

Psychotomimetic Agents



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I. Introduction	59
II. Chemistry and Descriptions of the Psychotomimetic Drugs	62
A. Lysergic Acid Diethylamide and Analogs	62
B. Lysergamides from the Convolvulaceae spp.	70
C. Ibogaine	76
D. Substituted Tryptamines	77
E. Substituted Carbolines	87
F. Mescaline and Peyote	91
G. Methoxyamphetamines (Methoxyphenylisopropylamines)	96
H. Marijuana, Its Components and Their Analogs	103
I. Anticholinergic Psychotomimetics	116
J. <i>Amanita</i> spp.	120
K. Minor, Mystical, and Marginal Materials	122
III. Mechanism of Action	126
IV. Medical Applications and Hazards	131
References	135

I. INTRODUCTION

In Volume I of this treatise, Dr. D. F. Downing presented much of the known information, as of 1964, concerning the origins, syntheses, and medical applications of the psychotomimetic drugs (Downing, 1964). In the intervening decade there has been an explosion of scientific information published in this area of psychopharmacology.

At the time of the first review, some of the botanical sources of potential psychopharmacological agents were academic curiosities and in no way to be considered agents of abuse. Although many of the snuffs, "magic" mushrooms, and intoxicating cacti were recognized and their chemical principles identified, it has been the careful use of the exquisite analytical tools of recent years which has led to a better chemical definition and understanding of these

drugs. The concurrent development of facile chemical synthetic methods have made these heretofore botanical rarities relatively easily available for pharmacological study.

In some cases, the drug in question may have been widely used and abused (marijuana is an example). The enthusiasm to investigate the detailed composition of the plant, to prepare and make available its active components for study, and to explain the mechanisms of its action was financially supported by several governmental funding sources, responding to the public awareness of an emerging drug problem.

In some cases, the drugs of abuse, or of potential abuse, are themselves the outgrowth of just this scientific sophistication and industry. The synthesis of psychopharmacologically active chemicals present as active components in plants has led naturally to the synthesis of analogs. The increased understanding of mechanisms of action of these materials has led to the preparation and study of new chemicals that might themselves also be active.

There should be no surprise, then, that the growth of scientific and medical knowledge, paralleling the widespread increase of interest within our current generation in drug-induced changes of all types, has led to patterns of drug abuse that were not predicted 10 years ago. In Downing's review, no mention was made of abuse, for at that time this potential was thought to be minor. Today drug abuse is a fact, and the public concern attached to it is attested to by the appearance of this volume which is dedicated principally to drug abuse rather than to drug use.

The medical consensus is that there is little potential for medical utility in psychotomimetic agents. Without exception, they are classified legally as Schedule I dangerous drugs for they have "... no currently accepted medical use in treatment in the United States" (U.S. Congress, 1970). In the opinions of a minority of physicians and medical researchers these materials can be, and have been, misused, but have a real potential for proper use in some forms of psychotherapy and emotional disturbance. These points will be touched upon in the section below on medical applications. It must be remembered that it is only in the eyes of a proponent that incorrect or excessive usage of a drug is called *misuse*; when the drug in question is socially and legally unacceptable, such use becomes *abuse*, and this describes the current attitude toward the psychotomimetics.

Even the term "psychotomimetic" has undergone some evolution in this recent period. This term was originally introduced (Gerard, 1956) as a synthetic word embracing the term "psychosis" with the Greek "mimesis" implying literally the imitation of psychosis. The early concept of the drug-induced imitation of psychosis stems from the descriptions by Stocking (1940) in which he referred to mescaline-induced intoxication as a "mescaline psychosis" and closely related the drug-induced state with spontaneous schizophrenia. Alles has used (1959) the contracted form, "psychotogen."

The term "psychodysleptic" was introduced by Delay (1959) but has found no currency in the United States. The term "hallucinogenic" is frequently encountered, but is misleading because of the scarcity of generated hallucinations. Occasionally encountered are such words as "phrenotropic, schizogens, psychotica, phantastica, eidetic, mysticomimetic, misperceptinogenic, and illusinogenic." Osmond (1957) proposed a host of possible terms employing the etymologically awkward prefix "psyche-" (psychezymic, psycherhexic, psychephoric, psychehormic, psycheplastic, psychelytic, and psychedelic).

The term "psychedelic" has come into wide social use in reference to the psychotomimetic drugs, although it is rarely found in the scientific literature because of a subtle connotation of approval of drug use associated with it.*

The recent association of drug use and various art and music forms known as the psychedelic style indicates the mood of approbation associated with this term. Such broad usage will probably ultimately provide the word needed authority, but for the present review, the term "psychotomimetic" will be used.

An early and often-quoted description of the psychotomimetic state was written at the time the concept of "model psychosis" was in favor. "Psychotomimetic agents are substances that produce changes in thought, perception, mood and, sometimes, in posture, occurring alone or in concert, without causing either major disturbances of the autonomic nervous system or addictive craving, and although, with overdosage, disorientation, memory disturbance, stupor, and even narcosis may occur, these reactions are not characteristic" (Osmond, 1957). The author's desire in proposing this definition was to exclude the many unrelated psychotropic drugs such as anaesthetics, analgesics, and hypnotics. The belief that these chemicals produced a typical "psychotic" state became less prevalent during the last decade, and the research use of such drugs in this direction has been discontinued. In its place there has been an increase in the exploration of the "psychedelic" nature of the induced intoxication, with a paramedical enthusiasm for their capability to unleash, and allow the realization of, unsuspected creative potential. (The literal origin of the term "psychedelic" is mind-releasing.) A number of vocal proselytizers emerged in the mid-1960's and seemed to catalyze an extraordinary awareness and approval of drugs in

* An interesting exchange occurred between Humphry Osmond and Aldous Huxley concerning the proper word to be coined for this class of drugs. Huxley suggested the term "phanerothyme" in the couplet (*personal communication to ATS, 1969*):

"To make this mundane world sublime

Take half a gram of phanerothyme"

Osmond replied:

"To sink in hell or soar angelic,

You'll need a pinch of psychedelic"

Osmond apparently had the last word.

the younger generation. Many changes occurred with accelerating rapidity during this period: the increased enthusiasm for drug-induced experiences (LSD as probably the principal vehicle), an emergence of explosive and self-centered attitudes (of art, music, and writing, the "psychedelic" style mentioned above), and a generalized transfer of sense of authority from parent (school, government) to peer ("Don't trust anyone over 30"). In response to this youthful curiosity and rebellion, laws and regulations have been designed to proscribe the personal use of these materials. Any effective clinical study of the psychotomimetic drugs has been made virtually impossible as a result of these proscriptions.

This chapter will be based upon the outline used by Downing in the corresponding chapter in Volume I. The information presented there will be only briefly reviewed. The emphasis will be to cover in finer detail the scientific contributions of the intervening 10 years. The extensive chemical history will not be recapitulated, but rather an emphasis will be placed upon relationship between structure and activity, where this is now known. Several theories explaining the action of the psychotomimetic agents have recently been proposed, and they are best discussed in light of parallel theories for the biochemical origins of schizophrenia.

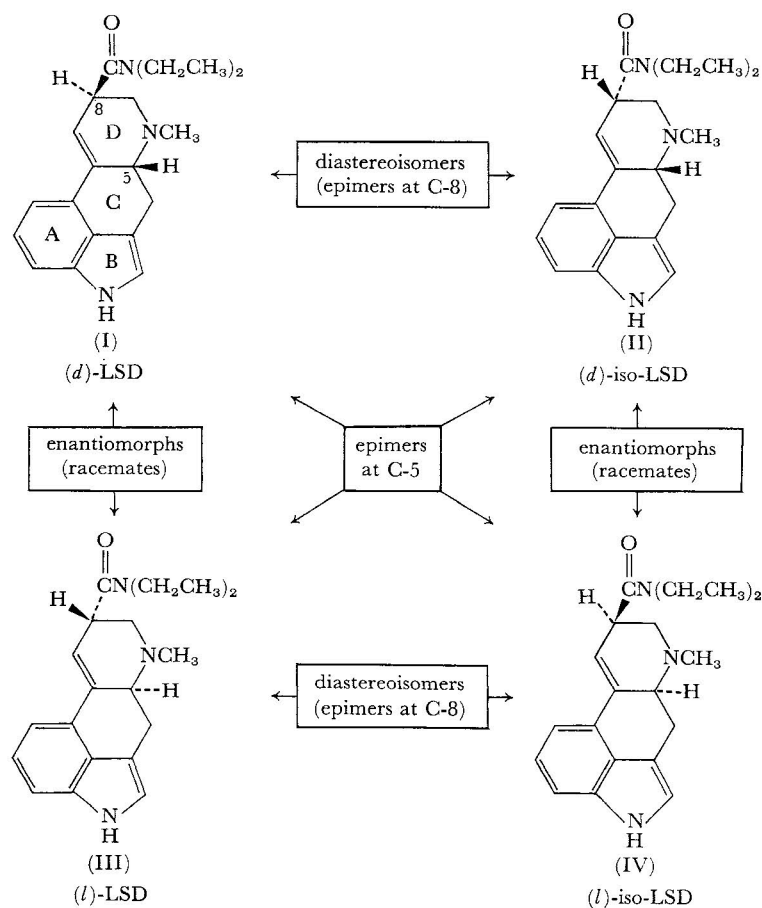
II. CHEMISTRY AND DESCRIPTIONS OF THE PSYCHOTOMIMETIC DRUGS

No attempt will be made here to organize these drugs in any pattern that would make pharmacological sense. The listings are quite arbitrary, and follow botanical logic, and in the case of synthetic materials, structural logic. The extensive bibliography of Downing's will not be duplicated except for the needed leading references that will make this review independently complete. Human pharmacology, to the extent that it is reported in the medical literature, will be included along with the chemistry where appropriate.

A. Lysergic Acid Diethylamide and Analogs

Lysergic acid diethylamide (LSD) (I) is certainly the most widely known of the psychotomimetic drugs and is still one of the most widely abused. It does not occur in nature, although its practical synthesis depends upon a heterocyclic ring system that can only (in practical terms) be obtained from plant sources, lysergic acid (see Scheme 1).

The term "LSD-25" is a common abbreviation for lysergic acid diethylamide and is derived from the initials of its chemical name in German, *lysergsaure diethylamid*. The number 25 was a code used by the chemist to identify the compound in a blind form for the pharmacologists who would study its biological properties. It was originally synthesized in conjunction

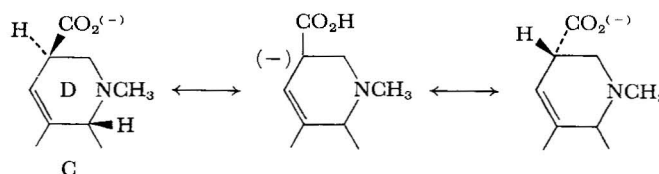


SCHEME 1

with a study of ergotlike amides that might imitate the structure and the biological properties of nikethamide, also a *N,N*-diethylamide (Stoll and Hofmann, 1938). Its profound psychological effectiveness and potency was accidentally discovered some 5 years later and has served as an observation that has given rise to an unprecedented volume of investigative research, both in scientific as well as in social areas. An interesting reproduction of these earliest notes has recently appeared (Hofmann, 1970).

Since there are two optical centers in the LSD molecule, there are four isomers possible, and these have been prepared as individual compounds (Stoll and Hofmann, 1955). They are shown in relationship to one another in structures (I)–(IV) (Scheme 1). All of the native ergot alkaloids have the 5,8-*trans* configuration of the hydrogen atoms as shown in (I), and it is only this isomer that is invested with psychotomimetic activity. During its synthesis

from lysergic acid, at least by the older methods, there is epimerization of the 8 position of ring D, with the generation of appreciable amounts of *d*-iso-LSD II as shown in Scheme 2. The two materials are easily separated chromatographically and there is no involvement of the C-5 position. In samples of



SCHEME 2

valid *racemic* LSD, both centers are inverted, and the scarce (and biologically inert) *l*-LSD (III) is present in mixture with *d*-LSD in precisely 1:1 ratios. This later isomer can again be equilibrated with the iso counterpart [*l*-iso-LSD (IV)] by base-catalyzed isomerization of either *l*-lysergic acid or of *l*-LSD.

The earliest reported synthesis of this type of amide from lysergic acid employed intermediates of mixed anhydrides, and there was invariably the generation of the iso isomers (through epimerization) which had to be separated chromatographically. Stoll and Hofmann's original synthesis (1943) employed hydrazine for the cleavage of the native amide group of the parent ergot alkaloid, and after conversion to the azide of lysergic acid, was reacted with diethylamine to a mixture of (I) and (II). The use of trifluoroacetic anhydride (Pioch, 1956) simplified the synthesis, but still produced these mixtures. A nonisomerizing anhydride reaction was introduced in 1959, employing sulfur trioxide as the other acid (through the use of a DMF-SO₃ complex) (Garbrecht, 1959). Although there is little if any isomerization, there apparently is the generation of some lysergic acid monomethylamide by degradation of the dimethylformamide solvent. A synthesis employing the acid chloride of lysergic acid has been advanced, but it is uncertain if these complications are circumvented (Frey, 1963). Very recently a general synthesis of lysergic acid amides, apparently without isomerization and in good yields, has appeared (Johnson *et al.*, 1973), but no specific details on its applicability to LSD were given. The great majority of synthetic procedures being promoted in the drug underground employ the DMF-SO₃ process of Garbrecht, and indeed most illicit laboratories reported by the authorities seem to have stockpiles of condemnatory chemicals such as lithium hydroxide and Triton-B. Recently, the use of carbonyldiimidazole, the peptide synthesis intermediate, has been observed in LSD synthesis (A. T. Shulgin, unpublished data, 1973).

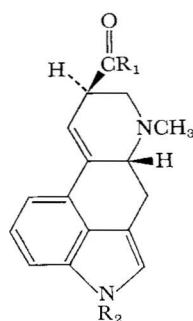
The psychopharmacology of LSD has been described at length in literally hundreds of books and essays, and need not be repeated here. The range of

dosages employed is from a minimum threshold level of about 25 μg , to an accepted full-blown "psychedelic trip" at 10 times this level. Higher levels have been recorded, but there seems to be some built-in limitation to toxicity, in that at extreme levels (several milligram amounts) severe nausea and vomiting is provoked which serves as a purge (Reynolds and Peterson, 1966).

Although much work has been reported on LSD itself, both pharmacologically and clinically, there has been very little psychopharmacological study made of its many known structural analogs. The largest number of structural variations has involved the nature of the substituents on the amide nitrogen. Since all of the syntheses mentioned incorporate a primary or secondary amine at the last step to constitute the amide portion of the final molecule, it is not surprising that a large number of these analogs have been prepared and studied. Only a few of these have been explored in human subjects. Rothlin (1957) held that the ethyl group is unique for the psychic changes associated with the LSD intoxication. The *N,N*-diethyl compound is of full activity whether the indolic nitrogen is free or acetylated, but the removal of one of the ethyl groups (i.e., to form LAE-32, see Table I) drops the potency by a full order of magnitude. Rothlin has reported that the *N*-monomethyl-, *N,N*-dimethyl-, *N*-monopropyl-, and *N,N*-dipropylamides of lysergic acid produce autonomic effects at submilligram levels but none of the psychological disruptions seen with the ethyl compounds. A number of other investigators have reported, however, that LSD-like activity can be demonstrated with some of the close homologs. Zsigmond *et al.* (1961) have reported both the *N,N*-dimethylamide (DAM-57) and the morpholinoamide (LSM-775) active in man. Both Abramson (1959) and Cerletti (1959) have found some of these amide homologs to be quantitatively less active than LSD but to have the same qualitative effects. The dosage values of Cerletti have been taken from his graphic presentation and are presented as approximations in Table I. Similarly, a number of studies by Abramson and Rolo (1967) have been made on the *N,N*-methyl ethyl-, the *N,N*-methyl propyl-, and the *N,N*-ethyl propylamides. They found the last named to have activity in man at best only a fraction of that of LSD and the others to be only weakly active, but the purpose of these studies was to assay these homologs for their capability to generate cross-tolerance, and few details are given for their drug effects per se.

Substitution on the indolic nitrogen, insofar as it has been studied, has little effect on the activity of the compound. The full LSD-like activity of the *N*₁-acetyl analog mentioned above from Rothlin's work, has been confirmed by Hofmann (1960) and Cerletti (1959). Methylation or hydroxymethylation of the indole-nitrogen decreases the potency; Stoll (1947) indicated that 500 μg of the *N*₁-methyl product was needed to produce an effect in human subjects equivalent to that resulting from 50 μg of LSD. The results of these changes are also tabulated.

TABLE I

HUMAN POTENCY OF LSD ANALOGS WITH VARIOUS NITROGEN SUBSTITUTIONS^{a,b}

R ₁	R ₂			
	—H	—CH ₃	—COCH ₃	—CH ₂ OH
$\text{—N} \begin{array}{l} \text{CH}_2\text{CH}_3 \\ \text{CH}_2\text{CH}_3 \end{array}$	LSD-25 ++++ (std)	MLD-41 +++ (g,h) ++ (e,f)	ALD-52 ++++ (a,b,g,h)	OML-632 +++ (g,h)
$\text{—N} \begin{array}{l} \text{CH}_2\text{CH}_3 \\ \text{H} \end{array}$	LAE-32 ++ (a) + (g,h)	MLA-74 + (d,g)	ALA-10 + (d,g)	
$\text{—N} \begin{array}{l} \text{CH}_2\text{CH}_3 \\ \text{CH}_2\text{CH}_2 \\ \\ \text{CH}_2\text{CH}_2 \end{array}$	LPD-824 ++ (g,l) + (d,h)	MPD-75 + (d,g)		
$\text{—N} \begin{array}{l} \text{CH}_2\text{CH}_2 \\ \text{CH}_2\text{CH}_2 \text{---} \text{O} \end{array}$	LSM-775 +++ (g,j) ++ (c)			
$\text{—N} \begin{array}{l} \text{CH}_3 \\ \text{CH}_3 \end{array}$	DAM-57 ++ (g,h)			
$\text{—N} \begin{array}{l} \text{CH}_3 \\ \text{CH}_3 \end{array}$	LME + (i)			
$\text{—N} \begin{array}{l} \text{CH}_2\text{CH}_3 \\ \text{CH}_3 \end{array}$	LMP + (i)			
$\text{—N} \begin{array}{l} \text{CH}_2\text{CH}_2\text{CH}_3 \end{array}$				

TABLE 1—Continued

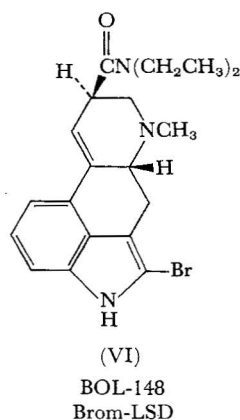
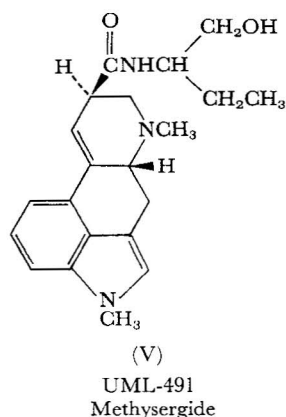
R ₁	R ₂			
	—H	—CH ₃	—COCH ₃	—CH ₂ OH
$\begin{array}{c} \text{CH}_2\text{CH}_3 \\ \\ \text{—N—} \end{array}$	LEP +++ (i)			
$\begin{array}{c} \text{CH}_2\text{CH}_2\text{CH}_3 \\ \\ \text{—N—} \\ \\ \text{CH}_2\text{CH}_2\text{CH}_3 \end{array}$	++ (k)			
$\begin{array}{c} \text{CH}_2\text{CH}_2\text{CH}_3 \\ \\ \text{—N—} \\ \\ \text{H} \end{array}$	LA-111 + (c)			

^a + + + +, Equipotent to LSD (50–100 μ gm being active); + + +, ca. a third as active as LSD; + +, ca. a tenth as active; +, weakly active.

^b Key to references:

- (a) Rothlin (1957).
- (b) Hofmann (1960).
- (c) Hofmann (1963a).
- (d) Information from Sandoz; quoted in Usdin and Efron (1972).
- (e) Stoll (1947).
- (f) Jacob (1967).
- (g) Cerletti (1959).
- (h) Abramson (1959).
- (i) Abramson and Rolo (1967).
- (j) Gogerty and Dille (1957).
- (k) Hofmann (1959).
- (l) Murphree *et al.* (1958).

The third nitrogen of LSD (the ring D piperidine nitrogen that is methylated) has been modified chemically [methyl replaced with cyano, with carboxamide, and with hydrogen (Inoue *et al.*, 1972)], but there have been no clinical studies of these compounds. Among the somewhat more complex amide derivatives, a number of hydroxylated amides are known. The α -hydroxyethylamide and β -hydroxyisopropylamide (ergometrine) are discussed in Section II,B on ololiuqui, wherein they occur naturally. The butanolamide of *N*₁-methylysergic acid [methysergide, UML-491, Sansert (V)] is commonly prescribed as a prophylactic for migraine. It has received some currency as a “legal” (i.e., prescribable) substitute for LSD in psychotherapy, and there are reports of its abuse (Lucas and Falkowski, 1973). The compound is about 0.5% the potency of LSD (Abramson and Rolo, 1967).



Methysergide has been used as an exploratory tool on the activities of other psychotomimetic drugs. Sai-Halasz (1962) reported that at levels themselves inactive (1–2 mg orally, 0.5 mg intramuscularly) led to a sensitization of the experimental subject to normally trivial dosages of dimethyltryptamine (XVII). Another well-studied substitution derivative of LSD is the 2-bromo analog, BOL-148 (VI). This compound is an even more potent serotonin antagonist than LSD (Cerletti and Rothlin, 1955). It is a very weak psychotomimetic, being less than 5% the potency of LSD (Stoll and Hofmann, 1955; Jacob, 1967).

Removal of the double bond in ring D, either by hydrogenation (to form 9,10-dihydro-LSD) or by hydration (to form lumi-LSD) appears to destroy all psychic activity (Cerletti, 1959). As to optical isomers, both *d*-iso-LSD (II) and *l*-LSD (III) are also inactive (Cerletti, 1959), the latter even at 400 times the effective dosage of LSD (Murphree *et al.*, 1960). The fourth isomer, *l*-iso-LSD (IV), produces no effects in man at 20 times the active dose of LSD (Hofmann, 1959).

The largest number of structural analogs of LSD that have been prepared involve the opening of one or more of the rings of the parent lysergic acid system. The compounds with the piperidine ring (ring D) opened [see (I)] are encountered as natural products in the several Convolvulaceae discussed in Section II,B on ololiuqui. The opening of ring C (by cleavage of the 10–11 bond to the indole “4 position”) results in a series of *N*- α -disubstituted tryptamines. Additionally, analogs are known with the indolic nitrogen replaced with sulfur (benzothiophenes) and with an aliphatic chain (tetralins). A recent review covers this chemistry (Campaigne and Knapp, 1971), but there is apparently no human psychopharmacology as yet known.

With the extreme upsurge in popularity and paramedical usage of LSD in the last decade, coupled with the enactment of several laws designed to curb its use, there has been an understandable effort to establish analytical

techniques for its detection. The two problems inherent in such analysis are consequences of unique properties of LSD in man. It is of such potency that analysis of a single dosage unit requires, by definition, techniques useful to microgram quantities, and it is apparently completely metabolized in man so that the search for traces of unchanged drug in the excretory products is futile.

All of the conventional analytical procedures are of limited value from the forensic viewpoint in that most of the spectrographic analyses cannot distinguish LSD from its iso analogs (which are generally not pharmacologically active nor illegal), and most of the chromatographic analyses cannot distinguish LSD from its close homologs (also of decreased activity, and also not illegal). As an example (Bailey *et al.*, 1973) the mass spectral patterns of a number of lysergic acid amides were substantially the same as those found for the iso counterparts, and thin-layer chromatographic separation procedures that could easily separate the normal compound from their epimers did not resolve, for example, LSD from the *N*-methyl-*N*-propyl isomer.

It is currently recognized that for legal purposes the use of infrared spectroscopy is a necessary technique for the establishment of chemical identity, and even here there are some noteworthy limitations. Mesley and Evans (1969) have found that KBr pellets can change spontaneously into polymorphic forms on standing; and spectra of the free base (as an oil), which, of course, circumvents the problems inherent in the identity of the accompanying salt, are complicated by spontaneous crystallization during the course of analysis. If the sample in question is a mixture of LSD and iso-LSD (commonly encountered in old samples or in those of illegal origin), separation of the two diastereoisomers is generally required before any quantitative results are possible. This can be done by column chromatography (Martin and Alexander, 1967) or by liquid chromatography (Wittwer and Kluckhohn, 1973). Fluorometric analysis has been advanced as an exceptionally sensitive technique (Dal Cortivo *et al.*, 1966; Dougherty, 1971), but being dependent to a large degree upon the indole ring and the conjugated $\Delta^{9,10}$ of ring D, there is a woeful lack of selectivity, and it cannot be properly employed in structural assignment.

A number of analyses depend upon chromatographic changes resulting from photolysis of LSD in aqueous solutions which generally produces the inactive lumi-LSD (Stoll and Schleintz, 1955; Hellberg, 1957) or in some organic solvent (Anderson, 1969) which produces a cascade of fluorescent degradation products easily revealed by thin-layer chromatography. The specificity of this latter test has not been established.

Analysis of body fluids for evidence of LSD usage is complicated by the absence of unchanged LSD in both plasma and urine following the administration of the drug. There is extractable fluorescent material from human plasma, and if this is accepted as LSD, it appears that there are only extremely low levels to be found. One hour after a nominal dosage, the observed level

is 5 ng/ml, which further decreases at a plasma half-time of about 4 hours (Aghajanian and Bing, 1964). When the subject is known to have been exposed to LSD, such a fluorescent assay is acceptable, but if the identity of drug involved in the exposure is unknown, there can be no identification possible with currently known techniques. Urine analysis is equally complicated. Following known LSD usage, there can be extracted from urine, following enzymatic hydrolysis, a fraction that upon UV irradiation gives acceptable levels for LSD (Faed and McLeod, 1973). Recently, two radio-immune assays have been made available for LSD analysis (Taunton-Rigby *et al.*, 1973; Loeffler and Pierce, 1973). One involves coupling of LSD to human serum albumin through the amide group, thus showing broad cross-reactivity to a number of ergot derivatives, the other is linked through the aromatic centers and is highly specific for the diethylamide structure. Both are extremely sensitive.

B. Lysergamides from the Convolvulaceae spp.

1. BOTANY AND CHEMISTRY

Although the many alkaloids associated with both the lysergic acid ring system and the isomeric clavine system have classically been associated with the rye fungus "ergot" or *Claviceps purpurea*, it is now well documented that most of the nonpeptide examples are also common components of a number of plants of the morning glory group.

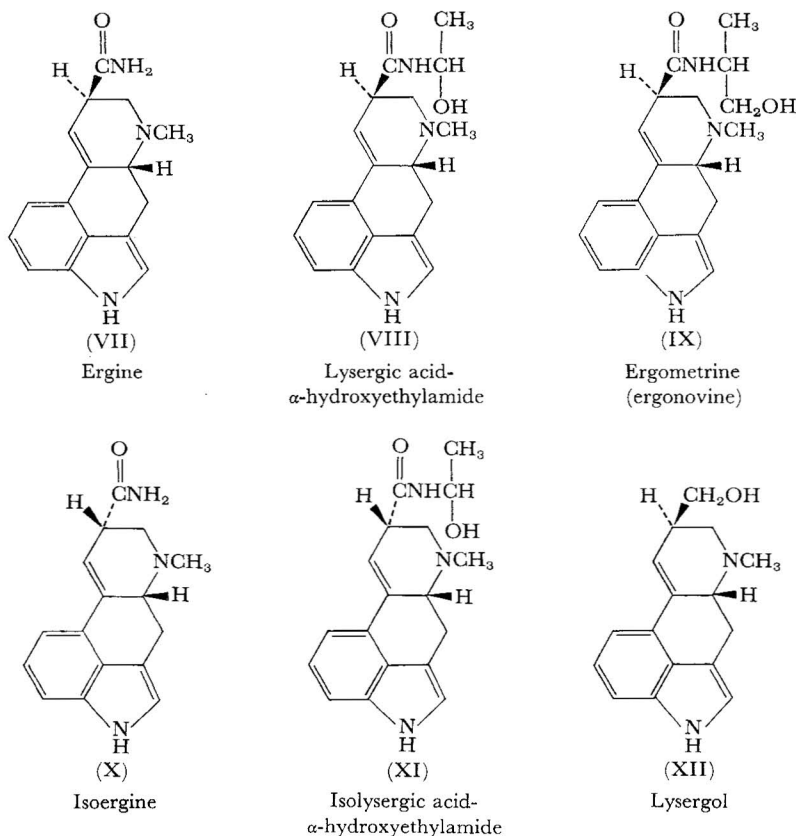
The best documented of these is the Convolvulaceae known by the Aztec name of ololiuqui, and botanically as *Rivea corymbosa*. It was first described and illustrated by the Spanish in the latter part of the sixteenth century. Its religious role was to produce a delirious state of hallucination and divine communication. It was also used broadly throughout Mexico as a medicine and anaesthetic. Schultes (1941) reviewed this history and made a firm connection between ololiuqui and the seeds of the plant *Rivea corymbosa*.

A second morning glory was recognized by MacDougall (1960) as a different plant, used by the Zapotecs sometimes with and sometimes in place of ololiuqui. The seeds of this plant were called *Badoh negro*, and the plant identified as *Ipomoea violacea*. There are many known species of *Ipomoea* but most of these have proved to lack alkaloids (Der Marderosian and Youngken, 1966). However, in addition to the several varieties known of *I. violacea* (syn., *I. tricolor*) mention should be made of the species *I. sidaefolia* [which is now equated to *R. corymbosa* (Schultes, 1941)] and of the unexplored morning glory *I. carnea*, a South American plant with an intoxicating seed known as *matacambra* (A. T. Shulgin, unpublished data, 1973).

The third morning glory plant that has found use as an intoxicant is Hawaiian baby woodrose or *Argyria nervosa*. This plant appears to be of Old

World origin, and has been used historically in India as a medicine. Its roots are reputed to be effective in the treatment of nervous system disorders (Dutt, 1887) and its leaves of value as a topical stimulant. It is the seed of this plant, however, that has proved to be the richest source yet discovered of the ergot like alkaloids in the family Convolvulacea.

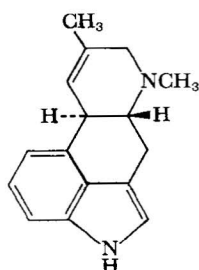
The chemistry of these several plants unfolded readily because of the many studies made in the area of the ergot alkaloids. The two principal alkaloids found in all of the Convolvulaceae so far studied are the amide of *d*-lysergic acid [ergine (VII)] and the diastereoisomeric amide of *d*-isolysergic acid [isoergine (X)]. These two bases have the same absolute configuration



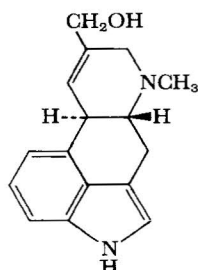
as is found with *d*-LSD and *d*-iso-LSD, but, of course, the amide nitrogen is unsubstituted. The monohydroxyethylamides of each of these two materials are also principal components of the various morning glories; *viz.*, lysergic acid- α -hydroxyethylamide (VIII) and isolysergic acid- α -hydroxyethylamide (XI). These two carbinolamides are the principal ergot products of culture medium synthesis from *Claviceps paspali*, from which they can be prepared in

concentrations of grams per liter of culture medium. These compounds, although well documented as components in the Convolvulaceae, are possibly lost in several of the analyses of alkaloid composition. They are extremely unstable, and are very readily degraded into acetaldehyde and the corresponding amide, ergine or isoergine. In these instances their presence will be measured only by the elevated levels of the derived amides. The three-carbon homolog, ergometrine [ergonovine (IX)] may also be found in these plant groups, but the iso epimer (ergometrinine) is present at best in trace amounts. Lysergol (the reduction product of lysergic acid) (XII) is found as a component of *R. corymbosa*, but neither it nor its epimer isolysergol can be detected in anything more than trace amounts in any of the other genera discussed here.

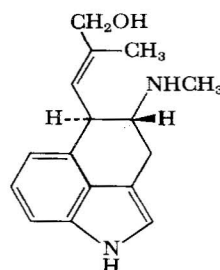
Three major clavine alkaloids are consistently reported as being present in the Convolvulaceae; *viz.*, agroclavine (XIII), elymoclavine (XIV), and chanoclavine (XV).



(XIII)
Agroclavine



(XIV)
Elymoclavine



(XV)
Chanoclavine

A number of reports have appeared that give amounts or that give ranges of alkaloids that are found present in any of these several plant products. A compilation of these is presented in Table II but a few problems must be noted: that all alkaloid levels have been normalized to 100% of total alkaloids and in the cases of low total levels these values are only approximate; that a number of the *Ipomoea* results are ranges found for a number of varieties of plants; and that some analyses of alkaloid content were conducted under conditions that would convert the carbinolamides to the derived lysergamides, so that the reported levels might reflect only the conversion end product, not the actual plant content.

In addition to those alkaloids itemized in Table II, Chao and Der Marderosian (1973) have identified in *A. nervosa* a number of minor components based on chromatographic behavior. These are festuclavine, lysergene, isolysergol, molliclavine, setoclavine, osisetoclavine, penniclavine, and ergometrinine. Hylin and Watson (1965) have also observed the latter two in *A. nervosa*.

TABLE II
RANGES OF ALKALOIDS FOUND IN SEVERAL PLANT PRODUCTS^a

Compound	<i>A. nervosa</i>	<i>R. corymbosa</i>	<i>I. violacea</i>
Ergine (VII)	23% (a) 25% (c)	54% (b) 48% (d)	58% (b) 10-16% (c) ^d 5-50% (d) ^e
Lysergic acid- α -hydroxyethylamide (VIII)	6% (a)	^b (b)	^b (b)
Isoergine (X)	31% (a) 18% (c)	17% (b) 35% (d)	8% (b) 18-26% (c) ^d 9-17% (d) ^e
Isolysergic acid- α -hydroxyethylamide (XI)	4% (a)	^c (b)	^c (b)
Ergometrine (IX)	8% (a) tr (c)		8% (b)
Elymoclavine (XIV)	4% (a)	4% (b)	8% (b)
Chanoclavine (XV)	3% (a)	4% (b)	8% (b)
Lysergol (XII)	tr (a)	4% (b)	
Agroclavine (XIII)	1% (a)		
Total alkaloids	0.3% (c)	0.012% (b)	0.06% (b)(d)
(% of dry weight of seed)	0.6% (a)	0.04% (d)	0.04-0.08% (c) 0.02-0.04% (e)

^a Key to references:

(a) Chao and Der Marderosian (1973).

(b) Hofmann (1971).

(c) Hylin and Watson (1965).

(d) Genest (1965).

(e) Taber *et al.* (1963).

^b Probably converted during analysis to acetaldehyde and ergine.

^c Probably converted during analysis to acetaldehyde and isoergine.

^d Range observed for two varieties of *I. violacea*; viz., Heavenly Blue and Pearly Gates.

^e Range observed for five varieties of *I. violacea*, viz., Flying Saucers, Heavenly Blue, Major Tall, Pearly Gates, and Wedding Bells (d).

2. PHARMACOLOGY

Studies of the pharmacological effectiveness of these seeds in man have led to a number of apparent contradictions. Osmond (1955) reported that the consumption of from 60 to 100 seeds of *R. corymbosa* led to a state of apathy and listlessness. There is mentioned an increase of visual sensitivity, followed by an extended feeling of well-being. Recently, verbatim accounts of these experiments have been published (Hoffer and Osmond, 1967a). Kinross-Wright (1959) reported that studies of dosages of up to 125 seeds were without any ascertainable effects whatsoever. On the contrary, Isbell mentioned unpublished studies (in Isbell and Gorodetzky, 1966) where he had

found that with only 6 seeds (again, of *R. corymbosa*) there was generated a slight sedation accompanied by nausea. These contradictory reports can be resolved (Wasson, 1963) by the fact that these seeds have a hard coat, and when consumed unmodified can pass through the digestive system intact. In native use, the seeds are finely ground, soaked in water, and, after being strained, yield a filtrate that is actually consumed.

A study was made to evaluate clinically the alkaloid mixtures as found in the extracts of *R. corymbosa* and as synthetically reconstituted from purified components (Isbell and Gorodetzky, 1966). Human subjects were given (1) crude extracts of *Ipomoea violacea*, totaling 5 mg of alkaloids, including ergine as the principal component, and also containing isoergine, chanoclavine, elymoclavine, and ergometrine, all in a ratio of about 7:1:1:1:1; (2) 5 mg of a reconstituted mixture that approximated the composition of the seeds of *R. corymbosa*, containing ergine, isoergine, ergometrine, chanoclavine, elymoclavine, and lysergol in exact ratios of 9:5:2:2:1:1; or (3) 100 μ g of LSD. Both the *I. violacea* extracts and the reconstituted *R. corymbosa* componentry were clearly different from the LSD trials, in that there was little sensory distortion and no reports of hallucinations.

Only a few limited pharmacological studies have been made on the individual drugs. Ergine in the rabbit produces strong autonomic symptoms such as mydriasis, piloerection, and hyperthermia, as well as motor restlessness (Cerletti *et al.*, 1963). On the rat uterus it has only 4% of the anti-serotonin activity of LSD. Conditioned avoidance studies with isoergine in the rat (Vogel *et al.*, 1972) support its role as a psychoactive agent. Lysergic acid hydroxyethylamide appears, in uterus response studies of the guinea pig and rabbit (Glasser, 1961), to be about half as potent as its homolog ergometrine, and in mice and rabbits it shows a sympathomimetic response very similar to that described for ergine. This is indicative of potential LSD-like activity. Similar stimulatory effects are reported in animal studies for both elymoclavine and lysergol (Yui and Takeo, 1958).

The human pharmacology of ergine, interestingly, predates its discovery as a major component in the Convolvulaceae. Following the discovery of the high potency of LSD, a large number of analogs were prepared at the Sandoz Laboratories, and many of these assayed in limited clinical experiments. Hofmann (1963a) has described the psychopharmacology of both ergine and isoergine. Following an i.m. 500- μ g dose of ergine there was nausea, followed by a narcoticlike physical and mental fatigue with a high sensitivity to noises. These effects developed in about an hour, and were followed by a period of sleep; in 5 hours there was complete return to the normal state. A similar sedative-hypnotic course of activity was reported by Solms (1956a,b) in which his subjects displayed a decrease of psychomotor activity, a feeling of sinking into nothingness, a desire to sleep, followed by sleep itself.

Hofmann (1963a) has described the action of isoergine in man. Following

the administration of 2.0 mg orally, there was a feeling of mental emptiness and unreality, but no indication of specific sensory distortion. Ergometrine has, of course, been extensively used in clinical work as an oxytocic following the latter stages of labor at dosages frequently in excess of a milligram, and although nausea can be encountered as an undesirable side reaction, there appears to be no adverse effects of a psychopharmacological nature. None of the remaining alkaloids reported in these botanicals has been evaluated as chemical individuals in man.

It appears that the agents that are responsible for the human activity of these plants are ergine and isoergine, and possibly the corresponding α -hydroxyethylamides of lysergic acid which could serve as metabolic precursors. In the case of *A. nervosa*, with a typical weight of 100 mg/seed, an alkaloid content of 0.5% with a composition of at least 50% of the above four presumed responsible ingredients, and an expected effective dosage of 5 mg, there would be 10 seeds required for activity. This is a number completely in keeping with the popular use of Hawaiian baby woodrose as an intoxicant. Similarly, the *R. corymbosa* seed is somewhat less than half the weight of the *A. nervosa* seed, and with some one-tenth the alkaloid content, it is consistent that several hundred seeds would be required for biological activity.

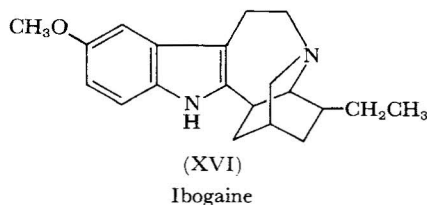
3. MISUSE AND LEGAL STATE OF MORNING GLORY SEEDS

It was in the summer of 1963 that the biological potential of morning glory seeds became widely broadcast throughout a very drug-conscious youth group, and within weeks every major news vehicle gave this "new problem" wide coverage.* There were a number of notes in medical journals in the following months concerning toxicity cases, but in general the fad quickly died out. Reference may occasionally be found to the fraudulent misidentification of morning glory seeds as some more salable hallucinogen (Miller, 1970). Occasions have arisen in which the intact seed content of the *A. nervosa* has been used as a masking for LSD in the hope that the complex composition of the seed would obscure the presence of LSD (A. T. Shulgin, unpublished data, 1973). Simple thin-layer chromatography can easily reveal LSD in admixture with these natural alkaloids. A botanical description of the plant materials involved has appeared for the use of the forensic scientist (McJunkins *et al.*, 1968) as have chromatographic screening methods for the ready distinction of morning glory seeds from others that might be mistaken for them (Brackett *et al.*, 1966). At the present time, neither these botanicals themselves nor any of their known components is proscribed by law.

* *New York Times*, July 11, 1963, p. 31; *Time*, July 19, 1963 p. 49; *Newsweek*, July 22, 1963, p. 59.

C. Ibogaine

Ibogaine (XVI) is the principal alkaloid isolated from the bark of the root of the African plant *Tabernanthe iboga*. In the first volume a review of its



native reputation as a centrally active stimulant was presented, as were some of the chemical studies associated with its complex structure. At that time there were only the original field reports of its biological activity, and no clinical studies had been made of the isolated pure alkaloid.

Recent animal pharmacological studies of ibogaine have shown a reduction of aggressiveness in mice (Kostowski *et al.*, 1972). This, together with the studies of Schneider and Sigg (1957) that demonstrated central stimulation and yet anticonvulsive properties, led to a hypothesis that ibogaine may indeed be a hallucinogenic in man.

This conclusion is not borne out by the several recent clinical studies that have appeared. Schmid (1967) has studied a range of oral dosages in human volunteers from 10 to over 100 mg, and has observed an intoxicated state generated, followed by mild sedation. He observed no hallucinations. A similar picture of its activity is presented by Naranjo (1969). He found ibogaine to be active orally at about 300 mg and parenterally at about one-fourth this dosage. He compared it directly with harmaline as a "fantasy enhancing" drug for psychotherapeutic use. These studies have been expanded to make comparisons between the pure alkaloid and the total botanical material itself, as well as with a number of pharmacologically (but not chemically) related psychotomimetics, such as LSD, harmaline, and MDA (see LXXIX) (3,4-methylenedioxyamphetamine) (Naranjo, 1973). The original French literature (see Landrin, 1905) that alleges hallucinogenic behavior and epileptic-like madness with ibogaine is not supported by these results. Rather they agree with descriptions of native usage (Dybowski and Landrin, 1901) that seemed to be similar to alcohol: the generation of an intoxicated state, of mild stimulation, followed by sedation. Schultes (1967) has mentioned that there is little evidence in recent studies among the West African tribes of the use of *T. iboga* as a vision-producing narcotic. Rather, it is used in a medical context.

Ibogaine was placed in the listings of the Federal Food, Drug and Cosmetic Act in 1967 (Federal Register, 1967) following a limited appearance of the alkaloid on the East Coast and a popularization of its reputation as a

hallucinogenic drug. A recent paper describes techniques for the isolation and identification of the drug from biological materials (Dhahir *et al.*, 1972).

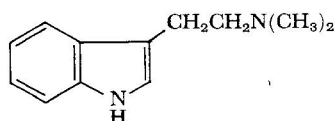
D. Substituted Tryptamines

1. BOTANICAL SOURCES

All of the known psychotomimetic drugs of the simple indole structure of tryptamine can be related either botanically or chemically to *N,N*-dimethyltryptamine (DMT). This is the simplest of the substituted tryptamines that is centrally active as a psychotomimetic, and it is the major component in a number of highly potent snuffs used throughout the New World. The principal botanical origins are two genera of the family Leguminosae and one of the family Myristicaceae.

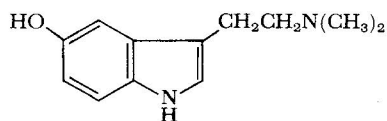
The first two genera are *Anadenanthera* and *Mimosa*. Until recently the plants giving rise to the snuff *yopo* or *cohoba* of Colombia, or *vilca* in Peru and Bolivia, were known by the generic name *Piptadenia*. Recently, Altschul (1964) has argued that both morphological and chemical factors require a reassignment to the genus *Anadenanthera* and most of the literature since 1970 employs the latter terminology. As is conventional, the species names remain unchanged and will serve to integrate new reports with the older literature.

Anadenanthera peregrina is the best studied of these plants and has been shown to contain five alkaloids. The two principal bases are *N,N*-dimethyltryptamine [DMT (XVII)] and the 5-hydroxy analog, bufotenine (XVIII), one of the few alkaloids found naturally in the animal as well as the plant kingdom (Stowe, 1959). The three minor alkaloids often also found present



(XVII)

N,N-Dimethyltryptamine (DMT)

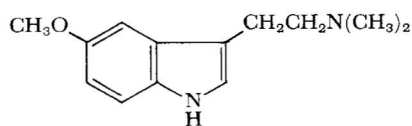


(XVIII)

Bufotenine

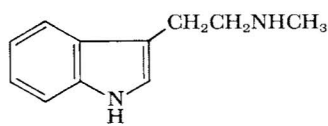
are closely related biosynthetically, *viz.*, 5-methoxy-*N,N*-dimethyltryptamine (XIX), *N*-monomethyltryptamine (XX), and 5-methoxy-*N*-monomethyltryptamine (XXI) (Legler and Tschesche, 1963). Both *N* oxides of DMT and bufotenine have also been reported as being present in *A. peregrina* (Fish *et al.*, 1955). A second species, *A. colubrina*, contains mainly bufotenine (Pachter *et al.*, 1959). There has also been reported an Argentinian species *Piptadenia macrocarpa* (Iacobucci and Ruveda, 1964) that contains these two primary alkaloids as principal components.

A second genus, *Mimosa*, is known best for the Brazilian member *M. hostilis*, whose roots give rise to a hallucinogenic drink known as *vinho de Jurema*. The principal alkaloid present is *N,N*-dimethyltryptamine (XVII)



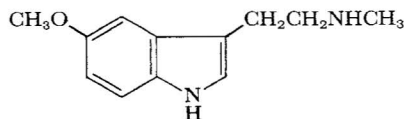
(XIX)

5-Methoxy-*N,N*-dimethyltryptamine
(5-OCH₃-DMT)



(XX)

N-Monomethyltryptamine



(XXI)

5-Methoxy-*N*-methyltryptamine

(Pachter and Hopkinson, 1960). The contradiction inherent in that a plant source of an intoxicating drink contains primarily an alkaloid that is only active parenterally is yet to be resolved.

In the northern part of South America (Brazil, Colombia, and Venezuela) there is wide usage of a snuff known as *parica*, *epena*, or *yakee*, which is prepared from the resin of the tree, *Virola theiodora*. This resin contains the remarkable level of some 10% by weight of 5-methoxy-*N,N*-dimethyltryptamine (XIX) (Holmstedt, 1965; Agurell *et al.*, 1969). At least a half-dozen additional species of *Virola* have been shown to contain the alkaloids (XVII), (XIX), or (XX) (Holmstedt *et al.*, 1964; Agurell *et al.*, 1969; Cassidy *et al.*, 1969; Corothie and Nakano, 1969). The bis-*N*-demethyl homolog of (XIX), 5-methoxytryptamine, has been reported in *Virola peruviana* (Lai *et al.*, 1973). *Epena* samples received from the Tucano and Waica Indians show, in addition to *N,N*-dimethyltryptamine, bufotenine and 5-methoxy-*N,N*-dimethyltryptamine as well as their monomethyl homologs (XX) and (XXI) (Holmstedt and Lingren, 1967). Several new carboline derivatives were also noted as present in these snuffs and will be discussed in the section on methoxyharmans.

Not only is there uncertainty in the assignment of drug to botanic source (see Wassen, 1967; Schultes, 1967; Altschul, 1967; Wassen and Holmstedt, 1963, for reviews attempting to afford some concordance to the many field observations) but also in the chemical area the problems are further multiplied by the fact that some analyses are performed on actual snuff samples (bearing some local native name and often of uncertain plant origin) and some on the plants themselves. The latter are usually well documented but often not accurately associated with the specific drug end product.

Recently, *N,N*-dimethyltryptamine (XVII) has been shown to be the principal alkaloid in the leaves of *Banisteriopsis rusbyana*, and no carboline derivatives are present. The *Banisteriopsis* group is discussed under methoxyharmans since the harmine-type carboline derivatives are their principal components. This is a second

indication of the oral appreciation of a parenterally active drug in that the Kofan Indians of Ecuador add leaves of *B. rusbyana* to the *Banisteriopsis* brews to increase the intensity and duration of the visual effects experienced (Der Marderosian *et al.*, 1968a). One might wonder if there is some component of their orally active native brews that does not contribute to the activity but provides some synthetic that would make the mixture orally active. How does, after all, a person discover a snuff? Most of the activities of the New World Indians have been directed to survival in the jungle, the need to secure food, or to protect himself. However, there are many plant sources of drugs containing dimethyltryptamine or methoxydimethyltryptamine which are only active parenterally, and their native abuse has been only through the use of snuffs. Since there is no apparent value of snuffs in either food getting or in self-defense, the interesting anthropological question remains unanswered as to how native tribes discover materials that are active only through some parenteral route of administration.

These several indolic chemicals form the framework for the presentation of the many known psychotomimetic indoles. They are to be discussed in chemical, not botanical, presentation.

2. DIMETHYLTRYPTAMINE (DMT)

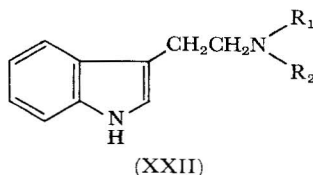
The psychotomimetic properties of *N,N*-dimethyltryptamine (XVII) were first discovered by Szara (1956) who reported that intramuscular administration of about 1 mg/kg produced LSD-like psychotic effects that were of very rapid onset and of relatively short duration. The onset of psychological symptoms appears in 3–5 minutes and has been completely dissipated within an hour. Potency and chronology have been confirmed in a number of clinical repetitions. Turner and Merlis (1959) have found only vague restlessness at levels of 25 mg im and give the lowest effective dose in man as 50 mg. Orally, even 350 mg was without effect.

A number of factors can influence the subject's response to the drug. Pretreatment of a normal individual with methysergide (30–40 minutes if administered orally, 10 minutes if intramuscularly) at dosages that are well below those needed to produce psychological effects alone (1–2 mg) greatly exaggerate the effects of *N,N*-dimethyltryptamine (Sai-Halasz, 1962). On the other hand, in schizophrenic subjects, there is a reduced response which is delayed in appearance (Boszormenyi and Brunecker, 1957). The relationship of *N,N*-dimethyltryptamine in the problem of mental illness is possibly important as both it and the monomethyl homolog (XX) have been identified in human urine (see Section III). Highly sensitive analytical procedures have been developed (Walker *et al.*, 1973; Wyatt *et al.*, 1973a) with a limit of detectability of DMT of about 4 ng/ml. These workers found no differences between schizophrenic populations and normals. A blood enzyme system

capable of synthesizing DMT has been described (Wyatt *et al.*, 1973b). One of the metabolic products of *N,N*-dimethyltryptamine is the 6-hydroxy analog; the question of its role in DMT activity is discussed below.

3. HOMOLOGS OF *N,N*-DIMETHYLTRYPTAMINE

The most completely studied homolog of DMT is *N,N*-diethyltryptamine (DET or T-9) [(XXII), $R_1 = R_2 = C_2H_5$]. Its human activity was discovered by Szara at about the same time as DMT (Szara, 1957). It was first explored clinically in Hungary by Boszormenyi *et al.* (1959) who likened it to mescaline rather than to LSD in that after an initial period of nausea, most test subjects developed a meditative, pleasant, euphoric mood, often with depersonalization. Unlike the rapid actions of DMT, the onset of action of



DET takes some 45 minutes following intramuscular administration, and the effects last some 3 hours. Like DMT, DET is metabolized both to the 6-hydroxy analog and to indoleacetic acid. Much of the clinical study concerning this drug is directed toward the role of, or the significance to be associated with, the appearance of this hydroxylated metabolite. There appeared to be some correlation between the extent of its generation and the intensity of drug effect (Szara *et al.*, 1966), but parallel trials of the drug with normal subjects and schizophrenic subjects showed only slight differences in metabolism. Both groups generated about 5% of 6-hydroxy-*N,N*-diethyltryptamine and about twice this amount of indoleacetic acid.

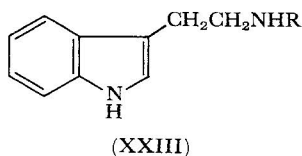
The *N,N*-di-*n*-propyl homolog of DMT [(XXII), $R_1 = R_2 = C_3H_7$] appears to parallel the diethyl counterpart both in potency and in chronology. Faillace *et al.* (1967) found in their clinical studies that in 10–15 minutes following the intramuscular administration of between 0.7 and 1.3 mg/kg the first effects were noted, that peak intensity was achieved between 45 and 90 minutes, and that the effects were largely dissipated after a total of 3 hours. This short duration and abrupt termination of effect has prompted its study in the psychotherapy treatment of alcoholic patients (Soskin *et al.*, 1973; Grof *et al.*, 1973). At levels of about 1 mg/kg enzymatic changes were sought (in aldolase and creatine phosphokinase activity) that might be similar to those reported as occurring in spontaneously psychotic patients, but none was observed (Meltzer *et al.*, 1970).

The human effectiveness of the diallyl analog [(XXII), $R_1 = R_2 = -CH_2CH=CH_2$] has been established (Szara and Hearst, 1962), but the di-*n*-butyl analog apparently is not active, at least at 1.0 mg/kg (Szara, 1970).

It is difficult to assess the value that can be given to reports of biological activity and potency that come from sources that exist outside the usual areas of academic research and scientific publication. An incalculable quantity of research has been done extracurricularly by philosophers, chemists, and pharmacologists, or by unenfranchised scientists, in the area of the isolation, preparation, and evaluation of unknown drugs. The most popular chemical families are two that are the most easily available synthetically, the substituted tryptamines, discussed here, and the substituted phenethylamines, to be discussed below. The results of these studies, if they appear at all, are generally anonymous, and can be found in underground publications devoted to the drug culture. The only validity that can be claimed for the details that are presented is that they are unquestionably tried and retried by tireless experimenters, and if myths live long, they may have merit.

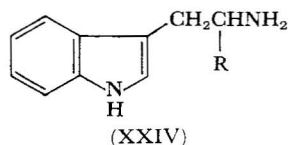
With this in mind, three comments should be made. It is "knowledge" within the anonymous underground drug publications that not only is the *N,N*-dipropyltryptamine homolog mentioned above active orally but also that the diisopropyl counterpart is especially so. Interestingly, there is a contradiction to the published literature, as well! Szara (1957) has indicated in a published table that *N,N*-diethyltryptamine is orally active at 60 mg. Apparently in drug abuse circles, some 5 times this quantity is required for psychotomimetic effects. *N,N*-Dimethyltryptamine appears to be orally inactive in quantities in excess of a gram.

Little is known of the monosubstituted tryptamines. *N*-Methyltryptamine



[(XX); (XXIII) $R = CH_3$] has been mentioned as a minor component in *Anadenanthera* spp. It has also been identified in the bark of *Virola theiodora* (Cassidy *et al.*, 1969), a plant that is one of the principal sources of the carbo-line psychotomimetics. In comparison with dimethyltryptamine, monomethyltryptamine produces less central stimulation in the dog, and the monopropyl homolog [(XXIII), $R = n-C_3H_7$] is without activity (Conner, 1954). The *n*-hexyl homolog [(XXIII), $R = n-C_6H_{13}$] has been found inactive in a limited number of subjects (Szara, 1967). The mono-*tert*-butyl derivative [(XXIII), $R = t-C_4H_9$] has the reputation of oral activity (see above discussion concerning anonymous street knowledge), but dosage details are not known.

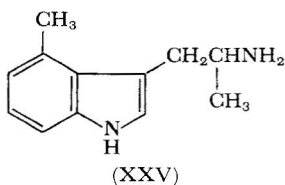
Two α -alkyl homologs of tryptamine have been clinically evaluated. α -Methyltryptamine [(XXIV), R = CH₃, Monase-M] is the more active



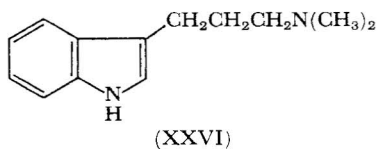
(Hollister *et al.*, 1960; Murphree *et al.*, 1960) producing at 20 mg dosages orally a psychotomimetic reaction that is equated, in experienced volunteers, to 50 μ g of LSD (Murphree *et al.*, 1961) or to 60 mg DET (Szara, 1961a). The activity is of surprisingly slow onset (3–4 hours) and of unusually long duration (up to 24 hours). This compound is alleged to have been the traveling drug of Ken Kesey's Merry Pranksters. The α -ethyl homolog [(XXIV), R = C₂H₅, Monase] appears to produce in experienced subjects more of a talkative intoxication and less of any LSD-like effects (Murphree *et al.*, 1961). The time of onset is more conventional (30–90 minutes, 6–12-hour duration) but it is an order of magnitude less potent (150 mg orally required for biological activity). This compound was marketed by Upjohn for a period for use in modest dosage levels as an antidepressant.

A single mention has been made of the antidepressant utility of a ring-substituted homolog, 4 α -dimethyltryptamine (XXV), but no details are presented (Hoffer and Osmond, 1967b).

One additional homologous system has been evaluated in man. This is the three-carbon chain homolog (XXVI) of *N,N*-dimethyltryptamine. This compound, intramuscularly administered to normal subjects at levels of up



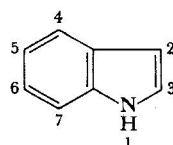
4 α -Dimethyltryptamine



to 80 mg, gave no central stimulation (Turner and Merlis, 1959).

The human pharmacological data concerning the *N*-alkyl and α -alkyl derivative of tryptamine are presented in Table III.

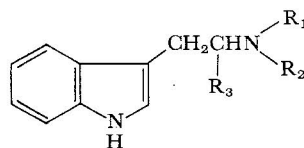
The principal ring-substituted derivatives of *N,N*-dimethyltryptamine that have been pharmacologically evaluated in man are the hydroxyl analogs (and their esters and ethers) and the fluoro analogs. Three of the four available positions of the indole nucleus command interest for three totally different reasons. The 4-substituted products are from natural (botanical) sources and came into the scientific literature as the active components of several hallucinogenic mushrooms; the 5-substituted materials are of interest



(XXVIII)

Indole numbering

TABLE III
HUMAN POTENCY OF ALKYLATED TRYPTAMINES



(XXVII)

R ₁	R ₂	R ₃	Effective dosage (mg)	Route		Ref. ^a
				im	Oral	
CH ₃	CH ₃	H	70	+	—	(a)
C ₂ H ₅	C ₂ H ₅	H	60	+	± ^b	(b,c)
C ₃ H ₅	C ₃ H ₅	H	60	+	+	(d)
<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	H	60	+	+	(e)
<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	H	50	?	+	(c)
<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	H	70	—	—	(f)
<i>t</i> -C ₄ H ₉	H	H	?	?	+	(c)
H	H	CH ₃	20–40	?	+	(g,h)
H	H	C ₂ H ₅	150	?	+	(i)

^a Key to references:

(a) Szara (1956).

(b) Szara (1957).

(c) See text.

(d) Szara and Hearst (1962).

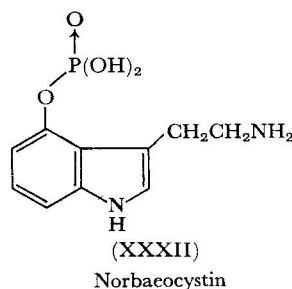
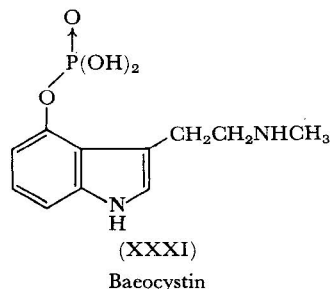
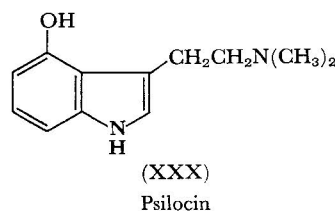
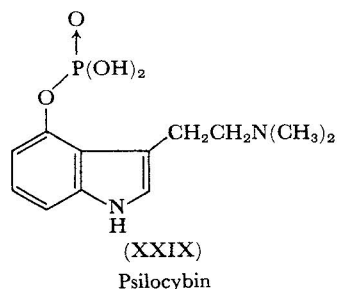
(e) Faillace *et al.* (1967).

(f) Szara (1970).

(g) Murphree *et al.* (1960).(h) Hollister *et al.* (1960).(i) Murphree *et al.* (1961).^b Reports of oral activity at 60 mg (b) but not at 200 (c).

because one of the principal neurotransmitters is serotonin, 5-hydroxytryptamine; and the 6-substituted analogs have been studied since they are products of one of the principal metabolic pathways in man for many of the psychotomimetic alkyl derivatives of the tryptamines.

The history of the ancient Aztec drug *teonanacatl*, its identification with the mushroom *Psilocybe mexicana*, and the isolation and identification of the alkaloid psilocybin (XXIX) as being the principal component have been superbly reviewed by Heim and Wasson (1959). The mushrooms most closely associated with the Mexican mushroom rites are *Psilocybe mexicana* and related species, *P. aztecorum*, *P. caerulescens*, and *P. zapotecorum*, as well as *Stropharia cubensis*. The *Psilocybe* group has proved to occur worldwide, and many of the



dozen or so species so far studied contain one or both of the alkaloids, psilocybin and the free hydroxy counterpart, psilocin (XXX). One species, *P. baeocystis*, has been shown to contain both a demethylated (Leung and Paul, 1967) and a didemethylated homolog [(XXXI) and (XXXII), respectively] (Leung and Paul, 1968).

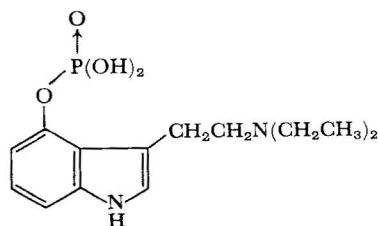
The other genera that have proved to contain psilocybin (*Conocybe*, *Copelandia*, and *Panaeolus*) are also found widely distributed. One species of the last-named, *Panaeolus sphinctrinus*, has been found to contain in addition to psilocybin, serotonin (5-hydroxytryptamine) and 5-hydroxytryptophane (Tyler and Gröger, 1964). The presence of the *N,N*-dimethyl homolog of serotonin in mushrooms is discussed below.

Psilocybin is the principal active agent in the *Psilocybe mexicana*, being present in 0.2–0.4% of the dry weight. A single dosage of from 4 to 8 mg of the pure chemical completely duplicates a 2-gram ingestion of the dried mushroom itself, which would constitute some 30 individual plants. Psilocin is present in *P. mexicana* only in trace amounts, but separate experiments have

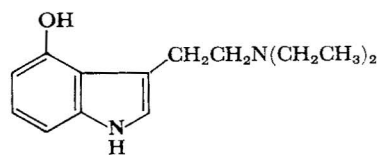
shown that it is pharmacologically equivalent to psilocybin at doses proportional to their respective molecular weights (Wolbach *et al.*, 1962). The earliest written reports of individual studies of the total mushroom (experiments of Heim, of Hofmann, of Brack, and of Cailleux) of early clinical trials of the synthetic psilocybin (reports of Delay) are collected in the review of Heim and Wasson (1959).*

Further clinical evaluation frequently employed the sublingual route using 5–10 mg of psilocybin (Delay *et al.*, 1958; Rinkel *et al.*, 1960), although doses of up to 30 mg were encountered (Malitz *et al.*, 1960).

Although the *N*-dealkylated homologs are as yet untested clinically, the *N,N*-diethyl homologs of psilocybin and of psilocin have been studied in man (Leunder and Baer, 1965). These compounds [CEY-19, (XXXIII); CZ-74, (XXXIV)] in dosages of from 5 to 20 mg appear to resemble psilocybin in the



(XXXIII)
CEY-19



(XXXIV)
CZ-74

qualitative nature of their action but to be of shorter duration. Maximum effects are obtained in an hour, and 2 hours later the subject is for the most part recovered, thus providing a valuable time course for psychiatric therapy.

Indoles substituted in the 5 position are of special interest since this is the ring-substitution pattern found in the neurotransmitter serotonin. The two 5-substituted compounds associated with the psychotomimetic area are bufotenine (XVIII) and its methyl ether 5-methoxy-*N,N*-dimethyltryptamine (XIX).

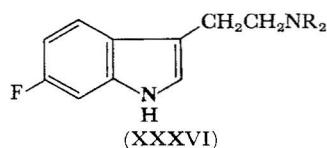
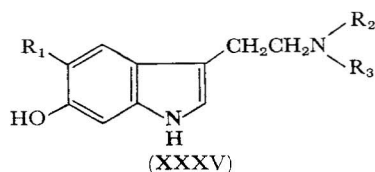
Confusion exists in the reports of human activity of bufotenine. Although it is regularly referred to as a "well-established hallucinogen" that produces "psychotic episodes" (and in fact has been listed as a Schedule I drug in the Controlled Substances Act as a hallucinogenic substance with reports of abuse) this assignment comes from a single report in the literature (Fabing and Hawkins, 1956). The studies that led to this article occurred at about the time of a New York Academy of Science Symposium on psychotomimetic drugs (March, 1957) and so received wide currency. This pharmacological

* Interestingly, it was only through human titration that the isolation and concentration of the active fractions of the mushroom extracts could be followed since animal assays were ineffective (Hofmann, 1971).

assignment has been challenged in that the compound has been shown to lead to severe cardiovascular excitement (Isbell, in Wassen and Holmstedt, 1963) which might account for the extreme facial discoloration consistently noted with the drug. The visual disturbances are possibly associated with increases of intraocular pressure (Fischer, 1968). The administration of the pure chemical as a snuff, at 10 mg, led to some lachrymation and flushing, but even at 40 mg elicited no central effects (Turner and Merlis, 1959). These same authors found that rapid intravenous administration of the chemical to schizophrenic patients provoked salivation, hyperventilation, and facial reddening. The compound is clearly not active orally at up to 100 mg (Hofmann, 1963b; Isbell, see Wassen and Holmstedt, 1963).

5-Methoxy-*N,N*-dimethyltryptamine has been shown to be a centrally active drug in animal studies (Gessner and Page, 1962; Gallagher *et al.*, 1964) and to be active parenterally in man. Like *N,N*-dimethyltryptamine, it is not active orally, although the *N,N*-diisopropyl homolog, as with the hindered dialkyl tryptamines mentioned earlier, is effective by the oral route (A. T. Shulgin, unpublished data, 1974). 5-Methoxy-*N,N*-dimethyltryptamine is extremely closely related chemically to the neurotransmitter serotonin, 5-hydroxytryptamine. It has been suggested that it might play the part of an endogenous psychotogen (Bennington *et al.*, 1965), a hypothesis which is supported by the reports of the compound appearing in the urine of schizophrenic subjects, but not in that of normal controls (Narasimhachari and Himwich, 1972). However, there are contradictory reports that 5-methoxy-*N,N*-dimethyltryptamine may occur in the urines of both populations (Fischer and Spatz, 1970; Sireix and Marini, 1969) and that it cannot be found in either population (Siegel, 1965). If the material is present at all, it is clearly excreted at levels of less than 100 $\mu\text{g/day}$ and possibly less than 10 $\mu\text{g/day}$. Support for some *in vivo* biosynthetic connection between these compounds comes from the observation of the presence of the methyl ether of serotonin (5-methoxytryptamine) as a normal hypothalamic component in the rat (Green *et al.*, 1973). The conversion *in vitro* of serotonin and melatonin-like compounds to biologically active carbolines will be discussed below.

Much interest became concentrated on tryptamines substituted in the 6 position, when it was found that *N,N*-dimethyltryptamine, *N,N*-diethyltryptamine (Szara, 1961b), and α -methyltryptamine (Szara, 1961a) were in part metabolized by hydroxylation at this position. The observation of a good correlation between the psychological changes associated with *N,N*-diethyltryptamine and the level of 6-hydroxy-*N,N*-diethyltryptamine [(XXXV), $R_1 = \text{H}$, $R_2 = R_3 = \text{C}_2\text{H}_5$] excreted suggested that this hydroxylation product might indeed be the active form of the original drug (Szara *et al.*, 1966). In fact, animal studies with 6-hydroxy-*N,N*-dimethyltryptamine suggested that the compound was indeed more potent than its parent (Szara and Hearst, 1962). However, animal studies with a number of



N-methyl analogs were not consistent with this. 6-Hydroxy-5-methoxy-*N,N*-dimethyltryptamine [(XXXV), $R_1 = \text{OCH}_3$, $R_2 = R_3 = \text{CH}_3$] appeared to be less potent than 5-methoxy-*N,N*-dimethyltryptamine (Taborsky *et al.*, 1966) and 6-hydroxy-5-methoxytryptamine [(XXXV), $R_1 = \text{OCH}_3$, $R_2 = R_3 = \text{H}$] was less potent than 5-methoxytryptamine (Taborsky *et al.*, 1965). In animal studies (Uyeno, 1969) as well as human studies (Rosenberg *et al.*, 1963), 6-hydroxy-*N,N*-dimethyltryptamine [(XXXV), $R_1 = \text{H}$, $R_2 = R_3 = \text{CH}_3$] was inactive at 1 mg/kg, whereas *N,N*-dimethyltryptamine is clinically effective at this dosage.

This metabolically available site (6 position) was blocked with a fluoro-group in a number of these *N,N*-dialkyltryptamines. 6-Fluoro-*N,N*-dimethyltryptamine [(XXXVI), $R = \text{CH}_3$] was again found to be less active than the parent *N,N*-dimethyltryptamine in animal studies (Kalir and Szara, 1966). However, clinical studies with the ethyl homolog [(XXXVI), $R = \text{C}_2\text{H}_5$] has shown that it produces most of the somatic effects of the comparison drug *N,N*-dipropyltryptamine without any of the psychological changes. It is proposed as an "active placebo" in controlling experiments with possible hallucinogenics (Faillace *et al.*, 1967). The present evidence indicates that chemical substitution on the 6 position of the tryptamine system destroys the psychotomimetic potential of the compound.

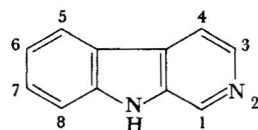
The two simplest dialkyltryptamines have been listed as scheduled drugs, as have both psilocybin and psilocin, and bufotenine (Federal Register, 1967). Analytical procedures for distinguishing psilocybin from psilocin have appeared as a legal aid in the routine screening of mushrooms (Heim *et al.*, 1966). There is a growing popularity in the use of the plant material rather than the specific chemical, and the problems associated with appropriate legislation are not yet solved (Hall, 1973). Procedures for the analysis of *N,N*-dimethyltryptamine, the 5-hydroxy, and the 5-methoxy counterparts, both by gas liquid chromatography (GLC) and mass spectral analysis of the silyl derivatives, have also appeared (Narasimhachari *et al.*, 1971).

E. Substituted Carbolines

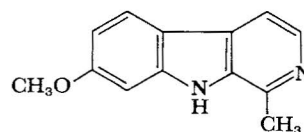
For many years there has been an intoxicating, psychotomimetic drink known to be used in South America under any of several names, principally *ayahuasca*, *caapi*, or *yaje*. It is well established to come from some of the many

species of the plants of the genus *Banisteriopsis*, and to contain alkaloids with structures based upon the carboline ring system (XXXVII). In reviewing the known correlations between plant identification and intoxicating drink identification, Pinkley (1969) has pointed out several of the difficulties still unresolved. There is a large number of species to be found in this genus, and there is rarely a firm connection between plant and drink. Usually a mixture of plants is employed, and it is completely uncertain if a compound such as dimethyltryptamine, commonly found in these drinks but known to be orally inactive, might truly be an active component, and that the carbolines present might serve a passive role of inhibiting the enzyme systems that normally inactivate it following oral administration. Such enzymatic inhibitory capability is well established (Udenfriend *et al.*, 1958). An example of unresolved confusion may be observed in the studies of the plant *Prestonia amazonica*, the alleged source of an intoxicating drink. It has been reported to contain dimethyltryptamine but no carbolines (Hochstein and Paradies, 1957), but it is now thought to be misidentified (Schultes and Raffauf, 1960) and actually to consist of mixtures of species of *Banisteriopsis* (Schultes, 1957). Yet in the *Banisteriopsis* species *B. rusbyana* dimethyltryptamine has been reported (Poisson, 1965) and confirmed (Der Marderosian *et al.*, 1968a; Agurell *et al.*, 1968b) as being the principal alkaloid present.

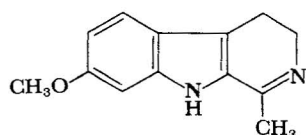
The principal species that has been identified with the native drink is *B. caapi*. This plant contains the 1-methyl-7-methoxy derivative of carboline, harmine (XXXVIII), and its dihydro and tetrahydro derivatives [harmaline (XXXIX) and tetrahydroharmine (XL) (leptoflorine)] (Hochstein and



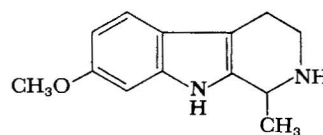
(XXXVII)
 β -Carboline



(XXXVIII)
Harmine



(XXXIX)
Harmaline

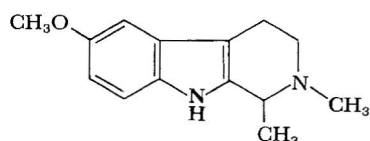


(XL)
Tetrahydroharmine (leptoflorine)

Paradies, 1957), although the first documented sample brought out by Spruce in the middle of the nineteenth century proved to contain only harmine (Schultes *et al.*, 1969). The harmine alkaloids have previously been

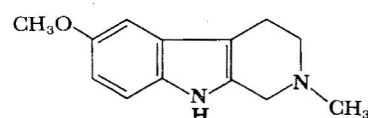
known to be components of the seeds of the Old World plant *Peganum harmala* as well as a number of other plants with medical, if not hallucinogenic, reputation (see Downing, 1964). Most of the *Banisteriopsis* spp. studied contain harmine,* usually accompanied by one or more of the closely related biosynthetic allies. *Banisteriopsis argentea* contains all three [(XXXVIII), (XXXIX), and (XL)] (Ghosal *et al.*, 1971). It is believed that *B. inebrians* contains only harmine (O'Connell and Lynn, 1953; Der Marderosian *et al.*, 1968b), but chromatographic evidence has been obtained suggesting the presence of the dihydro derivative, harmaline (Poisson, 1965).

Two alkaloids, recently reported as trace components of several plants involved in *ayahuasca*-like hallucinogen beverages, are of keen biochemical interest in that they have the aromatic methoxyl group at the carboline 6 position. This is the position of the oxygen atom in serotonin [5-HT, see (CXXIII)]. Agurell *et al.* (1968a) have reported 6-methoxy-2-methyltetrahydroharman (XLI) as a component of *Anadenanthera peregrina*, a plant closely



(XLI)

6-Methoxy-2-methyltetrahydroharman



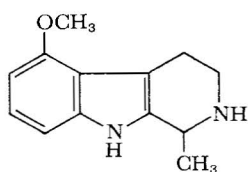
(XLII)

6-Methoxy-2-methyltetrahydrocarboline

associated with the tryptamine-containing snuffs. Also present in trace amounts was found the corresponding carboline, 6-methoxy-2-methyltetrahydrocarboline (XLII). The latter compound has also been observed in another snuff plant, *Viola theiodora* (Agurell *et al.*, 1968a), a plant which apparently also has oral activity (Schultes, 1969a). Several epena snuffs of uncertain plant composition have been shown to contain (XXXVIII), (XXXIX), and (XL) (Holmstedt and Lindgren, 1967). The biological significance of these 6-methoxy-substituted derivatives, the biological activities of several related compounds (see below), and the possible role of serotonin in brain metabolism will be discussed in Section III.

A 5-methoxy-substituted harman, a positional analog of tetrahydroharmine, has been observed and reported by Ghosal *et al.* (1971) as a component of *Banisteriopsis argentea*. This compound, 5-methoxytetrahydroharman (XLIII) is representative of an extremely rare class of heterocyclics, those that are based upon the indole ring and which are substituted at the indolic 4 position. The resemblance to psilocin (XXX) is provocative. Two

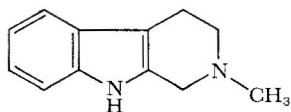
* A number of synonyms exist for harmine. Telepathine reflects its reputation to produce a clairvoyant state, yageine stems from the native name *yaje* for the drink derived from *Banisteriopsis caapi*, and banisterine comes from *Banisteria*, an older name for the genus *Banisteriopsis*. The name "harmine" derives from the first source of this alkaloid, *Peganum harmala*, commonly known as harmel.



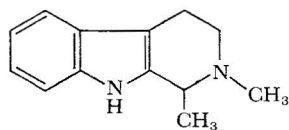
(XLIII)

5-Methoxytetrahydroharman

alkaloids without substituents on the aromatic ring have been reported as being components of psychotomimetic plants. The carboline (XLIV) has been observed as a trace component in *Banisteriopsis rusbyana* (Aguirell *et al.*, 1968b), and the corresponding harman (XLV) is present in *B. argentea* (Ghosal *et al.*, 1971).



(XLIV)



(XLV)

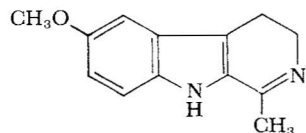
The case is true for *ayahuasca* as it is for most psychotomimetic concoctions derived from plant sources; the pharmacological studies of the total plant extract are observed by the anthropologist in the field, and the studies on the pure chemical components of the plant are reported by the physician in the clinic. There are several reports of the native terminology, superstition, botanical assignments, and the usage of these intoxicating brews (Lewin, 1931; Granguillhome, 1962; Deulofeu, 1967; Pinkley, 1969) but very few clinical reports of the effects of the component alkaloids in pure states.

There are only four reports of human psychopharmacology on specific chemicals in this area. Studies on harmine by Pennes and Hoch (1957) on mental patients showed threshold hallucinogenic activity at doses of between 150 and 200 mg. i.v. Slotkin *et al.* (1970) investigated the metabolism of harmine in man and studied the dynamics of its *O*-demethylation and conjugation. In these studies, they employed intravenously in normal subjects about a fifth the dosage reported by Pennes and Hoch, but still observed consistently similar effects (bradycardia, hypotension, and light-headedness). Slotkin *et al.* had administered the drug over a 5-7-minute period, and reported a 90% drop in plasma levels within minutes of the end of the injection. Pennes and Hoch employed a 20-30-minute injection period. The latter authors reported harmine to be orally inactive at levels of approximately a gram.

Naranjo (1967) has described clinical evaluations of a number of the substituted harmans. He found harmaline (XXXIX) to be more active than harmine, leading to the development of a profound mentally disturbed state

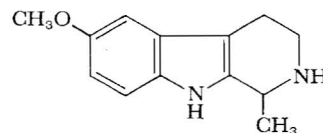
at oral doses of 4 mg/kg. It was active intravenously at one-fourth this level. The tetrahydro isomer tetrahydroharmine (XL) appeared to be less active, the equation of 300 mg tetrahydroharmine = 100 mg harmaline resulting from a single human trial.

In the analogous 6-methoxyharman series, Naranjo has reported the analog of harmaline, 6-methoxyharmalan (XLVI) to be orally active with threshold effects noted at oral levels of 1.5 mg/kg. The same levels of the



(XLVI)

6-Methoxyharmalan



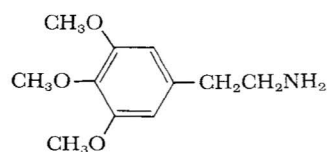
(XLVII)

6-Methoxytetrahydroharman

tetrahydro counterpart, 6-methoxytetrahydroharman (XLVII) led to "mild effects." It is uncertain if the totally aromatic analog, 6-methoxyharman, was evaluated. The psychic changes associated with the most thoroughly studied member of this series, harmaline, have been discussed at length (Naranjo, 1969) and compared with several other pharmacologically related psychotomimetic drugs (Naranjo, 1973).

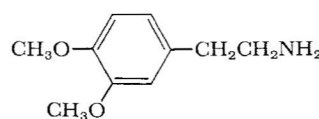
F. Mescaline and Peyote

The cactus alkaloid mescaline (XLVIII) is one of the earliest known, and one of the best studied of all the psychotomimetic drugs. It is the principal component of the peyote cactus, *Lophophora williamsii*. This cactus has proved to be one of the richest sources of alkaloids, with a present count of over fifty constituents, mostly bases with the parent structures of phenethylamines or



(XLVIII)

Mescaline



(XLIX)

DMPEA

isoquinolines (Kapatia and Fayez, 1973). A number of the simpler alkaloids, mono- and disubstituted hydroxy- and methoxyphenethylamines, have recently been found widely distributed throughout the cactus world (Aguere, 1969b). The stimulants hordenine, *N*-methyltyramine, and tyramine, for example, all known to be present in *L. williamsii* (McLaughlin and Paul, 1965, 1966), have been found, one or the other, in *Ariocarpus* spp. (Braga and McLaughlin, 1969; McLaughlin, 1969; Neal *et al.*, 1971a) and species of the genera *Pelecyphora* (Neal *et al.*, 1972), *Coryphantha* (Hornemann *et al.*, 1972),

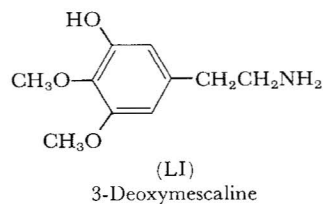
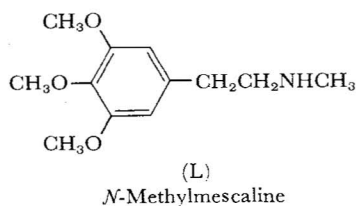
Oregonia (Neal *et al.*, 1971b), *Cereus*, *Echinopsis*, *Helianthocereus*, and *Lepidocoryphantha* (Aguirell, 1969b).

A dioxygenated phenethylamine, 3,4-dimethoxyphenethylamine (DMPEA) (XLIX) has been identified as a component of *L. williamsii* (Lundström and Agurell, 1968) as well as in a number of other cacti, *viz.*, in *Stetsonia coryne* (Aguirell *et al.*, 1971), in *Pelecypora aselliformis* (Neal *et al.*, 1972), and in seven species of *Trichocereus* (Aguirell, 1969a; Agurell *et al.*, 1971). This compound has sparked particular interest in the last decade since it has been shown to be contributory to a "pink spot" reported to be a component found exclusively in the urine of schizophrenic patients (Friedhoff and Van Winkle, 1962). Its close chemical similarity to mescaline, and the known psychotomimetic potency of mescaline, made this an appealing lead in the argument of an endogenous source of mental disorders. The correlation between the pink spot and XLIX was established with certainty chemically (Creveling and Daly, 1967), but there has been much conflicting comment on the association of this chromatographic indicator and clinical diagnosis. There have been reports that the material is exclusively in the urines of the mentally ill, present in all populations, derived from some exogenous origin, or that it is not present at all. These reports have been summarized by Siegel and Tefft (1971) who recognized interferences from drug metabolites (phenothiazines) and relative insensitivity in many of the analytical procedures employed. Their studies employed extremely sensitive probes (dansyl derivatives and mass spectrometry) and they concluded that DMPEA is present in all human urine samples. In any event the compound is clearly inactive in man (Shulgin *et al.*, 1966; Hollister and Friedhoff, 1966; Charalampous and Tansey, 1967).

Mescaline itself has been observed in a number of novel cactus species. The *Trichocereus* genus has been a most rewarding source. *Trichocereus pachanoi* is a Peruvian plant, known by the common name of San Pedro (*aguacolla* in Ecuador), that has long been involved in magic and in medicine (Poisson, 1960). Mescaline and several of the tetrahydroisoquinolines and related phenethylamines seem to constitute the alkaloid fraction. Additional *Trichocereus* species that have been shown to contain mescaline are *T. terscheckii* (Reti and Castrillon, 1951), *T. bridgesii* and *T. werdermannianus* (Aguirell, 1969a), and *T. cuzcoensis*, *T. fulvilanus*, *T. taquimbalensis*, and *T. validus* (Aguirell *et al.*, 1971). Two additional genera are reported to contain mescaline, *Stenonia coryne* (Aguirell *et al.*, 1971) and *Pelecypora aselliformis* (Neal *et al.*, 1972). The original reports of the presence of mescaline in *Opuntia cylindrica* [syn., *Austracylidropuntia cylindrica* (Turner and Heyman, 1960)], thought to be San Pedro, were apparently based upon misidentified samples of *Trichocereus pachanoi* (Aguirell, 1969b). Reanalyses of authentic samples of *O. cylindrica* have shown no traces of mescaline present.

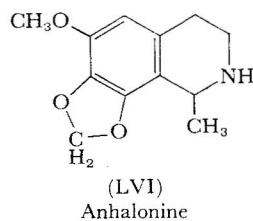
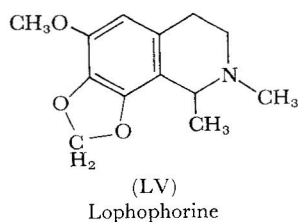
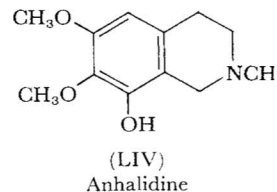
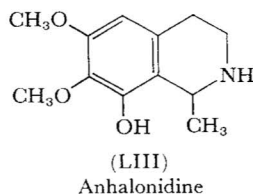
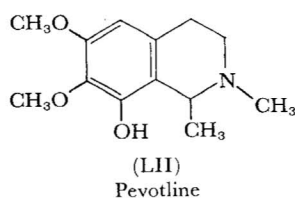
Two simple homologs of mescaline present in *L. williamsii* have also been

shown to occur in other cacti. *N*-Methylmescaline (L), present in peyote (Späth and Bruck, 1937), has been reported as a component of *Pelecyphora aselliformis* (Neal *et al.*, 1972). 3-Deoxymescaline [3-hydroxy-4,5-dimethoxyphenethylamine, (LI)], present in *L. williamsii* (Aguirell and Lundström,



1968) and proposed as a biosynthetic precursor of several of the phenolic tetrahydroisoquinolines (Paul, 1973), has been observed in one of the few nonpeyote cacti known to contain such heterocyclic alkaloids, *Trichocereus pachanoi* (Aguirell, 1969b).

Five of the variously substituted tetrahydroisoquinolines of the 23 known to be contained in the peyote plant *L. williamsii* (Kapatia and Fayez, 1973) warrant singling out and special mention. These are the three phenolic examples peyotline [pellotine (LII)], anhalonidine (LIII), and anhalidine (LIV), and the two methylenedioxy heterocyclics, lophophorine (LV) and anhalonine (LVI).

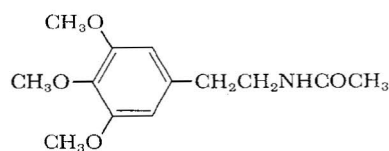


Three of these compounds have recently been observed as components of other cacti species. Anhalidine (LIV) has been reported found in *Pelecyphora aselliformis*, the only North American cactus other than *L. williamsii* known to contain mescaline (Aguirell *et al.*, 1971; Neal *et al.*, 1972). It is also found in *Stenonia coryne* (Aguirell *et al.*, 1971). Peyotline (LII) is reported present in *Pelecyphora aselliformis* (Neal *et al.*, 1972), and anhalonidine (LIII) has been

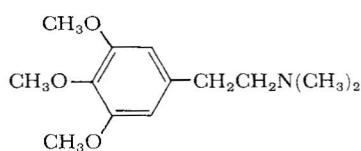
reported in *Trichocereus pachanoi* (Aguirell, 1969a) as well as *Stensonia coryne* (Aguirell *et al.*, 1971).

The human psychopharmacology of the intact plant *L. williamsii* can be correlated to a large measure to the content of mescaline that is contained in it. Most of the early medical literature made reference to some form of extract of the whole cactus, and so certainly represented a complex pharmacological picture. This early literature on tincture of peyote, on basic panpeyote, and on soluble (or injectable) peyote, has recently been summarized (Shulgin, 1973b).

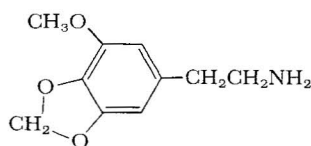
Of the pure chemicals that are obtainable from the cactus, and which have been studied in man, mescaline itself is the best studied. It is active, either orally or by parenteral administration, at about 350 mg, leading after an hour or so of external physical disruptive symptoms to a state of sensory and psychic intoxication that persists for several hours. The details of these states are the subject of a number of books (Beringer, 1927; Huxley, 1954). Of the simpler mescaline substitution products, *N*-methylemescaline (L) shows no effects either peripherally or centrally at levels that represent many times that which would be encountered in a nominal dose of peyote (A. T. Shulgin, unpublished data, 1973). *N*-Acetylmescaline (LVII), a trace component in



(LVII)

N-Acetylmescaline

(LVIII)

N,N-Dimethylemescaline (trichocerine)

(LIX)

Homomyristiclyamine
(lophophine)

the peyote plant, has been identified as a metabolite of mescaline in man (Charalampous *et al.*, 1966). It has been explored in acute trials in human subjects at levels between 300 and 750 mg total dosage. Only at the highest levels were any effects noticed, and they were summed up as being merely a mild degree of drowsiness. The homologous *N,N*-dimethylemescaline [trichocerine (LVIII)] has never been observed in peyote, although it has been observed in a number of closely related cacti. It is included here because of its close relationship to the monomethyl homolog and the known presence of

methylyating enzymes in the peyote plant (Paul, 1973). The compound has been found devoid of any central activity in humans even following parenterally administered dosages of more than 500 mg (Luduena, 1936). Another compound is homomyristicylamine [lophophine (LIX)], which also has never been observed in the peyote plant, but which presents an obvious theoretical potential as a biosynthetic precursor of the tetrahydroisoquinoline alkaloids such as lophophorine and anhalonine (Kapatia *et al.*, 1969). This compound is active in man at dosage levels of 150–200 mg, about twice the potency of mescaline (A. T. Shulgin, unpublished data, 1973). The qualitative description of its action is quite similar to that of mescaline in that there is a peaceful elevation of mood, the generation of an euphoric state, and the enhancement of visual perception, especially in the color sense. There are dissimilarities, particularly in that there is little if any nausea and there is no visual distortion. These latter differences disappear at dosages of 300 mg, and there is the generation of eyes-closed imagery similar to that observed with mescaline.

Four of the tetrahydroisoquinolines have been clinically evaluated. The pharmacological action of peyotline (LII) in human subjects is one of calming or sedation rather than that of a hallucinogen. Jolly (1896) has reported the production of an uneventful sleep in patients with a dosage of 50 mg. At levels of as much as 240 mg (total dosage) there are no indications of sensory distortions (Heffter, 1898). There is a dizziness and a generalized tiredness that undergoes a gentle transition into sleep. This latter quantity of drug is greater than that which would be encountered in a single dosage unit of peyote. It is certainly possible that peyotline could contribute to the pharmacological picture associated with peyote since this sedative action is noted at levels that might well be encountered in the total cactus. At low levels in man (15–30 mg) there has been described a calming effect, without overt hypnosis.

Anhalonidine (LIII), the homolog of peyotline in which the *N*-methyl group is absent, appears to act in man in a manner parallel to peyotline (leading to a heavy-headedness and sedation) but with only about one-fourth the potency. At oral levels of between 100 and 250 mg there was a marked sedation but no sensory changes whatsoever (Heffter, 1898). It is unlikely that this compound contributes to the reported action of panpeyote.

The two remaining tetrahydroisoquinoline principles of peyote are methylenedioxy ethers rather than phenols. The first of these is lophophorine (LV), the methylenedioxy analog of peyotline. This alkaloid has been considered the most toxic of the natural components of peyote, but this claim is based solely on animal studies. In man, oral dosages of 20 mg led to a distinct vasodilation accompanied by an immediate headache and a warm flushed feeling. These responses are lost within the hour. The level of lophophorine found in peyote varies over a wide range, and no estimate can be

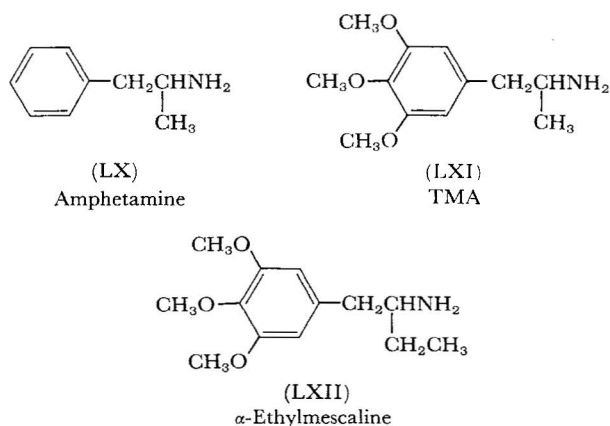
made concerning its contribution to the action of the entire plant. Anhalonine (LVI) is the methylenedioxy ether analog of anhalonidine and the *N*-demethyl homolog of lophophorine. This alkaloid appears to show pharmacological properties similar, both quantitatively and qualitatively, to its phenolic counterpart, anhalonidine. A single reported experiment with 100 mg orally (Heffter, 1898) led to an uneventful tiredness without any noticeable central effects of a sensory nature. The term "amorphous anhalonine" is occasionally encountered in the early literature on peyote. This has been shown not to be a single substance but a mixture of peyotline and lophophorine.

G. Methoxyamphetamines (Methoxyphenylisopropylamines)

Although only a few of the naturally available analogs and homologs of mescaline have been explored pharmacologically, and have proved to be psychotomimetic, it has been through the synthetic variations of this molecule that some of the structural requirements of hallucinogenesis have been uncovered. A principal metabolic detoxification route found with the phenethylamine molecule is one of deamination and oxidation to the corresponding phenylacetic acid. Not only phenethylamine but also the simpler mono- and disubstituted analogs are largely metabolized and inactivated by this transformation. Mescaline itself undergoes such a conversion to a limited degree in the human body (Charalampous *et al.*, 1966). Whereas phenethylamine is known to undergo such oxidative deamination readily, the α -methyl homolog, amphetamine (LX), is relatively refractory to such chemical changes, and, to an appreciable extent, is excreted unchanged in man (Smith and Dring, 1970). Although the pharmacological profiles of mescaline and amphetamine are completely different, it was thought that the interference to enzymatic disposal conferred by the sterically blocking α -methyl group might influence the effectiveness of mescaline.

The psychopharmacological action of the compound that results from the combination of the features of mescaline and amphetamine has been described (Peretz *et al.*, 1955). This compound is 3,4,5-trimethoxyamphetamine [3,4,5-trimethoxyphenylisopropylamine, TMA (LXI)], and it has been established as being an effective sensory distorting agent at levels of about 175 mg (Shulgin *et al.*, 1961). It is thus about twice as potent as mescaline.* An extension of this chain to the 4-carbon homolog [α -ethyl-mescaline (LXII)] produces a compound that lacks all central and peripheral activity in human subjects at acute levels as high as 220 mg (Shulgin, 1963).

* The carbon skeleton and positional location of the ether oxygen atoms in (LXI) [and in MDMA see (LXXIII)] are identical to that found in elemicin and myristicin, components of the spice nutmeg. These latter nitrogen-free essential oils have recently been shown capable of being converted into the above-mentioned amphetamine analogs under biological conditions (Braun and Kalbhen, 1972).



These two chemicals have laid the groundwork for all of the substances to be discussed below, namely, that the three-carbon chain, the phenylisopropylamine or amphetamine structure, has proved to be optimum for the generation of these sensory distortion effects. A decrease of the chain length to two carbons (the loss of the α -methyl group) usually retains the nature of psychic activity but with some decrease in potency. A lengthening of the chain to four carbons (the substitution of an α -ethyl group) changes the qualitative nature of the pharmacological response.

Variations of the substitution pattern of the methoxyl groups within this generalization of a three-carbon chain optimum have led to extensive changes in potency. Using (LXI) as a parent structure, there are five possible positional isomers. These have been synthesized (Shulgin, 1966a) and clinically evaluated in man (Shulgin *et al.*, 1969). The first of these positional isomers is 2,4,5-trimethoxyphenylisopropylamine, [TMA-2 (LXIII)]. This isomer has proved to be the most potent of all six, with an effective dosage level of 20 mg, about a twentieth that required for effective mescaline intoxication. The vicinal analog [2,3,4-trimethoxyphenylisopropylamine, TMA-3 (LXIV)] is without central activity. The symmetrical isomer [2,4,6-trimethoxyphenylisopropylamine, TMA-6 (LXVII)] has a substitution pattern common throughout the many plant products related to the chromones and the flavanoids. The central activity of (LXIII) and (LXVII) are similar to one another in that at threshold levels there is noted only an enjoyable light-headedness coupled with distinct euphoria and a minimum of perceptive distortion. At effective dosages there again is the nausea reminiscent of that seen with mescaline, and the visual distortions can become quite extensive; (LXVII) is about half as potent as (LXIII). The two remaining possible isomers have been titrated clinically, but have not been explored to establish the qualitative nature of their actions. 2,3,5-Trimethoxyphenylisopropylamine [TMA-4 (LXV)] is an effective central

intoxicant at a 90-mg dosage, and 2,3,6-trimethoxyphenylisopropylamine [TMA-5 (LXVI)] has similar activity at a third this level, i.e., 30 mg. Both are thus clearly more potent than mescaline.

A number of isomers of (LXI) have been studied wherein the variation is with the number of methoxy groups rather than with their position. Only one of the three possible monomethoxy analogs has been explored clinically. In animal studies, this compound [4-methoxyphenylisopropylamine, PMA (LXVIII)] is reported to have a hallucinogenic potential parallel to LSD (Smythies *et al.*, 1967). In man, however, some 75 mg is required (orally) for effective central activity, thus being closer to mescaline than LSD in potency. Arguments that this compound might be an active metabolite of amphetamine in cases of amphetamine-induced psychoses have been answered by the reported failure to observe this compound in human urine samples following heavy amphetamine administration. It could only be found as an excretory product following its own administration to human subjects (Angrist *et al.*, 1970).

Three of the six possible dimethoxyphenylisopropylamines have been explored pharmacologically. The compound most closely allied with both botanical and mammalian biochemistry is 3,4-dimethoxyphenylisopropylamine (LXIX). This base is the homolog of DMPEA (XLIX), and is slightly less potent than mescaline (Fairchild, 1963) in that levels of about 700 mg were required parenterally to produce the color syntheses and other sensory distortions ascribed to mescaline. The other two dimethoxy isomers that have been studied, 2,4-dimethoxyphenylisopropylamine (LXX) and 2,5-dimethoxyphenylisopropylamine (LXXI), are considerably more potent, being active at 70 and 45 mg orally, respectively (Shulgin *et al.*, 1969). In late 1970, 2,5-dimethoxyphenylisopropylamine (LXXI) appeared in the illicit drug market in the United States under the name DMA (dimethoxyamphetamine). More recently (in the spring of 1973) the 4-methoxy analog (LXVIII) also appeared in a flurry of abuse in both Canada and the United States. It was implicated in several deaths involving the cardiovascular system. In September, 1973 the Drug Enforcement Administration (formerly the Bureau of Narcotics and Dangerous Drugs) incorporated both of these drugs into the Controlled Substances Act.

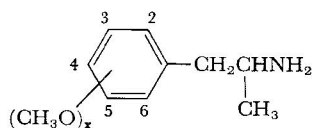
A single tetramethoxy analog is known, 2,3,4,5-tetramethoxyphenylisopropylamine (LXXII). It is effective in man at a dosage of 60 mg, i.e., six times as potent as mescaline. These data are compiled in Table IV.

Bases that contain a methylenedioxy ring in place of two adjacent methoxyl groups constitute a large family of compounds that parallel most of the above-mentioned polymethoxylated phenylisopropylamines. In nature, this form of biosynthetic relationship is frequently seen as noted within the tetrahydroisoquinoline alkaloids of peyote itself.

Just as there are six possible trimethoxy substitution isomers of am-

TABLE IV

THE METHOXY PHENYLISOPROPYLAMINES



Number of OCH ₃ groups	Position of OCH ₃	Name	Human potency index ^a
$X = 1$	4	PMA(4-MA) (LXVIII)	5
$X = 2$	3,4	DMA ^b (LXIX)	0.5
	2,4	^b (LXX)	5
$X = 3$	2,5	DMA ^b (LXXI)	8
	3,4,5	TMA (LXI)	2
	2,4,5	TMA-2 (LXIII)	20
	2,3,4	TMA-3 (LXIV)	<2
	2,3,5	TMA-4 (LXV)	4
	2,3,6	TMA-5 (LXVI)	12
	2,4,6	TMA-6 (LXVII)	10
$X = 4$	2,3,4,5	(LXXII)	6

^a Based upon mescaline (at 350 mg) = 1; the higher the potency, the larger the index. See text for literature references.

^b The initials DMA have appeared in the medical literature to represent the 3,4-isomer. In the forensic literature, the term "DMA" applies only to the abused isomer (LXXI).

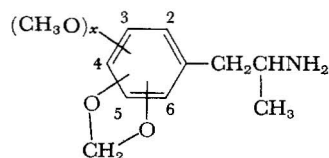
phetamine, so there are six possible methoxymethylenedioxy isomers. Five of these six have been described chemically and pharmacologically. Their trivial names relate the position of the oxygen substituents directly to the trimethoxy counterpart. The isomer that is the direct relative of mescaline (XLVIII) and homomylristylamine [lophophine (LIX)] is 3-methoxy-4,5-methylenedioxy-phenylisopropylamine [MMDA (LXXIII)]. This compound was synthesized and evaluated independently in two separate laboratories (G. A. Alles, 1962, personal communication to Fairchild, 1963; Shulgin, 1964a). The compound is active in man at 130 mg, and thus is nearly three times the potency of mescaline. Unlike mescaline, however, its actions are largely free of perceptual distortions and seem not to inflexibly command the complete attention of the subject. There is an element of choice in the degree of compliance to the intoxication, and there seems to be some valid access to memory material. These properties have been discussed in a recent monograph (Shulgin *et al.*, 1973) and seem to constitute a consistent distinction between a methylenedioxy compound and its dimethoxy counterpart. The methylenedioxy compound shows less potential for visual distortion, it is

generally more controllable in its extremes of central activity, and, as a rule, it is more potent.

The compound analogous to TMA-2 (LXIII) is 2-methoxy-4,5-methylenedioxyphenylisopropylamine [MMDA-2 (LXXIV)], a base only slightly less active in human trials (30 mg) than the trimethoxy counterpart. Two possible 2,3,4-trisubstituted compounds can exist that correspond to (LXIV). These are 2-methoxy-3,4-methylenedioxyphenylisopropylamine [MMDA-3a (LXXV)] and 4-methoxy-2,3-methylenedioxyphenylisopropylamine [MMDA-3b (LXXVI)]. Although the trimethoxy compound with this vicinal substitution pattern was not active, both of these compounds have been shown to be effective intoxicants, the first at a 35-mg dose (Shulgin, 1964b) and the second at 120 mg (Shulgin *et al.*, 1969). The fifth of these methoxy methylenedioxy isomers is 6-methoxy-2,3-methylenedioxyphenylisopropylamine [MMDA-5 (LXXVIII)] which corresponds exactly to TMA-5 (LXVI) both in substitution pattern and in potency (Shulgin, 1973b). No successful synthesis has yet been reported for 5-methoxy-2,3-methylenedioxyphenylisopropylamine [MMDA-4 (LXXVII)]. The analog to TMA-6 (LXVII) cannot, of course, exist.

Only three methylenedioxy compounds that are not trisubstituted have been studied in man. One is 3,4-methylenedioxyphenylisopropylamine [MDA (LXXIX)]. This compound is not particularly potent (typical dosage, some 120 mg or about three times the activity of mescaline), but its apparent consistency of action has led to its clinical study (Naranjo *et al.*, 1967). The 2,3-isomer is unknown. The remaining two are the dimethoxy derivatives, 2,5-dimethoxy-3,4-methylenedioxyphenylisopropylamine DMMDA (LXXX) and 2,3-dimethoxy-4,5-methylenedioxyphenylisopropylamine DMMDA-2 (LXXXI). They are active at 30 and 70 mg, respectively (Shulgin and Sargent, 1967), corresponding to twelve times and five times the potency of mescaline. These data are presented in Table V.

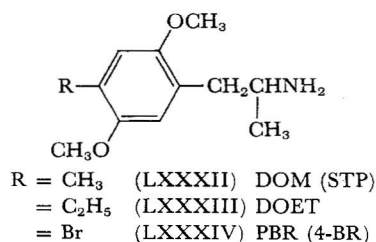
Another group to be discussed consists of compounds that have been prepared to exploit the apparent importance assigned to the 4 position of the aromatic substitution pattern. The argument has been extended that this positional sensitivity might be associated with a theoretical ease of metabolic attack at this position. Consistent with this approach, one should expect that the replacement of an easily attackable group (alkoxy) with one less amenable to removal (alkyl) might radically affect the pharmacological properties of the corresponding amine. The simplest such example, 2,5-dimethoxy-4-methylphenylisopropylamine [DOM, STP (LXXXII)], proved to be several times more potent than (LXIII) as a centrally active psychotomimetic. With an effective, not threshold, level of activity of 3 mg total dosage, it has about one-hundred times the potency of mescaline. Further, the nature and chronology of the intoxication is quite changed from that common to most of these chemicals discussed. Most noteworthy is the unexpected lengthening of

TABLE V
 THE METHYLENEDIOPHENYLISOPROPYLAMINES


Number of OCH ₃ groups	Position of OCH ₃ ^a	Name	Human potency index ^b
X = 0	—(3,4)	MDA (LXXIX)	3
X = 1	3(4,5)	MMDA (LXXXIII)	3
	2(4,5)	MMDA-2 (LXXXIV)	12
	2(3,4)	MMDA-3a (LXXXV)	10
	4(2,3)	MMDA-3b (LXXXVI)	3
	5(2,3)	MMDA-4 (LXXXVII)	?
	6(2,3)	MMDA-5 (LXXXVIII)	12
X = 2	2,5(3,4)	DMMDA (LXXX)	12
	2,3(4,5)	DMMDA-2 (LXXXI)	5

^a Methylenedioxy positions in parentheses.^b See Table IV.

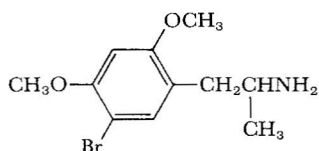
the time course of intoxication by a factor of three or more. Several clinical studies have appeared in the medical literature concerning this drug (Snyder *et al.*, 1967; Weingartner *et al.*, 1967). The 4-ethyl homolog [2,5-dimethoxy-4-ethylphenylisopropylamine, DOET (LXXXIII)] appears to be fully as potent as DOM (LXXXII), although at lower clinical levels the psychological changes noted seem to be somewhat more controllable and thus more constructive (Snyder *et al.*, 1971).^{*} The homologs of DOM carrying an



^{*} Originally the terminology employed for this series of 4-alkyl homologs was designed to indicate the loss of the oxygen of the 4 position (deoxy, DO) and then the initial of the remaining group (methyl, M; ethyl, E; etc). The term "DOM" stood for (LXXXII), and originally (LXXXIII) was called DOE. When this was recognized as a well-established abbreviation for deoxyephedrine (methamphetamine) the additional letter was added. The origin of the name "STP" for DOM is uncertain, but it has been claimed to stand for serenity, tranquility, and placidity; for serenity, tranquility, and peace; for stop the police; and for super-terrific psychedelic.

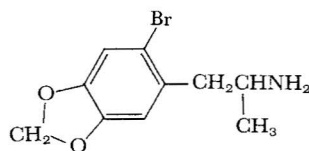
n-propyl, *n*-butyl, and *n*-amyl group in place of the methyl group at the 4 position have been synthesized and evaluated. The *n*-propyl (DOPR) is similar in potency and action to DOM and DOET, but the two higher homologs (DOBU and DOAM) are of reduced activity in man (Shulgin and Dyer, 1975).

Recently, yet another analog of this system has been described. In this compound the 4-methyl group has been replaced with a bromo substituent to produce 2,5-dimethoxy-4-bromophenylisopropylamine (LXXXIV) (Shulgin *et al.*, 1971; Barfknecht and Nichols, 1971). This compound has, in man, an effective response level of between 0.5 and 1.0 mg, thus it is several hundred times more potent than mescaline. Yet in the qualitative sense it presents more of the clinical picture that has been associated with MDA (LXXIX) (Shulgin *et al.*, 1971). A positional isomer has been described [2,4-dimethoxy-5-bromophenylisopropylamine (LXXXV)] which is much less potent than (100 mg for an effective intoxication), but which maintains,



(LXXXV)

2,4-Dimethoxy-
5-bromophenylisopropylamine



(LXXXVI)

2-Bromo-4,
5-methylenedioxyphenylisopropylamine

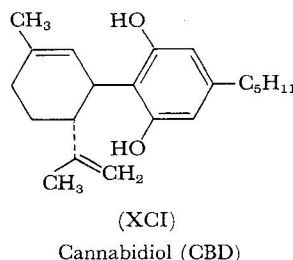
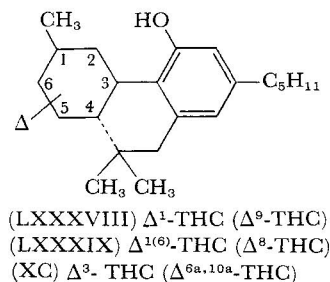
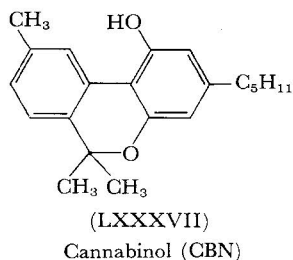
the MDA-like response. The 2-bromo analog of MMDA-2 [2-bromo-4,5-methylenedioxyphenylisopropylamine (LXXXVI)] is less active than mescaline (> 350 mg in man) and seems to produce an amphetaminelike response (Sepuveda *et al.*, 1972). The highly active isomer (LXXXIV) has been labeled with ^{82}Br and ^{77}Br and the kinetics of its distribution determined in man (Kalbhen *et al.*, 1974; Sargent *et al.*, 1975). The bromine atom is not metabolically removed, thus allowing continuous monitoring of the parent compound and its metabolites. There is a rapid accumulation in lung tissue, followed by deposition in the brain.

A final comment is in order concerning the frequent use of the term "amphetamines" to describe these compounds. All of the centrally active substances that have been discussed here contain the carbon skeleton of the amphetamine molecule. Yet almost none of them display the sympathomimetic stimulation associated with amphetamine use. The popular use of the term "amphetamines" has come to embrace a large number of currently used drugs that are stimulants, and which call upon these responses for their effectiveness. Examples of this are amphetamine itself (and its dextrorotatory isomer, dexedrine), methamphetamine, methylphenidate (Ritalin), phenmetrazine (Preludin) and mephenteramine (Wyamine). An excellent demonstration of the separation of these pharmacological areas may be seen

from the fact that the active optical isomer of DOM (LXXXII) is the R(−) form. The S(+) form shows only stimulant properties, yet it is this latter absolute configuration that is seen in the stimulative active isomer of amphetamine itself, S-(+)-dextroamphetamine (Shulgin, 1973a).

H. Marijuana, Its Components and Their Analogs

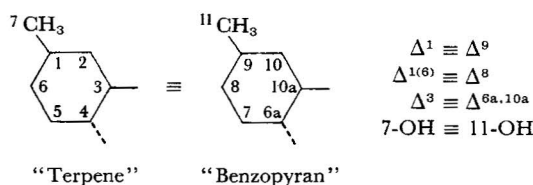
Research associated with the drug marijuana in the last decade has commanded an explosive expansion of effort. A number of reasons appear to have contributed to this enthusiasm. The determination of the exact structure of the major pharmacologically active component, tetrahydrocannabinol, led to a number of varied syntheses of it and its closely related congeners. The exponential increase of popularity of the drug, especially among middle class youth, led to an increased recognition of the potential social hazards which might result from lack of factual knowledge concerning the drug; therefore, federal grant funds to investigate almost any aspect of the drug were made easily available. Coupled with this was the concerted interest of the chemical and biological warfare groups within the military establishment in marijuanalike analogs as potential psychological war weapons. An outgrowth of this interest was the successful project to make available to scientific and medical researchers not only documented and consistent samples of the plant but also samples of the pure synthetic components. In 10 years syntheses of several natural products theretofore unobtainable or even incorrectly defined structurally were expanded from the milligram to the kilogram scale.



In Downing's review (1964) the early isolation and chemical characterization of several of the components of *Cannabis sativa* were outlined. The first cannabinoid,* cannabinol (LXXXVII), was isolated at about the turn of the century (Wood *et al.*, 1899) and synthesized by both Adams' group (Adams *et al.*, 1940b) and Todd's group (Ghosh *et al.*, 1940) some 40 years later. Two additional cannabinoids were isolated by these two research groups, *viz.*, tetrahydrocannabinol (THC) and cannabidiol (CBD). The former of these, now believed to be the major active component, was first described in terms that implied the isolation of a relatively pure product (Wollner *et al.*, 1942). Although the structures of these two components were known only in general terms, they led to a broad synthetic study of analogs. The position of the double bond in natural THC was unknown, but the conjugated isomer Δ^3 -THC† was synthesized and found to have marijuana activity. Further, natural cannabidiol was isomerizable into tetrahydrocannabinols of unknown double bond position and of unknown stereochemistry, which also proved active. A wealth of research papers appeared from Adams' laboratories that were based upon the cannabislike activity noted for the synthetic Δ^3 -THC, and which culminated with the report of variations in the 5-alkyl group that suggests biological activities of many hundreds of times that of the reference synthetic tetrahydrocannabinol, and thus presumably many tens of times that of natural THC (Adams *et al.*, 1948). This decade of structure-activity relationship study has been excellently and completely summarized by Loewe (1950). It is of interest that the first report (Mechoulam and Shvo, 1963; Gaoni and Mechoulam, 1964a) was a note added in proof to Downing's review article just 10 years ago, and the vast wealth of chemical and pharmacological knowledge that has stemmed from this has been accumulated in just 10 years.

* The term "cannabinoid" was introduced by Mechoulam and Gaoni (1967) to embrace the group of the 21-carbon compounds characteristically present in *Cannabis sativa*, as well as their analogs, homologs, and transformation products. The term has widely become used.

† There is as yet no accepted convention for positional notation of the cannabinoids. Two systems often found to be used interchangeably differ in the numbering of the terpene ring. One system, based upon terpene conventions, defines the methyl group as being located at the 1 position. The second, based upon a formal benzopyran nucleus, numbers from the aromatic ring, and the methyl group appears at the 9 position; this convention is inapplicable in compounds such as cannabidiol where no pyran ring exists. The following structures illustrate this relationship:



Natural tetrahydrocannabinol has been shown to be Δ^1 -THC (LXXXIII) and the stereoisomer orientation at the 3 and 4 positions trans. The double bond is easily isomerized by acid catalysis to give $\Delta^{1(6)}$ -THC (LXXXIX) of the correct structure of cannabidiol and of natural tetrahydrocannabinol (Gaoni and Mechoulam, 1966a; Hively *et al.*, 1966), apparently the only cannabinoid of this orientation of unsaturation to be a native constituent of the plant (Hively *et al.*, 1966, and see Table VI).

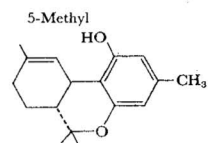
Approximately 30 cannabinoids are known at the present time, and these are listed in Table VI. This table is organized to emphasize two generalities that have become apparent in the last few years. One is the regular discovery of the presence of carboxylic acids that correspond to principal components of marijuana extract. These are felt to be biosynthetic precursors. They are found in higher amounts in botanical samples that are from the northern, or cooler, countries, and which are felt to be unripe and of low potency (Grlić, 1964). Decarboxylation can occur during the smoking process, leading to some increase in biological availability of the active cannabinoids. For this reason an analysis of just the extractable neutral fraction need not reflect the intoxicative potential of plant specimen. A second observation that appears to be general, is the regular presence of homologs of the cannabinoids wherein the pentyl (amyl) group is replaced with a propyl or a methyl. These minor components reflect the employment of divarinol (5-propylresorcinol) or orcinol (5-methylresorcinol) in place of olivetol (5-pentylresorcinol) in biosynthesis.* In some samples of marijuana, the propyl homologs are present in amounts comparable to the pentyl counterparts and may contribute to the overall pharmacological activity. It is recognized that some of the cannabinoids listed in Table VI could have been generated by the techniques of isolation (decarboxylation) and some may result from decomposition as a result of storage, irradiation, or air-exposure. Some of the proposed structures rest solely upon GLC and mass spectral analysis, with the substance itself not characterized chemically.

A number of additional classes of components have been isolated from the marijuana plant. Nitrogenous substances have been known to be present for

* Nomenclature problems exist concerning these homologs. When first identified, the three-carbon analogs were named as were the five-carbon counterparts, but incorporating the divarinol term; i.e., tetrahydrocannabinol gave rise (etymologically) to tetrahydrocannabivarin. It was proposed by Vree *et al.* (1972b) that a common suffix be maintained, and they suggested tetrahydrocannabivarol (and tetrahydrocannabinorcol for the 5-methyl homolog). It may be noted that if the seven-carbon homolog were discovered (this series orcinol, divarinol, olivetol, and sphaerophoral is regularly encountered in botanical systems) one would require the name "tetrahydrocannabisphaerophoral." The proposal of de Zeeuw *et al.* (1971) to employ THC (or pentyl-THC), propyl-THC, and methyl-THC (and eventually heptyl-THC) not only circumvents this but also allows easy naming of homologs of cannabinoids wherein the suffix is already committed by the structure of the molecule (i.e., propyl-cannabicyclol).

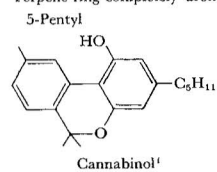
TABLE VI
TABULATION OF THE KNOWN CANNABINOIDS

Monophenols		Corresponding diphenols		Derivatives	
Phenol	Phenol carboxylic acid	Resorcinol	Resorcinol carboxylic acid	Ethers	Esters
Terpene ring cyclohexene					
5-Pentyl					
	Tetrahydrocannabinolic acid A ^b		Cannabidiolic acid ^{e,f}	Cannabidiol monomethyl ether ^{g,h}	Cannabitril ester of cannabidiolic acid ^h
	Tetrahydrocannabinolic acid B ^c				
Δ¹⁰-Tetrahydrocannabinol ^{g,h}					
5-Propyl					
Tetrahydrocannabivarin ⁱ (tetrahydrocannabivarol) ^j	Tetrahydrocannabivarolic acid ^m	Tetrahydrocannabidivarin (Tetrahydrocannabidivarol) ^{n,u}			

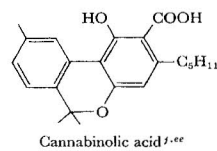


Tetrahydrocannabiorcol^{dd}

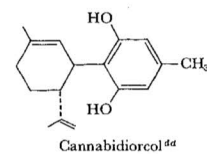
Terpene ring completely aromatic



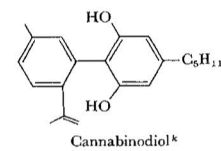
Cannabinol^l



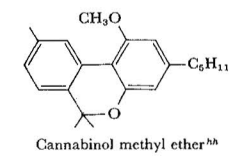
Cannabinolic acid^{j,ee}



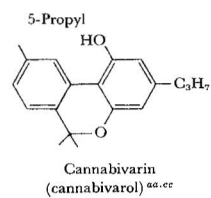
Cannabidiol^{dd}



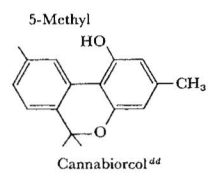
Cannabinodiol^k



Cannabinol methyl ether^{hh}



Cannabivarín
 (cannabivarol)^{aa,cc}

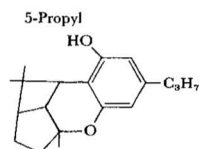


Cannabiorcol^{dd}

(Continued)

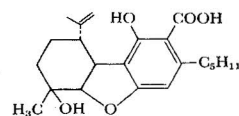
TABLE VI
TABULATION OF THE KNOWN CANNABINOIDS

Monophenols		Corresponding diphenols		Derivatives	
Phenol	Phenol carboxylic acid	Resorcinol	Resorcinol carboxylic acid	Ethers	Esters
Terpene ring opened					
5-Pentyl					
Cannabichromene ^{6,p,ff}	Cannabichromenic acid ^q	Cannabigerol ^{r,ff}	Cannabigerolic acid ^t	Cannabigerol methyl ether ^t	
				Cannabigerolic acid methyl ether ^t	
5-propyl					
Cannabivarichromene ⁹⁹					
Terpene ring doubled					
5-Pentyl					
Cannabicyclol ^{u,v,w}	Cannabicyclolic acid ^a				
				Cannabicitran ^{ff}	

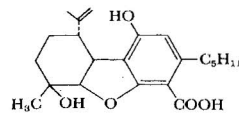


"Propyl" cannabicyclol⁸⁹

Terpene ring inverted
5-Pentyl



Cannabielsoic acid A^x



Cannabielsoic acid B^x

^a Gaoni and Mechoulam (1964a).

^b Korte *et al.* (1965a).

^c Mechoulam *et al.* (1969).

^d Adams *et al.* (1940a).

^e Schultz and Haffner (1958).

^f Kabelik *et al.* (1960).

^g Gaoni and Mechoulam (1966a).

^h Hively *et al.* (1966).

ⁱ Wood *et al.* (1899).

^j Mechoulam and Gaoni (1965a).

^k van Ginneken *et al.* (1972).

^l Gill *et al.* (1970).

^m Paris *et al.* (1973).

ⁿ Vollner *et al.* (1969).

^o Gaoni and Mechoulam (1966b).

^p Claussen *et al.* (1966).

^q Shoyama *et al.* (1968).

^r Gaoni and Mechoulam (1964b).

^s Yamauchi *et al.* (1968).

^t von Spulak *et al.* (1968).

^u Mechoulam and Gaoni (1967).

^v Crombie and Ponsford (1968).

^w Shani and Mechoulam (1970).

^x Shoyama *et al.* (1972b).

^y Shoyama *et al.* (1972a).

^{aa} Vree *et al.* (1971).

^{bb} Vree *et al.* (1972a).

^{cc} Merkus (1971).

^{dd} Vree *et al.* (1972b).

^{ee} Shoyama *et al.* (1970).

^{ff} Bercht *et al.* (1974).

^{gg} de Zeeuw *et al.* (1973).

^{hh} Bercht *et al.* (1973).

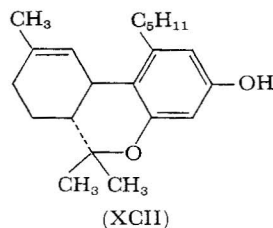
ⁱⁱ Turner *et al.* (1973).

^{jj} The cannabichromenes and cannabigerols are related through an oxidative step, rather than by a simple double bond addition as is true with the other listed monophenol-diphenol pairs. This interconversion has been proposed as a biosynthetic step (Mechoulam and Gaoni, 1967).

many years (Smith, 1891). Saleminck *et al.* (1965) have reported the presence of choline and trigonelline. Recently, several more complex, and pharmacologically active, alkaloids have been isolated and partially characterized (Klein *et al.*, 1971). Zamir-ul Haq *et al.* (1974) have identified carbazole, indole, and skatole in condensates of marijuana smoke. A number of studies have reported the presence of phenols as components of the plant. Guaiacol and eugenol are present (Obata and Ishikawa, 1960), as are the closely related acids melilotic acid (*p*-hydroxycinnamic acid) and ferulic acid (3-methoxy-4-hydroxycinnamic acid) (Bate-Smith, 1962). The *p*-hydroxyphenethylamide of melilotic acid has been isolated from the roots of cannabis (Slatkin *et al.*, 1971). A number of additional phenols (cresol, *p*-ethyl and *p*-vinylphenol, catechol, and piceol) have been identified in marijuana smoke (Fentiman *et al.*, 1973). Sterols (Fenselau and Hermann, 1972) and triterpenes (Slatkin *et al.*, 1971) are present in plant extracts. Two flavones (apigenol and luteolol) have been identified in marijuana leaves by Paris and Paris (1973) as their glucosides. The essential oil fraction (Martin *et al.*, 1961) and terpene fraction (Nigam *et al.*, 1965) have also been analyzed. Strömberg (1974) has made an extensive gas-chromatography mass-spectroscopy of these fractions and has tentatively identified 11 terpenes. The sugar composition of marijuana has also been studied (Grose and Jones, 1973). There is no suggestion that any of these noncannabinoid compounds contribute appreciably to the pharmacological action of the entire plant.

The first synthesis of the principal cannabis cannabinoid, Δ^1 -THC (LXXXVIII), was reported in 1965 (Mechoulam and Gaoni, 1965b) employing the terpene aldehyde citral and a derivative of olivetol. Within the next few years a large number of additional syntheses were devised, either for the preparation of the two principal isomers of tetrahydrocannabinol [(LXXXVIII) and (LXXXIX)] or for the open ring resorcinol, cannabidiol (XCI). Several of these entailed the construction of the terpene ring from an appropriately substituted olivetol (Korte *et al.*, 1965b, 1966; Fahrenholtz *et al.*, 1966), but most exploited the concept that was suggested in the biosynthetic arguments, the reaction of an appropriate terpene directly with olivetol. The citral process was confirmed by Taylor *et al.* (1966), and was followed by methods employing pinene and verbenol (Mechoulam *et al.*, 1967), *p*-menthadiene-2,8-ol-1 (Petrzilka *et al.*, 1967), and Δ^2 -carene (Razdan and Handrick, 1970). The advantages of the last three mentioned routes is that optically asymmetric isomers are synthesizable (natural THC is the levorotatory isomer) avoiding the need of a resolution step in the synthetic process (Jen *et al.*, 1967). In the case of the use of pinene, as both optical enantiomorphs of verbinol are available, the unnatural (dextrorotatory) isomer of tetrahydrocannabinol was prepared [and found to be inactive in animal tests (Edery *et al.*, 1971)]. An unexpected observation was made in the case of the synthesis with menthadiene-2,8-ol-1; with manipulation of the quantity

of catalyst employed, a sizable amount of the positional isomer (XCII) of (LXXXVIII) can be formed (Bailey and Verner, 1972a). At the present

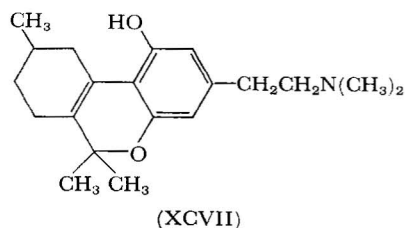
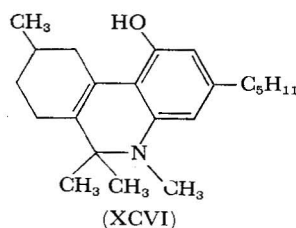
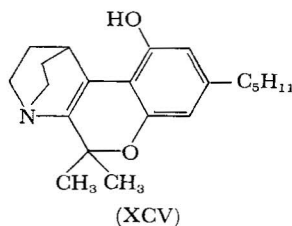
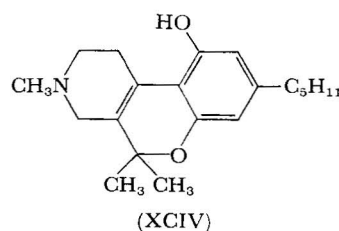
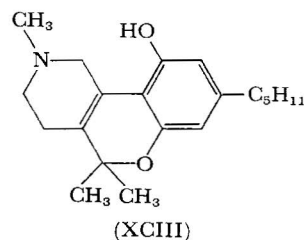


state of the art, it appears that the best and easiest route to quantities of either Δ^1 - or $\Delta^{1(6)}$ -tetrahydrocannabinol is a semisynthetic one. A major product of cannabis, and one that can be isolated from it in a high state of purity, is cannabidiolic acid. This, on decarboxylation and catalytic ring closure, yields THC of excellent purity (Gaoni and Mechoulam, 1971).

In this period, the chemistry of the more easily synthesized biologically active, but unnatural isomer with the Δ^3 position (XC) was not ignored. Although this compound was at best a tenth the potency of the natural isomer in man, in animal tests the variation of group on the 5 position of the resorcinol ring was known to radically affect its activity. The *n*-hexyl isomer, synhexyl, has been evaluated clinically but the exceptional activity of the dimethylheptyl isomer (XCIX) (Loewe, 1950) encouraged active research in a number of government laboratories. It was recognized that the original Adams compound, with three asymmetric carbon centers, might well be a mixture of isomers, and that one of them might be a major contributor to the five-hundredfold increase of potency of (XCIX) over (XC). These isomers have been separated and described (Aaron and Ferguson, 1968). The corresponding homolog with the double bond located in the "natural" positions (i.e., Δ^1 and $\Delta^{1(6)}$) has been synthesized (Petrzilka *et al.*, 1969) and seems to retain the exaggeration of potency associated with (XCIX), but pharmacological details are not yet published (Mechoulam, 1970, 1972a).

Another widely explored area of analogs are those that have a nitrogen atom at one point or another in the tetrahydrocannabinol molecule. Marijuana is one of the very few biologically active plants that does not exhibit its activity through the action of alkaloids, and the synthetic chemists have attempted to remedy this. A number of analogs of Δ^3 -THC (XC) have been prepared with nitrogen in place of carbon. In the cyclohexene ring C-1 (Pars *et al.*, 1966), C-6 (Anker and Cook, 1946), and C-5 (Lyle *et al.*, 1970) have been replaced, with additional structural modifications, to yield (XCIII), (XCIV), and (XCV). The pyran oxygen has been replaced (Hoops *et al.*, 1968) to produce the tetrahydrophenanthridine (XCVI). A nitrogen has been inserted in the chain in the manner of a phenethylamine (XCVII) (Pars and Razdan, 1971). A number of compounds with structures

further removed from that of THC have been described, diazepine and pyrimidine analogs (Greb *et al.*, 1972) and piperidinobenzopyrans (Harris *et al.*, 1967). These materials are without the natural Δ^1 double bond. The



only studies leading toward a nitrogen analog with the stereochemistry and unsaturation found in (LXXXVIII) is still at the model compound stage (Cushman and Castagnoli, 1973). Several substitution derivatives of THC that contain nitrogen in the substituent (to effect water solubility) have been described (Zitko *et al.*, 1972).

In the last 2 years a great deal of energy has been directed toward studying the metabolic fate of tetrahydrocannabinol in animals and in man. This research direction has resulted from the widely held belief that the nature of intoxication expressed by marijuana must invoke the *in vivo* generation of an active metabolite. Also, since the active components of marijuana are not found unchanged in urine, the interests of forensic chemists would be served by analytical procedures reflecting marijuana usage. The large number of metabolites which have been observed from *in vitro* and *in vivo* studies of both (LXXXVIII) and (LXXXIX), in many animal species, have been reviewed recently (Burstein; see Mechoulam *et al.*, 1972b). In general,

the chemical changes are hydroxylation (in either the methyl group, or the cyclohexene ring allylic to the double bond, and in the amyl chain), aromatization of the cyclohexene ring to cannabinol, or oxidation of the methyl group to a carboxylic acid. In man, there is principally 7-hydroxylation of Δ^1 -THC (Lemberger *et al.*, 1970, 1971a,b) to produce a compound that is indeed more potent than the original. This metabolite can be analyzed by conversion to cannabinol (Anderssen *et al.*, 1971), but in all cases must be freed from its native conjugated state by enzymatic pretreatment before successful isolation (Christiansen and Rafaelsen, 1969; Woodhouse, 1972). The aromatic cannabinol has been observed as a metabolite by McCallum (1973).

The reports of human activities and potencies of chemical substances related to marijuana may be considered in two groups: those that are natural products either derived from plant sources or synthesized, and those that are unnatural synthetic analogs.

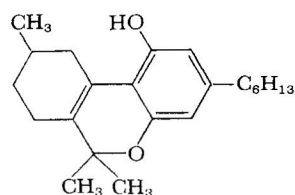
Of the natural compounds, there seems little question that the major tetrahydrocannabinol present, Δ^1 -THC (LXXXVIII) is largely responsible for the activity of the plant. A number of workers (Isbell *et al.*, 1967; Hollister *et al.*, 1968; Waskow *et al.*, 1970) have reported that it satisfactorily mimics the action of the drug, orally at levels of from 5 to 25 mg, and by inhalation at levels of from 2 to 10 mg. These are levels of tetrahydrocannabinol that are reasonably encountered in marijuana usage. Only low levels have been explored intravenously, and 0.5 mg appears to be without effect (Lemberger *et al.*, 1971a). However, 1.0 mg of the metabolite 7-hydroxy- Δ^1 -THC is unquestionably active (Lemberger *et al.*, 1972). Cannabichromene (see Table VI) is inactive in man at oral levels of about 200 mg (Isbell *et al.*, 1967) as is cannabinol (LXXXVII), either orally or by smoking, at levels of 150 mg. The diether of cannabidiol has been reported without activity at 25 mg levels when smoked (Isbell *et al.*, 1967), but as the free resorcinol (XCI) shows human activity by this route (R. Jones, unpublished studies and personal communication, 1972).

Interest in the unnatural synthetic analogs of the tetrahydrocannabinols has been generated by the extensive chemical and pharmacological studies in the 1940's of Adams and Loewe (see Mechoulam, 1973, for a review), where biological activity was found to sensitively reflect the chemical nature of the substituent at the 5 position of the resorcinol moiety. Two compounds have been extensively studied in man; the 5-hexyl homolog of (XC) [synhexyl (XCVIII)] and the 5-(1,2-dimethylheptyl) homolog [DMHP (XCIX)].

The pharmacological results from the original dog ataxia assay screening method (Loewe, 1950) have been shown to be similar to those obtained in primates (Edery *et al.*, 1971), and are, as far as has been determined, applicable to the expressed marijuanalike activity of these compounds in man. The most potent of the straight chain homologs is (XCVIII), known as synhexyl

or pyrahexyl in clinical studies. It was initially explored as an aid in morphine withdrawal (Himmelsbach, 1944; Williams *et al.*, 1946) wherein it showed little value. However, it was shown to display cannabislike effects at oral levels of 60 mg, although this same level intramuscularly was substantially without effect. In chronic studies allowing an *ad libitum* consumption (60–2400 mg/day) the initially experienced euphoria gave way to a state of lassitude. The subjects felt that the preparation was stronger than marijuana (Williams *et al.*, 1946). A recent comparison of synhexyl with Δ^1 -THC (Hollister *et al.*, 1968) revealed that a mean dosage of about 100 mg was necessary to parallel the intoxication found with the THC standard. There is apparently only a single experiment with the parent of this Adams series, the 5-amyl compound (XC). Isbell *et al.* (1967) found it to be without effect at a dosage of 30 mg parenterally.

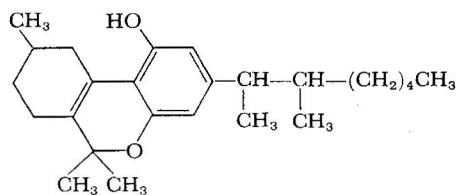
By far the best studied of the alkyl homologs of (XC) is the dimethylheptyl



(XCVIII)

Synhexyl

Pyrahexyl



(XCIX)

Adams' nine-carbon compound

DMHP (Dimethylheptylpyran)

CA-101

SKF-5350 (Smith, Kline, and French)

EA-1476 (Edgewood Arsenal)

RA-122 (Roger Adams)

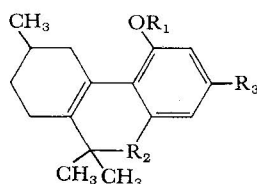
PL-5895

226,048 (A. D. Little)

EA-2233 (Edgewood Arsenal code for the acetate esters)

homolog (XCIX). A number of the codes used to define it are listed under the structure. A wealth of information concerning this unusual compound has become available with the recent declassification of the army research work of the 1950's. Since this compound has three asymmetric centers, it is capable of existence in eight isomeric forms. Initially, the mixture of those that were obtained synthetically was assayed as being some 500 times more potent than the reference THC analog (XC) by dog studies, and since this reference compound was a tenth to a fifteenth as active as natural tetrahydrocannabinol, one might expect (XCIX) to be 30–50 times more active than Δ^1 -THC in man. Human studies have indicated, however, that the racemic mixture as obtained synthetically is about a tenth this expected activity. Sim (1970) has reported that oral application of from 2 to 4 mg leads to a slow onset of a

relatively severe postural hypotensive state that can persist for several days. Jasinski *et al.* (1971) also studied its oral effects over a similar range and found that the initial responses were, in addition to the hypotensive presentation, a long-acting sedation. They reported psychological effects at higher dosages. An early army report (D.O.D., 1963) breaks this down to 0.5–1.0 mg, fatigue, thirst, and headache noted; 1.5–3.0 mg, postural hypotension and blurring of vision; and 3.5–4.0 mg, psychomotor retardation, lasting up to 48 hours. These effects are in agreement with the comments of Mechoulam (quoted in Ben-Zvi *et al.*, 1971) who stated that experienced marijuana users who had assayed illicitly produced DMHP had confirmed that it had a prolonged action but that it was mostly unpleasant.



	R ₁	R ₂	R ₃
EA-1465	H	O	—CH(CH ₃)C ₇ H ₁₅
EA-1476	H	O	—CH(CH ₃)CH(CH ₃)C ₅ H ₁₁
EA-1477	H	O	—C ₅ H ₁₁
EA-1507	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{N}(\text{CH}_3)_2 \end{array}$	O	—C ₅ H ₁₁
EA-1542	H	NH	—C ₅ H ₁₁
EA-1543	$\begin{array}{c} \text{O} \\ \nearrow \\ \text{P}-\text{CH}_3 \\ \searrow \\ \text{OCH}(\text{CH}_3)_2 \end{array}$	O	—C ₅ H ₁₁
EA-1544	H	S	—CH ₃
EA-1545	H	O	—CH ₃
EA-2233	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{CH}_3 \end{array}$	O	—CH(CH ₃)CH(CH ₃)C ₅ H ₁₁

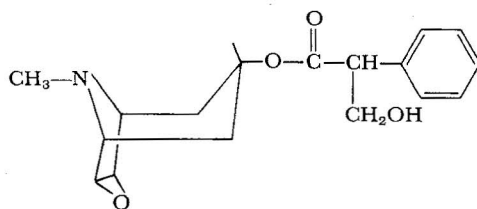
The acetyl derivatives of the mixture (XCIX) have proved to be considerably more stable than the free phenols, and perhaps somewhat more potent. Sim (1970) has reported an increase in blood pressure and colored hallucinations observed at doses of a milligram, and at higher levels, a reversal in blood pressure and an unexpected hypothermia. However, the government reports (D.O.D., 1963) describe only hypotension and lethargic state at dosages of up to 4 mg, and have considered it to be equipotent to the free phenol.

The isomers inherent in the structure (XCIX) have been resolved (Aaron and Ferguson, 1968) and have been separately explored clinically. Sidell *et al.* (1973) have compared, intravenously, the racemic acetate mixture and the two most active isomers are called #2 and #4 (both with the 1,2-dimethyl groups trans to one another). The isomer #2 showed erratic euphoric response at between 150 and 200 μg doses, but consistent hypotension. The isomer #4 was, if anything, more potent yet (100–200 μg total dose), but again hypotension was the principal response expressed. The initial reports of the *iv* activity of the racemic acetate esters as being consistently euphoristic (D.O.D., 1966) are not consistent with the reported lack of this activity in the #2 and #4 isomer mixtures and in pure isomer #4 were at its pharmacologically active level (*iv*) of 100–200 μg (D.O.D., 1967). One must conclude that isomers and derivatives in this chemical class can be exceptionally potent but that the nature of the activity is increasingly foreign to that deemed characteristic of marijuana.

A number of additional derivatives in this area have been studied pharmacologically in animals (see Hardman *et al.*, 1971), but many of the compounds reported are identified only by their EA numbers. Several of these are given in the accompanying tabulation on page 115.

I. Anticholinergic Psychotomimetics

A number of groups of drugs have been studied because of their capacity to imitate, pharmacologically, the action of an extremely potent natural alkaloid, scopolamine (C). This compound is the principal active agent in a large number of plants found around the world and used for centuries for their magic or mystical power. The belladonna plant, *Atropa belladonna*, was used in Europe in the Middle Ages as a witches' brew. Henbane, *Hyoscyamus niger*, was also widely cultivated throughout Europe as a hallucinogenic



(C)
Scopolamine

contribution to these brews, as has been mandrake, *Mandragora officinarum*. Pituri, *Duboisia hopwoodii*, has been broadly used by the Australian aborigines, and the many species of *Datura* have been used, mainly in the New World, for centuries for religious purposes and as a stupeficient. The principal active component in this diffuse botanical collection is scopolamine.

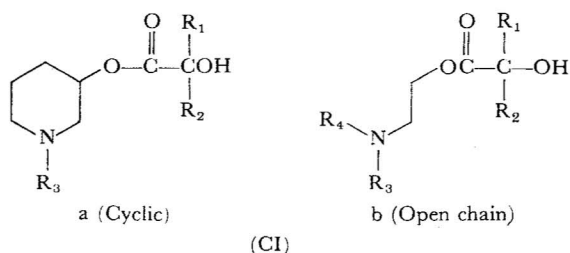
Issue may be taken with the classification of materials pharmacologically related to scopolamine as psychotomimetic drugs in the sense that it is employed in this review. Most of the drugs that have been discussed are characterized by sensory and intellectual distortion and synthesis, but an overriding property has been the retention of insight and the regular ability to recall most aspects of the intoxication state. It has been found with the clinical evaluation of most of the drugs to be discussed here that although there can be unmistakable hallucinogenesis, it is as a rule unrecalable because of the subject's induced amnesia, particularly of the delirium period.

Most of the drugs that are classified in this category have a consistent chemical feature—the ethanolamine group. In these drugs, the amine is always tertiary and often in a cyclic form such as piperidine, and the hydroxy group is esterified with an arylglycolic acid. The largest group of these compounds resulted from a study of potential antispasmodic drugs (Biel *et al.*, 1955) which were unusable because of undesirable side effects (Abood *et al.*, 1958). As in many other instances, the side effects that are considered undesirable from the clinical viewpoint are the very effects that contribute to a drug's misuse. It was found that 10 mg of *N*-methyl-3-piperidyl benzilate (JB 336, Table VII) led experimental subjects to a complete loss of contact with their environment, with the development of both visual and auditory hallucinations. In all materials that have been found to be active as psychotomimetics, there are evident and usually long-lasting signs of parasympatholytic activity (Abood *et al.*, 1959a), but the reverse is not true; many active anticholinergics in these studies are without central activity. Minor chemical changes (removal of the glycolic hydroxy group, quaternization of the piperidine nitrogen) eradicated the central action. Those compounds for which there are reports of human activity are organized in Table VII. The listed human dosage ranges are estimates in several cases. In some of the studies the intensities of response were compared at a set dosage schedule rather than determining the dose requirement to effect a given response. In others, only threshold responses were observed; thus, the maximum stated dose must be presumed to be the minimal for activity.

It should be noted that all of this work was reported during a period of only 3 years, yet this was 15 years ago. One should not infer that there was no further interest in the area. Quite the contrary, many extensive studies were made of analogs and homologs, especially in the area of heterocyclic variations in the piperidine ring. Biological data from pharmacological studies however have been obtained exclusively from animal studies so that the current status of structure-activity relationships (see Abood, 1968) may not properly display the psychotomimetic effectiveness of the compounds in question. There has been considerable interest in this area shown by the U.S. Army, but apparently none of this work has as yet been declassified. Two of the simplest of the compounds in Table VII, the *N*-methyl and the

TABLE VII

HUMAN ACTIVITY FROM VARIOUS COMPOUNDS



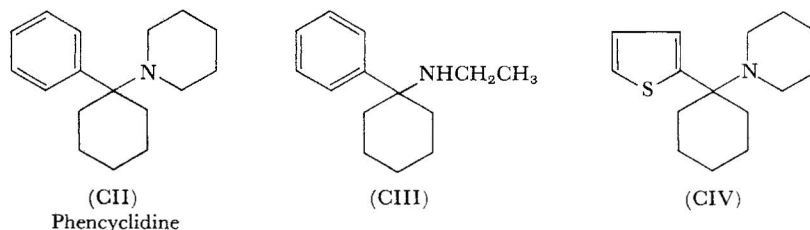
Name	R ₁	R ₂	R ₃	R ₄	a or b	Effective dosage range (mg) ^a	Ref. ^c
Benactyzine	Phenyl	Phenyl	Et	Et	b	50-200	(d)
JB 841	Phenyl	Phenyl	H	—	a	>100	(e)
						>20	(f)
JB 18	Phenyl	Phenyl	Allyl	—	a	>20	(f)
JB 868	Phenyl	Phenyl	—CH ₂	—	a	>20	(f)
			CH ₂				
			NH				
			N(CH ₃) ₂				
JB 344	Phenyl	2-Thionyl	Me	—	a	10-20	(e)
JB 318	Phenyl	Phenyl	Et	—	a	10-20	(a,c)
JB 851	Phenyl	Phenyl	—CH ₂	—	a	>10	(e)
			CH ₂				
			N(CH ₃) ₂				
JB 329 ^b	Phenyl	Cyclopentyl	Et	—	a	10	(e)
JB 840	Phenyl	Cyclohexyl	Me	—	a	10	(e)
Win 2299	2-Thionyl	Cyclohexyl	Et	Et	b	5-10	(b)
JB 328	Phenyl	Cyclohexyl	Et	—	a	5-10	(e)
JB 336	Phenyl	Phenyl	Me	—	a	5-10	(a)

^a Estimated from intensity of response or from threshold dosage. See text.^b This chemical has been investigated under the name "Ditrane." In this form it is a mixture of 30% piperidine and 70% ring-contracted 2-pyrrolidine.^c Key to references:

- (a) Abood *et al.* (1958).
- (b) Pennes and Hoch (1957).
- (c) Ostfeld *et al.* (1958).
- (d) Vojtěchovský *et al.* (1958).
- (e) Abood *et al.* (1959a).
- (f) Abood *et al.* (1959b).

N-ethyl piperidinyl benzylates (JB 336 and JB 318), have appeared in the illicit drug market recently, predominately on the East Coast. They have been added to the Schedule I class of Controlled Substances (Federal Register, 1970). Benactyzine has appeared on the "street" as a hallucinogen in 1968, sold under the name "DMZ." It is a component of a number of legitimate preparations and is uncontrolled.

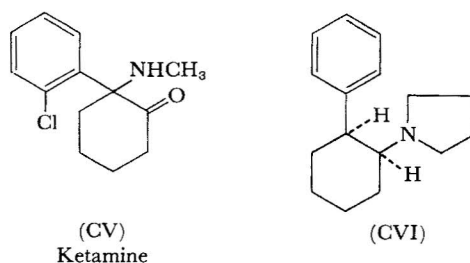
Another class of drugs should be considered here, not for their chemical structure but for pharmacological similarities. These are the dissociative anaesthetics related to phencyclidine, [Sernyl (CII)]. This synthetic base was developed in the 1950's and introduced into clinical study as an anaesthetic in 1957 by Parke Davis. It proved to have seriously limiting side effects upon emergence from anaesthesia, such as extreme excitement, visual disturbances, and delirium. Clinical investigations were discontinued in 1965,



but in 1967 the drug was made available for veterinary surgery. At about this time, there was an upwelling of availability and popularity of the substance in the young drug-oriented community where it was distributed under the name of PCP (abbreviations of the chemical name phenyl cyclohexyl piperidine) or peace pill (a corruption of PCP), and later under the name "hog." Although the first material available was certainly diverted from legitimate channels, the reasonably high potency of the drug (3–10 mg orally) and the exceptional simplicity of synthesis serve to encourage a mushrooming of illegal laboratories. It has been made available in every conceivable form and under many names. It has been used as a pharmacological diluent for marginally effective doses of LSD and marijuana. It has appeared as an outright fraud being sold under any name that might sell, such as mescaline or THC. The occasional appearance of a batch leading to distressing physical disturbances has been blamed upon synthetic error (Reed and Kane, 1970) but is probably explained best by incomplete purification from the highly toxic nitrile intermediate (D. MacLean, unpublished data and personal communication, 1972). The use of phencyclidine is still common, although the drug has been placed within Schedule III of the Controlled Substances Act. A number of minor chemical modifications have appeared [(CIII) and (CIV)] and have been accepted on the street as phencyclidine. These explorations employ variations in synthetic starting materials that may

reflect curiosity or possibly the awareness of the letter of the law in which phencyclidine alone is named as illegal.

A number of additional compounds can be considered as outgrowths of phencyclidine research, compounds that are being investigated as clinical drugs due to the pharmacological development of a useful dissociative state, but which seem still to have the disturbing side reactions which might make them marketable in the illegal drug trade. An example is an analog of phencyclidine wherein the phenyl group is replaced with an ethinyl group, giving a compound of similar activity (Weinstein *et al.*, 1973). Ketamine (CV) is only a tenth as potent as phencyclidine but appears to produce a rapid onset and short duration anaesthesia (Domino *et al.*, 1965), although there are still reports of undesirable psychotic changes similar to those seen with phencyclidine (Fine and Finestone, 1973). Another similar compound (CVI) has been clinically assayed as an anticholinesterase agent for the



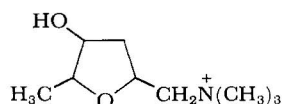
treatment of myasthenia gravis, but has been withdrawn because of severe sensory distortions (disorientation, dysphoria, and hallucination) observed at doses of some 50 mg *iv* (Wray and Cowan, 1973).

J. *Amanita* spp.

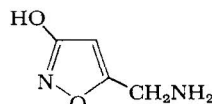
The *Amanita* genus of mushroom has been involved for centuries in a folklore of unusual occult or magical powers. The most famous species is the *A. muscaria*, an internationally distributed fungus readily recognized by its red crown covered with white flecks. This mushroom is known as the fly agaric, popularized in the United States by its portrayal in Disney's *Fantasia* and internationally believed to be the intoxicating factor in the Scandinavian *Berserkgang* (Fabing, 1956). These were the legendary monsters of the north countries who ate the mushroom (and sustained their intoxication by consuming one another's urine) to inspire maniacal capabilities. Wasson (1968) has critically challenged this role of the mushroom, and has advanced an exquisite argument that this plant might indeed be the legendary *Soma* of

classical reverence.* A number of other species of *Amanita* are known, and most have some reputation of toxicity associated with them. *Amanita phalloides* is commonly called the "death cup," *A. verna* the "destroying angel"; these common names are occasionally interchanged. Intentional autointoxication with these latter species can probably be attributed to the widespread reputation of *A. muscaria* as a hallucinogenic plant.

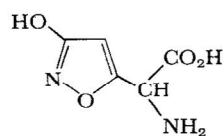
There has been a rather remarkable collection of compounds isolated from *A. muscaria*, including the only known vanadium organic substance ever found in plants (Bayer and Kneifel, 1972). Potentially culpable, pharmacologically, are bases such as muscarine (CVII), a cholinergic drug initially isolated from this mushroom and of high pharmacological significance (defining the muscarine effect) but apparently present in the intact mushroom



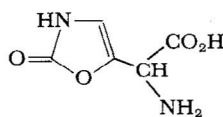
(CVII)
Muscarine



(CVIII)
Muscimol



(CIX)
Ibotenic acid



(CX)
Muscazone

at such low levels (2-3 ppm), and known to be relatively inactive orally, that it is not in any way responsible for the activity of the plant (Wilkinson, 1961). Bufotenine has been reported as being present (see above), as have atropine and scopolamine. The levels of these, however, are at most, present at levels of less than a part per million (atropine, 0.1 ppm; scopolamine, 0.5 ppm; Eugster, 1967). Further, although the presence of indolic materials has been noted, bufotenine could not be detected in European varieties.

Two chemicals have been isolated in substantial quantities from fresh *A. muscaria* and may well account for much of its reported effects. These are muscimol (CVIII) (Good *et al.*, 1965) and the corresponding α -amino acid ibotenic acid (CIX) (Takemoto *et al.*, 1964). The amino acid appears to be

* Wasson has alluded to "the celebrated mushroom in *Alice in Wonderland*" as being possibly *A. muscaria*. Graves (1970) has volunteered that Carroll had read about this in Cooke's *British Fungi* appearing in the *Gardener's Chronicle and Agricultural Gazette*, October, 1862. In fact, the Carroll mushroom has only been pharmacologically, not morphologically, described; the left-hand bit makes you taller and the right-hand bit makes you shorter (in the original manuscript, 1864, Carroll wrote that the top will make you grow taller, and the stalk will make you grow shorter). There is no suggestion that the mushroom was *A. muscaria*, however.

a major component present in concentrations of up to 0.1% of the fresh plant. A closely related heterocyclic isomer of muscimol has also been isolated; this is muscazone (CX). Although less active biologically, it occurs in varying quantities and may account for the variability of activity of the intact plant (Eugster, 1969). It can be generated from ibotenic acid by uv irradiation (Eugster, 1967) and may possibly be an artifact of the isolation procedures (Catalfomo and Eugster, 1970).

The other principal species of *Amanita* that have been studied for their toxic components are *A. phalloides* and *A. verna*. In these plants the toxic principles are cyclic polypeptides (Weiland, 1972; Frimmer, 1971). A high molecular weight toxin has been isolated and characterized as a hemolysin from *A. phalloides* (Seeger *et al.*, 1973). The early history of the discovery of these toxins has been thoroughly reviewed (Weiland and Weiland, 1959). The toxins are severe liver poisons (Brunswig *et al.*, 1972), and cases of intoxication rarely involve sensory distortion. Another species, *A. pantherina*, appears to resemble *A. muscaria* both as to chemical composition and the nature of induced intoxication (Anonymous, 1972). Unusual amino acids (with allenic and chloro groups) have been isolated from *A. solitaria*, but they are unexplored pharmacologically (Chilton *et al.*, 1968; Chilton and Tsou, 1972). There has been a recent upwelling of enthusiasm regarding the use of thiocetic acid as an antidote to poisoning from *Amanita* spp. (Culliton, 1974). This is by no means widely accepted (Alleva, 1975; Bartter, 1975).

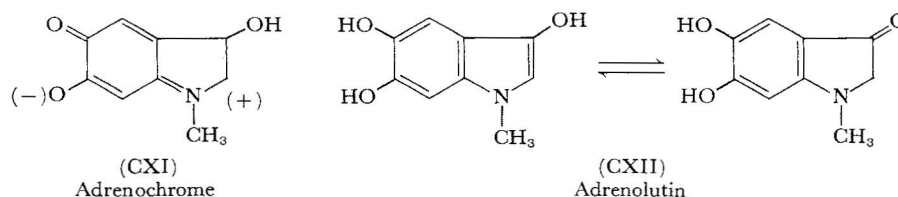
The syndrome of intoxication by *A. muscaria* is usually initiated by a period of drowsiness, followed in an hour or so by a state resembling alcohol intoxication. Following this there is a confusion accompanied by visual disturbances. Human experiments employing ibotenic acid have not satisfactorily duplicated these observations; studies employing up to 20 mg orally produced only slight facial flushing (Waser, 1967) and even at 75 mg the action was described as being weak and unlike that produced by the intact mushroom (Waser and Bersin, 1970). Muscimol, on the other hand, seems to elicit a feeling of lassitude at 5 mg with intoxication, dizziness, and mood elevation at twice this dose (Waser, 1967). With dosage levels of 15 mg there were visionary distortions but none of psychic reaction and psychotomimetic disruption that would be observed with LSD (Theobald *et al.*, 1968). The observation of unchanged muscimol in urine following such experiments (Eugster, see Waser, 1967) supports the argument of the effectiveness of recycling urine as a means of re-intoxication.

K. Minor, Mystical, and Marginal Materials

Many substances have been reputed to be psychotomimetics which are poorly defined chemically, botanically, or pharmacologically. Some of these lie in the area of folk reputation or current rumor; some stem from single

observations or isolated technical reports; and some are well-defined sociologically but seem to be found wanting in efforts to study them clinically employing Western scientific criteria. The merit of each cannot be evaluated without the application of some of the effort and curiosity lavished on the well-recognized areas discussed earlier; however, any or all of these might serve as a nucleus for the evolution of new families of psychoactive drugs in the future.

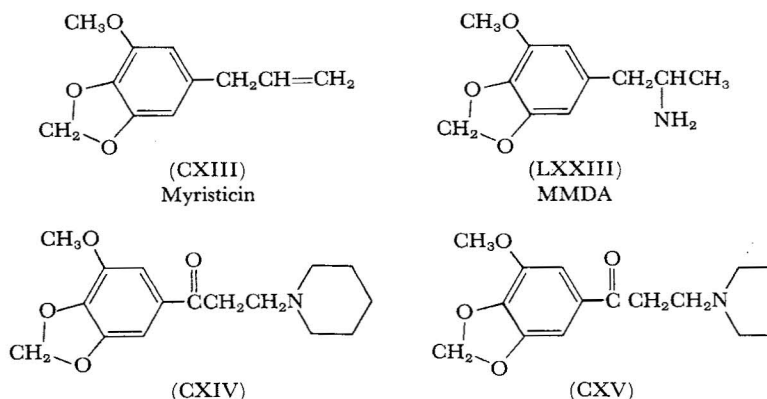
A body of literature has been built up over the last two decades concerning the possible role of some oxidation product of adrenalin as an *in vivo* psychotomimetic. It has been proposed, from chemical similarities between the neurotransmitter epinephrine (adrenalin) and mescaline, that some derivative of epinephrine might be generated abnormally in the body in mental illness (Osmond and Smythies, 1952). Adrenochrome (CXI) is an



oxidation product easily formed from epinephrine *in vivo*. This material was reported to be an extremely potent compound in humans, active in leading to central changes at submilligram dosages (Hoffer *et al.*, 1954). Another, and considerably more stable, oxidation product of epinephrine, is androlutin (CXII) which is also reported to be centrally active in humans (Hoffer, 1957). Early efforts to confirm or challenge these reports were faulted by the difficulties of obtaining and maintaining pure preparations of adrenochrome. Now that problems have been largely overcome, it is generally accepted that the initial reports cannot be duplicated. Grof *et al.* (1963) have noted sensory disturbances induced in normal subjects with 15–30 mg doses, but these were variable and reflected the source of the drug employed. Others have found the drug inactive (Rinkel and Solomon, 1957; Smythies, 1960), and efforts to detect it in blood samples from schizophrenic patients were futile (Szara *et al.*, 1958). The current chemistry and pharmacological position of these indoles have been recently reviewed (Heacock, 1971).

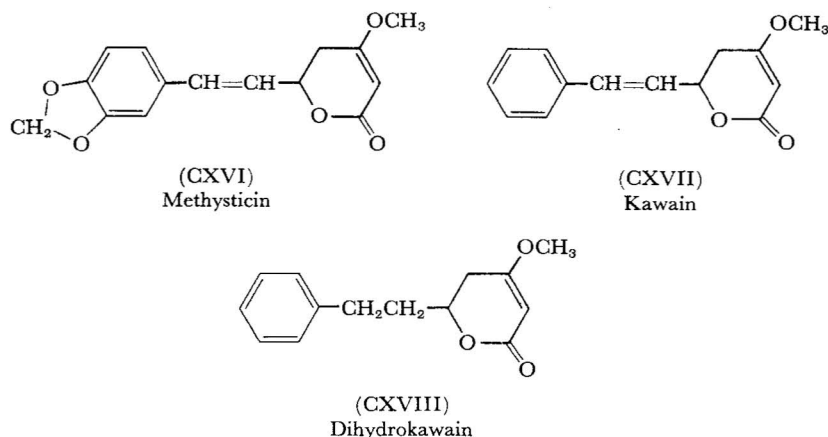
A number of plants, primarily associated with spices of one sort or another, have been implicated in the area of drug use. The purportedly active components in these cases are various essential oils, mainly hydroxy-, methoxy-, or methylenedioxy-substituted allylbenzene or propenylbenzene. An example of a spice frequently employed for intoxicating purposes is nutmeg, the seed of *Myristica fragrans* (Weiss, 1960; Weil, 1965). The principal aromatic essential oil present is myristicin (CXIII) which has the exact carbon and oxygen skeleton of MMDA (LXXIII) and which has been

implicated as a possible explanation for the pharmacological properties of nutmeg (Shulgin, 1966b). Studies have shown that the compound undergoes this chemical transformation in *in vitro* tissue homogenate preparations (Braun and Kalbhen, 1972), but *in vivo* metabolism studies in the rat and the guinea pig have revealed completely different amination products (CXIV and CXV) (Oswald *et al.*, 1971). No human metabolism has been studied,



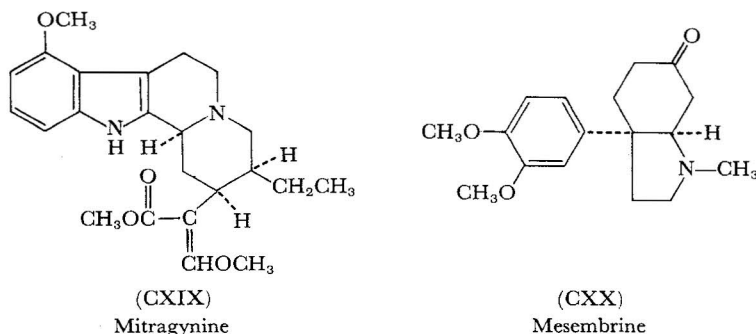
and the human pharmacology to these two heterocyclics is unknown. Recent studies of nutmeg (Isogai *et al.*, 1973a,b) have revealed the presence of a number of dimers of these simple phenyl propenes. The known chemistry and biochemistry of nutmeg has been recently reviewed (Forrest and Heacock, 1972). It should be noted that there is a good correlation between the substitution patterns that have been observed among the many aromatics in the essential oils and the patterns of the substituted phenylisopropylamines that have proved to be active psychotomimetics in man (Shulgin *et al.*, 1967).

Another botanical binomial renowned in the area of psychotropic pharmacology is *Piper methysticum*, the source of the drug kava-kava. This plant is the source of an extremely broadly used social intoxicant, employed throughout the South Pacific. The principal chemical components of this brew have been shown to be methysticin (CXVI), kawain (CXVII), and its dihydro derivative dihydrokawain (CXVIII) (Klohs *et al.*, 1959; Young *et al.*, 1966). A number of reports have described the pharmacological activity of the total plant material in man (Gajdusek, 1967; Holmes, 1967; Ford, 1967) as well as studies of the unresolved extracts in clinical studies of control of epileptiform seizures, but this clinical application has proved to be hopelessly beset with condemnatory side reactions (Pfeiffer *et al.*, 1967). Research activity has centered around the properties of these individual chemical components and their simple homologs such as ethysticin [352-Riker, the ethoxy homolog of methysticin (CXVI)]. The results have been largely



disappointing, with subjective responses equally divided between reports of stimulation, sedation, and no activity whatsoever (Pfeiffer *et al.*, 1967).

There are many plants which are difficult to deal with because of the uncertainty of their use or of the lack of information as to their active principles. *Mitragyna speciosa* has been used as an opium substitute in its native Southeast Asia (Holmes, 1907) and in Borneo as an intoxicant. The plant in Thailand is known as *kratom* and has been outlawed there. The principal alkaloid mitragynine (CXIX) represents structural features of both the carbolines and of ibogaine. Mitragynine shows analgesia and no dependence liability in animals, but no clinical data are available. Of additional interest is the presence of an indole ring, substituted with oxygen in the 4 position. Only psilocybin (XXIX), psilocin (XXX), and the recently reported base (XLIH), share this feature in the botanical world. Several species of *Mesembryanthemum* are known in Africa as khanna and have an age-old reputation



as a narcotic. Again, the plant use is difficult to document, but the major alkaloid present, mesembrine (CXX), is a methoxylated phenethylamine, bearing a passing resemblance to mescaline (XLVIII). Analogs containing uncyclized nitrogen but still the α -spiro substitution pattern are documented

components of the narcotic plant khanna, *Sceletium joubertii* (Arndt and Kruger, 1970). The active agent in the generation of psychotomimetic effects need not be a molecule of any complexity. Nitrous oxide (laughing gas) has been known for a century and has found its way into accepted medical use as an anaesthetic in spite of its well-documented proclivity to generate a sensory state of misinterpretation and illusion. Less well known, but perhaps even more dramatic is the ubiquitous gas, carbon dioxide. In admixture with oxygen (30% CO₂, 70% O₂, carbogen) there is the development of an intense and short-lived psychotomimetic episode that accompanies the expected state of physical distress.

Acorus calamus (rat-root) is used in northern Canada as a stimulant but contains no identified alkaloid. A principal component is asarone, a trimethoxyphenylpropene similar to myristicin (CXIII), and a recently established component of vermouth (Larry, 1973). The rhizomes of *Ararum canadense* (known as Canadian snakeroot) contain tetramethoxyallylbenzene, a potential precursor to tetramethoxyamphetamine, just as myristicin and elemicin are potential sources of MMDA and TMA (Bauer *et al.*, 1967). There was recently a brief appearance of silverweed, *Potentilla anserina*, as a marijuana substitute (Carter, 1971). The use and abuse of the classical stimulant khat, from the plant *Catha edulis*, has been recently reviewed (Getahun and Krikorian, 1973; Heacock and Forrest, 1974). Note has been made in the recent popular press of a possible intoxication principle to be found in catnip, *Nepeta cataria*. Activity has been reported in man (Jackson, 1969) but is presently uncertain (Hatch, 1972). The recent fad of "glue sniffing" may result from true CNS alteration but may be largely anoxia (Bass, 1970). *Abrus precatorius* seeds have been consumed (Gunn, 1969), and many largely innocent plants have been smoked from banana peel (Krikorian, 1968) to Scottish broom, *Genista carariensis* (Fadiman, 1965) to Queen Anne's lace, *Daucus carota*. *Salvia divinorum* (*pipiltzintzintli* of the Aztecs) is botanically and anthropologically well defined, but is completely unknown as to composition. The lists of psychotomimetic substances that lack one of the essential factors for complete definition (botany, chemistry, pharmacology, or anthropology) are long, and offer to provide the medical sciences rich information in the future. Many dozens of these have been compiled in a recent review (Schultes, 1970).

III. MECHANISM OF ACTION

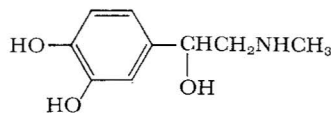
It is true with the psychotomimetic drugs as it is with all other drugs that the mechanism of action is not known. Results of the studies directed toward the search for such mechanisms are always expressed in terms of correlation: correlations between potency of action, chemical structure, functional group identity and physics, kinetics of body dynamics, organ and tissue distribution,

agonist or antagonist efficacy in competition with other drugs or normal biochemicals, and, for that matter, any phenomenon that can be measured or computed.

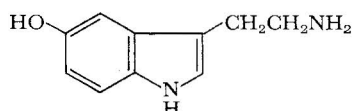
One of the most apparent correlations is between the chemical structures of the various classes of the psychotomimetics and the three principal neurotransmitters. These are acetylcholine (CXXI), epinephrine [adrenaline (CXXII)] and serotonin [5-HT, enteramine (CXXIII)]. An immediately



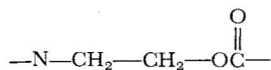
(CXXI)
Acetylcholine



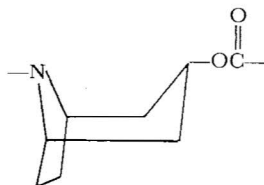
(CXXII)
Epinephrine



(CXXIII)
Serotonin



Acetylcholine skeleton



Atropine skeleton

appealing move is to classify the known families of psychotomimetics into groups that mimic chemically these three endogenous neurohumors. The acetylcholine transmitter is excellently defined by the antagonist that most effectively interferes with its action, the well-studied parasympatholytic, atropine. This drug has a spacing between the most polar portions of its molecular structure that is sterically superimposable to that of acetylcholine. In acetylcholine there is the separation of two carbon atoms, two methylene groups, between the nitrogen that is quaternized and the oxygen that supports the carbonyl of the substituent acid moiety. In atropine, although the separation is in fact three carbons rather than two, the conformation of the ring and bridge system maintains the same spatial configuration. In all of the cholinergic drugs discussed in Section II, I the exact chain of acetylcholine, an esterified ethanolamine, is inevitably present. The structure of epinephrine (CXXII) has the phenethylamine chain that is shared by all of

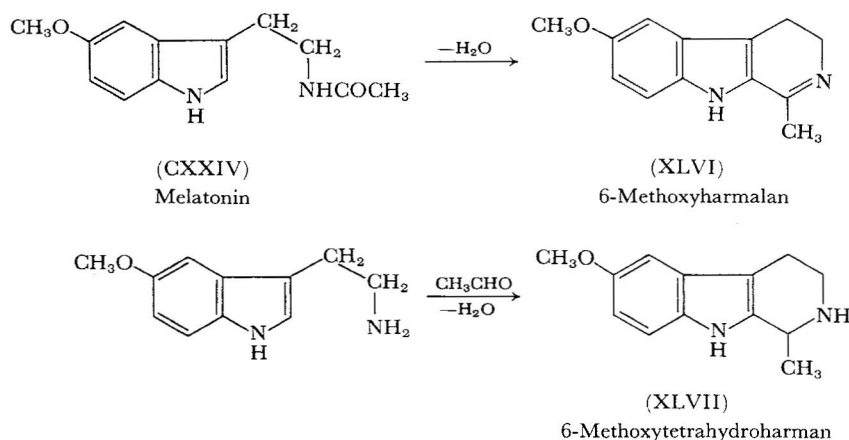
the mescaline analogs and homologs discussed in Section II,F. It is substituted with three oxygens, as is mescaline (XLVIII) and, although these are not methylated as is the case with mescaline, methylation occurs during the course of the metabolism of epinephrine. The third neurotransmitter, serotonin (CXXIII) is a substituted tryptamine, as are the many psychotomimetics mentioned in Section II,D.

In a general way, the subjective nature of the intoxicated state induced by these three broad chemical groupings can be similarly subdivided. All of the psychotomimetic drugs which are chemically related to the acetylcholine chemical structure have, without exception, the properties of generating an intoxicated state characterized by delusion and delirium, by the clear impairment of specific aspects of sensory and intellectual integrity as shown by the induced states of apraxia, aphasia, and agnosia, all usually hidden from the subject by amnesia throughout most of the period of intoxication. With the families of drugs related to the epinephrine group, as with those of indole structure related to serotonin, there is as a rule excellent recall of the illusions and interpretations experienced during intoxication. The distinction between these two latter families is primarily one of extrospection opposed to introspection from the viewpoint of a subject's participation within the drug-induced synthetic state. The many compounds chemically related to mescaline, and to the ring-substituted amphetamine family, lead to generally consistent reports of attention paid to external objects, to visual (and rarely auditory) syntheses which seem to have their origins in the physically surrounding environment, and to constructive interpretations resulting from such experiences being directed primarily to the relationship between the subject and his exterior world. On the contrary, the consensus of subjective reports concerning the psychiatric changes following experiments with the indole, or serotonin-related drugs, is that the reinterpretation of relationships is entirely within the individual. Here one reads of religious insight, re-evaluations of purpose and personal role, of coming to understand one's self in some new light (Shulgin, 1970).

This broad, and by no means generally accepted, categorizing of psychological or subjective response into subdivisions of chemical structure falls apart completely in all attempts to explain pharmacological action at the molecular level. The distribution of psychotomimetics in the intact body, the localization in specific organs or in specific sites of organs, the attempt to show agonistic or antagonistic action with specific regard to these neurotransmitters, the efforts to demonstrate degrees of cross-tolerance between one another—all have been relatively unsuccessful. As an example of contradiction, DET appears to act directly upon the serotonin receptors within the CNS (Winter, 1969) and yet the bromo analog of LSD, BOL, one of the most potent serotonin antagonists, is not an active psychotomimetic (Cerletti, 1959). These conflicting interpretations may largely result from the necessity

for the use of nonhuman experimental animals in most biochemical studies, to correlate to subjective phenomena that are expressible only in intelligent human subjects. Further, several of the families of drugs discussed earlier cannot be cataloged in any of the chemical classes. There are at present still no animal screens that satisfactorily predict human behavior or potency in the area of the psychotomimetic drugs.

A number of these attempts to relate chemical structure to established or hypothetical biochemistry are extremely appealing; for example, the presence of melatonin (CXXIV) as a pineal component and its origins from serotonin are well established. The close resemblance between this hormone and the carboline (XLVI) led to the proposal (McIsaac, 1961a) that such a dehydration might occur *in vivo* and that this latter compound might be an



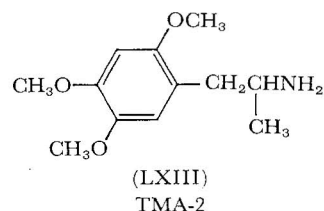
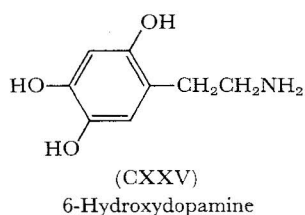
endogenous psychotogen. This cyclodehydration transformation is a standard chemical synthetic procedure *in vitro* and has been shown to occur, in the case of *O*-methyl serotonin and acetaldehyde, under physiological conditions (McIsaac, 1961b). The observations that these latter compounds are indeed psychotomimetic in man (see Section II,E) make the repeated failure to observe their presence in normal or abnormal human pineal preparations a disappointment. A similar invocation of biochemical mechanisms has been promoted for the activity of α -methyl amphetamines that have not been observed in their phenethylamine counterparts. The presence of a methyl group hindering the primary amine is well known to inhibit the effectiveness of the monoamine oxidase enzyme system usually involved in deamination, and, indeed, simple compounds such as amphetamine are excreted in part unchanged whereas the parent phenethylamine is completely metabolized and inactivated. Yet mescaline is a phenethylamine that is apparently not an effective substrate for the MAO system, and further, the presence of the α -ethyl group, rather than maintaining the increased psychotomimetic

activity of the α -methyl over the unmethylated homolog, actually decreases it. The relationship of epinephrine to adrenochrome has been discussed, but has not been a satisfactory demonstration of the effectiveness of the latter compound in humans, nor a demonstration of its presence in either mentally sound or mentally disturbed subjects.

An entirely separate approach to the attempt to explain the actions of these compounds in man has been to inquire into their physical properties and the possible ways in which these might influence absorptivity or membrane interaction. Most of the known psychotomimetic drugs are aromatic compounds, and in almost all of these the aromatic ring is quite electron-rich. Aromatic properties such as molecular orbital densities (Snyder and Merrill, 1965; Kang and Green, 1970), ultraviolet absorptivity phenomena (Bailey and Verner, 1972b), fluorescence (Antun *et al.*, 1971), or strength of charge-transfer complexes (Sung and Parker, 1972) have been correlated with known psychotomimetic potencies. Recently, strong arguments have been made to support a serotonin receptor as a site of action. The chemical similarities between the indolic psychotomimetic drugs and serotonin are apparent, but some successful studies of cross-tolerance (*vide* the review by Brawley and Duffield, 1972) suggest that chemically unrelated drugs may also act here. The nature of drug-receptor interaction has been explored (Berridge and Prince, 1974) and employed in the ranking of known psychotomimetic agents (Dyer and Grant, 1973; Dyer *et al.*, 1973). In all cases, anomalous compounds exist which must be apologized for to allow a good correlation to remain. Yet these all permit prediction of biological activity of unexplored chemicals, and these hypotheses cannot be judged until such trials are made.

A tangent to the search for the mechanism of action of the psychotomimetics in man is the search for the capacity of their generation in the intact individual, regardless of their mechanism of action, as a possible contribution to mental illness. The roles of melatonin-to-carboline and epinephrine-to-adrenochrome conversion have already been mentioned as being unobserved as of the present. However, in the area of *in vivo* biochemistry, the various processes of methylation (and possible demethylation) are well established and have been found to apply to the area of the psychotomimetics. Enzymes exist in rabbit lung (Axelrod, 1961), in rat and human brain (Saavedra and Axelrod, 1972), and in human blood (Wyatt *et al.*, 1973b) for the *N*-methylation of tryptamine to *N*-monomethyltryptamine and to the well-established psychotomimetic, *N,N*-dimethyltryptamine (DMT, see Section II,D). In fact, DMT has been observed as a component of the urine of schizophrenic patients under monoamine oxidase inhibitor treatment (Tanimukai *et al.*, 1970), and the provision of tryptophan (a tryptamine precursor) and methionine (a methyl group source) has been shown to exaggerate the symptoms presented by schizophrenic patients (Pollin, *et al.* 1961). These

biochemical transformations within the brain involve methyltransferase systems effective only on indole amines (Morgan and Mandell, 1969), but similar *O*-methyltransferases are intimately involved in the metabolism of the several compounds in the dopamine-norepinephrine-epinephrine metabolic pathway. Dimethoxyphenethylamine has been discussed earlier and represents a typical convergence structure although it is not established either as a normal metabolite or as a psychotomimetic drug. Nonetheless, most psychotomimetic compounds related to the phenethylamines are *O*-methyl ethers and are known to be able to be demethylated *in vivo* (Sargent *et al.*, 1967), just as the catecholamine family is known to be readily *O*-methylated *in vivo* (Axelrod, 1966). There is widespread interest in 6-hydroxydopamine (CXXV) because it is a biologically producible oxidation product of



dopamine, an extremely effective sympatholytic (Malmfors and Thoenen, 1971) and bears a strong chemical resemblance to the active trimethoxyamphetamine [TMA-2, (LXIII)]. These *O*-methylation exchange reactions have also been shown to have disruptive effects on mental patients (Hall *et al.*, 1969). It seems apparent that the metabolic catabolism within the norepinephrine family of sympathomimetic neurotransmitters will eventually intersect with the anabolic transformations found within the mescaline family of psychotomimetics and that some structure common to both will become apparent as a possible natural neuroleptic agent.

IV. MEDICAL APPLICATIONS AND HAZARDS

The earliest application of the psychotomimetic drugs in the area of medical science involved a definition and description of the "model psychosis." One of the earliest rationalizations for research in this pharmacological area was the thesis that the intoxication exhibited by any of the psychotomimetic drugs was a clinically valid reproduction of the schizophrenic state. This clinical enthusiastic portrayal was gradually felt to be inadequate from the practitioner's point of view, and it fell out of favor in experimental psychiatric circles. From the resulting nadir of experimental disapproval the psychotomimetic state has recovered some of its former position and is now considered as an "artificially inducible state" that duplicated an altered state of consciousness similar to those seen in states of spontaneous mental distress. Early in the study of psychotomimetic drugs

psychiatry students were encouraged to undergo an experience with some psychotomimetic drug since it was felt that they would be more sympathetic to the trials of their patients.

A euphemism that has come into popular usage in this area of medical practice is the use of a drug "as an adjunct to psychotherapy." Within psychotherapy there is a rich value given to anything that can release and expose any personal information in the hidden history of the patient. Most of these drugs, without question, release the reservations that maintain privacy over such information and thus allow a free exchange of communication. Hoffman has described the psychotherapeutic values of these psychotomimetic drugs in the following terms (Hofmann, 1971):

1. They are able to release the patient from his autistic fixation and isolation by shattering and transforming his customary setting. As a result, the patient can obtain a more satisfactory relationship with the therapist.
2. Following the general psychic activation elicited by these drugs the resistance of the ego disappears, and forgotten or repressed memories may be evoked. Even experiences of early childhood are often remembered. This is of major importance for the success of psychotherapy, particularly when the experiences concerned are those which have led to psychic trauma.

A large number of the research papers that have recently appeared involving the psychotomimetic drugs have appeared employed under the phrase, "psychotherapeutic adjuncts." These are studies of drug-induced increased rapport within the constrictive framework of analytical therapy. It would appear that it shall only be under this umbrella that any psychiatric research shall be conducted with the psychotomimetic drugs.

There have been a number of reported studies of the therapeutic use of the psychotomimetic drugs in cases of alcoholism. The rationale to this approach has been that of shock therapy, that the dramatic, inescapable insights resulting from an intense LSD experience might encourage the patient to review his drinking problem. There have been literally dozens of such investigations since the first trials in 1953, and at present it appears that the overall results are disappointing. A less vigorous approach employing modest amounts of DPT, to facilitate communication with the patient rather than to overwhelm him, appears to have promise (Soskin *et al.*, 1973; Grof *et al.*, 1973). There has been a recent summary of this medical application (Abuzzahab and Anderson, 1971).

Another area of medical research involving the use of psychotomimetic drugs has been in the treatment of the terminally ill patient. A number of drugs have been explored in this application, including LSD, MDA, and the alkyltryptamines. In some instances there has been relief from otherwise

intractable pain, a result of the depersonalization, the out-of-bodyness that can be a property of a psychotomimetic episode. This is, of course, at best a temporary measure. More dramatic has been the relief from the fear of dying. Needless to say, not only is there a medical controversy in this application, but the ethical and religious problems raised are complex. Nonetheless, there is limited but enthusiastic inquiry being made in this direction in a number of hospital laboratories.

A most promising, but unfortunately now largely neglected, area of research has been on the effects of some of the psychotomimetic drugs on pre-adolescent schizophrenic and autistic children (Bender, 1970). Bender found that the chronic application of modest dosages of LSD to her young patients decreased the fantasies and bizarre behavior patterns, and generated an insightful and realistic attitude toward their environment. There were none of the hallucinatory or untoward responses known from adult usage, but then there had been a gradual building up of dose levels in most cases, and the subjects may have become tolerant to these latter effects. Also in the area of medical research, mention must be made of the work of Fischer and co-workers employing psilocybin as an exploratory agent in the study of the sense modalities of man (Fischer *et al.*, 1969, 1970; Hill *et al.*, 1969; Hill and Fischer, 1970).

There have been many reports over the last few years that give weight to the possible hazards to be associated with the use of the psychotomimetic drugs. In most instances these problems are real and are properly studied so that the risks involved in a medical application can be evaluated against the potential values. However, in this area of research, as in many other areas that have become charged with social and political overtones, there is an unfortunate enthusiasm with some researchers to search only for negative findings, to emphasize hazards out of context in the hope that such statements might dissuade the potential drug user from exploration with these chemicals.

At the behavioral level, one of the most widely observed complications of psychotomimetic drug use is the generation of an extended psychotic state. It is felt that in most of such instances there was a preexisting instability and that the function of the drug was that of precipitant. A closely related phenomenon is the "flashback." This term refers to the spontaneous recurrence of some aspect of the intoxication syndrome, at a time when there is no exposure to the drug in question. The fact that both phenomena (the extended or the short-term unstable state) can occur without the use of drugs at all, and that they are not observed in clinical studies with these compounds, suggest that at most, the psychotomimetic drug serves a catalytic role. However, these points do emphasize the need of care in the selection of experimental subjects. With chronic usage of psychotomimetic drugs, very little is known factually since there have been no scientifically controlled studies whatsoever. Such observations as have been made have come from sociological studies in

groups where both the drug identity and history are undocumentable. A term has come into medical parlance, the "amotivational syndrome," to describe a listless and indifferent state that has occasionally been associated with people in the drug subculture. As is so frequently the case, it is difficult to determine if this attitude resulted from involvement in drugs, or might in fact have contributed to just this involvement. These unanswered questions are as much sociological as medical.

At the biochemical level, there have been serious questions raised concerning chromosome damage and teratogenic potential. In 1967 several reports appeared (Cohen *et al.*, 1967a,b) that suggested a connection between LSD use and chromosome damage. There followed a cascade of reports, some confirming and some failing to confirm these findings. With regard to embryonic development, there are a number of clear-cut cases of LSD-induced teratogenesis in experimental animals (Alexander *et al.*, 1967; Auerbach and Rugowski, 1967). A search within human populations for evidence of corresponding effects through increased spontaneous abortion rate or high incidence of fetal malformation has yielded inconclusive evidence. These observations both as to preconceptual (chromosome) and post-conceptual (teratogenic) hazard have been thoroughly reviewed (Dishotsky *et al.*, 1971) and the following generalities seem to be valid, at least for LSD. The drug is unlikely to be mutagenic in any concentration encountered in human experimentation, but there may be a slightly increased chance of birth defects associated with LSD usage during pregnancy. The admonition concerning the use of any drug during the first trimester of pregnancy is still excellent advice.

Unfortunately, research into the possible medical utility of the psychotomimetic drugs is currently under drastic curtailment for a number of reasons. Within the medical community there is general feeling that these chemicals, by their very nature, cannot be used beneficially. It follows that all experimental studies are therefore improper. This attitude is reflected in the structure of current legislation, wherein all of the recognized abusable psychotomimetic drugs are listed in Schedule I of the Controlled Substances Act. This section contains only those drugs that have a high potential for abuse, that lack evidence of safety in use, or that have no currently accepted medical use in treatment. Although the structure of the law permits research with these materials, there is no question but that the requirements of approved research protocols and associated paperwork has had a chilling effect. As an example of these complexities, the prime supplier of LSD, Sandoz Laboratories, has consigned its inventory to the National Institute of Mental Health, and this group is now the only legal source of the drug. And here again there are requirements of research approval.

Although there may be no legal synthesis of LSD and other related drugs, there is a broad structure of illegal drug supply prompted by the demands of

a steadily growing popularity of the use of such drugs. Over the last 10 years there has been an unprecedented upsurge of curiosity and participation concerning psychotomimetic drugs. The exact reasons and causes are difficult to assign, but the evidence is clear. Whereas LSD and mescaline were once the exclusive province of scientific, academic, and literary circles, they have been catapulted into wide recognition and broad popularity. The use of marijuana has become so widespread that it is not even considered as a drug with many in the younger generation. There has been a flood of writings on consciousness alteration usually with the involvement of some psychotomimetic drug. The concept of "psychedelic" has pervaded our society—in color, in sound, and in life-style—and the association of this with drug usage is inescapable.

And where there is a market, there is a supply. There has been a development of a chemical sophistication in the illicit underground that is hard to believe. There is a steady flow of publications revealing in complete detail the procedures for the home preparation of one drug or another. Although in many instances there is clearly some illegal drug preparation involved, in many others advantage is taken of the fact that minor modifications of chemistry easily sidestep the specific entries named in the law. And here lies one of the greatest and most subtle of the hazards to be associated with this class of drugs. Not only is there broad misrepresentation of the identities of drugs that are continuously available from such clandestine sources, but also on occasion a new drug appears and is made available to a wide population. And all too often this is a drug that has little, if any, body of pharmacological study associated with it; in fact, it may well be a chemical unknown to the scientific literature. The possibilities of mischief and tragedy are obvious.

This then is the current state, not only of the chemistry but also of the social and medical situation, concerning the psychotomimetic drugs. The tide is still running toward the increased use and abuse of these substances, and the recent strengthening of legal proscriptions seems not to have had its desired effect. Perhaps the problem will level off with a diversion of interests into other areas; perhaps some means will be found to effectively control this drug problem without simply exchanging one drug for another. To sustain the logarithmic explosion of the last decade for yet another would be, without question, detrimental to our society.

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