HALLUCINOGENS, CNS STIMULANTS, AND CANNABIS

A. T. Shulgin

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COMMON CHARACTERISTICS OF SOME DRUGS

The drugs known variously as the hallucinogens, the Central Nervous System (CNS) stimulants, and cannabis are by name and reputation a varied collection of materials. A hallucinogen is, broadly, a substance that creates some unexplained and unconfirmable imagery, a CNS stimulant clearly invokes some anatomical or physiological site of action, and cannabis is the generic name of a plant. Also included in this apparently disparate group are substances which are best referred to as delusionary agents; drugs that induce sensory deprivation and distortion that effectively achieve a clinical state of anesthesia. However, there are unifying features of this heterogeneous collection that all share in common:

1. They are drugs that are being used by an increasingly large minority within the society as psychotropic agents;
2. They are drugs that are being used for their effective modification of sensory integrity, whether for believed virtues of self-understanding, self-instruction, religious insight, or simple escape;
3. They are drugs that are disapproved of by the majority within the society and which have, in several instances, been made illegal;
4. They are drugs that are certainly habituating, thus leading to a degree of psychological dependence, but drugs which appear to be, without exception, free of known capability of leading to a physiologically dependent state or addiction, seen frequently with the three classes discussed earlier; the narcotics, the barbiturates, and alcohol;
5. Except for the phenethylamine analogues, they are drugs that have not received official recognition of medical utility and are only rarely employed in medical practice;
6. They are drugs that have evolved from the plant kingdom, although many of the currently employed substances are synthetic modifications of the parent botanical prototypes.

Consideration of the dosage must be made concerning a number of these drugs. With some, primarily the stimulants, usage at low levels is medically acceptable and encouraged for both anorexogenic and mood modifying effects. It is only when the user has become tolerant of excitatory properties and increases the dosage to the level that produces a psychotomimetic intoxication, that the drug is generally condemned. With

others, there may be such expressions of excitation or perhaps some sedative depression at large dosages, but the sought after intoxication and sensory distortion syndrome is expressed at smaller levels of use. External, obvious symptoms of physical change are evident only in instances of overdosage.

The discussion that follows is based on chemical, rather than pharmacological lines. Where appropriate, some comparative descriptions of the nature of action will be made, but to a large measure this presentation is intended to serve as a reference body of chemical structure, botanical source, and terminology.

THE INDOLE FAMILY

The most potent, the most famous, and the most notorious of all the drugs to be discussed in this chapter are chemically based on the indole nucleus. These are chemical substances that are, at least in origin, completely derived from the plant kingdom. There are the ergot-like alkaloids from the fungi and the *Convolvulaceae* families, the carboline group of bases stemming primarily from the South American vines of the genus *Banisteriopsis*, and the compounds that account for the activity of the New World snuffs; relatives of a compact family of compounds related to the parenterally active tryptamine bases.

The most widely known drug of this entire group is the semisynthetic compound, lysergic acid diethylamide, LSD-25. The stereochemical structure of the active (*d*-) isomer is shown in Figure 1. Although the chemical was first synthesized in 1937, its extraordinary activity was not recognized until 1943,[1] and not reported until 1947.[2,3] Within a few years, it had been introduced and received broad experimental evaluation within both medical and experimental social circles of the U. S.

Hundreds of minor chemical variations of LSD have been synthesized, and a number of these have been evaluated in human subjects. One of the first extensive reports of such a study[4] has shown the exquisite sensitiveness of the relationship of chemical structure to biological activity. Shortening one of the two amide ethyl groups to a methyl group (LME, Figure 2; R^1=methyl, ethyl; R^2, R^3 = H) or lengthening one to a propyl group (Figure 2 LEP, R^1 = ethyl, propyl; R^2, R^3 = H) greatly reduces its activity as a psychotomimetic. The LSD isomer, the *N*-methyl-*N*-propyl counterpart, or the mono-ethyl homolog (LAE) are virtually without activity. Bromination at the indolic 2-position (Figure 2, R^1 = ethyl; R^2 = Br; R^3 = H) reduced the high potency of LSD. Changes within the D-ring, either the hydrogenation of the double bond, conversion to the *l*-isomer, or structural rearrangement to the *cis*-configuration, all result in an inactive molecule.

It is only with substitution on the indolic nitrogen, that psychotomimetic potency is maintained or enhanced. The methyl and acetyl counterparts (Figure 2; R^1 = ethyl; R^2 = H; R^3 = CH_3, $COCH_3$) are comparable to LSD in human potency.[5]

Another group of highly potent alkaloids, closely related to LSD chemically, but total strangers in the botanical sense, are the ergot-like bases isolated from the various *Convolvulaceae* of the morning glory group.

The New World drug, Ololiuqui is known to

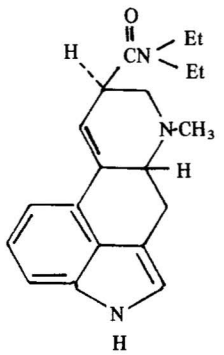

FIGURE 1.

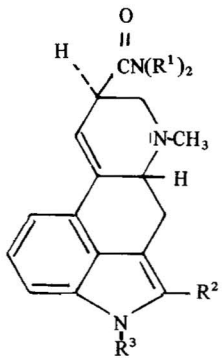

FIGURE 2.

come from the seeds of the plant *Rivea corymbosa.*[6] These are brown in color and are known locally as "badoh", but they are used interchangeably with the black seeds (badoh negro) of the larger and more dramatic morning glory, *Ipomoea violacea.* The composition of these two species has been found to be essentially identical.[7] The major alkaloids present were found to be ergine (*d*-Lysergic acid amide, Figure 2; R^1, R^2, R^3 = H) and the enantiomorph isoergine (*d*-Isolysergic acid amide, identical with ergine, but with the opposite epimeric configuration on the carbon atom that carries the amide carbonyl group). These two compounds have been shown to have some activity in man, but it is possible that their presence in the natural seed as the extremely labile acetaldehyde condensates (the hydroxyethylamides) may explain the activity of the seed compared to the lack of activity of the ergot isolates.[8]

A third major alkaloid present in both species is Chanoclavine (Figure 3), an open ring analog of the ergoline series of compounds, which is present to about 10% in the ergine-isoergine content, but completely unexplored in humans.

Yet, another morning glory relative, the Hawaiian Baby Woodrose, or *Argyreia nervosa,* has found extensive usage as a hallucinogenic plant source. Both ergine and isoergine have been shown to be present in exceptionally large amounts,[9,10] but penniclavine (Figure 4), a minor component of both the *Rivea* and *Ipomoea* species, is also present as a major component. Again, its pharmacology in man is unknown. A recent study of this potent plant material[11] revealed the presence of more than a dozen additional alkaloids, and it is certain that some of them must play some role in the explanation of the hallucinogenic

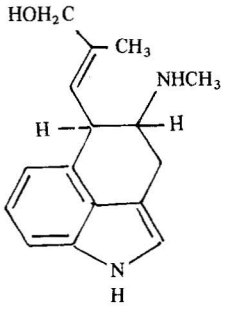

FIGURE 3.

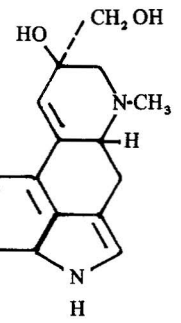

FIGURE 4.

effectiveness of this plant. The large Hawaiian Wood Rose (*Ipomoea tuberosa*) is interestingly without alkaloids and biological activity.

Ibogaine is yet another indole alkaloid that should be mentioned briefly under this heading. Basically, it is an indole in structure (Figure 5) and has a polycyclic structure superficially similar to that of LSD. Second, it shows psychotomimetic properties at large dosages[12] and due to a brief, but active flurry of illegal appearance as a street drug, has been included into the BNDD listings of dangerous drugs. It is synthetically unobtainable, being isolated only from the African plant, *Tabernanthe iboga.* Modifications of the structure are unknown, both chemically and pharmacologically.

The carbolines represent a chemical class of simpler chemical structure and some biochemical logic from the point of view of rationale of action. They are tricyclic indole substances represented by the general structural formula in Figure 6.

Of these substances the best studied are those of the harmine family, found in the plants of the genera *Peganum* (of the Old World) and *Banisteriopsis* (formerly *Banisteria,* of the New World). The extract of this latter vine is known as Ayahuasca (or Caapi or Yaje), and has been used for generations by Indians in the Amazon and Orinoco river basins, as an orally active hallucinogen.

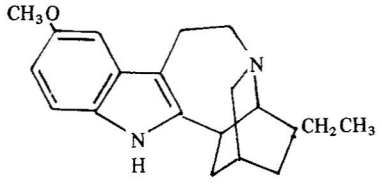

FIGURE 5.

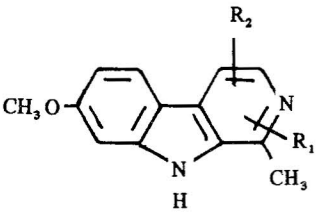

FIGURE 6.

The principal alkaloids of this plant group were recognized early as being related to harmine (Figure 6) through various degrees of hydrogenation in the pyridine ring. The major alkaloid in *Banisteriopsis caapi* has been reported to be the dihydro counterpart, harmaline (Figure 6, R^2 = H_2).[13] This isomer may be the major contributor to the action of the plant product Ayahuasca, as the tetrahydro analog (tetrahydroharmine, Leptoflorin, Figure 6, R_1, R_2 = H_2). Although clearly present as an alkaloidal component,[14] it appears be less active than harmaline in humans.[15]

A parallel family of compounds carries the methoxy group in the indolic 5-position (Figure 7). This group is implicated more logically in human metabolism (as analogs of serotonin) but has been identified as components of plant intoxicants only very recently.

The *Virola* snuffs of northern South America have long been associated with the *Piptadenia* group of intoxicants known as Yaje. Although originally thought to be related to nutmeg, these are now known to contain alkaloids.[16] These are positional isomers of the harmaline series and are more potent. Here, the major alkaloid is the tetrahydro isomer[17] (Figure 7, R^1 = CH_3, R^2 = H), but the two dehydrogenation products (6-methoxyharmalan and 6-methoxyharman, Figure 7, with one and two double bonds in the pyridine ring) are clearly present.[18] Theoretically, these plant products are derivable from the brain hormone melatonin. This potential route to an endogenously-produced psychotogen has been advanced as a clear and simple explanation of mental illness,[19] but it has not yet received experimental support.

A recent report describes two *N*-methylated carbolines present in Virola (Figure 7, R^1 = H, R^2 = CH_3 and R^1 = R^2 = CH_3).[20] Their contribution to the hallucinogenic effects of the plant are not known.

A major alkaloid of this snuff, and of many other South American plant medicines such as Parica (Epena)[21] and the Caribbean counterpart Cohoba is the simple indole, dimethyltryptamine (DMT). This base (Figure 8, R^1, R^2 = H, R^3 = CH_3) has been identified as a component of a large number of New World hallucinogens and has been extensively evaluated in clinical studies.[22] It has been detected in the urine of schizophrenic patients[23] and may be involved in the abnormal metabolism associated with mental illness.

There are a large number of hallucinogens closely related to dimethyltryptamine chemically. 5-Methoxydimethyltryptamine (Figure 8, R^1 = H, R^2 = OCH_3, R^3 = CH_3) which accompanies DMT in many of the South American snuffs, is an extremely rapidly acting chemical (effective within seconds), and like DMT, is only active parenterally. The phenolic analog, 5-hydroxy-*NN*-dimethyltryptamine is known as bufotenine. Although it is legally classified as an hallucinogenic substance, there is little medical justification for this assignment.[24]

The alkyl homologs of DMT (diethyltryptamine and dipropyltryptamine, DET and DPT, Figure 8, R^1 = R^2 = H, R^3 = CH_2CH_3 and $CH_2CH_2CH_3$, respectively), are progressively longer-acting and less potent.[25] It has been reported that the diisopropyl isomer and the *N*-monotertbutyl homolog are active orally, but this has not been confirmed in the published literature.

An unusual compound within the dialkyltryp-

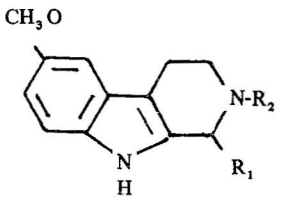

FIGURE 7.

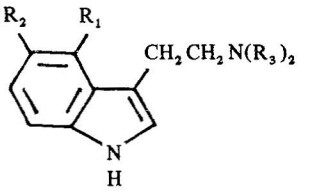

FIGURE 8.

tamine family is the 4-hydroxy analog, psilocin, and its pharmacologically equivalent phosphate ester, psilocybin (Figure 8, R^1 = OH or $OPO(OH)_2$, R^2 = H, R^3 = CH_3). These orally active hallucinogens have been isolated from, and completely account for, the central activity of the Mexican sacred mushroom, Teonanacatl.[26] These mushrooms were found to be of the Genus *Psilocybe*,[27] but recently a number of other fungi have been identified as sources of these alkaloids.[28] Synthetic modifications of these basic structures have indicated that the diethyl homolog of psilocin (SZ-74, Figure 8, R^1 = OH, R^2 = H, R^3 = CH_2CH_3) is somewhat less potent than psilocin, but acts more rapidly, quite the opposite action of DET compared to DMT.[29] There are no reports of studies in humans of the higher homologs.

THE PHENETHYLAMINE FAMILY

The simplest of the central stimulants and the parent structure to a large number of active compounds, both as sympathomimetic stimulants and as psychotomimetics, is the chemical phenethylamine (Figure 9, R^1 = R^2 = R^3 = R^4 = R^5 =H). Although this compound is not active in the human due to its extremely rapid metabolic removal, modifications of it have proven to be resistant to in vivo destruction. Alkalylation of the carbon next to the amine group (Figure 9, R^4) leads to central stimulants, whereas ether substitution upon the aromatic ring (R^1,R^2,R^3) leads to hallucinogenic compounds. The latter pharmacological property appears to be the more dominant, as changes simultaneously in both areas of the molecule yield hallucinogens that are of increased potency, but do not promote appreciable stimulation.

One of the best documented hallucinogenic plants known is the Peyote cactus (*Anhalonium lewinii, Lophorphora williamsii*) which contains mescaline as its principal alkaloid. (Figure 9, R^1 = R^2 = R^3 = OCH_3, R^4 = R^5 = H). A number of nitrogen substituted analogs are also present, the *N*-methyl and the *N*-acetyl analogs, but they are known to be biologically inert, and probably do not contribute to the reported pharmacology of the entire plant.

Several tetrahydroisoquinoline derivatives are biosynthetically derivable from mescaline and its precursors, and some of these have been observed as plant components. Of the four best-studied compounds, two are phenolic (anhalonidine, Figure 10, R^1 = R^2 = OCH_3, R^3 = OH, R^4 = CH_3, R^5 = H; and pellotine, R^1 = R^2 = OCH_3, R^3 = OH, R^4 = R^5 = CH_3) and 2 are methylenedioxy ethers (anhalonine, Figure 10, R^1 = OCH_3, R^2, R^3 = $-OCH_2O-$, R^4 = CH_3, R^5 = H; and lophophorine, R^1 = OCH_3, R^2, R^3 = $-OCH_2O-$, R^4 = R^5 = CH_3). The best accumulation of the sparse-known pharmacology of these peyote components can be found in the appendices of La Barre's study of the peyote cult.[30]

Structure modifications of the mescaline molecule can be arranged in two pharmacologically justified groups. One, accepting the *a*-methyl substitution pattern as a necessity to circumvent the metabolic clearing of the drug, has led to the discovery of a wealth of aromatic substitution derivatives that have uncovered many active hallucinogens. The other, exploiting the excitatory consequence of the *a*-methyl substitution pattern, has led to a family of sympathomimetic stimulants.

The first of these modifications, the presentation of the amphetamine carbon skeleton, coupled with a freedom of rearrangement of the groupings of mescaline, has led first to the discovery of TMA (Figure 11, R^1 = H, R^2 = R^3 = R^4 = OCH_3)[31] followed by positional isomers, the most potent of which has been the 2,4,5-counterpart (TMA-2, R^1 = R^3 = R^4 = OCH_3, R^2 = H).[32] The incorporation of the methylenedioxy ring into this general structure, a feature found regularly in the peyote tetrahydroisoquinoline alkaloids, leads to a further increase in potency.[33] The retention of the

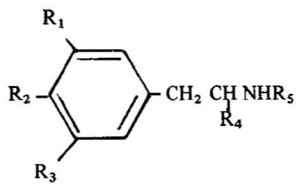

FIGURE 9.

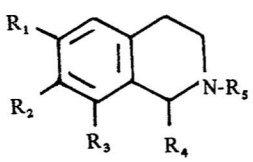

FIGURE 10.

2,4,5-substitution pattern, but with the incorporation of unusual groups into the 4-position, has led to several extremely potent compounds.

The 4-methyl and the 4-ethyl homologs of 2,5-dimethoxy-phenylisopropylamine (DOM, STP, Figure 11, $R^1 = R^4 = OCH_3$, $R^2 = H$, $R^3 = CH_3$; and DOET, $R^1 = R^4 = OCH_3$, $R^2 = H$, $R^3 = CH_2CH_3$) are both effective antidepressants at modest levels (15 μg/kg) and clearly psychotomimetic at higher dosages.[34] The 4-bromo analog (Figure 11, $R^1 = R^4 = OCH_3$, $R^2 = H$, $R^3 = Br$), effective at 4 μg/kg in man, is the most potent of the substituted phenethylamines described in the medical literature.[35]

The second of the structure-modification groups stemming from the skeleton of phenethylamine modified by an alpha-methyl substituent has emphasized changes on the aliphatic chain portion of the molecule, with no substitution whatsoever on the aromatic ring. The results of this have been the development of a number of sympathomimetic stimulants which do not present central distortions, at least within reasonable dosages.

A host of α- and N-alkyl substituted derivatives have been prepared by the pharmaceutical chemist, evaluated by the experimental pharmacologist, and promptly exploited and abused by the socially active drug subculture. The N-methyl homolog of amphetamine (Benzedrine and Dexadrine, Figure 12, $R^1 = R^2 = R^3 = H$) is methamphetamine (Figure 12, $R^1 = R^2 = H$, $R^3 = CH_3$). This chemical has no medical virtue over amphetamine itself, but has been abused greatly

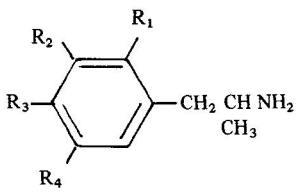

FIGURE 11.

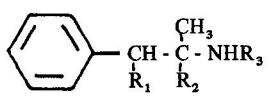

FIGURE 12.

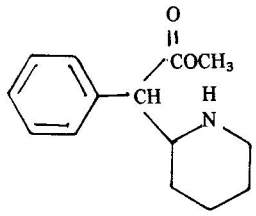

FIGURE 13.

for its stimulant action. In an effort to circumvent abuse, the homolog mephentermine has been substituted as a decongestant inhalent, but this chemical (Wyamine®, Figure 12, $R^1 = H$, $R^2 = R^3 = CH_3$) promptly found an abuse market as an excitant.[36] The beta-hydroxy analogs of these chemicals, members of the *Ephedra* botanical group, have been long known as stimulants. A number of these have come into the pharmacological literature (ephedrine and phenylpropanolamine, Figure 12, $R^1 = OH$, $R^2 = H$, $R^3 = H$ or CH_3) and encountered the illicit drug trade.

Most frequently noted are those drugs that are distributed as prescribed chemicals and are employed as acceptable stimulants, but which are found in broad abuse through simple overavailability. Ritalin® (methylphenidate) (Figure 13) has become a major problem in Sweden, and is frequently a "street" problem in the U.S. Preludin® (phenmetrazine, Figure 14) is also occasionally encountered and deserves additional attention.

HETEROCYCLIC SYSTEMS

The only heterocyclic system mentioned so far has been the indole system and it is indeed paramount in most alkaloidal chemical systems. However, many other heterocyclic systems are known in the plant kingdom and many have evolved intoxicants that are extremely effective in man.

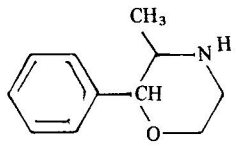

FIGURE 14.

The tropane family of alkaloids is represented in two classes of drugs, the local anesthetics and central stimulants associated with cocaine and the parasympatholytics related to scopolamine. Other natural alkaloid families are the purines (caffeine) and the isooxazoles (active components of the *Amanita muscaria* mushroom). Only a very few synthetic heterocyclics that are unrelated to some plant source, are known.

Cocaine (Figure 15, $R^1 = CH_3$, $R^2 = OCOC_6H_5$ [benzoyl]) is obtained from the leaves of the South American plant, *Erythroxylon coca*. For many centuries, it has been used as a stimulant by the Andean Indians, and the knowledge of its effectiveness as a local anesthetic is over 100-years old. From the medical viewpoint, cocaine has served valuably both per se as a topical anesthetic and as a chemical model that has led to the synthesis of a wealth of related anesthetics that are much safer for injection. Procaine (Figure 16) exemplifies this family of benzoate esters and has been known for 65 years. The social use (misuse?) of cocaine can be considered in two lights. The native use (mentioned above) is restricted to the mountainous areas of western South America and has recently been summarized in an extensive report.[37]

A clearer abuse of cocaine has stemmed from its popularization during the pre-World War II period as an intoxicant. It was popularly administered parenterally by direct inhalation of the crystalline alkaloid.

In the last year or two, cocaine has become a

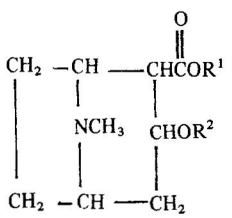

FIGURE 15.

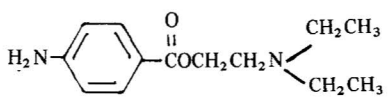

FIGURE 16.

widely touted fad in the drug subculture, but its inherent expense, rather than its illegal classification (along with the parent compound ecgonine, Figure 15, $R^1 = R^2 = H$, as a schedule 2 controlled substance[38]) appears to be limiting its use. The more readily obtainable anesthetic phencyclidine (vide infra) is commonly offered and frequently accepted as "inexpensive cocaine".

A second family of drugs that stems from the tropane carbon skeleton is based on the structure of scopolamine (Figure 17, R^1, R^2 is an epoxide ring). It and the related base atropine (Figure 17, $R^1 = R^2 = H$) are the principal alkaloids in a variety of intoxicating plants. A number of species of the *Datura* genus have been employed as intoxicants and for religious purposes both in North[39] and South[40] America. Henbane (*Hyosyamus niger*) and Nightshade (*Atropa belladonna*) are native to the eastern Mediterranean regions and Mandrake (*Mandragora officinarum*) probably had its origins in western Asia; these have been known and used since prehistoric times. Even on the Australian continent, intoxicating members of the *Solanaceae* family are found. Pituri (*Duboisia hopwoodii*) also contains the belladonna alkaloids and its leaves are chewed or smoked for their hallucinogen potential.[41] A recent report describes the presence of a tropane alkaloid identical to atropine, but with a 3,4,5-trimethoxycinnamyl acid moiety, rather than tropic acid.[42] The plant, which is native to Australia, is interestingly of the genus that provides cocaine (*Erythroxylon*).

There has been only a small degree of recent social abuse of such plants, although the presence of "stramonium" in a number of over-the-counter medications has led to the expected amount of exploration. Of more concern, is the growing availability of a large number of synthetic substitutes for scopolamine, which although of similar pharmacology, are immensely more potent and easily manufactured.[43] A number of such

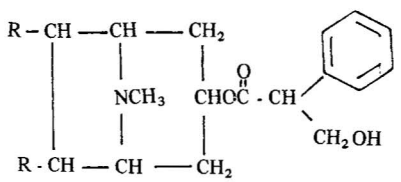

FIGURE 17.

compounds have been developed by the Lakeside Laboratories, and have been extensively explored in human subjects, both clinically and illegally. Examples of this family are JB-329 (Ditran®, Figure 18, $R^1 = C_2H_5$, R^2 = cyclopentyl), JB-318 (Figure 18, $R^1 = C_2H_5$, R^2 = phenyl) and JB-336 (Figure 18, $R^1 = CH_3$, R^2 = phenyl). The latter two homologs have received wide distribution in the eastern regions of the U.S. and have recently been included in the listing of drugs subject to control by the Bureau of Narcotics and Dangerous Drugs.

The best known of all the heterocyclic stimulants is the ubiquitous purine, caffeine. It is a mild euphoriant, yet by no means can be called a psychotomimetic and is a major component of a large number of socially acceptable drinks, yet it cannot gracefully be classified as a drug. Coffee and tea are major sources (containing perhaps 2% caffeine) found in our society; cacao, Maté, and kola are drinks of comparable strength used elsewhere.

Caffeine (Figure 19, R = CH_3) is the most effective stimulant of the methylated xanthines. However, a number of compounds are being explored which are 7-substituted theophylline derivatives and show potentially disruptive central effects at higher levels of use. Dimethazan (Figure 19, R = $CH_2CH_2N(CH_3)_2$) is being explored as an antidepressive in geriatric patients, and Fenethylline (Captagon, Figure 19, R = $CH_2CH_2NHCH(CH_3)CH_2C_6H_5$), an amalgamation of the structures of caffeine and of methamphetamine which has been sold through the over-the-counter market in Germany as a psychostimulant and antidepressant. Recent abuse through overuse has caused it to be withdrawn.

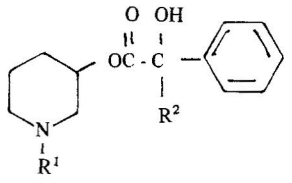

FIGURE 18.

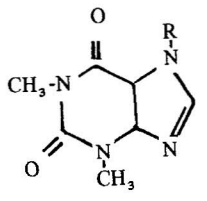

FIGURE 19.

An unusual family of heterocyclics, identified as components of the hallucinogenic mushroom *Amanita muscaria* (fly agaric), is the isooxazoles. The thesis of a masterful study[44] is that the legendary drink Soma can be identified with this mushroom but the discrepancies between the reported pharmacology of intoxication following use of the isooxazole alkaloids and the excesses associated through use of Soma (according to the *Rig Veda*) still leave the assignment open to question. The chemistry of the plant has, however, been worked out well. Early, it was felt that muscarine, a potent parasympathomimetic, was responsible for the action of the mushroom, as it was clearly present (and in fact derived its name from the species title). The amounts present, however, cannot begin to account for the action of the fungus. Also, atropine, scopolamine, and bufotenine have been noted to be present in the plant, but the first two are present in too small amounts to account for activity, and the last is known to be active only through parenteral routes.

Two isooxizole alkaloids have been well established as principal components of the mushroom and can account for a large measure of its activity.[45] These are muscimol (Figure 20, R = H) and the corresponding amino acid, ibotenic acid (Figure 20, R = COOH).[46] Variants of these two structures are unknown and thus unexplored.

A small family of compounds, unnatural in the sense that it is derived from no known botanical source, is represented by the compound phencyclidine (Figure 21, R^1, $R^2 = (CH_2)_5$). This compound is not psychotomimetic or "psychedelic" from any point of view, but has become broadly used for two simple reasons; it is potent (5 to 10 mg is a thorough dose producing anesthesia without loss of consciousness) and it is exceptionally inexpensive to synthesize in large quantities, with neither skill nor expert equip-

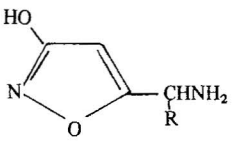

FIGURE 20.

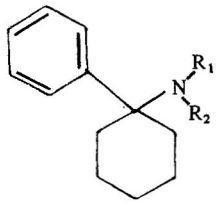

FIGURE 21.

ment. A large number of variations are potentially available through minor variations in the molecule. A recent report from the BNDD indicates the appearance of the mono-ethyl analog (Figure 21, R^1 = H, R^2 = CH_2CH_3), an analog of phencyclidine that is reported to be of equivalent potency in humans.[47] Another chemically related psychotomimetic and anesthetic (Ketamine, Figure 22) has been introduced into human clinical studies,[48] and has served to show the chemical versatility potentially available within this family. It is only 1/10 the potency of phencyclidine.

NONNITROGENOUS SYSTEMS

A number of intoxicants, psychotomimetics or hallucinogens, are known that do not fit any simple classification. These include the terpenacious or etherial fractions of many plants, the broad problem of *Cannabis* (marijuana) and its currently assumed active components, and last but not least, the unending list of fads, rumors, put-ons, and fables that are believed active by the young drug-oriented subject.

A great number of plants have the reputation of leading to some form of intoxicated state following the ingestion of some reasonable quantity of their oil-rich portions. These range from the Oil of Calamus, noted in biblical times,[49] to the oils of absinthe to zingiber, all of which have found their way into the pharmacopoeias and dispensatories of the last century. They all share in common a distillation fraction that is rich in nitrogen-free aromatic ethers, usually carrying an allyl or propenyl side chain.

Little is known specifically about these neutral compounds in human pharmacology, but studies have been made on the many amination products that are easily derived from them chemically, and to a large measure they have proven to be active as psychotomimetics.[50] The mechanism of action of intoxication of the essential oils is completely unclear, but it has been shown that at least one of the group of essential oils, safrole, is not converted to an amphetamine, but to one of several tertiary amino-methylenedioxypropiophenones.[51] If these are proven to be centrally active, they well may account for the chemistry of plant oil intoxication.

The question of pharmacological mechanism of marijuana intoxication and the medical significance of the many components that have been reported in the extracts of the parent plant (*Cannabis sativa*) has prompted a bewildering body of largely trivial information. A number of historical and scientific reviews have recently appeared and symposia representing the current state of the art occur about once a month. The following points seem to be well established, and are generally agreed upon. Delta-*l*-tetrahydrocannabinol (Figure 23, R = amyl) is clearly a major component of the resin fraction of the marijuana plant; it is biologically active in man, and certainly contributes to, if not accounts for, the primary action of the entire plant. A principal companion is the two-ring counterpart cannabidiol (Figure 24, R = amyl) which is capable of generating tetrahydrocannabinol under certain conditions and

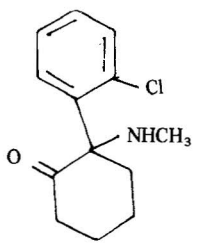

FIGURE 22.

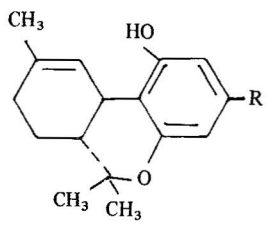

FIGURE 23.

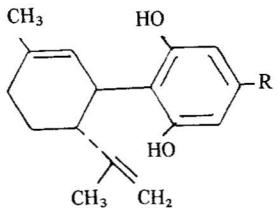

FIGURE 24.

might influence the latter's metabolic disposition. The propyl homologs of both of these compounds occur in the *Cannabis* resin (Figures 23, 24; R = propyl), but only to a small degree. They are of reduced activity and probably do not contribute to the activity of the resin to a significant extent. A principal metabolite of tetrahydrocannabinol (THC) is the isomeric hydroxylation product (Figure 25). This is produced rapidly, but is still controversial as to whether this represents an active form of the drug. A proven component of the original plant, and at least one of the metabolic end products, is cannabinol (Figure 26), but it is not felt to contribute to the overall pharmacological picture of marijuana intoxication.

A large number of extremely active cannabinoid analogs have been prepared with the double bond located in the 3,4-position (Figure 27) and their action in animal and in man appears to be extremely sensitive to the exact identity of the alkyl group R. The homolog with nine carbons (R = $-CH(CH_3)CH(CH_3)CH_2CH_2CH_2CH_2CH_3$) is probably the most potent, but does not imitate the human pharmacology of marijuana with any clinical satisfaction. None of these latter compounds occur in nature. Recent reviews have summarized the chemical[52] and the metabolic[53] research in the marijuana area.

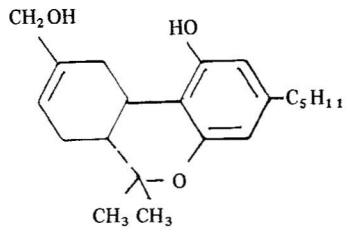

FIGURE 25.

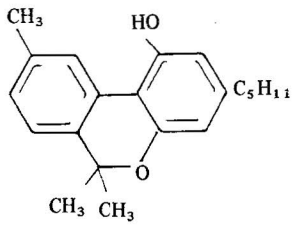

FIGURE 26.

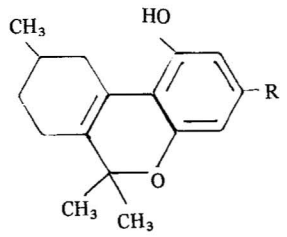

FIGURE 27.

REFERENCES

1. Hofmann, A., Notes and documents concerning the discovery of LSD, *Agents and Actions*, 1, 148, 1970.

2. Stoll, W. A., Ein neues in sehr kleinen mengen wirksames Phantastikum, *Arch. Neurol.*, 64, 483, 1949. (Presented at the 108th meeting of the Swiss Soc. Psychiat., Nov. 22, 1947, Zurich.)

3. Stoll, W. A., Lysergsäure-diäthylamid, ein Phantastikum aus der Mutterkorngruppe, *Schweiz. Arch. Neurol. Neurochir. Psychiat.*, 60, 279, 1947.

4. Abramson, H. A. and Rolo, A., Comparison of LSD with Methysergide and Psilocybin on test subjects, in *The Uses of LSD in Psychotherapy and Alcoholism*, Abramson, H. A., Ed., Bobbs-Merrill Co., New York, 1967.

5. Hofmann, A., Psychotomimetic Agents, in *Drugs Affecting the Central Nervous System*, Medicinal Research Series, Vol. 2, Burger, A., Ed., Marcel Dekker, New York, 1968.

6. Schultes, R. E., A contribution to the knowledge of *Rivea corymbosa:* the narcotic Ololiuqui of the Aztecs, Bot. Museum, Harvard, 1941.

7. Hofmann, A., The active principles of the seeds of *Rivea corymbosa* and *Ipomoea violacea, Psychedelic Rev.*, 1, 302, 1964.

8. Hofmann, A., Teonanácatl and Ololiuqui, two ancient magic drugs of Mexico, *Bull. Narc.*, 23, 3, 1971.

9. Hylin, J. W. and Watson, D. P., Ergoline alkaloids in tropical wood roses, *Science*, 148, 499, 1965.

10. Miller, M. D., Isolation and identification of lysergic acid amide and isolysergic acid amide as the principal ergoline alkaloids in *Argyreia nervosa*, a tropical wood rose, *J.A.O.A.C.*, 53, 123, 1970.

11. Der Marderosian, A. H. and Chao, J., The indole alkaloid constituents of *Argyreia nervosa* Burm. f. Bojer. (convolvulaceae), *Die Gesellschaft Arzneipflanzenforschung* (abs.), Vienna, 1970.

12. Naranjo, C., Ibogaine: A psychotherapeutic picture of its use in humans, *Clin. Toxicol.*, 2, 209, 1969.

13. Hochstein, F. A. and Paraoies, A. M., Alkaloids of *Banisteria caapi* and *Prestonia amazonicum*, *J. Amer. Chem. Soc.*, 79, 5735, 1957.

14. Bernauer, K., Notiz über die Isolierung von Harmin und (+)-1,2,3,4-Tetrahydro-harmin aus einer indianischen Schnupfdroge, *Helv. Chim. Acta*, 47, 1075, 1964.

15. Naranjo, C., Psychotropic Properties of the Harmala Alkaloids, in *Ethnopharmacologic Search for Psychoactive Drugs*, Efron, D. H., Ed., U.S. Government Printing, Washington, D.C., 1967, 385.

16. Schultes, R. E. and Homstedt, B., *De Plantis Toxicariis e Mundo Novo Tropicale Commentationes II* (The vegetal ingredients of the myristicaceous snuffs of the northwest Amazon), *Rhodora*, 70, 781, 1968.

17. Cassady, J. M., Tyler, V. E., Williams, M., and Blair, G. E., The isolation of 6-methoxytetrahydroharman from *Virola cuspidata* and *N*-monomethyltryptamine from *Virola theiodora, Proc. Sym. Biochem. Physiol. Alkaloids*, Halle (Saale), 1970.

18. Cassady, J. M., Blair, G. E., Raffauf, R. F., and Tyler, V. E., The isolation of 6-methoxyharmalan and 6-methoxyharman from *Virola cuspidata, Lloydia*, 34, 161, 1971.

19. McIsaac, W. M., A biochemical concept of mental disease, *Postgrad. Med.*, 30, 111, 1961.

20. Agurell, S., Holmstedt, B., Lindgren, J.-E., and Schultes, R. E., Identification of two new β-carboline alkaloids in South American hallucinogenic plants, *Biochem. Pharmacol.*, 17, 2487, 1968.

21. Wassén, S. H. and Holmstedt, B., The use of Paricá, an ethnological and pharmacological review, *Ethnos*, 5, 1, 1963.

22. Szara, S., Dimethyltryptamine: its metabolism in man; the relation of its psychotic effect to the serotonin metabolism, *Experientia,* 12, 441, 1956.
Arnold, O. H. and Hofmann, G., Zur Psychopathologie des Dimethyltryptamine: ein weiterer Beitrag zur Pharmakopsychiatrie: vorlaufige Mitteilung, *Wein Z. Nervenheilk*, 13, 438, 1957.

23. Tanimukai, H., Ginther, R., Spaide, J., Bueno, J. R., and Himwich, H. E., Detection of psychotomimetic N,N-dimethylated indoleamines in the urine of four schizophrenic patients, *Brit. J. Psychiat.*, 117, 421, 1970.

24. Fabing, H. D. and Hawkins, R. J., Intravenous bufotenine injection in the human being, *Science*, 123, 886, 1956.
Turner, W. J. and Merlis, S., Effect of some indolealkylamines on man, *Arch. Neurol. Psychiat.*, 81, 121, 1959.

25. Szara, S., DMT (N,N-dimethyltryptamine) and homologues: clinical and pharmacological considerations, in *Psychotomimetic Drugs*, Efron, D. H., Ed., Raven Press, New York, 1970, 275.

26. Hofmann, A., Heim, R., Brack, A., and Kobel, H., Psilocybin, ein psychotroper Wirkstoff aus dem mexikanischen Rauschpilz, *Psilocybe mexicana*, Heim, *Experientia*, 14, 107, 1958.

27. Heim, R. and Wasson, R. G., Les champignons hallucinogénes du Mexique, Ed. du Muséum National d'Histoire Naturelle, Paris, 1958.

28. Hofmann, A., Teonanácatl and Ololiuqui, two ancient magic drugs of Mexico, *Bull. Narc.*, 23, 3, 1971.

29. Leuner, H. and Baer, G., Two new short-acting hallucinogens of the psilocybin group, *Neuro-psychopharm.*, 4, 471, 1965.

30. La Barre, W., *The Peyote Cult*, Schocken Books, New York, 1969.

31. Peretz, D. I., Smythies, J. R., and Gibson, W. C., A new hallucinogen: 3,4,5-trimethoxyphenyl-β-aminopropane, with notes on the stroboscopic phenomenon, *J. Ment. Sci.*, 101, 317, 1955.
Shulgin, A. T., Bunnel, S., and Sargent, T., The psychotomimetic properties of 3,4,5-trimethoxyamphetamine, *Nature*, 189, 1011, 1961.

32. Shulgin, A. T., The six trimethoxyphenylisopropylamines (trimethoxyamphetamines), *J. Med. Chem.*, 9, 445, 1966.

33. Shulgin, A. T., Psychotomimetic Amphetamines: Methoxy 3,4-dialkoxyamphetamines, *Experientia*, 20, 366, 1964.

34. Snyder, S. H., Faillace, L. A., and Weingartner, H., DOM (STP), a new hallucinogenic drug, and DOET: effects in normal subjects, *Amer. J. Psychiat.*, 125, 113, 1968.
Hollister, L. E., Macnicol, M. F., and Gillespie, H. K., An hallucinogenic amphetamine analog (DOM) in man, *Psychopharmacologia*, 14, 62, 1969.

35. Shulgin, A. T., Sargent, T., and Naranjo, C., 4-Bromo-2,5-dimethoxyphenylisopropylamine, a new centrally active amphetamine analog, *Pharmacology*, 5, 103, 1971.
Barfknecht, C. F. and Nichols, D. E., Potential Psychotomimetics. Bromomethoxyamphetamines, *J. Med. Chem.*, 14, 370, 1971.

36. Angrist, B. M., Schweitzer, J. W., Gershon, S., and Friedhoff, A. J., Mephentermine psychosis: misuse of the Wyamine inhaler, *Amer. J. Psychiat.*, 126, 149, 1970.

37. United Nations, Report of the Commission of Enquiry on the Coca Leaf, Economic and Social Council, 1950, Special Supplement No. 1, Lake Success, New York.

38. Public Law 91-513, Schedules of Controlled Substances, U.S. Government Printing Office, Washington, D.C., 1971.

39. Gayton, A. H., Ph.D. Thesis, University of California, 1928.

40. Bristol, M. L., Tree datura drugs of the Colombian Sibundoy, *Botan. Mus. Leafl., Harvard Univ.*, 22, 165, 1969.

41. Lewin, L., *Phantastica, Narcotic and Stimulating Drugs*, Routledge and Kegan Paul, London, 1964, 138.

42. Johns, S. R., Lamberton, J. A., and Sioumis, Tropine 3,4,5-trimethoxycinnamate., a new alkaloid from *Erythroxylum ellipticum (Erythroxylaceae), Aust. J. Chem.*, 23, 421, 1970.

43. Abood, L. G., The psychotomimetic Glycolate esters, in, *Drugs Affecting the Central Nervous System*, Medicinal Research Series, Vol. 2, Burger, A., Ed., 1968, 127.

44. Wasson, G., *Soma: Divine Mushroom of Immortality*, Harcourt, Brace and World, New York, 1970.

45. Waser, P. G., The pharmacology of *Amanita muscaria*, in *Ethnopharmacologic Search for Psychoactive Drugs*, Efron, D. H., Ed., U.S. Government Printing Office, Washington, D.C., 1967, 419.

46. Catalfomo, P. and Eugster, C. H., *Amanita muscaria*: present understanding of its chemistry, *Bull. Narc.*, 22, 33, 1970.

47. Godefroi, E. F., Maddox, V. H., and Parcell, R. F., Process for producing a depressant-like effect on the central nervous system, U.S. Patent 3,097,136, 1963.

48. Domino, E. F., Chodoff, P., and Corssen, G., Human pharmacology of CI-581, a new intravenous agent chemically related to phencyclidine, *Fed. Proc.*, 24, 268, 1965.

49. Exodus 30:23.

50. Shulgin, A. T., Sargent, T., and Naranjo, C., The chemistry and psychopharmacology of nutmeg and of several related phenylisopropylamines, in, *Ethnopharmacologic Search for Psychoactive Drugs*, Efron, D. H., Ed., U.S. Government Printing Office, Washington, D.C., 1967, 202.

51. Oswald, E. O., Fishbein, L., Corbett, B. J., and Walker, M. P., Identification of tertiary aminomethylenedioxy-propiophenones as urinary metabolites of safrole in the rat and guinea pig, *Biochim. Biophys. Acta*, 230, 237, 1971.

52. Mechoulam, R. and Gaoni, Y., Recent advances in the chemistry of hashish, *Fortsch. Chem. Org. Naturst.*, 25, 175, 1967.

53. Mechoulam, R., Marijuana chemistry, *Science*, 168, 1159, 1970.