopsis* which are woody climbers (lianas) capable of growing up to several meters by attaching themselves to the trunks of large trees. According to Schultes (61) and others, this generic name supersedes the formerly used incorrect generic name, *Banisteria*. For example, *Banisteria caapi* Spruce ex Griseb., is now correctly called *Banisteriopsis caapi* (Spruce ex Griseb.) Morton.

TABLE 3. *Representatives of the Malpighiaceae which contain hallucinogenic indoles.*

Genus, species	Origin of material tested	Constituents and plant part	References
Banisteria caapi Spruce ("caapi" in Brazil and Columbia, "yage" in Columbia and Ecuador and "ayahuasca" in Peru and Bolivia)	Napo River, near Iquitos, Peru	A. Harmaline, tetrahydroharmine (leaf, stem), harmine (bark, wood)	(34, 61, 66)
	Brazil	B. Harmine	(55)
Banisteria chrysophylla Lam.	———	Unnamed alkaloid (leaf)	(83)
Banisteria lutea Ruiz.	———	Harmine	(83)
Banisteria metallicolor A. Juss. (*B. lutea* Ruiz.)	———	Harmine	(83)
Banisteriopsis inebrians Morton. (Same native names as *B. caapi*	Columbia	Harmine (leaf, stem)	(56, 83)
Banisteriopsis sp. (A decoction known as "Natem" used by Aguarunas Indians in North Peru)	Peru	Harmine, (stem) and either harmaline or 6-methoxy-*N*-dimethyltryptamine (stem), *N*-dimethyltryptamine (leaves)	(58)
Cabi paraensis Ducke	Brazil	A. Harmine (leaf, twigs) B. Harmine (shrub)	(11, 55, 83)

Several species are used in the preparation of a narcotic decoction known by various synonyms in South America. These include, "caapi" (Brazil and Columbia), "yage" (Columbia and Ecuador), and "ayahuasca" (Peru and Bolivia). The narcotic preparations are basically prepared from the same or closely related plants in this family. Different species are indigenous to various areas. For example, the species used most frequently in Brazil, east Columbia and the Amazon basin of Peru and Bolivia is *Banisteriopsis caapi*. *Banisteriopsis quitensis*, *B. inebrians*, and *B. rusbyana* are used in the western most fringe of the Amazon

basin, in Ecuador and Peru and along the Andean foothills of Columbia. *Tetrapterys methystica* R. E. Schultes, a closely related genus, is used in Brazil and Columbia (61). Others include, *Banisteriopsis longialata* Ruiz ex. Ndz. and *Banisteriopsis metallicolor* (61). One of the nonmalpighiaceous plants, *Prestonia amazonica* (Benth.) Macbride (*Haemadictyon amazonicum* Spruce) of the family Apocynaceae, has been thought to be used in admixture with *Banisteriopsis* in some areas of South America (61). Hochstein (34) reported that this plant contained *N,N*-dimethyltryptamine. However, it is presently felt that there was a misidentification of plant material in this case (63).

Several names including, telepathine, yageine, and banisterine have been used to describe the alkaloids obtained from some of the species given above. Later, it was thought that all of these referred to harmine (19), however, Hochstein (34) did find three alkaloids in *B. caapi* (See table 3) and identified them as harmine harmaline and 1,2,3,4-tetrahydroharmine, shown in fig. 1. According to Hofmann (39) and Chen and Chen (9), banisterine, telephathine and yageine are all identical with harmine.

Historically, harmine has been known for over a hundred years to be a constituent of *Peganum harmala* (zygophyllaceae). In addition, harmaline and harmalol have been isolated from this plant (19), however, the use of *Peganum* as a narcotic apparently is quite limited if it is used at all for this purpose.

Details of the structure confirmation and synthesis of harmine and related compounds is further discussed by Downing (19). A three step synthesis of biogenetic interest envolving the conversion of tryptamines into harmans is also given in this reference. Leete (51) further gives plausible routes from tryptamine through eleagnine to the harman type structure. One study given involves the administration of anthranilic acid-carboxyl-^{14}C to *Peganum harmala* which led to the formation of radioactive peganine (51), however, no direct biogenetic studies on the formation of harmine in this plant or *Banisteriopsis* species is given (2, 51).

Schultes (64–66) describes the psychotomimetic activity of a concentrated decoction of *Banisteriopsis inebrians*. In a self experiment his reactions involved initial giddiness and nervousness, then profuse sweating and nausea, followed by a period of lassitude accompanied by a play of colors, mainly hazy blue. Deep sleep with dreams accompanied by feverishness followed.

The hallucinogenic activity of pure harmine has been investigated (19) but once again the crude preparation appears to show greater psychic action. High oral doses (300–400 mg) of pure harmine are necessary to produce psychotomimetic effects, while lower doses iv (150–200 mg) and sc (25–75 mg) produced hallucinations and euphoria respectively (39). Hochstein (34) states that because pure harmine has a low psychotomimetic effectiveness in relation to the *B. caapi* extracts, both harmaline and/or *d*-tetrahydroharmine may have substantial hallucinogenic activity of their own.

Because few members have been investigated in the malpighiaceae (83) it is difficult to say what potential this family holds for new potential hallucinogens. However, it is obvious that a careful reinvestigation of all available members in the genera *Banisteriopsis* and *Cabi* will lead to clarification of some of the problems encountered and discussed above. A recent report by Bristol (7) is an example.

MYRISTICEAE

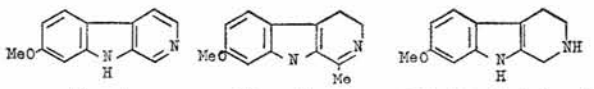
From several species of *Virola* in this family (to which nutmeg also belongs) is prepared a potent intoxication snuff known as yakee, epená or paricá. The ethnological and botanical background of this preparation is extensively reviewed by Schultes (60) and Wassén (79–80).

Yakee has widespread use throughout the Amazon region of Columbia, the adjacent north-westernmost Brazil, and the Orinoco drainage area of Columbia and Venezuela. Essentially, three species are used which include *Virola calophylloidea* Markgraf, *Virola calophylla* Warburg, and *Virola elongata*.

The snuff is prepared by first stripping the bark from the trunks of the trees. The red resin exuding from the inner bark is scrapped off with a knife and placed into an earthenware pot. This is then slowly heated in order to reduce the material to a thick paste. The paste is then sun-dried, powdered and mixed with ashes of the bark of a wild cacao tree to obtain the potent snuff (62). The snuff powder is blown into the nostrils using V-shaped or bifurcated tubes or bamboo tubes (62, 79, 80).

At first, Schultes (62) suggested that the active principle may be the essential oil, myristicine and, although Shulgin (67) points out that two psychotomimetics (3,4,5-trimethoxyamphetamine (TMA) and 3-methoxy-4,5-methylenedioxyamphetamine (MMDA)) are possible theoretical derivatives from it, their presence has not been established.

More recently, Holmstedt (42, 43) has detected the presence of 5-methoxy-*N*,*N*-dimethyltryptamine as a major component of *Virola* snuff and *N*,*N*-dimethyltryptamine (DMT) and 5-hydroxy-*N*,*N*-dimethyltryptamine (bufotenine) as minor constituents. Although the psychic effects of the major component are not known with certainty, the psychotomimetic effects of the latter two are at least documented (39, 71). These surely account for the effects of paricá.



Harmine Harmaline 1,2,3,4-tetrahydroharmine

FIG. 1. *Harmaline and related alkaloids.*

A point should be made here regarding a few recent references which have used native names alone to describe plant material. This practice can only lead to confusion. For example, Biocca (5) describes the detection of harmine, dihydroharmine and tetrahydroharmine in paricá. Fortunately, it is mentioned that the material is one of the *Banisteriopsis* species from which these alkaloids have been previously obtained and not *Virola*. Likewise with Marini-Bettolo (53) who describes the presence of *N*,*N*-dimethyltryptamine and bufotenine in epená. Again, because the author mentions that the material consists of seeds of a woody Leguminosae, one would surmise that is was probably a species of *Piptadenia*, since the alkaloids are characteristic for this genus. Still another, Bernauer (3), refers to the isolation of harmine and (+)-1,2,3,4-tetrahydroharmine from an Indian snuff powder, "Epena." Here, one would guess that this might refer to *Banisteriopsis* again, however, this genus is not used as a snuff Thus confusion ensues.

Since the U.S.D.A. survey (83) has not covered this family, it is once again difficult to forecast what a detailed study will uncover. Certainly, more members of the genus *Virola* warrant study.

CONVOLVULACEAE

This family is generally well known as the morning glory family. Its members are herbs or shrubs, usually with twining stems, mostly spirally arranged variable leaves, tuberous roots or rhizomes, and characteristic companulate or funnel-shaped showy flowers (77).

The use of certain members for their laxative resins or glycoresins is well known. Less prominent and more recent is the knowledge that certain genera have been found to contain hallucinogenic indole alkaloids.

Briefly, recent ethnobotanical studies have uncovered the use of *Ipomoea violacea* L. (*Ipomoea tricolor* Cav.), known as "badoh negro" and *Rivea corymbosa* (L.) Hallier filius (*Turbina corymbosa* (L.) Raf. or *Ipomoea corymbosa* (L.) Roth.) known as "ololiuqui" in the uplands of southern Oaxaca in Mexico for divinatory and hallucinatory purposes. As seen by the various Latin names given here, taxonomic confusion and disagreement still reigns in the family.

The historical, taxonomic, ethnobotanical, pharmacognostical, chemical, and pharmacological aspects of the use of morning glory seeds as narcotics has been given in several recent articles (13–18). The results are summarized in table 4 with pertinent references given.

TABLE 4. *Representatives of the Convolvulaceae which have been shown to contain hallucinogenic indole alkaloids.*

Genus, species	Origin of material tested	Constituents and plant part	References
Rivea corymbosa ("Ololiuqui")	San Bartolo, Yautepec and Huautla, Mexico	Seeds contained ergine (0.0065%), isoergine (0.0020%), chanoclavine (0.0005%), elymoclavine (0.0005%), lysergol (0.0005%)	(35–40)
Ipomoea violacea ("badoh negro")	"	Seeds contained ergine (0.35%), isoergine (0.005%), chanoclavine (0.005%), elymoclavine (0.005%), ergometrine (0.005%)	(35–40)
Rivea corymbosa	Cienfuegos, Cuba	Ergot-type alkaloids found in embryo but not in seed coat, seed membranes or resinous layer under seed coat of seeds. (0.071–0.077% total, based on ergometrine equivalents)	(72)
Ipomoea and *Convolvulus* species	Commercial flower seed packages purchased in Canada and England	All but three of sixteen species and varieties showed van Urk-reacting substances in seeds. Ergine, isoergine, ergometrine, ergometrinine, elymoclavine, penniclavine and chanoclavine tentatively identified.	(73)
Rivea corymbosa	Cienfuegos, Cuba	"	(73)
Rivea corymbosa	Cienfuegos, Cuba	Ergine and isoergine found in leaf and stem but not in root of greenhouse plant	(74)
Ipomoea violacea	Yautepec, Mexico and various commercial seed supplies in the U.S. and drug gardens around the world	Of the seeds of 29 different species and varieties of Ipomoeas, three species of *Convolvulus* only *Ipomoea violacea* and its varieties ("Badoh negro" from Mexico, 'Heavenly Blue', 'Pearly Gates', 'Summer Skies', 'Blue Star,' 'Flying Saucers', and 'Wedding Bells') showed presence of chanoclavine, ergine, isoergine, ergometrine, penniclavine, and elymoclavine. Total indole assay ranged from 0.005–0.079%. Indole alkaloids also detected in vegetative tissues	(13–18)
Rivea corymbosa	Oaxaca and Ocozocaotla, Mexico	Same constituents as above. Indole alkaloids also detected in vegetative tissues	(13–18)
Ipomoea rubrocaerula Hook. (*Ipomoea violacea* L.)	Various drug gardens around the world	Of about 10 different species of *Ipomoea*, *I. rubro-caerula* showed the presence of ergoline derivatives previously isolated including ergonovine and lysergic acid α-hydroxyethylamide	(31)

TABLE 4. *Continued.*

Genus, species	Origin of material tested	Constituents and plant part	References
Ipomoea coccinea L.	"	Seeds found to contain elymoclavine	(31)
Ipomoea rubrocaerulea Hook. var. *praecox* (*Ipomoea violacea* L.)	Various sources including seed	Only this plant and another variety ('Pearly Gates') of about 24 species examined showed presence of ergine, isoergine, chanoclavine, elymoclavine, and other indole alkaloids in seeds	(4)
Ipomoea violacea L. (different varieties)	Various sources	Of 10 different lots of seeds only varieties of *I. violacea* L. ('Heavenly Blue', 'Pearly Gates', 'Wedding Bells') showed presence of ergoline derivatives. Total percent indole alkaloids (calculated as ergine) ranged from 0.009 to 0.020%.	[a]
Ipomoea violacea L. (different varieties)	Seed supply house, Canada	Of 10 different varieties of morning glories only those of *I. violacea* ('Wedding Bells', 'Heavenly Blue', 'Pearly Gates', 'Flying Saucers') showed high percent total indole alkaloids, (calculated as ergometrine) in seeds	(24)
Ipomoea violacea L. (different varieties)	"	Of three samples tested, 2 varieties of *I. violacea* L. ('Pearly Gates' and 'Wedding Bells') showed percent total indole alkaloids (calculated as ergometrine) of 0.041 and 0.023 respectively, in seeds	(26)
Ipomoea violacea L. varieties and *Rivea corymbosa*	Various commercial seed supply houses	Of 16 varieties of morning glory seeds examined, only nine samples contained indole alkaloids. Six of these varieties of *I. violacea* viz. 'Flying Saucers', 'Heavenly Blue', 'Pearly Gates', and 'Wedding Bells' plus 'Major Tall' (mixture of *I. violacea* and *I. purpurea*) and ololiuqui (*Rivea corymbosa*) showed the presence of chanoclavine, ergometrinine, ergine, isoergine, lysergol, and ergometrine. Percent total indole alkaloids as well as percent ergine, isoergine and clavines is given for these six	(25)
Ipomoea violacea L. varieties and *Rivea corymbosa*	"	Essentially the same results as above obtained in study on 11 commercially available varieties of morning glories.	(27)
Ipomoea violacea L. varieties and *Rivea corymbosa*	"	Sixty-five samples of morning glory seeds from nine species and thirty-three horticultural varieties analyzed. Again, only *I. violacea* and *R. corymbosa* showed consistent high values	(29)

TABLE 4. *Continued.*

Genus, species	Origin of material tested	Constituents and plant part	References
		values for total indole alkaloids (0.023–0.066%) based on fresh weight using an ergometrine standard curve and recalculating for a molecular weight of 262.	
Ipomoea violacea L. varieties (incorrectly named *I. purpurea*)	Commercial seed supply sources in Hawaii	Found per gram of fresh seed the following: 'Pearly Gates' (78 μg isoergine and penniclavine and 69 μg ergine) and 'Heavenly Blue' (219 μg isoergine and penniclavine and 81 μg ergine). Values are ergonovine maleate equivalents	(44)
Aryreia nervosa ('Baby Hawaiian wood rose')	"	Found per gram of fresh seed of this plant, 555 μg isoergine penniclavine and 780 μg of ergine. Value is ergonovine maleate equivalent	(44)
Ipomoea muelleri	Gascoyne district of Western Australia	Detected presence of ergine and isoergine qualitatively, using *I. violacea* as a control	(23)
Ipomoea violacea varieties and *Rivea corymbosa*	Commercial seed suppliers	Seeds and aerial portions of 3 *I. violacea* varieties ('Heavenly Blue', 'Flying Saucers', 'Pearly Gates') shown to contain significant amounts of indole alkaloids. Roots, callus tissue, and callus medium of these 3 varieties; the callus tissue and callus medium of *Rivea corymbosa* contained traces of indole alkaloids.	(68)
Ipomoea argyrophylla Vatke	Kenya	Ergosine, ergosine and agroclavine isolated from the seeds	(69)
Ipomoea leptophylla Torr.	Puerto Rico	Seeds showed at least 6 indole alkaloids on the TLC. Identified chanoclavine, ergine, isoergine, and ergonovine. Percent total indole alkaloids is 0.02	(b)
Ipomoea rubra (*I. setifera* Poir.)	Puerto Rico	Seeds showed at least 3 indole alkaloids by TLC. Percent total indole alkaloids is 0.038	"
Ipomoea tamnifolia	Tuscaloosa, Florida (Herbarium specimen coll. in 1878)	Seeds showed presence of trace indole alkaloids by TLC	
Ipomoea cardiophylla	Chihuahua, Mexico (Herbarium specimen coll. in 1885)	Seeds showed at least 4 indole alkaloids by TLC	"
Stictocardia tiliafolia (Desr.) Hall.	Herbarium specimen, Panama	Seeds showed at least 6 indole alkaloids by TLC. Chanoclavine, ergine, isoergine, ergonovine, and elymoclavine identified	"

TABLE 4. *Continued.*

Genus, species	Origin of material tested	Constituents and plant part	References
Argyreia speciosa (Sweet)	Herbarium specimen, Australia and Hawaii	Seeds of all of these showed the presence of large amounts ergoline alkaloids including chanoclavine, ergine, isoergine, ergonovine and others	
Argyreia nervosa	Herbarium specimen, Polynesia and Queensland	"	"
Argyreia acuta (Lam.)	Herbarium specimen, China	"	"
Argyreia barnesii (Merrill) Van. Oostr.	Herbarium specimen, Philippines	"	"
Argyreia wallichii	Herbarium specimen, Burma	"	"
Argyreia capitata	Herbarium specimen, China	"	"
Argyreia spendens	Herbarium specimen, China	"	"
Argyreia osyrensis	Herbarium specimen, China	"	"
Argyreia wallichii	Herbarium specimen, China	"	"
Argyreia aggregata	Herbarium specimen, India	"	"
Argyreia hainanensis	Herbarium specimen, China	"	"
Argyreia obtusifolia	Herbarium specimen, China	"	"
Argyreia pseudorubicunda	Herbarium specimen, Sumatra	"	"

[a]Alexander, T. G. Personal Communication.
[b]Der Marderosian, A. H. To be published.

With respect to the information given in table 4, one should be aware that many names are synonymous and that references to horticultural varieties can be confusing (13). Needless to say, voucher specimens should be kept of all material analyzed. If possible, seeds should be planted, plants grown and identifications made on the whole mature plant. Identifications based on seed material alone are possible in some cases and difficult or impossible in others, especially in variety differences where frequently the color of the flower of the mature plant is the only difference.

Reference to table 4 reveals that, of the genera examined for hallucinogenic indoles, *Ipomoea*, *Rivea*, and *Argyreia* stand out. These are all closely related members of the convolvulaceae and there is indication of some pattern of distribution of ergoline type alkaloids in them. It has already been pointed out (18, 29) that this may be a potentially useful chemotaxonomic tool. Genest (29) discusses

this and other parameters of chemotaxonomic interest including lipid content of the seed oil, alkaloids other than those of the indole type, resins, sterol fractions, pigments of the seed coat and volatile matter.

One should not assume from table 4 that these are all the genera and species examined. Each reference article sited includes the results of negative tests for indole alkaloids in different members of the family. For example, Genest (29) has examined over 65 samples of morning glory seeds and Der Marderosian,[3] over 120. In the recent survey by Der Marderosian mentioned here, the following were examined, 78 species of Ipomoea, 9 species of *Convolvulus*, 16 species of *Argyreia*, 8 species of *Quamoclit*, 3 species of *Cuscuta*, and one species each of *Jacquemontia, Merremia, Exogonium*, and *Calystegia*. The presence of indole alkaloids in the species given in table 4 (23–40) are reported here for the first time.

It is of extreme interest to note from table 4, that only one member, *Ipomoea aryrophylla* Vatke, contains ergot alkaloids of the peptide type ergosine and ergosinine. This is the first case where this type of alkaloid has been isolated from higher plants (69). Earlier, the same research group (35) was the first to report ergoline type alkaloids in higher plants. These findings can only be explained as examples of parallel or convergent evolution of a highly specific biogenetic pathway since ergoline and peptide-type ergot alkaloids have previously only been reported in the lower fungi.

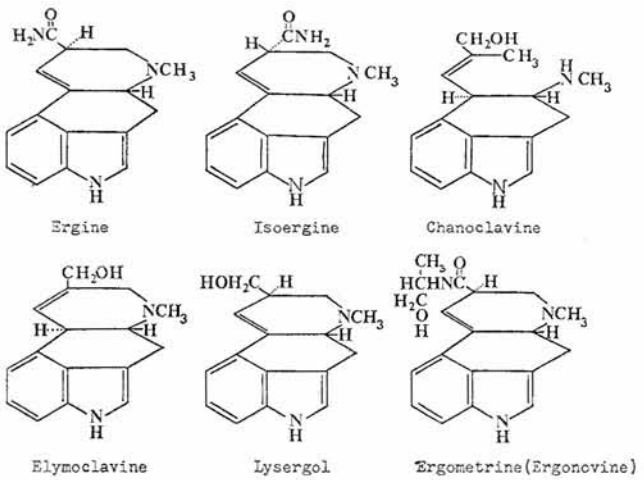


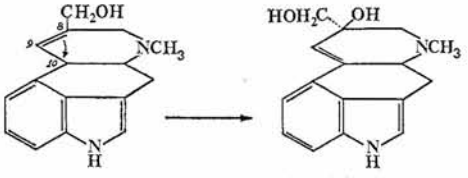
FIG. 2. *Ergoline type alkaloids isolated from* Ipomoea violacea *and* Rivea corymbosa.

Thus far, the ergoline type alkaloids reported in the convolvulaceae include, ergine (lysergic acid amide), isoergine (isolysergic acid amide), chanoclavine, elymoclavine, lysergol, ergometrine (ergonovine), ergometrinine, agroclavine, penniclavine, and lysergic acid-α-hydroxyethylamide. The two peptide type ergot alkaloids isolated include ergosine and ergosinine (table 4). Structures of some of these are seen in fig. 2.

Because of the unusual occurrence of these types of indole alkaloids in higher plants, it was deemed of interest to investigate whether their biogenesis proceeded along routes previously established in ergot. It was known from previous studies (13, 31, 73, 74) that the vegetative parts, as well as the seeds of *Ipomoea* species contained ergot-type alkaloids. Gröger (32) determined that the alkaloid content of the stems was always greater than that of the leaves and that generally it

[3]Der Marderosian, A. To be published.

reached its highest value at the end of the growing season. In a preliminary study to determine the site of alkaloid biosynthesis, Gröger (32) analyzed leaf-slips that had taken root in nutrient solution. However, he could find alkaloids neither in the leaves or roots. In an attempt to rule out any destructive process which inhibits the accumulation of alkaloids, he applied ^{14}C labelled elymoclavine onto the leaves of this plant to study its fate. He found that most of it was rapidly metabolized and degraded to unknown products. Some was changed to penniclavine which probably involves hydroxylation at position 8 in the D-ring and migration of the double bond from the 9 to the 10 position.



Elymoclavine Penniclavine

FIG. 3. *Conversion of elymoclavine into penniclavine.*

Later, Gröger (33) carried out more direct experiments which involved feeding labelled L-tryptophan and mevalonic acid to *Ipomoea rubro-caerulea* Hook. (*I. violacea* L.) plants growing in nutrient solution. He found in one experiment that both of these precursors were utilized for alkaloid biosynthesis in the stems with a specific incorporation of 2% for L-tryptophan and 13% for mevalonic acid. Thus these may be considered the precursors of ergoline in higher plants. It was unusual to find that the specific incorporation by the alkaloids isolated from seeds is much less than those isolated from the stems. Gröger (33) gave three interpretations to these results which include the possibility that the alkaloids are formed only in the stems and migrate into the seeds, or that the applied radioactive compounds did not reach the seeds or finally that during the length of the experiment, no measurable alkaloid formation took place in the seeds.

A second experiment supported the first possibility to some extent and so did a third experiment where no incorporation took place after injecting L-tryptophan into the seeds. However, experiments with seeds in different stages of development are necessary to clarify this.

There is little doubt now that ingestion of a sufficient quantity of either *Ipomoea violacea* or *Rivea corymbosa* seeds properly prepared can produce psychotomimetic effects. At first there was some confusion about this, but the problem has essentially been resolved (82). Because these seeds have a hard, impervious seed coat, and can pass through the alimentary tract intact, it is necessary that they be properly ground or soaked in water prior to ingestion. Natives prepared the seeds by grinding them on a grinding stone, then soaking them in cold water for a short time, and finally passing the mixture through a cloth strainer. The filtrate is ingested.

Hofmann (40) ascribes the psychic effects of these seeds to *d*-lysergic acid amide, isolysergic acid amide, elymoclavine, and lysergol. Some of these compounds had been known to be psychotomimetic prior to their isolation from these seeds. Some were tested pharmacologically during the course of studies on compounds related to LSD.

Essentially, *d*-lysergic acid amide can induce indifference, a decrease in psychomotor activity, and the feeling of sinking into nothingness accompanied by a desire to sleep. Isolysergic acid amide can cause tiredness, apathy, and a feeling of unreality. Elymoclavine and lysergol produce an excitation syndrome in various animals (39).

One report by Isbell (47) indicates that the crude extracts of both *Ipomoea violacea* and *Rivea corymbosa* are sedative rather than psychotomimetic in action. Ingram (46) reports a case of a student who ingested *Ipomoea tricolor* (*I. violacea*), and Cohen (10) a suicide following morning glory seed ingestion. One reference mentions morning glory seeds in a statistical study of the use of hallucinogenic drugs among college students (54).

By now it is obvious that the continued examination of the Convolvulaceae can only lead to more interesting discoveries of future interest to the botanist, pharmacognosist, chemist, and pharmacologist alike.

OTHER PLANT FAMILIES OF INTEREST

Up to now all the commonly known families and their members have been considered, but there also exists another body of miscellaneous information regarding the presence of hallucinogens or potential psychotomimetic indoles scattered in various plants in different families.

There are the harmala bases, harmine, harmaline, and harmalol, and related compounds, which occur in *Peganum harmala*, and harman in *Zygophyllum fabago* (6) both of the Zygophyllaceae. These bases occur in at least eight families including the Leguminosae, Rutaceae, Rubiaceae, and Passifloraceae (75).

The indole alkaloid gramine is found in *Acer saccharinum* of the Aceraceae, *N,N*-dimethyl-5-methoxytryptamine is found in *Dictyoloma incanescens* of the Rutaceae (57), 5-methoxy-*N*-methyltryptamine has been isolated from *Phalaris arundinacea* of the Gramineae (83). Obviously, not all of these are necessarily used as hallucinogens, or have psychotomimetic principles, but plants related to these might.

Also, we find the interesting African shrub *Tabernanthe iboga* which contains ibogaine as the principle alkaloid of at least 12 in this plant. This is in the

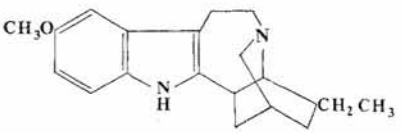


FIG. 4. *Structure of ibogaine.*

Apocynaceae. Extracts of the root have been reported to produce excitement, drunkenness, mental confusion and probably hallucinations at high doses (19, 41).

Finally, we come to *Mitragyna speciosa* of the Rubiaceae. It contains mitragynine, the principal alkaloid of this intoxicant of Borneo. Chemically it is related to 1,2,3,4-tetrahydroharmine and it also has a substitution at position 4 like psilocin (19). However, it is not known with certainty whether mitragynine is a true hallucinogen. The leaves of *M. speciosa* are chewed or prepared in various ways for its narcotic or psychotropic effects. It is used as a substitute for opium (41). Similarly, yohimbine which has a 1,2,3,4-tetrahydroharmine residue like mitragynine is capable of producing psychic effects (19).

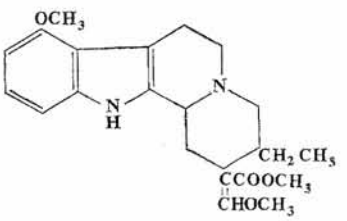


FIG. 5. *Structure of mitragynine.*

These are but a few of the interesting leads which offer potential for a continuing search for new psychotomimetic agents in higher plants. There remains only the pursuit.

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