CHAPTER 3

BASIC PHARMACOLOGY AND EFFECTS

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3.0 INTRODUCTION: WHAT ARE THE HALLUCINOGENIC DRUGS?

This chapter is intended to present an overview of the current knowledge of the hallucinogenic drugs, in a format that will be of value to a readership composed of forensic scientists, prosecution and defense lawyers, law enforcement, pharmacologists, chemists, toxicologists, and other scientists. This review will cover a very narrow area, a small sliver of the immense world of psychopharmacological agents.

A possible alternative title for this chapter could have been "The Psychedelic Drugs," but it will be another 20 years before that word will become acceptable in the text of a technical volume directed towards the scientific community. To many, this word conjures up an image of the 1960s, with its Vietnam war protests, its love-ins, its wildly colored posters and raucous music, and of the drugs that were widely associated with that era. Even today, a third of a century later, the editorial advisers of scientific journals and government granting agencies are loath to use that terminology.

There is a yet older alternative term, "Psychotomimetic Drugs," which is discounted for a different reason. Its etymological origin, the imitation of psychosis, gives an inaccurate description of the effects that are produced. These states may be mysterious, instructive, fascinating, and to some quite frightening, but they are not "crazy" states as one would infer from that name. The nature of the effects of all these drugs was considered pathological a few decades ago, and the transient changes they effected in the experimental subject were seen as disruptive and negative. It was believed at that time that the major value to be obtained from them, as research tools in medicine, was that they allowed the creation of an authentic state of psychosis (of limited duration) in an otherwise normal individual. Their medical research value was, according to the philosophy of those years, that interning psychiatrists, those who would be called upon to treat madness, could get insight into the schizophrenic state.

Some researchers came up with another interpretation of the actions of

these materials, the previously unacknowledged potential for personal inquiry and self-discovery, and what might be called the mystical or spiritual nature of the drug experience. It became apparent to some researchers that these were not simply agents of mental disruption but, rather, potentially valuable research and therapy tools. The psychotomimetic concept gradually disappeared from the literature and is today almost unknown.

There are several newly proposed euphemisms for these drugs, such as "entheogens," "empathogens" or "entactogens" (the finding of God within us, the experience of empathy for others, or the touching of our inner psychic nature); all of these have both rational justifications and avid supporters, but to some extent they are no more than further efforts to avoid the term "psychedelic."

The term "hallucinogen" is, of course, a euphemism as well, but it is one that is, at the moment, medically acceptable. Quite literally, this term should only be used to define drugs that give rise to hallucinations, states wherein the subject is unaware of the fact that what he or she is experiencing is unreal. With rare exceptions, there are no hallucinations observed or reported in the use of the drugs in this review. There are some plants in the Solanaceae family that can produce a mental state that is characterized by a dream-like hypnogogia with an accompanying syndrome of confusion and amnesia, plants and compounds that could be classified with some validity as hallucinogenic agents. Datura, Belladonna, Mandrake, Henbane – all of these are rich in the atropine/scopolamine family of alkaloids that could more rightly be called the drugs of hallucination, and in which amnesia is a major symptom. However, these compounds are not included as part of our coverage. Nor are the anesthetic parasympatholytics such as PCP or ketamine which can consistently produce a delusional, out-of-body state. The word "hallucinogen" is also not correct for the description of this area of pharmacology.

The psychotropic agents described in this chapter lack a proper name that would define a unique collection of drugs that produce an alteration of one's state of consciousness in a generally predictable manner, for a reasonably short period of time, and without any lasting sequelae in most people. No such term exists at the present time. For the purposes of this review, these drugs will be referred to as hallucinogens.

The diversity of pharmacological effects resulting from the use of these drugs has never been acknowledged as deserving the attention of the scientific or medical world. Historically, the Western cultures have viewed these particular forms of intoxication as being somehow demonic. They were expressions of some toxic psychosis produced by the use of a so-called magical or sacred plant, or of some toxin derived from it. A large body of human experience was dismissed as simply being a form of poisoning, either from the plant, or an

active isolate of it, or a synthetic modification of that isolate. What was accepted as a mystical or religious experience by some people was dismissed by others as being some form of blasphemy. Our present medical ethic is that any agents capable of producing such changes of states of consciousness are deemed dangerous to the physical and mental well-being of individuals given the many social and economic side-effects of drug proliferation and use. As such, currently any extensive research for possible scientific and medical benefit is largely not practiced or not held in high regard.

A number of different properties of the hallucinogens have been used in organizing reviews. There is their relationship to specific neurotransmitters, or the subjective nature of the human response to them, or the molecular structure. The neurotransmitter argument is appealing but not completely satisfactory. With the clear and obvious division of the hallucinogenic drugs into two large classes, the phenethylamines and the tryptamines, it is most tempting to view them in relation to the two major neurotransmitters, dopamine and serotonin. These two biochemicals have the structures of a phenethylamine and a tryptamine, respectively. It would be much simpler if those drugs that were phenethylamines invoked the dopaminergic systems, and those that were tryptamines were active through some serotonergic mechanism. The explanation would not only be short but simple in concept. However, there is a terribly complex crossover between drug classes and neuroreceptors, and no easily described relationship is yet apparent. There is certainly no one-to-one correspondence.

Most of the hallucinogenic drugs, be they phenethylamines or tryptamines, are intimately involved as ligands of the serotonin (5-HT) receptors (currently 5-HT_2 is the preferred favorite) in some balance of agonist/antagonist interplay, but the dopamine receptors are involved with many of them as well. Efforts to group them by the known receptor relationship have made no sense when the nature of action or the potency were considered. Arrangements by potency have given a listing that was more like a check-list than a logical progression. Animal behavior ranking, or toxicity measures, were intrinsically faulted in that the experimental animal is not the human subject, and the principal reason for any study of these compounds is to investigate subjective responses reported by people.

All efforts to organize drugs for correlative purposes by these very subjective responses have been unsatisfactory. The qualitative nature of the induced responses are extremely variable from subject to subject, and they have never been brought into a framework that is broadly acceptable. Each person's change of consciousness is unique to him or her, and the efforts to find threads of commonality have been unsuccessful. It is the quantitative measure of response that shows greater consistency.

So, the molecular structures are usually accepted as the basis of organization, and the potency of a drug in humans as the single measure of its efficacy. This review is based upon these two properties. Nine drugs are used as archetypes and shall be the reference starting points for the discussion of the potency and activity of a large collection of related drugs. In short, this is a structure/activity relationship (SAR) review.

The usual presentation format that is seen as an SAR review is a series of tables, with a parent skeleton substituted with numbered Rs, then a listing of the things that the R represents. This is the structure half of the concept of SAR. The activity half is a listing of numerical values such as potency, toxicity, receptor binding kinetics, orbital computations – something that the experimental scientist can use on the "other axis" for plotting his or her own findings with these compounds. The pharmacologist can make an easy correlation between his or her own experimental animal findings and human activity. The neurochemist can evaluate the receptor binding, the effectiveness of a compound as agonist or antagonist, or relate brain regional distribution to central activity.

So the one axis of this correlation is easily defined: it is the chemical structure modified by a cascade of substituents. The other axis is the effectiveness reported in human clinical studies. This is based on a complex set of qualitative actions, which must somehow be reduced to a number that represents potency. There are three major dimensions of quality of action that contribute to this end-number. The nature of the altered state of consciousness can be described as involving intoxication, introspection, and escape. Let me try to give form to each of these parameters of drug effect.

Intoxication can be equated to "getting high." This property brings into play the disinhibition and diffuseness that is familiar to anyone who has become inebriated from consuming too much alcohol. Often, superimposed on this "high" is an amplification of sensory inputs that can be expressed in any of several ways. Visual amplification is often seen, colors may be brighter, or they may be completely new. Changes in the delineation of shapes or edges of objects are often commented upon. Movement of things immobile can be distracting. Unexpected interpretations of the significance of familiar things are common. One may report lights flashing, being enveloped by darkness, or feeling surrounded by chaos. Changes in sound interpretation can occur. These are all part of the intoxication character of the hallucinogenic drug.

Introspection is the phenomenon of "going inside." It is the viewing of one's own psyche as opposed to viewing one's relationship with the external world. The Jungians might refer to it as a dialog with the unconscious. Here, one can have access to early memories, down to and including (according to some analysts) the birth trauma and, according to others, earlier lives. Some of

these compounds can be valuable adjuncts to psychotherapy sessions by allowing the subject to circumvent the denial and fear, allowing a deep acceptance of oneself. Relationships with one's contemporaries, with one's trusted lover, with one's parents or children, are potentially exposed.

Escape is "being out there." The immediate external world and the immediate internal world are both abandoned. A person may feel as if he or she were on some "astral plane" or at some "cosmic level" that makes the acknowledgement of the real world quite unnecessary. This aspect of the state of consciousness change may be perceived as the ultimate escape by the user. Some philosophies call it ecstasy, and others call it death.

Any attempt to categorize the effects of a hallucinogenic drug must reckon with each of these areas: the intoxication, the introspection, and the escape. The need to put a quantitative number on the potency of such a drug is an exercise in weighing and measuring, in an objective way, values that are totally subjective. Any SAR will always be firm and objective as to the "S" (structure), but be necessarily loose and subjective as to the "A" (activity). This chapter is a presentation of the "R" (relationship) between the "S" and "A" properties, using the nine classic hallucinogens and their immediate analogues.

3.1 THE PHENETHYLAMINES

The first of the two major groups of the hallucinogens is called the phenethylamines. These are compounds of extremely simple structure, involving a molecular combination that constitutes a benzene ring (the "phen" composed of carbon and hydrogens atoms), a two carbon chain (the "ethyl," also carbon and hydrogen atoms), and a new atom known as a nitrogen (the amine). So, the phenethylamine system is a ring, attached to a chain, attached to a nitrogen atom (see Figure 3.1).

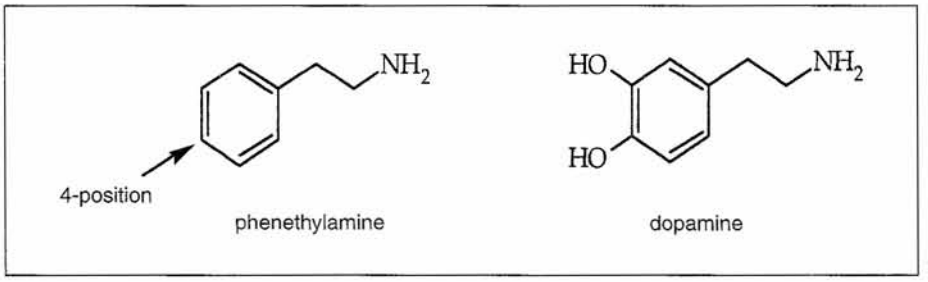


Figure 3.1
Chemical structures of phenethylamine and dopamine

The parent phenethylamine is closely associated with the neurotransmitter dopamine, a vital brain neurotransmitter. It is a phenethylamine with two hydroxyl substituents at the benzene 3- and 4-positions.

3.1.1 MESCALINE ANALOGUES

The first of these classic hallucinogens is indeed a classic in every sense, being the first example of an isolate from a sacred plant that was assigned a chemical structure, and was found to be responsible for the activity of the plant itself. This is the compound mescaline, 3,4,5-trimethoxyphenethylamine seen in Figure 3.2.

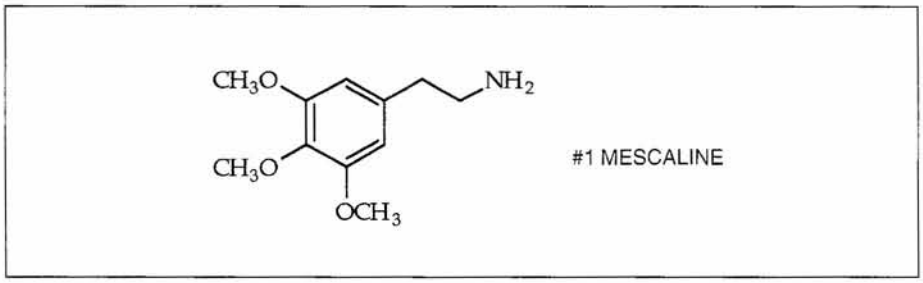
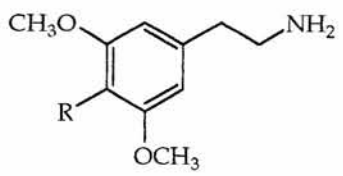


Figure 3.2
Chemical structure of mescaline

The plant from which it was first isolated is a small cactus found in the southwest of the United States and the north of Mexico. Its common name is Peyote, and its botanical binomial is *Anhalonium lewinii* or *Lophophora williamsii.* Its human pharmacology was described in 1896 and its structure was verified by synthesis 23 years later. Although a large number of psychoactive plants have been known since antiquity, this isolated compound remained the only structurally identified hallucinogen until after World War II. The second structurally characterized hallucinogen (LSD) was a synthetic derivative of an ergot alkaloid and was described in the 1940s. In the years since then, there has been a flood of new information; some of it has come from the identification and characterization of plant products, and much of it has come from the methodical synthetic variations of these isolates.

Most of the structural variations of mescaline that have been studied in a clinical environment have had modifications on one or more of the three substituents on the benzene ring. These are organized into two groups, those with variations at the 4-position, and those with other variations.

The 4-position-modified compounds are shown below (Table 3.1) with the nature of the 4-substituent, the common name, the code names, the potency (orally, in man) in milligrams, and the potency relative to mescaline (called mescaline units, or M.U.). In some of these entries (as with other listing later in this chapter), the greater than symbol (>) indicates the highest level that had been evaluated, and that there had been no pharmacological action noted at that level. There is a corresponding (<) usually found in the potency relative to mescaline column, since there can be no placement of relative activity when there is no known activity. This symbol does not imply that the compound



mescaline analogues substituted at the 4-position

Table 3.1

Mescaline analogues substituted at the 4-position

R =	common name	code	potency (mg)	M.U.
CH_3O-	mescaline	M	200–400	1
CH_3CH_2O-	escaline	E	40–60	6
$CH_3(CH_2)_2O$-	proscaline	P	30–60	7
$(CH_3)_2CHO$-	isoproscaline	IP	40–80	5
$CH_3(CH_2)_3O$-	buscaline	B	>150	<1
$(CH_2CH_2)CHCH_2O$-	cyclopropylmethyl	CPM	60–80	5
$CH_2=CHCH_2O$-	allyloxy	AL	20–35	10
$CH_2=C(CH_3)CH_2O$-	methallyloxy	MAL	40–65	6
$CH\equiv CCH_2O$-	propynyloxy	PROPYNYL	>80	<2
CH_3-	4-desoxymescaline	DESOXY	40–120	4
$C_6H_5CH_2CH_2O$-	phenescaline	PE	>150	<1

either is or is not active. This relationship to the action of mescaline has been occasionally called the Mescaline Unit measure within the substituted phenethylamine hallucinogenic drugs, following the fact that mescaline was the earliest known example of this family and the least potent example. Thus, for correlation purposes, all activity values are 1 or greater.

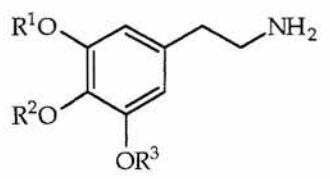
A generality is apparent; there is an increase in potency following an increase in chain length of the aliphatic group attached to the oxygen atom at the 4-position of mescaline, at least to a total of three atoms. The n-butyl homologue has not been reported to be active and no higher homologues have been clinically assayed. The introduction of certain structural parameters into this chain (branching, a small ring, or a double bond) maintains the compound's capability of provoking central activity, but the effect of a triple bond is uncertain. The removal of the oxygen atom from the 4-methoxy group

of mescaline yields the compound DESOXY, which proves to have an activity that is difficult to classify. The removal of additional oxygen atoms yields 3,5-dimethyl-4-methoxyphenethylamine which produces a potent rage response in the cat but which has not been evaluated in man and thus has not been entered in Table 3.1.

Retaining all three of the oxygen atoms in the 3,4,5-positions that are defined by mescaline, but varying the substituent on other than just the 4-position has led to compounds that are no more potent than mescaline, if active at all. This was designed as an indirect way of exploring any pharmacological or metabolic sensitivity that might be displayed by changes to neuroreceptor specificity by simple changes in the steric bulk at these geographic locations. The compound lophophine is not yet known as a natural product despite the trivial name. It is, however, a logical bioprecursor of the several 6-methoxy-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline alkaloids, such as anhalonine, lophophorine and peyophorine, which are natural components of the peyote cactus, *Lophophora williamsii.* (See Table 3.2.)

Table 3.2

Other alkoxylated mescaline homologues



other alkoxylated mescaline homologues

R^1=	R^2=	R^3=	common name	code	potency (mg)	potency M.U.
CH_3O-	- OCH_2O -		lophophine	L	>200	<1
CH_3O-	CH_3O-	CH_3CH_2O-	metaescaline	ME	200–350	1
CH_3O-	CH_3O-	$CH_3(CH_2)_2O$-	metaproscaline	MP	>240	<1
CH_3O-	CH_3CH_2O-	CH_3CH_2O-	asymbescaline	ASB	200–280	1
CH_3CH_2O-	CH_3O-	CH_3CH_2O-	symbescaline	SB	>240	<1
CH_3CH_2O-	CH_3CH_2O-	CH_3CH_2O-	trescaline	TRIS	>240	<1

Some isotopic analogues of mescaline should be mentioned here. One labelled form of mescaline that has been studied in man, is the radioactive isomer with ^{14}C- at the benzylic position. It has been studied as a metabolic tracer. A study was made in humans using three different quantities of mescaline (350mg, 4mg, and 60μg) but with a constant amount of radiocarbon

label. This measured the stochiometry of the amine-oxidase enzyme system that is responsible for the disposition of mescaline in humans. The ratio of the deamination metabolite 3,4,5-trimethoxyphenylacetic acid to unchanged mescaline was a measure of this enzyme's participation capability in this route of metabolism. Two of the five stable deuterated analogues of mescaline have also been studied in humans. The α,α-dideutero mescaline would be compromised by this conversion to the phenylacetic acid, but still could be valuable as a measure of the chiral position sensitivity of metabolism as the separate R and S isomers, but the β,β-dideutero analogue of mescaline has been made and evaluated. Also, the 4-trideuteromescaline (4-D) has been explored as a separate and new drug. The question asked here is whether any of these hydrogen atom positions represent reaction sites that might contribute to the understanding of the mechanism of action of mescaline. In both of these analogues, the observed psychopharmacological activity was in the 200–400mg range in humans, indistinguishable from mescaline itself. The three possible remaining deutero-analogues (the 3,5-dimethoxyl group hexadeuteromescaline, the ring 2,6-dideuteromescaline and the di-alpha-deuteromescaline) are unexplored.

One additional isomer of mescaline and one dimethoxyphenethylamine have been studied in humans. The mescaline isomer is isomescaline (IM) which maintains the three methoxyl groups of mescaline but in effect has the side chain relocated next to one of them (see Figure 3.3).

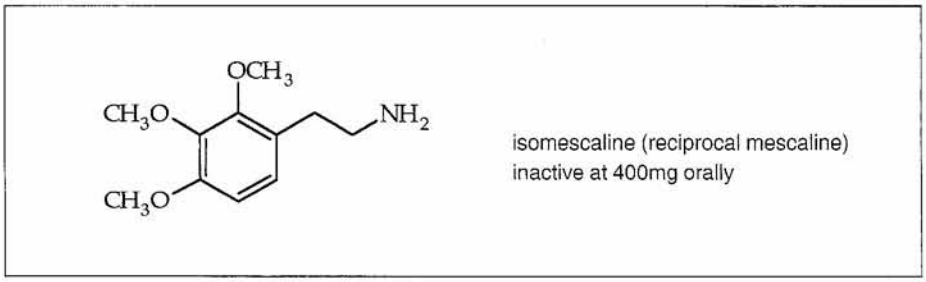


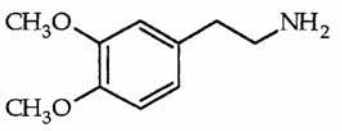
Figure 3.3
Chemical structure of isomescaline

This compound was perhaps the first synthetic mescaline analogue to be studied in humans. A report was published In 1936 stating that it was not active at dosages where mescaline would be fully effective, but that in schizophrenic patients it would intensify the psychotic symptoms that they experienced. To my knowledge, these studies have never been confirmed.

3,4-Dimethoxyphenethylamine (DMPEA) shown in Figure 3.4 is of particular interest in that it has been reported to be present in the urine of schizophrenic patients.

The wide publicity given this so-called "pink spot" inspired a great deal of speculation as to some possible biochemical significance of this compound in

Figure 3.4
Chemical structure of O,O-dimethyldopamine



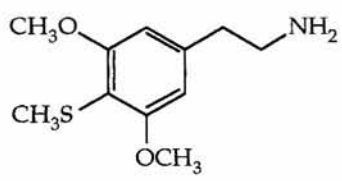
DMPEA, O,O-dimethyldopamine
inactive at 1000mg orally
inactive at 10mg iv

relation to mental illness. Some people could, and some could not confirm its presence in the urine of schizophrenic patients. Some researchers reported the presence of this compound in the urine of normals as well, and other researchers couldn't find it anywhere. Might DMPEA be some metabolic endogenous psychotomimetic, or might it be simply some dietary component? Its close structural resemblance to the neurotransmitter dopamine lent appeal to the causality association. The answer came from the direct assay of the chemical in humans as a possible psychoactive agent; it is not active. Neither is the 3,4-methylenedioxyphenethylamine counterpart, MDPEA, at least at dosages of up to 300mg orally. The 4-ethoxy homologue of DMPEA (MEPEA) has been assayed to 300mg orally, and it also has little if any psychopharmacological activity. The totally unsubstituted analogue with the backbone skeleton that defines this entire section on phenethylamines, is phenethylamine (PEA) itself. It is a natural component of the human nervous system and has received much lay press as a component of chocolate and as a "love drug," but the pharmacological truth is that it is not an active compound in humans. Studies with oral administrations of 1600mg and i.v. injections of up to 50mg have been without observed response.

3.1.2 THIOMESCALINE ANALOGUES

The replacement of the 4-position oxygen of mescaline with a sulfur atom provides the archetype of a second class of hallucinogenic drugs, 4-thiomescaline shown in Figure 3.5. From a purist's point of view, this is a true analogue, in that the relationship between oxygen and sulfur is one of their being neighbors vertically in the periodic table.

Figure 3.5
Chemical structure of thiomescaline



#2 THIOMESCALINE

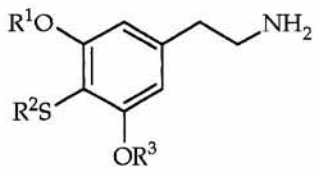
Although thiomescaline (or 4-thiomescaline, 4-TM) is a relatively recent synthetic compound (first prepared and with activity discovered in 1977), its unexpectedly high potency inspired the synthesis and evaluation of perhaps 20 analogues of which nearly half are more potent than mescaline.

The highest levels of activity have been associated with compounds that are homologated at this 4-position. This theme will be played again and again in the discussion of the comparative activities of both the substituted phenethylamines and (later) the substituted amphetamines. It is the structural manipulation of this 4-position, the position opposite to the aliphatic chain, that provides the greatest swings of biological activity as well as affording the highest potency compounds.

Homologation to the four-carbon n-butyl chain maintained a relatively high potency. However, the compounds that represent a further extension of this series to the amyl or higher bid fair to be active but have not yet been reported in the synthetic literature. (See Table 3.3.)

A completely parallel set of compounds has been made with the meta-oxygen of mescaline, rather than the para-oxygen, having been replaced with a sulfur atom. In general this series of isomers is of a somewhat reduced potency when compared with the 4-thio counterparts. An added complexity is the fact that when both the sulfur atom and the ethoxy group are meta to the aliphatic

Table 3.3
4-Thiomescaline homologues



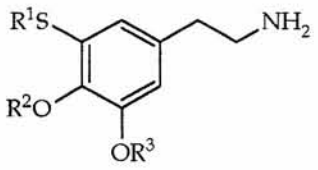
4-thiomescaline homologues

R^1=	R^2=	R^3=	common name	code	potency (mg)	potency M.U.
CH_3-	CH_3-	CH_3-	4-thiomescaline	4-TM	20–40	10
CH_3-	CH_3-	CH_3CH_2-	4-thiometaescaline	4-TME	60–100	4
CH_3-	CH_3CH_2-	CH_3-	4-thioescaline	4-TE	20–30	10
CH_3-	$CH_3(CH_2)_2$-	CH_3-	4-thioproscaline	4-TP	20–25	10
CH_3-	$CH_3(CH_2)_3$-	CH_3-	4-thiobuscaline	4-TB	60–120	4
CH_3-	CH_3CH_2-	CH_3CH_2-	4-thioasymbescaline	4-TASB	60–100	4
CH_3CH_2-	CH_3-	CH_3CH_2-	4-thiosymbescaline	4-TSB	>240	<1
CH_3CH_2-	CH_3CH_2-	CH_3CH_2-	4-thiotrescaline	4-T-TRIS	>200	<1

chain, there are two possible isomers that can exist. All such isomers have been made, and the findings of their evaluation are shown below. One additional note: two of the given weights are preceded by an approximate symbol (~). This is not an indication that the weight of material administered is unknown, but that there were indeed effects produced by these compounds but they could not correctly be classified as hallucinogenic. The reports of 3-TASB indicate a strong adrenergic component with extensive stimulation. Those of 5-TASB suggest some neurological hyperactivity and extended physical malaise.

Table 3.4

3-Thiomescaline homologues



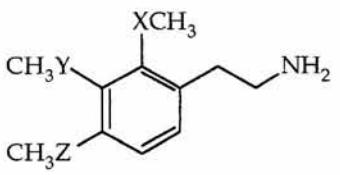
3-thiomescaline homologues

R^1=	R^2=	R^3=	common name	code	potency (mg)	potency M.U.
CH_3-	CH_3-	CH_3-	3>thiomescaline	3-TM	60–100	4
CH_3-	CH_3CH_2-	CH_3-	3-thioescaline	3-TE	60–80	5
CH_3CH_2-	CH_3-	CH_3-	3-thiometaescaline	3-TME	60-100	4
CH_3-	CH_3-	CH_3CH_2-	5-thiometaescaline	5-TME	>200	<1
CH_3CH_2-	CH_3-	CH_3CH_2-	3-thiosymbescaline	3-TSB	>200	<1
CH_3CH_2-	CH_3CH_2-	CH_3-	3-thioasymbescaline	3-TASB	~160	<1
CH_3-	CH_3CH_2-	CH_3CH_2-	5-thioasymbescaline	5-TASB	~160	<1
CH_3CH_2-	CH_3CH_2-	CH_3CH_2-	3-thiotrescaline	3-T-TRIS	>160	<1

As neither of these effects are mescaline-related, the potency × mescaline column is proper at <1.

There are three possible sulfur analogues of isomescaline and all three have been synthesized and assayed. None have the action of mescaline, which is surprising considering the several-fold enhancement of potency that usually accompanies the replacement of an oxygen atom with a sulfur atom. (See Table 3.5.)

This lends additional weight to the intrinsic inactivity of the parent, isomescaline.



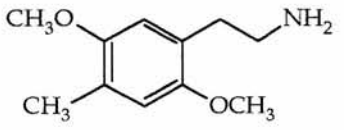
thioisomescaline isomers

X=	Y=	Z=	common name	code	potency (mg)	potency M.U.
S	O	O	2-thioisomescaline	2-TIM	>240	<1
O	S	O	3-thioisomescaline	3-TIM	>240	<1
O	O	S	4-thioisomescaline	4-TIM	>160	<1

Table 3.5
Thioisomescaline isomers

3.1.3 2,5-DIMETHOXY-4-METHYLPHENETHYLAMINE (2C-D) ANALOGUES

All of the above described compounds have the basic ring orientation of three vicinal oxygens (or their sulfur analogues). Mescaline has this adjacency pattern, and it is one of the two patterns that have been widely studied as hallucinogens. The second is the so-called 2,4,5-trisubstitution arrangement. The prototype for this orientation is the 2-carbon homologue of DOM shown in Figure 3.6 and discussed later under 3.1.6).



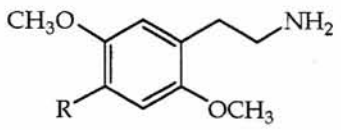
#3 2C-D (LE-25)

Figure 3.6
Chemical structure of 2,5-dimethoxy-4-methylphenethylamine

This is the first of a large number of 2C compounds, so named for the fact that they have the 2-carbon chain of the phenethylamine. The following letter has generally been chosen to reflect either the substituent at the 4-position, or the parent from which it had been derived.

This reference compound, 2C-D, is the simplest of the entire series. It is of relatively low potency relative to many examples in this group, but it has two properties that call for special comment.

Table 3.6
2C-D and its 4-alkyl homologues



2C-D and its 4-alkyl homologues

R=	common name	code	potency (mg)	potency M.U.
H-	2,5-DMPEA	2C-H	?	
CH_3-	4-methyl-2,5-DMPEA	2C-D (LE-25)	20–60	8
CH_3CH_2-	4-ethyl-2,5-DMPEA	2C-E	10–15	24
$CH_3CH_2CH_2$-	4-propyl-2,5-DMPEA	2C-P	6–10	40

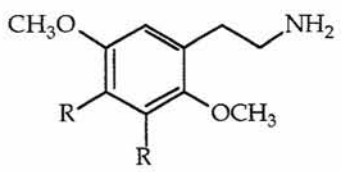
It has been very successfully explored in clinical trials in Germany under the name of LE-25, as an adjunct to psychotherapy. Some of the dosage regimens there were quite high (100 or more milligrams) but in its evaluation as a hallucinogenic drug, the lower range was published. The proteo-homologue, 2,5-dimethoxyphenethylamine (2,5-DMPEA), remains unassayed. Its major interest is the fact that it can play the role of a starting material (both synthetically and logically) for many of these surprisingly potent phenethylamines. It is generally believed that it would have little activity orally, due to its potential deamination by the hepatic monoamine oxidase systems, but this is difficult to rationalize in light of the extraordinarily high potency of many of the 4-substituted analogues which should be equally effective substrates.

As the chain lengthens, the potency increases but there is a change in the qualitative nature of the induced effects. The ethyl homologue, 2C-E, is a most extraordinary drug, evoking for many subjects a dramatic recall of forgotten events, with a remarkable ability to interpret and analyze them. The alteration of one's state of consciousness is dramatic, often quite frightening, and yet consistently allowing a complete recall. The extension by just a single carbon atom more, to give 2C-P, produces a yet more potent compound but one which is physically uncomfortable and considered to be unpleasant. No further homologation has been studied.

A completely separate type of homologation has been reported, with two groups located between the methoxyl groups of 2,5-DMPEA. This family has been explored along with the 3-carbon homologue amphetamines, and they have proven to be exceptionally potent compounds.

Table 3.7

3,4-Dialkyl homologues of 2C-D



3,4-dialkyl homologues of 2C-D

R	R	common name	code	potency (mg)	potency M.U.
CH_3-	CH_3-	3,4-dimethyl-2,5-DMPEA	2C-G	20–35	10
-$CH_2CH_2CH_2$-		3,4-trimethylene-2,5-DMPEA	2C-G-3	16–25	14
-$CH_2(CH_2)_2CH_2$-		3,4-tetramethylene-2,5-DMPEA	2C-G-4	?	
-$CH(CH_2)_2CH$- CH_2		norbornyl-2,5-DMPEA	2C-G-5	10–16	24
-CH=CH-CH=CH-		1,4-dimethoxynaphthyl-2-ethylamine	2C-G-N	20–40	10

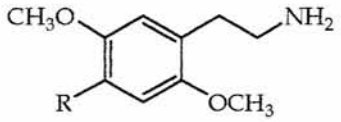
The tetramethylene homologue is entered here because it has been synthesized but the clinical study of it has not yet been completed. A great number of fascinating analogues are suggested by this collection, such as the 3,4-diethyl (or the two distinct methyl ethyl isomers) or multiple ring systems of the norbornyl type with heteroatoms in them. Synthetically, these should present few problems.

An exceptionally rich family of compounds has come from the substitution of groups at the 4-position of 2C-D which are not simple alkyl homologues. There seems to be little if any correlation between either the size or the electronegativity of the group, and the potency of the resulting phenethylamine. The iodine-analogue, one of the most potent of the series, has proven to be a valuable ligand for positron emission tomography, as it has been substituted with radio iodine and, as is so rarely the case in receptor-site studies of labelled ligands, the heavy atom here is intrinsic to the activity of the molecule. An enigma is 2,4,5-trimethoxyphenethylamine, a positional isomer of mescaline (the 3,4,5-counterpart). It is devoid of activity even at doses that with mescaline would be fully effective. (See Table 3.8.)

And yet, the addition of an alpha-methyl group to mescaline (a move that presumably protects it from oxidative deamination) only doubles the potency, whereas the same protective modification of this "inactive" isomer (to give the

Table 3.8

4-Substituted analogues of 2C-D



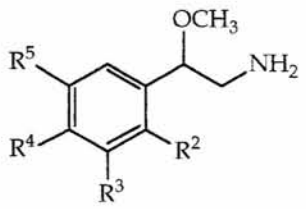
4-substituted analogues of 2C-D

R	common name	code	potency (mg)	potency M.U.
F-	4-fluoro-2.5-DMPEA	2C-F	>250	<1
Cl-	4-chloro-2,5-DMPEA	2C-C	20–40	10
Br-	4-bromo-2,5-DMPEA	2C-B	12–24	16
I-	4-iodo-2,5-DMPEA	2C-I	14–22	16
CH_3O-	2,4,5-trimethoxy-PEA	TMPEA	>300	<1
NO_2-	4-nitro-2,5-DMPEA	2C-N	100–150	2
$(CH_3)_2CHO$-	4-isopropoxy-DMPEA	2C-O-4	>60	?
CH_3S-	4-methylthio-DMPEA	2C-T	60–100	4
CH_3Se-	4-methylseleno-DMPEA	2C-SE	~100	~3

compound TMA-2), there is an increase of more than an order of magnitude. The 4-methylthio analogue (2C-T) is included here for comparative purposes. but it is the starting point for a large family to be discussed below.

Another location for structural variation is the β-position on the aliphatic side chain where one might place a methoxyl group. This is the position of the hydroxyl group on the neurotransmitters norepinephrine and epinephrine (noradrenaline and adrenaline) as well as on the natural phenethylamine ephedrine. This collection has been referred to as the BOX family. (See Table 3.9.)

Three O-demethyl compounds in this BOX group have been clinicall studied in humans. The β-hydroxy analogue of BOD is 4-methyl-2,5-dimethoxyphenyl-β-ethanolamine (BOHD). It has a side-effect of causing a precipitous drop of both systolic and diastolic blood pressure. At an ora dosage of 50mg a drop of 36mm was observed and no further assays were conducted with this compound. There were no indications of hallucinogeni activity. The analogous derivative of BOH is 3,4-methylenedioxyphenyl-β-ethanolamine (BOHH). In the early literature it is occasionally referred to b the name MDE but this code has now been exclusively assigned to the N-eth



phenethylamines substituted with a β-methoxy group

R2	R3	R4	R5	common name	code	potency (mg)	potency M.U.
CH_3O-	H-	Br-	CH_3O-	4-bromo-2,5-dimethoxyphenyl-M[a]	BOB	10–20	20
CH_3O-	H-	CH_3	CH_3O-	4-methyl-2,5-dimethoxyphenyl-M	BOD	15–25	15
H-	-OCH_2O-		H-	3,4-methylenedioxyphenyl-M	BOH	80–120	3
H-	CH_3O-	CH_3O-	CH_3O-	3,4,5-trimethoxyphenyl-M	BOM	>200	<1

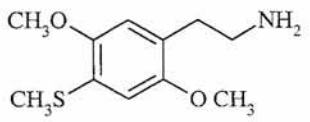
[a] "M" stands for β-methoxyethylamine

Table 3.9

Phenethylamines substituted with a β-methoxy group

homologue of MDMA. It is inactive at an oral dosage of 100mg. The corresponding dimethoxy compound (3,4-dimethoxyphenyl-β-ethanolamine, DME) has been studied at doses of up to 115mg and is without psychoactivity.

3.1.4 2,5-DIMETHOXY-4-METHYLTHIOPHENETHYLAMINE (2C-T) ANALOGUES



#4 2C-T

Figure 3.7

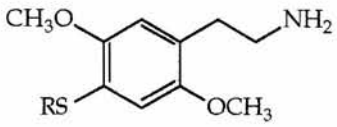
Chemical structure of 2,5-dimethoxy-4-methylthio-phenethylamine

This modestly active methylthio-analogue of 2C-D has proven to be a rewarding starting point for an extensive study of sulfur-contained homologues and analogues. These are presented in a format of increasing mass and complexity of the substituents; the number suffix of the code name simply reflects the sequence of synthesis. (See Table 3.10.)

The optimum alkyl substitution seems to be two to three carbons, with 2C-T-2, 2C-T-4 and 2C-T-7 being both potent and similar in effect to LSD. The >30mg dosage indicated for 2C-T-15 indicates that this level showed some suggestion of activity, but the final active range had not yet been determined.

Table 3.10

Chemical structures of 2C-T and its alkyl and heteroalkyl analogues



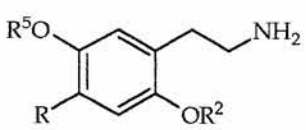
alkyl homologues and heteroalkyl analogues of 2C-T

R	common name	code	potency (mg)	potency M.U.
CH_3-	4-methylthio-2,5-DMPEA	2C-T	60–100	4
CH_3CH_2-	4-ethylthio-2,5-DMPEA	2C-T-2	12–25	16
$CH_3(CH_2)_2$-	4-n-propylthio-2,5-DMPEA	2C-T-7	10–30	15
$(CH_3)_2CH$-	4-i-propylthio-2,5-DMPEA	2C-T-4	8–20	20
s-C_4H_9-	4-s-butylthio-2,5-DMPEA	2C-T-17	60–100	4
t-C_4H_9-	4-t-butylthio-2,5-DMPEA	2C-T-9	60–100	4
c-C_3H_5-	4-cyclopropylthio-2,5-DMPEA	2C-T-15	>30	?
c-$C_3H_5CH_2$-	4-cyclopropylmethylthio-2,5-DMPEA	2C-T-8	30–50	8
$CH_3O(CH_2)_2$-	4-(2-methoxyethyl)thio-2,5-DMPEA	2C-T-13	25–40	10
FCH_2CH_2-	4-(2-fluoroethyl)thio-2,5-DMPEA	2C-T-21	8–12	30
	—— with an N-hydroxy substitution ——			
CH_3CH_2-	4-ethylthio-N-hydroxy-DMPEA	HOT-2	10–18	24
$CH_3(CH_2)_2$-	4-n-propylthio-N-hydroxy-DMPEA	HOT-7	15–25	14
s-C_4H_9-	4-s-butyl-N-hydroxy-DMPEA	HOT-17	70–120	3

The final compound of the first group on this list deserves some additional comment. One, it is a novelty, being the first hallucinogenic material with six different elements in it (C, H, N, O, S and F), and as the hydrochloride salt, that number becomes seven. Secondly, it carries an ideal atom for radiolabelling the material for PET scanning. The introduction of ^{18}F should be readily achieved, and the drug might well be a potent ligand for the serotonin receptors involved with the action of the hallucinogenic drugs. And lastly, the presence of the fluorine atom at the end of the aliphatic chain suggests the possibility of lipophobic and hydrophobic chain terminals such as β,β,β-trifluoroethylthio-2,5-DMPEA. These are discussed below with the amphetamine homologues, and are presently completely unexplored.

The small second group on this list is from a small study of psychoactive hydroxylamines. The generic family name is HOT for "N-HydrOxyThio" and the assigned serial number corresponds to those of the corresponding 2C-T compound. The hallucinogenic potency of these analogues is very similar to the primary -NH2 counterparts. The 2,4,6-substituted positional isomer of 2C-T-4, is, 4-isopropylthio-2,6-dimethoxyphenethylamine (ψ-2C-T-4). In preliminary evaluations, it appears to be an active compound in the 10–20 milligrams range, but more studies are needed to firmly establish the dosage and the nature of the intoxication produced.

I learned of a remarkable study that had been methodically carried out but never published, in which the methoxy groups of a number of the 2C- family were replaced with ethoxy groups. As there are two methoxy groups, there are three possible homologues: the 2-methoxy-, the 5-methoxy- or both methoxys can be lengthened. These compounds were called the TWEETIO compounds in a humorous way of pronouncing the simplest of them, a compound with an ethoxy (or EtO-) group at the 2-position, vis., 2-EtO-something. (See Table 3.11.)



the TWEETIO homologues of several 2C- compounds

R	dosage (parent)	R^2	R^5	code	trial dose (mg)	comments of trial
Br	12–24	Et-	Me-	2CB-2-ETO	15	30–50 prolongs action
		Et-	Et-	2CB-DI-ETO	>55	restless sleep, only
CH_3-	20–60	Et-	Me-	2CD-2-ETO	60	intimate, no intox, 4 hrs
		Me-	Et-	2CD-5-ETO	50	12 hour duration
		Et-	Et-	2CD-DI-ETO	>55	mild, 4 hr duration
C_2H_5-	10–15	Me-	Et-	2CE-5-ETO	15	16–24 hr duration
I	14–22	Et-	Me-	2CI-2-ETO	5	50 mg longer duration only
CH_3S-	60–100	Et-	Me-	2CT-2-ETO	50	mild, 4 hr duration
		Me-	Et-	2CT-5-ETO	30	15 hr duration
EtS-	12–25	Et-	Me-	2CT2-2-ETO	50	9 hr duration
		Me-	Et-	2CT2-5-ETO	20	16 hr duration
		Et-	Et-	2CT2-DI-ETO	50	only longer with higher dose
iPrS-	8–20	Et-	Me-	2CT4-2-ETO	25	dosage affects duration only
PrS-	10–30	Et-	Me-	2CT7-2-ETO	20	fast, out at 5 hrs

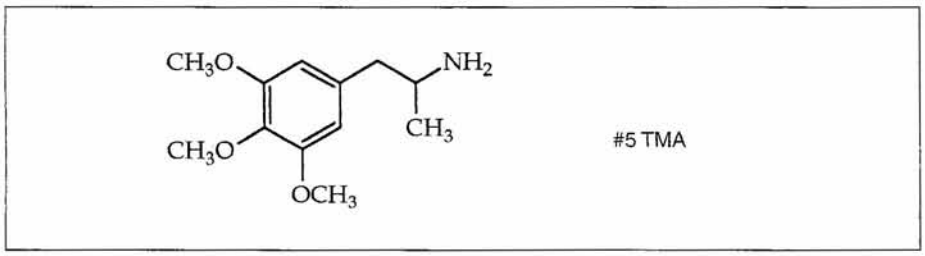
Table 3.11
The TWEETIO homologues of several 2C-compounds

In most of these listings the human studies involved only two subjects, never more than six. For this reason, ranges are not given, only typical dosages, and the short statement of effect is simply a terse abstract of the reports that were written. Some generalities are possible. Homologation at the 2-position appears to lead to a shorter duration and a decrease in potency. Homologation at the 5-position can enhance the potency and increase the duration to a remarkable degree. With 2CE-5-ETO for example, the administration of Valium or Halcion allowed sleep, but did not abort the long duration of action. Longer ether chains such as the propoxy groups have not been synthesized as yet.

3.1.5 3,4,5-TRIMETHOXYAMPHETAMINE (TMA) ANALOGUES

The first synthetic modification of the mescaline molecule that was found to be hallucinogenic was the alpha-methyl homologue, 3,4,5-trimethoxyamphetamine. This simple structural manipulation, the adding of a methyl group adjacent to the amine function, is a well documented change that in general protects the amine from metabolic deamination.

Figure 3.8
Chemical structure of TMA



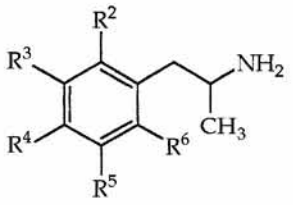
The prototype for this change was the design of amphetamine itself as a metabolically stable stimulant from the extremely labile compound phenethylamine. With very few exceptions, the alpha-methyl homologues of the above-described phenethylamines are more potent and longer-lived in the human subject. From the historic view, the amphetamine derivative was discovered first in most cases, but the more logical structure-activity presentation in this review calls for the progression from the two-carbon phenethylamine to the three-carbon amphetamine. In the case of TMA, a continuous extension of this alpha-group led to the alpha-ethyl homologue alpha-ethylmescaline (AEM) which showed no human activity at over 200mg, and the longer-chained homologues were not evaluated. This alpha-homologation is discussed below for some of the 2,4,5-trisubstituted analogues.

A large number of positional variations have been explored, based on this prototype. In general, as the number of methoxy groups increases, the character of central action of the drug progresses from that of a stimulant to

that of a hallucinogen, with a trisubstitution pattern being the most effective example of this latter action. And, in general, the most effective locations for the three substituents are in the 2,4,5- or the 2,4,6-orientations. Special attention should be paid to the first entry in the above table, for 4-methoxyamphetamine (4-MA). The earliest clinical studies with this compound were inspired by the frequency with which patients were seen displaying a schizophrenic-like syndrome, that was in fact a consequence of chronic excessive amphetamine use. One of the metabolites of amphetamine in humans is 4-hydroxyamphetamine. (See Table 3.12.)

Table 3.12

Alkoxy analogues of TMA



alkoxy analogues of TMA

R²	R³	R⁴	R⁵	R⁶	common name	code	potency (mg)	potency M.U.
H-	H-	[a]MeO-	H-	H-	4-methoxy-A[b]	4-MA (PMA)	50–80	5
MeO-	H-	MeO-	H-	H-	2,4-dimethoxy-A	2,4-DMA	>60	?
MeO-	H-	H-	MeO-	H-	2,5-dimethoxy-A	2,5-DMA	80–160	2.5
H-	MeO-	MeO-	H-	H-	3,4-dimethoxy-A	3,4-DMA	in 100's	<1
H-	MeO-	MeO-	MeO-	H-	3,4,5-trimethoxy-A	TMA	100–250	1.7
H-	MeO-	[c]EtO-	MeO-	H-	4-ethoxy-3.5-dimethoxy-A	3-CE	30–60	7
H-	MeO-	[d]BzO-	MeO-	H-	4-benzyloxy-3.5-dimethoxy-A	3C-BZ	100–180	2
MeO-	H-	MeO-	MeO-	H-	2,4,5-trimethoxy-A	TMA-2	20–40	10
EtO-	H-	MeO-	MeO-	H-	2-ethoxy-4.5-dimethoxy-A	EMM	>50	?
MeO-	H-	EtO-	MeO-	H-	2,5-dimethoxy-4-ethoxy-A	MEM	20–50	10
MeO-	H-	MeO-	EtO-	H-	2,4-dimethoxy-5-ethoxy-A	MME	~60	~5
MeO-	H-	OEt-	OEt-	H-	4,5-diethoxy-2-methoxy-A	MEE	nt	
EtO-	H-	OMe-	OEt-	H-	2,5-diethoxy-4-methoxy-A	EME	nt	
EtO-	H-	EtO-	MeO-	H-	2,4-diethoxy-5-methoxy-A	EEM	nt	
EtO-	H-	EtO-	EtO-	H-	2,4,5-triethoxy-A	EEE	nt	
MeO-	H-	[e]PrO-	MeO-	H-	2,5-dimethoxy-4-(n)-propoxy-A	MPM	>30	?
MeO-	MeO-	MeO-	H-	H-	2,3,4-trimethoxy-A	TMA-3	>100	?
MeO-	MeO-	H-	MeO-	H-	2,3,5-trimethoxy-A	TMA-4	>80	?
MeO-	MeO-	H-	H-	MeO-	2,3,6-trimethoxy-A	TMA-5	~30	~10
MeO-	H-	MeO-	H-	MeO-	2,4,6-trimethoxy-A	TMA-6	25–50	8
MeO-	MeO-	MeO-	MeO-	H-	2,3,4,5-tetramethoxy-A	TA	>50	?

[a] "Me" represents a methyl group
[b] "A" represents the word amphetamine
[c] "Et" represents an ethyl group
[d] "Bz" represents a benzyl group
[e] "Pr" represents an n-propyl group
"nt" not yet clinically tested in humans

The question was asked that, if 4-MA were metabolized by O-demethylation to this same metabolite, might it be the causative agent for the dementia? 4-MA is indeed metabolized to this hydroxy derivative but there is no evidence that it is psychoactive. But an entirely separate issue has come up, in that there is a

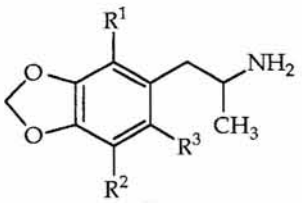
considerable amount of 4-MA (called PMA but distributed as "Ecstasy") is being distributed in the current rave scene, and a number of fatalities have followed its use. At the level of about 1mg/kg (in humans) it is a light hallucinogen with some pressor side-effects. At twice this dosage, there can be a considerable cardiovascular disturbance, and with several of these tablets taken at once (not uncommon in the rave scene) the user can face a lethal crisis.

N-Methylation of primary amines became the structural challenge. If MDA went to MDMA with such beauty, maybe other primary amines would become magical with a similar N-methylamine.

A common analogue of the vicinal dimethoxy structure, found frequently in nature, is the methylenedioxy group. These two substitution patterns are biosynthetically close cousins, and many of the essential oils found in spices and as food fragrances have one or the other of these systems present. Safrole is the cousin of methyleugenol, myristicin of elemicin, and apiole or dill apiole of tetramethoxyallylbenzene. (See Table 3.13.)

Table 3.13

Alkoxy methylenedioxy analogues of TMA



alkoxy methylenedioxy analogues of TMA

R^1	R^2	R^3	common name	code	potency (mg)	potency M.U.
H-	H-	H-	3,4-methylenedioxy-A[a]	MDA	80–160	2.5
CH_3O-	H-	H-	2-methoxy-3,4-methylenedioxy-A	MMDA-3a	20–80	6
H-	CH_3O-	H-	3-methoxy-4,5-methylenedioxy-A	MMDA	100–250	1.7
H-	H-	CH_3O-	2-methoxy-4,5-methylenedioxy-A	MMDA-2	25–50	8
CH_3O-	CH_3O-	H-	2-5-dimethoxy-3,4-methylenedioxy-A	DMMDA	30–75	6
H-	CH_3O-	CH_3O-	2-3-dimethoxy-4,5-methylenedioxy-A	DMMDA-2	>50	?

[a] "A" represents the word amphetamine

This same parallel in structures may be seen in the alkoxylated amphetamine derivatives usually with a small increment of increased potency given to the methylenedioxy example. Efforts to enlarge the methylenedioxy ring by homologation of MMDA and MDA were synthetically achieved, but the hallucinogenic activity was lost. The products (3-methoxy-4,5-ethylenedioxyamphetamine, MEDA, homologue of MMDA, and 3,4-ethylenedioxy-N-methylamphetamine, EDMA or MDMC, homologue of MDA or, more accurately, of MDMA) were not active at 200mg, and so fall in the less-than-mescaline classification. Similarly, the second possible positional isomer of

MMDA-3a is known (4-methoxy-2,3-methylenedioxyamphetamine, MMDA-3b) and has been clinically explored at up to 50mg without any central effects being noted. With the methylenedioxy in that 2,3-orientation, next to the amphetamine chain, two more isomers are possible. The 2,3,5-arrangement has been named MMDA-4 and the 2,3,6-counterpart is known as MMDA-5; no human activity for either compound has been reported in the literature. There cannot be, of course, a MMDA-6 as the 2,4,6 orientation lacks adjacent oxygen atoms.

A large number of nitrogen-substituted homologues of the MDA-related amphetamines have been synthesized and assayed, with listed potencies again compared to mescaline as being the reference standard, and most of them have been found to be relatively inactive. The N-methyl homologue of MDA is MDMA, which turned out to be not a hallucinogen but rather a mild stimulant that produced a most gentle and friendly altered state of consciousness, one that permitted both easy personal interaction and complete recall. It had seen extensive use as a clinical adjunct in psychotherapy, but with its appearance on the street in 1985 under the name of "Ecstasy" or "X," it was placed in Schedule I of the Controlled Substances Act by the Drug Enforcement Administration. It has been only in the last few years that moves to start human research with it again, mostly abroad, have become successful. The other two active members of this subfamily (MDE and MDOH) are very similar to MDA in their qualitative effects. Interestingly, the ring-methyl homologue of MDMA (2,N-dimethyl-4,5-methylenedioxyamphetamine, MADAM-6) is devoid of either stimulant or hallucinogenic activity in humans, at a dosage of 280mg. The corresponding ring-methoxy analogue (N-methyl-2-methoxy-4,5-methylenedioxyamphetamines, METHYL-MMDA-2) can also be viewed as a mono-substituted analogue of MDMA. It has been assayed in humans up to 70 milligrams orally, and is without activity.

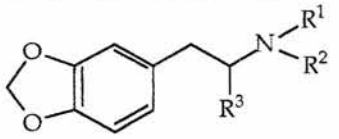
The ethanolamine amide (MDHOET) shows central effects at higher doses that are anesthetic, in the manner of ketamine. (See Table 3.14.)

Of all the compounds of this group that had been assayed for pain suppression in mice, this compound was the most effective. Two phentermine analogues showed some toxicity, and neither had the visual effects of a hallucinogenic drug nor the magic of MDMA. The parent α,α-dimethylhomologue of MDPEA (the α-methyl homologue of MDA) is MDPH and it is of about the same potency as MDA. The N-methyl homologue is MDMP and was virtually inactive at 110mg, and no higher level has yet been explored.

The group of compounds apparent from the ETHYL-J and METHYL-K in the table below speak of a structure activity relation study that was never carried out. The syntheses were straight forward, and the collection of names was clear. The named alkyl group (the METHYL, the ETHYL or the PROPYL) was the

Table 3.14

Nitrogen-substituted homologues and analogues of MDA



nitrogen-substituted homologues and analogues of MDA

R^1	R^2	R^3	common name	code	potency (mg)	potency M.U.
H-	H-	H-	MDPEA[a]	MDPEA	>300	<0.5
H-	H-	Me-	MDA[b]	MDA	80–160	2.5
H-	H-	Et-	α-ethyl-MDPEA	BDB	150–230	1
H-	H-	$(Me)_2$	α,α-dimethyl-MDPEA	MDPH	160–240	1
Me-	H-	Me-	N-methyl-MDA	MDMA[c]	80–150	2.5
Me-	H-	Et-	N-methyl-α-ethyl-MDPEA	MBDB	180–210	1
Me-	H-	Pr-	N-methyl-α-propyl-MDPEA	METHYL-K	>100	<2
Me-	H-	$(Me)_2$	α,α-dimethyl-MDPEA	MDMP	>110	<2
Me-	Me-	Me-	N,N-dimethyl-MDA	MDDM	>150	<1
Me-	HO-	Me-	N-hydroxy-N-methyl-MDA	FLEA	100–160	2
Et-	H-	Me-	N-ethyl-MDA	MDE	100–200	2
Et-	H-	Et-	N,α-diethyl-MDPEA	ETHYL-J	>65	?
Et-	H-	Pr-	N-ethyl-α-propyl-MDPEA	ETHYL-K	>40	?
Pr-	H-	Me-	N-(n)-propyl-MDA	MDPR	>200	<1
iPr-	H-	Me-	N-(i)-propyl-MDA	MDIP	>250	<1
Bu-	H-	Me-	N-(n)-butyl-MDA	MDBU	>40	?
$(C_3H_5)CH_2$-	H-	Me-	N-cyclopropylmethyl-MDA	MDCPM	nt	
Al-	H-	Me-	N-allyl-MDA	MDAL	>180	<1
$CH{\equiv}CCH_2$-	H-	Me-	N-propargyl-MDA	MDPL	>200	<1
$C_6H_5CH_2$-	H-	Me-	N-benzyl-MDA	MDBZ	>150	<1
HO-	H-	Me-	N-hydroxy-MDA	MDOH	100–160	2
MeO-	H-	Me-	N-methoxy-MDA	MDME	>180	<1
$HO(CH_2)_2$-	H-	Me-	N-(β-hydroxyethyl)-MDA	MDHOET	>50	?
$MeO(CH_2)_2$-	H-	Me-	N-(β-methoxyethyl)-MDA	MDMEOET	>180	<1

[a] "MDPEA" represents 3,4-methyleneioxyphenethylamine
[b] "MDA" represents 3,4-methylenedioxyamphetamine
[c] "MDMA" is not hallucinogenic, see text
"nt" Not yet clinically tested in humans.
The BDB and MBDB codes are derived from the exact chemical names for these two compounds, i.e., 1-(1,3-benzodioxol-5-yl)-2-butanamine and N-methyl-1-(1.3-benzodioxol-5-yl)-2-butanamine.
The MDPH and MDMP are codes derived from the commercial names for the molecular skeleton, i.e., 3,4-methylenedioxyphentermine and 3,4-methylenedioxymephentermine.

substituent on the nitrogen atom of the 3,4-methylenedioxyphenethylamine basic skeleton, and the letter employed (the J or the K) representing the α-substituent (the α-H and the α-I were not used, as the indicated molecule already has a trivial code, but the J was the α-ethyl, the K was α-propyl, and so on). All of the synthetic chemistry was easily completed, but the loss of hallucinogenic potency with the heavier substituents quickly discouraged further exploration in people.

Another N-alkyl homologue of these simple amphetamine derivatives merits special mention. PMA was mentioned above as a drug requiring close attention. The N-methyl homologue of this compound has recently been seen in the street trade, first as an impurity in PMA and then as an agent in its own

right. This material, called para-methoxy-methamphetamine or PMMA, is active at something over 100 milligrams, but it still produces cardiovascular stimulation without much virtue as a hallucinogen. Its easy availability may be because it can be made directly by the synthetic procedures used for MDMA, but with the use of the rather innocent anethole (anise camphor) in place of isosafrole which is being closely watched by the government. The corresponding analogue of 2,5-DMA (N-methyl-2,5-dimethoxyamphetamine, DMMA or methyl-DMA) is without human activity at 250mg.

3.1.6 2,5-DIMETHOXY-4-METHYLAMPHETAMINE (DOM) ANALOGUES

Another starting point for the viewing of a family of amphetamine homologues of the phenethylamine family is the drug DOM, or STP as it became known on the street in the 1960s. It is an unusually potent amphetamine derivative that was designed as an analogue of TMA-2. (See Figure 3.9.)

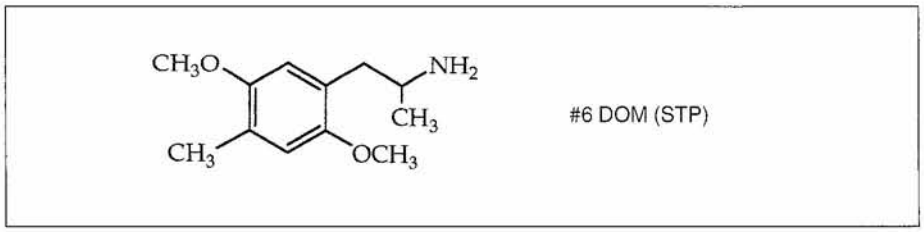


Figure 3.9
Chemical structure of DOM (STP)

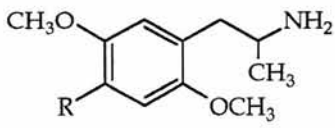
The unusually high potency of TMA-2 was ascribed to the group found at the 4-position, the methoxy group, as indicated by the fact that it was only through homologation at this position that higher potency and hallucinogenic activity were maintained. The replacement of the methoxyl function with a methyl group would interfere with its metabolism, as the methyl group cannot be removed by any obvious hydrolysis scheme. It was believed that if DOM were to act as a receptor agonist and it could not be easily destroyed metabolically, it would be a very potent drug. If it was not intrinsically active but did indeed occupy the receptor, it might well block some endogenous psychotogenic factor, and thus serve as a prophylactic or treatment for spontaneous mental illness. It proved however, to be intrinsically active, and has served as a pilot structure for many analogues.

The first structural variations were changes made on the 4-alkyl group. As it was lengthened, the activity was found to increase, and then it abruptly dropped off. The compounds with longer chain lengths were apparently evaluated simply up to the point where it could be said that the activity was no longer increasing. The one intriguing homologue that lies in the middle of the range of high potencies is the isopropyl isomer, DOIP. In the study that

provided the above values, this isomer was investigated. At dosages of 4 and 10mg, there were substantially no effects. Apparently there are "valid changes in the mental state" in the 20 to 30mg range, but these are not described. In any event it appears that the isopropyl analogue does not compete in potency with the ethyl or the propyl counterparts. The β-fluoroethyl isomer is compelling evidence that the ethyl chain is enough for holding on to full activity, and that there is the potential for making extensive modification at the outer end of that ethyl group. (See Table 3.15.)

Table 3.15

4-Alkyl homologues of DOM



4-alkyl homologues of DOM

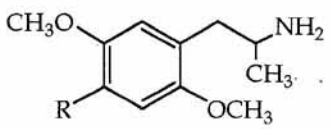
R=	common name	code	potency (mg)	potency M.U.
CH_3-	4-methyl-2,5-dimethoxy-A[a]	DOM	3–10	50
CH_3CH_2-	4-ethyl-2,5-dimethoxy-A	DOET	2.0–6.0	80
$CH_3(CH_2)_2$-	4-(n)-propyl-2,5-dimethoxy-A	DOPR	2.5–5.0	80
$(CH_3)_2CH$-	4-(i)-propyl-2,5-dimethoxy-A	DOIP	>10	?
$CH_3(CH_2)_3$-	4-(n)-butyl-2,5-dimethoxy-A	DOBU	>3	?
$(CH_3)_2CHCH_2$-	4-(i)-butyl-2,5-dimethoxy-A	DOIB	>10	?
$CH_3CH_2CH(CH_3)$-	4-(s)-butyl-2,5-dimethoxy-A	DOSB	>25	?
$(CH_3)_3C$-	4-(t)-butyl-2,5-dimethoxy-A	DOTB	>10	?
$CH_3(CH_2)_4$-	4-(n)-amyl-2,5-dimethoxy-A	DOAM	>10	?
FCH_2CH_2-	4-(β-fluoroethyl)-2,5-dimethoxy-A	DOEF	2.0–3.5	100

[a] "A" represents the word amphetamine

Considering this remarkably potent compound along with the expectedly potent β-fluoroethylthio- compound 2C-T-21 mentioned above, one could speculate that a small lipophobic (and hydrophobic) atom at the end of a short aliphatic (and thus lipophilic) chain in the appropriate receptor site makes for a remarkable agonist. If this is valid, what might be the activity of the rather easily made analogues with groups such as CHF_2CH_2- or CF_3CH_2- in these positions?

Two homologues, one ring analogue, and two heterocyclic structural modifications of DOM warrant mention. Neither the N-methyl homologue (N,4-dimethyl-2,5-dimethoxyamphetamine, BEATRICE) nor the 5-ethoxy homologue (5-ethoxy-2-methoxy-4-methylamphetamine, IRIS) have shown any psychopharmacological activity at oral dosages that would be completely effective with DOM itself. The closure of the chain-methyl group with the adjacent benzylic carbon to create a three-member ring produces a compound (2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine, DMCPA) which is an effective hallucinogen in the 10–20mg range. The incorporation of the oxygen atom at the DOM 5-position into a furan ring has led to two heterocyclic analogues of DOM. The furanyl-2-methyl and 2,2-dimethyl compounds are 6-(2-aminopropyl)-5-methoxy-2-methyl-2,3-dihydrobenzofuran (F-2) and 6-(2-aminopropyl)-2,2-dimethyl-5-methoxy-2,3-dihydrobenzofuran (F-22) and were, as with the two homologues mentioned above, inactive at oral dosages (15mg) that would have been effective for the parent compound, DOM.

Instead of an alkyl group at the sensitive 4-position, there have been a number of compounds synthesized and assayed with other subsituents at that position. (See Table 3.16.)



4-substituted analogues of DOM

R=	common name	code	potency (mg)	potency M.U.
CH_3-	4-methyl-2,5-dimethoxy-A[a]	DOM	3–10	50
Cl-	4-chloro-2,5-dimethoxy-A	DOC	1.5–3.0	150
Br-	4-bromo-2,5-dimethoxy-A	DOB	1.0–3.0	150
I-	4-iodo-2,5-dimethoxy-A	DOI	1.5–3.0	150
NO_2-	4-nitro-2,5-dimethoxy-A	DON	3.0–4.5	80

[a] "A" represents the word amphetamine

Table 3.16

4-Substituted analogues of DOM

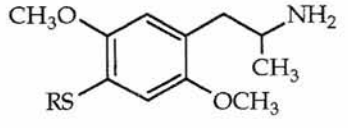
The halides that have been tried have been extremely active, and the two heavier ones have enjoyed an extensive popularity as serotonin receptor site ligands (the methyl-bearing DOM is included in this table for comparison). The second of these, DOI, is commercially available, both as the racemate and

as the separate optically active isomers. Animal studies on the 4-fluoro analogue (DOF) have suggested that it is several times less potent than DOB and DOI, but no human studies on it have yet been reported. Two positional isomers and two N-alkyl homologues of these halogenated amphetamine derivatives have been clinically explored, and all are less active than their parent prototypes. The interchanging of the 5-methoxy group and the bromine atom of DOB produces META-DOB (5-bromo-2,4-dimethoxyamphetamine) which proved to develop a complex toxic syndrome in the 50 to 100mg range. The relocation of the 2-methoxy group to the 3-position produces 4-Br-3,5-DMA (4-bromo-3,5-dimethoxyamphetamine) which is a remarkably effective anesthetic to skin surfaces at 4 to 10 mg orally. The N-methyl homologue of DOB (4-bromo-2,5-dimethoxy-N-methylamphetamine, METHYL-DOB) produced a long-lasting broad array of physical discomfiture at 8mg and was not explored higher. The N,N-dimethyl homologue of DOI was called IDNNA (2,5-dimethoxy-N,N-dimethyl-4-iodoamphetamine) and, although not active at levels where DOI would be, it led to an extensive series of some 15 mono- and di-N-alkylated amines related to DOI. They were prepared for studies of ^{131}I labelled compounds for rat pharmacology (and eventual ^{122}I PET scanning agents for human studies) but none of them had been clinically explored.

What other hetero-atoms could be brought into that 4-position? The obvious one is suggested by the thiomescaline and 2C-T which call upon the sulfur atom. This is the series of compounds called the "Aleph" group, made with the 4-position sulfur substituted in place of the 4-position oxygen atom. (See Table 3.17.)

Table 3.17

4-Thioalkyl analogues of DOM



4-thioalkyl analogues of DOM

R=	common name	code	potency (mg)	potency M.U.
CH_3-	4-methylthio-2,5-dimethoxy-A[a]	Aleph (DOT)	5–10	40
CH_3CH_2-	4-ethylthio-2,5-dimethoxy-A	Aleph-2	4–8	50
$CH_3(CH_2)_2$-	4-(n)-propylthio-2,5-dimethoxy-A	Aleph-7	4–7	50
$(CH_3)_2CH$-	4-(i)-propylthio-2,5-dimethoxy-A	Aleph-4	7–12	30
C_6H_5-	4-phenylthio-2,5-dimethoxy-A	Aleph-6	>40	?

[a] "A" represents the word amphetamine

There are examples of chains up to three carbons in length (the n-propyl group) and the activity gives no indication of beginning to diminish. There is much manipulation possible here, with longer chain alkyls, branched chain alkyls, with small rings, with fluoro-atoms, and it is all still unexplored. One observation is needed. In the broader clinical studies with some of the Aleph compounds, a sizable individual variation was noted, so care must be taken in the exploration of new levels of new compounds. Some people may be unduly sensitive or insensitive.

The determination of the effects of replacing the oxygen atom in active compounds with a sulfur atom has been extended into several families of the hallucinogens.

This substitution has been thoroughly explored with the 4-alkyl-2,5-dimethoxyamphetamines DOM and DOET. With DOM, each of the oxygen atoms separately and both of the oxygen atoms together have been replaced with sulfur, and with one, the sulfoxide was made as well. There is 5-methoxy-4-methyl-2-methylthioamphetamine (2-TOM) which is active at 60–100mg, 2-methoxy-4-methyl-5-methylthioamphetamine (5-TOM) which is active at 30–50mg, and 4-methyl-2,5-bis-(methylthio)amphetamine (BIS-TOM) which shows no activity even at 160mg. The sulfoxide of 5-TOM (2-methoxy-4-methyl-5-methylsulfinylamphetamine, TOMSO) also was without activity at 150mg. The two oxygen atoms in DOET have also been replaced with sulfur. There is 4-ethyl-5-methoxy-2-methylthioamphetamine (2-TOET) which is inactive at 65mg, and 4-ethyl-2-methoxy-5-methylthioamphetamine (5-TOET) which is an active hallucinogenic drug in the 12–25mg range.

The two other possible oxygen substitutions of DOT have been synthesized and evaluated; this completes the three theoretical thio-analogues of TMA-2. 4,5-Dimethoxy-2-methylthioamphetamine and 2,4-dimethoxy-5-methylthioamphetamine (Ortho-DOT and Meta-DOT respectively) were without any central effects at levels of 25mg orally.

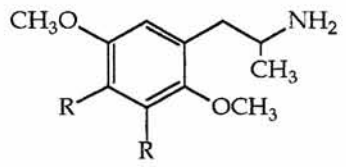
Two of the methylenedioxyamphetamine compounds have also been similarly modified. The 2-methoxy group of MMDA-3a is replaced with a methylthio group giving 3,4-methylenedioxy-2-methylthioamphetamine, or 2T-MMDA-3a. It is not active at a dosage of 12mg. The second analogue has one of the oxygens of the methylenedioxy group changed to a sulfur. This is 6-(2-aminopropyl)-5-methoxy-1,3-benzoxathiol (4-T-MMDA-2) and it shows no activity at 25mg orally.

The last group of hallucinogens that has been derived by structural manipulation of DOM is the Ganesha series. This is a collection of 3,4-dialkyl derivatives similar to those that were seen earlier in the 2C-G family, but these are the corresponding amphetamines. Interestingly, the difference between the two

families (the normally more potent 3-carbon amphetamine set and the less potent2-carbon phenethylamines) is substantially lost. (See Table 3.18.)

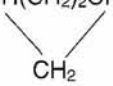
Table 3.18

3,4-Dialkyl homologues of DOM



3,4-dialkyl homologues of DOM

R	R	common name	code	potency (mg)	potency M.U.
CH_3-	CH_3-	3,4-dimethyl-2,5-dimethoxy-A[a]	G	20–32	10
-$CH_2CH_2CH_2$-		3,4-trimethylene-2,5-dimethoxy-A	G-3	12–18	20
-$CH(CH_2)_2CH$-		norbornyl-2,5-dimethoxy-A	G-5	14–20	18



[a] "A" represents the word amphetamine

The 3,4-dimethyl compounds (G vs. 2C-G) are equipotent. The three-carbon G-3 is half-again more potent than the 2-carbon 2C-G-3. But the norbornyl two-carbon compound 2C-G-5 is believably more active than the three-carbon G-5 listed here. It would seem that within this 3,4-disubstituted-2,5-dimethoxy family, as the substituent become more bulky, the phenethylamine analogue assumes the role of being the more potent. The analogous G-4 and G-N have not been evaluated in humans.

This review to date has considered the relatives of the 3,4,5-trisubstitution ring pattern (modest activity) and the considerably more potent 2,4,5-trisubstitution pattern. As was noted in the comments comparing TMA-2 with TMA-6, the 2,4,6-orientation bids fair to be every bit as important as the 2,4,5-system, although it has as yet been almost unexplored, either chemically or pharmacologically. A nomenclature that has been used to refer to this branch which is parallel to the 2,4,5-group, is to use the code name of the drug and precede it with the Greek letter psi. This was introduced above with the compound Ψ-2C-T-4. Thus, the lead drug of this section (DOM or 2,5-dimethoxy-4-methylamphetamine) becomes Ψ-DOM (2,6-dimethoxy-4-methylamphetamine). Clinical studies have shown it to be active as a hallucinogen in the 15–25mg range, with a mescaline equivalency of 15. There is too little data at the present time to determine any quantitative relationship between the 2,4,5-normal series and the 2,4,6-Ψ-series, but it appears quite possible that the two parallel families are, at least as to their quantitative properties, quite similar.

Just as the addition of a carbon atom in the form of an N-methyl group (converting a primary amine -NH_2 to a secondary amine -$NHCH_3$) largely dispels the hallucinogen property, so does the addition of a carbon atom in the form of an extension on the alpha-methyl group of the amphetamine chain (converting an alpha-methyl to an alpha-ethyl group). Again, with DOM as an illustration, the homologue with an alpha-ethyl group is an antidepressant, but not hallucinogenic in any way. This drug, 1-(2,5-dimethoxy-4-methylphenyl)-2-amino-butane, was developed by Bristol Laboratories under the name Dimoxamine, although in the early literature it had the code name Ariadne. A parallel is given in the tryptamine world below, with the comparison of alpha-methyl tryptamine with Monase, the alpha-ethyl homologue, also an antidepressant.

3.2 THE TRYPTAMINES

The drugs to be covered in this section of this review contain a skeleton of two-rings known as an indole. This, with an aminoethyl chain attached to its 3-position, becomes indolethylamine, commonly known as tryptamine. The phenethylamine versus tryptamine balance can be seen in the comparison of the chemical structures of the two major central neurotransmitters, dopamine and serotonin. In these diagrams, the positions of maximum sensitivity for producing hallucinogenic activity, the 4-position in the phenethylamine family, and the 5-position in the tryptamine, are indicated. Each is occupied in the native neurotransmitter by a hydroxyl group. (See Figure 3.10.)

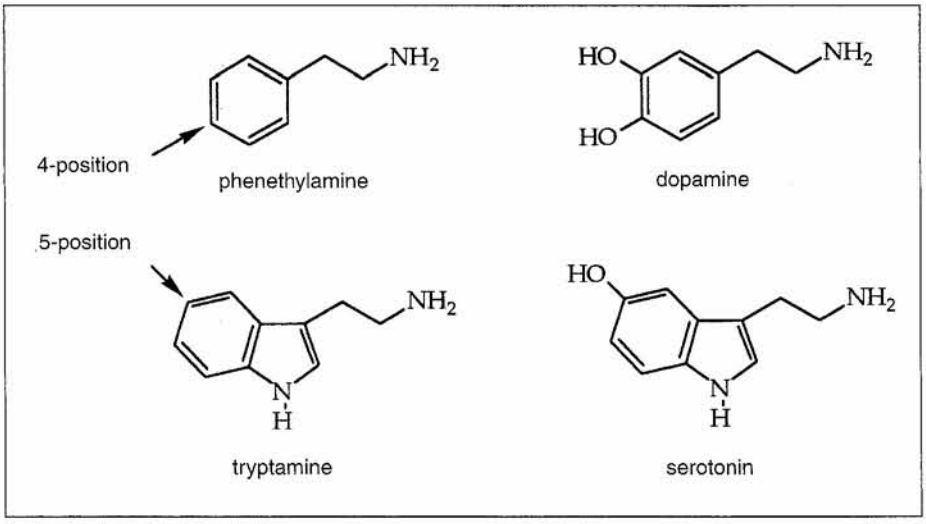


Figure 3.10
Chemical structures of dopamine and serotonin and their similarity to phenethylamine and tryptamine respectively

The pharmacological universe would be a neat and simple place if the hallucinogens that were phenethylamines were to work via the dopamine

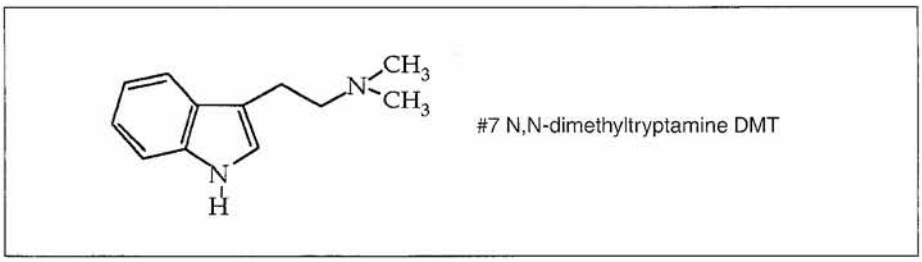
receptors and those that were tryptamines were to use the serotonin receptors: a sort of a structural allegiance. The universe is far from simple. All hallucinogens involve one or more of the serotonin subtypes, but the dopamine system is frequently involved as well.

There are structural consistencies between the two families, and differences as well. In both groups, the simplest and most structurally open examples are subject to metabolic oxidative deamination, which can be minimized by placing a methyl group alpha to the basic nitrogen atom. And in both groups, the placement of a non-polar group (as a methoxy group) at the position of the neurotransmitter's binding hydroxy group (4- with the phenethylamines, and 5- with the tryptamines) greatly enhances central activity and versatility of response. In contrast, whereas the substitution of groups on the nitrogen eradicates activity in the phenethylamines, it is an essential structural feature with the tryptamines (unless there is an amphetamine-like alpha-methyl group present).

3.2.1 N,N-DIMETHYLTRYPTAMINE (DMT) ANALOGUES

There is a very wide distribution of the two hallucinogens DMT (discussed here) and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT, discussed below) throughout the plant kingdom. But both are also well-established normal constituents in human urine, blood, and cerebral spinal fluid. Efforts to find a relationship between levels of these natural alkaloids and the mental health of humans have been futile. They are always there but at very small levels. When these levels are increased through some parenteral route of self-administration, a short-lived but intense hallucinogenic crisis can occur. DMT is the most convenient compound to use as a base reference point. (See Figure 3.11.)

Figure 3.11
N,N-Dimethyltryptamine (DMT)



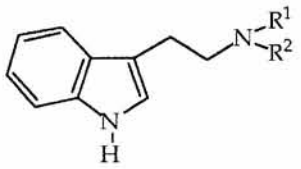
It, like mescaline in the phenethylamine group, is one of the oldest, best documented, and least potent of the entire system.

A number of homologues of DMT have been synthesized, and evaluated in human subjects. (See Table 3.19.)

Not all of these chemicals have been rigidly defined by the rigors of the "scientific method," double blind experiments with placebo controls. In fact,

Table 3.19

N,N-Dialkyl homologues of DMT



N,N-dialkyl homologues of DMT

R^1	R^2	common name	code	potency (mg)	potency x-DMT
H-	H-	tryptamine	T	>100	<1
H-	Me-	monomethyltryptamine	NMT[a]	50–100	1
H-	s-Bu-	mono-(s)-butyltryptamine	NSBT	50–75	1
H-	t-Bu-	mono-(t)-butyltryptamine	NTBT	~20	~4
H-	Am-	mono-(n)-amyltryptamine	NAT	>100	<1
H-	He-	mono-(n)-hexyltryptamine	NHT	>100	<1
Me-	Me-	dimethyltryptamine	DMT	60–100	1
Me-	Et-	methyl-ethyltryptamine	MET	80–100	1
Me-	Pr-	methyl-(n)-propyltryptamine	MPT	>50	?
Me-	iPr-	methyl-isopropyltryptamine	MIPT	10–25	4
Me-	Bu-	methyl-(n)-butyltryptamine	MBM	250–400	0.3
Et-	Et-	diethyltryptamine	DET	60–150	1
Et-	iPr-	ethyl-isopropyltryptamine	EIPT	24–40	3
Pr-	Pr-	di-(n)-propyltryptamine	DPT	~100	1
iPr-	iPr-	diisopropyltryptamine	DIPT[b]	40–100	1
Al-	Al-	diallyltryptamine	DAT	80	1
Bu-	Bu-	di-(n)-butyltryptamine	DBT	>100	<1
—$(CH_2)_4$—		pyrrolidyltryptamine	pyr-T	~100	1

[a] Several of these latter codes employ the first letter "N" for nitrogen rather than "M" for mono-. This latter has been reserved for the methyl group.
[b] Extreme auditory harmonic distortion, with no visual changes at all.

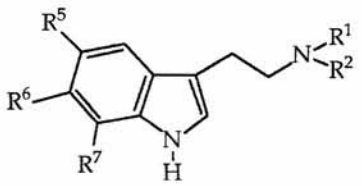
very few of the human studies on any of the hallucinogens have been structured in this way. The simple reason is that all clinical studies, at least with new and previously unexplored compounds that might show some of the subjective properties of this class of drugs, depend upon the awareness of the test subject of the nature of the experiment and the potential range of effects that might be expected. Thus, many studies are single trials in single individuals, with the results commingled in the effort to bring some statistical validity to any conclusions found. Several of the values in the listings above are findings in one or two individuals only.

A logical extension of this family of DMT homologues embraces substitutions on the aromatic ring of the indole. A collection of aromatic-substituted

ring-substituted compounds is shown in the Table listing. Analogues that are substituted on the indolic 4-position will be considered separately. (See Table 3.20.)

Table 3.20

Ar, N-Substituted analogues of DMT; nothing at 4-position



Ar, N-substituted analogues of DMT; nothing at 4-position

R^5	R^6	R^7	R^1	R^2	common name	code	potency (mg)	potency x DMT
HO-	H-	H-	H-	H-	serotonin	5-HT	–	–
HO-	H-	H-	CH_3-	CH_3-	5-hydroxy-N,N-dimethyltryptamine	bufotenine	8–16	7[a]
CH_3O-	H-	H-	Ac-	H-	melatonin	melatonin	1–3	[b]
CH_3O-	H-	H-	CH_3-	CH_3-	5-methoxy-N,N-dimethyltryptamine	5-MeO-DMT	6–20	7[c]
CH_3O-	H-	H-	CH_3-	iPr-	5-methoxy-N-isopropyl-N-methyltryptamine	5-MeO-MIPT	4–6	16
CH_3O-	H-	H-	Et-	Et-	5-methoxy-N,N-diethyltryptamine	5-MeO-DET	1–3	40
CH_3O-	H-	H-	Pr-	Pr-	5-methoxyl-N,N-dipropyltryptamine	5-MeO-DPT	6–10	10
CH_3O-	H-	H-	iPr-	iPr-	5-methoxyl-N,N-diisopropyltryptamine	5-MeO-DIPT	8–12	8
CH_3O-	H-	H-	-$(CH_2)_4$-		5-methoxyl-N,N-tetramethylenetryptamine	5-MeO-pyr-T	0.5–2	[d]
CH_3S-	H-	H-	CH_3-	CH_3-	5-methylthio-N,N-dimethyltryptamine	5-MeS-DMT	15–30	4
CH_3O-	CH_3O-	H-	CH_3-	iPr-	5,6-dimethoxy-N-isopropyl-N-methyltryptamine	5,6-MeO-MIPT	>75	<1
-OCH_2O-		H-	CH_3-	CH_3-	5,6-methylenedioxy-N,N-dimethyltryptamine	5,6-MDO-DMT	?	?[e]
-OCH_2O-		H-	CH_3-	iPr-	5,6-methylenedioxy-N-isopropyl-N-methyltryptamine	5,6-MDO-MIPT	>60	<1
-OCH_2O-		H-	iPr-	iPr-	5,6-methylenedioxy-N,N-diisopropyltryptamine	5,6-MDO-DIPT	?	?[e]
H-	HO-	H-	CH_3-	CH_3-	6-hydroxy-N,N-dimethyltryptamine	6-OH-DMT	>80	<1
H-	CH_3O-	H-	CH_3-	iPr-	6-methoxy-N-isopropyl-N-methyltryptamine	6-MeO-MIPT	>50	<1

Table 3.20 (continued)

R^5	R^6	R^7	R^1	R^2	common name	code	potency (mg)	potency x DMT
H-	F-	H-	Et-	Et-	6-fluoro-N,N-diethyltryptamine	6-F-DET	>80	<1[f]
H-	H-	CH_3O-	CH_3-	iPr-	7-methoxy-N-isopropyl-N-methyltryptamine	7-MeO-MIPT	>70	<1

[a] administered parenterally – see comments below
[b] sedation, dream-state
[c] smoked – not orally active
[d] not hallucinogenic – produces long-lived amnesia and unconsciousness
[e] clinical trials started, not yet completed
[f] with autonomic effects similar to those of DET but without the hallucinogen component, this has found clinical value as an active placebo in human experiments

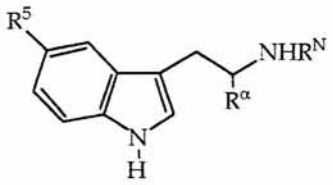
It is immediately obvious from the representation that substitution in the 5-position is needed for maximum activity (the 4-substituted isomers will be discussed below).

For a number of reasons, some pharmacological and some political, the compound 5-hydroxy-N,N-dimethyltryptamine, bufotenine, deserves special comment. From the pharmacological point of view, the compound is clearly active, but the nature of this activity is difficult to classify. The early studies that report effects in humans followed intravenous administration, and the responses noted (anxiety, panic, visual distortion, intense flushing) have been ascribed to extreme cardiovascular action and possible increases in interocular pressure. No effects have been observed following intranasal or oral administration. Recent studies with snuffs from roasted red seeds of the South American trees of the *Anadenanthera* species have proved highly active and yet careful analysis have shown that the only alkaloid present was bufotenine. Yet there are several reports in the medical literature of human studies where the compound is reported to be without activity.

The political aspects deal largely with the law. In the earliest studies, the comment was made that some of the observed effects were reminiscent of LSD. This prompted the inclusion of bufotenine into the legal structure as a hallucinogen, and it has been referred to in this way ever since. This alkaloid can be found in a number of plants and animals and is, in fact, a normal component of human urine. A recent event involving the smoking of dried toad venom may lead to a legal challenge of consuming a Schedule I drug (bufotenine) and questions such as its presence in the venom, its pyrolytic stability, and its pharmacological nature should be well defined ahead of time.

A number of tryptamines have been studied that imitate the structural pattern of amphetamine, where an alpha-alkyl group effectively protects the molecule from enzymatic deamination. (Table 3.21.)

Table 3.21
α,Ar, N-Substituted tryptamines



5,α,N-substituted tryptamines

R^5	R^α	R^N	common name	code	potency (mg)	potency x-DMT
H-	CH_3-	H-	α-methyltryptamine	α-MT, IT-290	15–30	3
H-	CH_3-	CH_3-	α,N-dimethyltryptamine	α,N-DMT	50–100	1
H-	Et-	H-	α-ethyltryptamine	α-ET, Monase	100–160	0.5
CH_3O-	CH_3-	H-	α,O-dimethylserotonin	α,O-DMS	3–5	20
CH_3O-	CH_3-	CH_3-	α,N,O-trimethylserotonin	α,N,O-TMS	10–20	5
CH_3O-	Et-	H-	5-methoxy-α-ethyltryptamine	5-MeO-α-ET	~70	1

A close structural analogue of the neurotransmitter serotonin is seen in α,O-DMS. Serotonin, when administered orally, is not available to the brain for two reasons. It is polar (with the 5-hydroxyl group exposed), and is rapidly deaminated by monoamine oxidase attack. A methyl group on the oxygen decreases the hydrophilicity, and a methyl group on the alpha-position affords metabolic protection, resulting in a very potent, orally active hallucinogen. The drug α-ET was made available commercially by the Upjohn company under the name Monase, and was an effective antidepressant. It was withdrawn due to some side-effects, and shortly thereafter began to be sold on the street market as a substitute for MDMA. It was placed in Schedule I as a hallucinogen by the DEA.

Three related compounds deserve specific mention. The 4-methyl homologue of α-MT, α,4-dimethyltryptamine (α,4-DMT), is orally active in humans at 20mg and produces some feelings of unreality, with neurological toxicity including skin flushing and eye dilation. The 4-hydroxy analogue (4-HO-α-MT) has been observed by some to evoke visual changes, accompanied by dizziness and mild depression. In the 15–20mg range (orally) there is occasional tachycardia, headache, and diarrhea. And the complete relocation of the 3-(2-aminopropyl)-chain of α- MT to the 5-position creates an isomer called 5-IT which, with 20mg orally produces a state of increased heart rate, anorexia, diuresis and slight hyperthermia, all lasting about 12 hours. None of these materials could be called hallucinogens.

Quite a different story follows the inclusion of a methyl group at the indolic 2-position, in both of the two above groups.

With the aryl, N-substituted analogues of DMT, three compounds are of specific interest. These are the three 2-methyl homologues of DMT, 5-MeO-DMT and DET. The first of these, 2,N,N-trimethyltryptamine (2,N,N-TMT) is orally active in the 50 to 100mg range. This is a potency very similar to the prototype DMT, but with this compound there is oral activity. It is as if just the presence of some aliphatic entity in the space between the indole ring and the 3-side-chain, whether it is an alpha-methyl or a 2-methyl, effectively protects the molecule from the monoamine oxidase. A similar protection from oxidative deamination, although at a considerable drop in potency, is seen with the 2-methylation of 5-methoxy-N,N-dimethyltryptamine. This base, 5-MeO-2,N,N-TMT, is orally active in the dose range of 75–150mg, down by a factor of 10 from the 5-MeO-DMT parent. The corresponding homologue of DET is 2-Me-DET. It is orally active with doses in the 80 to 120mg range.

One example of a 2-methylated-alpha-methyltryptamine has been studied in humans. This is 2,alpha-dimethyltryptamine, or 2,α-DMT. It leads to a gentle, pleasurable intoxication with oral doses in the 300–500 mg range.

3.2.2 PSILOCYBIN ANALOGUES

An unusual collection of tryptamines has its origins in the fungal world. These compounds are unique in that they have a 4-indolic hydroxyl group (or an ester group that can be metabolized to a hydroxyl group) and yet they are orally active. The natural prototypes are psilocybin itself, and the two demethylated homologues baeocystin and norbaeocystin. (See Figure 3.12.)

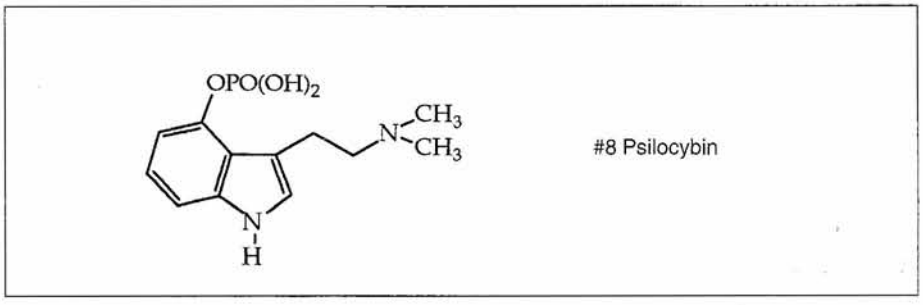
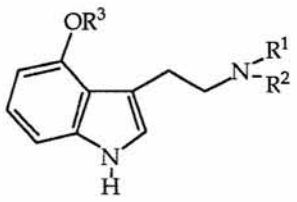


Figure 3.12
Chemical structure of psilocybin

These compounds have been found in various combinations, along with the dephosphorylated analogue psilocin, in perhaps a hundred species of mushrooms, largely of the *Psilocybin* genus. (See Table 3.22.)

It has now been established that the phosphate group is metabolically removed, revealing the free phenolic compound as the intrinsically active drug in humans. That it should be centrally active at all may involve a structurally

Table 3.22
Psilocybin analogues



Psilocybin analogues

R^1	R^2	R^3	common name	code	potency (mg)	potency x-DMT
H-	H-	PO_3H_2	norbaeocystin		?	
H-	CH_3-	PO_3H_2	baeocystin		6–10	10
CH_3-	CH_3-	H-	psilocin	CX-59	7–10	10
CH_3-	CH_3-	PO_3H_2	psilocybin	CY-39	10–15	6
CH_3-	Et-	H-	4-hydroxymethylethyl-T[a]	4-HO-MET	10–20	6
CH_3-	Pr-	H-	4-hydroxymethylpropyl-T	4-HO-MPT	?	
CH_3-	iPr-	H-	4-hydroxymethylisopropyl-T	4-HO-MIPT	12–25	5
CH_3-	iPr-	CH_3-	4-methoxymethylisopropyl-T	4-MeO-MIPT	20–30	3
Et-	Et-	H-	4-hydroxydiethyl-T	CZ-74	10–20	6
Et-	Et-	PO_3H_2	4-phosphoryloxydiethyl-T	CEY-19	15–25	4
Pr-	Pr-	H-	4-hydroxydipropyl-T	4-HO-DPT	?	
iPr-	iPr-	H-	4-hydroxydiisopropyl-T	4-HO-DIPT	15–20	4
iPr-	iPr-	Ac-	4-acetoxydiisopropyl-T	4-AcO-DIPT	6–10	10
Bu-	Bu-	H-	4-hydroxydibutyl-T	4-HO-DBT	>20	?
-$(CH_2)_4$-		H-	4-hydroxytetramethylene-T	4-HO-pyr-T	>20	?

[a] "T" stands for tryptamine

allowable close association and intermolecular neutralization between the acidic hydroxy group and the basic amine group. The generalization that all ester substituted 4-hydroxytryptamines are saponified before being active may not be valid. The doubled potency of the 4-AcO-DIPT over that of 4-HO-DIPT (in the above table) and the speed of onset (10 to 20 minutes) suggests that it might be absorbed directly from the stomach as the unsaponified ester.

Two compounds defy classification in the above tables, but they were designed for that exact reason – to challenge the structure-activity relationships (SAR) that derive from this data base. They incorporate the 4-oxygen atom of psilocin and the 5-oxygen atom of bufotenine. The compounds are the 4,5-methylenedioxy analogues of DMT and of DIPT. Both of them (4,5-MDO-DMT

and 4,5-MDO-DIPT) are of unknown potency in humans, although the latter has been assayed up to 25mg with some activity. This challenge has not yet been answered.

3.3 SIGNIFICANT OTHERS

3.3.1 LSD ANALOGUES

The last large class of hallucinogenic compounds that has been extensively studied as to structure activity relationships is represented by the well-known prototype, LSD. (See Figure 3.13.)

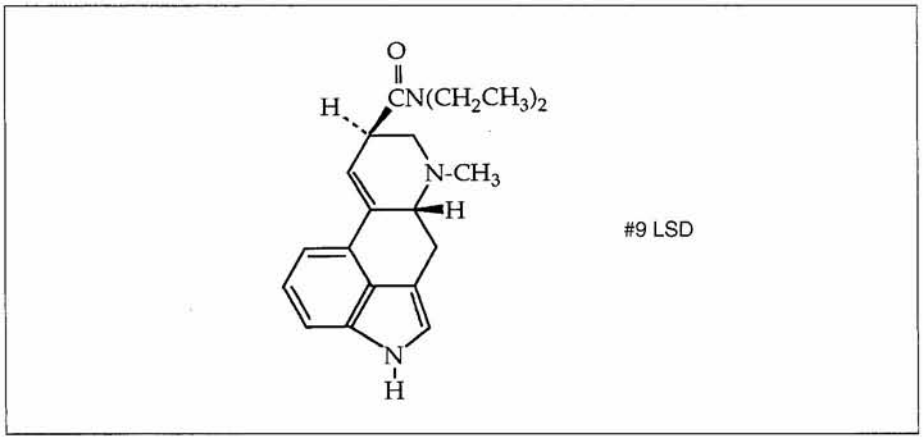


Figure 3.13
Chemical structure of LSD

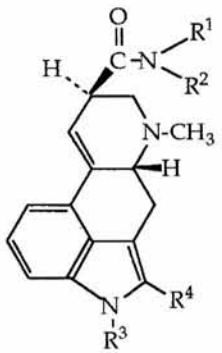
This is a synthetic base, derived from the lysergic acid nucleus that is best known from the ergot alkaloids. This family of compounds was originally discovered in the rye fungus and was responsible for the lethal outbreaks of Saint Anthony's Fire in the Middle Ages. (See Table 3.23.)

These compounds are now known to be present in morning glory seeds and helps explain their use in older Western cultures.

A great number of homologues and analogues of LSD have been studied. The most easily available group consists of variations of substituents on the amide group, often accompanied with substituents on the indolic pyrrole ring. No material in this group has shown a potency that exceeds that of LSD itself. It must be remembered that a number of these studies are statistically weak, as the number of subjects was very limited. All of these studies were conducted on compounds with the absolute configuration shown. Prolonged exposure of LSD to basic conditions promotes the isomerization of the carbon atom at the 8-position (that bears the carboxamide function) resulting in the generation of the inactive d-iso-LSD. Trials with the two unnatural diastereoisomers (l-LSD and l-iso-LSD) have been shown to be free of any LSD-like effects at rather

Table 3.23

Amide analogues and pyrrole derivatives of LSD



amide analogues and pyrrole derivatives of LSD

R^1	R^2	R^3	R^4	common name	code	potency (mg)	potency x-LSD
H-	H-	H-	H-	LA-amide, ergine	LA-111	0.5–1	0.1[a]
Me-	H-	H-	H-	LA-methylamide		~0.5	0.2[a]
Me-	Me-	H-	H-	LA-dimethylamide	DAM-57	0.5–1.2	0.1
Et-	H-	H-	H-	LA-ethylamide	LAE-32	0-5–1.6	0.1
Et-	H-	Ac-	H.	1-acetyl-LA-ethylamide	ALA-10	~1.2	0.1
Et-	H-	Me-	H-	1-methyl-LA-ethylamide	MLA-74	~2	0.05
Et-	Me-	H-	H-	LA-methylethylamide	LME-54	[b]	
Et-	Et-	H-	H-	LA-diethylamide	LSD-25	0.05–0.2	1
Et-	Et-	H-	Br-	2-bromo-LSD	BOL-148	>1	<0.1
Et-	Et-	Ac-	H-	1-acetyl-LSD	ALD-52	0.1–0.2	1
Et-	Et-	Me-	H-	1-methyl-LSD	MLD-41	0.2–0.3	0.3
Et-	Et-	Me-	Br-	l-methyl-2-bromo-LSD	MBL-61	>10	<0.01
Et-	Et-	Me-	I-	l-methyl-2-iodo-LSD	MIL	?[c]	
Pr-	H-	H-	H-	LA-propylamide		>0.5	<0.2
Pr-	Me-	H-	H-	LA-methylpropylamide	LMP	>0.1	<1[d]
Pr-	Et-	H-	H-	LA-ethylpropylamide	LEP-57	[b]	
Pr-	Pr-	H-	H-	LA-dipropylamide		>1	<0.1
Al-	Al-	H-	H-	LA-diallylamide	DAL	>1	<0.1
[f]	H-	H-	H-	ergonovine		10	0.01
[g]	H-	H-	H-	methylergonovine		2	0.05
[g]	H-	Me-	H-	methysergid[e]	UML-491	4–8	0.02
$-(CH_2)_4-$		H-	H-	LA-pyrrolidineamide	LPD-824	~0.8	0.1
$-(CH_2)_4-$		Me-	H-	1-methyl-LA-pyrrolidineamide	MPD-75	>1.6	<0.05
$-(CH_2)_2O(CH_2)_2-$		H-	H-	LA-morpholineamide	LSM-775	0.3–0.6	0.2

Table 3.23 (continued)

"LA" is the abbreviation for lysergic acid

"LSD" is the abbreviation for lysergic acid diethylamide

[a] sedative action or autonomic changes in humans; not hallucinogenic

[b] active but less so than LSD; no numbers available; used in cross-tolerance studies with LSD

[c] often used in human ^{11}C PET scanning; activity unknown

[d] used as a legal decoy against LSD prosecutions

[e] this is the prescription antimigraine drug Sansert; when used at 10× the usual dose, there is an LSD-like intoxication

[f] 1-hydroxy-2-propyl

[g] 1-hydroxy-2-butyl

large dosages. This reinforces the extreme stereoselectivity of the LSD structure, and the isomeric purity of the compounds studied. Exposure of an aqueous solution of LSD to light, especially sunlight with its UV component, causes a rapid loss in potency. Here this is due to the addition of a molecule of water to the 9,10-double bond in ring D. This product is called lumi-LSD and it is also inactive in humans.

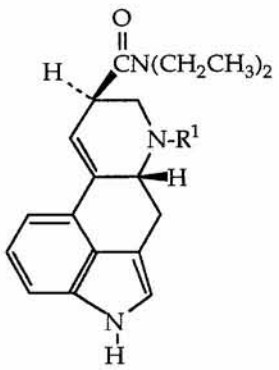
A second area of structural modification of the LSD molecule is the homologation of the alkyl group located on the nitrogen atom at the 6-position. These are best called 6-substituted nor-lysergic acid diethylamides, and are synthetically considerably more challenging than the amide homologues. (See Table 3.24.)

Here, apparently, there is considerable indifference to the nature of the alkyl group that is attached to the molecule, suggesting that this would be an ideal location for a radioactive label for PET scanning, with a β-haloethyl group carrying an iodine or a fluorine atom. Earlier work employed the halogen at the pyrrole 2-position which, although easily made, was an inactive molecule, at least as a hallucinogen.

There are several additional hallucinogens which are properly part of this review but which have been unexplored as to structural variations. They are shown in the sections below.

Table 3.24

5-Alkyl homologues of 5-nor-LSD



5-alkyl homologues of 5-nor-LSD

R^1	common name	code	potency	
			(μg)	x-LSD
H-	nor-LSD		>500	<0.2
Me-	6-methyl-nor-LSD	LSD-25	50–200	1
Et-	6-ethyl-nor-LSD	ETHLAD	40–80	2
Pr-	6-propyl-nor-LSD	PROLAD	80–175	1
Al-	6-allyl-nor-LSD	ALLYLAD	50–150	1
Bu-	6-n-butyl-nor-LSD	BULAD	>400	<0.3
Φ-$(CH_2)_2$-	6-(β-phenethyl)-nor-LSD	PHENETHYLAD	>350	<0.3

nor-LSD is the abbreviation for nor-lysergic acid diethylamide

3.3.2 IBOGAINE

Ibogaine is a complex alkaloid found as a major component in the African shrub Tabernanthe iboga. It has been drawn in the accompanying diagram in a manner that emphasizes its tryptamine skeleton, and the three-dimensional birdcage ring complex. (See Figure 3.14.)

This cage system contributes one of the elements of chirality to ibogaine that is not obvious to a non-chemist. Looking at it from one of the vertices, the N-E-I order on rotation can be clockwise or counterclockwise. The second chiral center is the carbon that holds the ethyl group. Thus there are two diastereoisomeric forms possible, each with two optical isomers. The positional isomer with the aromatic methoxyl group at the indolic 6-position rather than at the 5-position, is also found in the plant and is called tabernanthine.

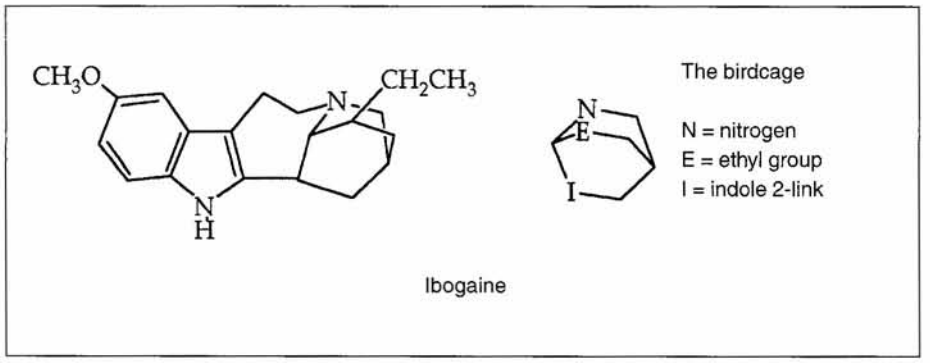


Figure 3.14
Chemical structure of ibogaine

Ibogaine is an active hallucinogen in the 400 milligram area and has been clinically studied for the treatment of heroin addiction. In this latter role, the dosages employed may range as high as 1500mg. A primary human metabolism is via O-demethylation to give the free phenol 12-hydroxyibogamine. This metabolite, misnamed nor-ibogaine in the literature, appears to be pharmacologically active in its own right.

The native use of this plant is in Gabon, where it is used in the Bwiti sacramental initiation ceremonies. The material used is called eboka, and is taken from the root of the *Tabernanthe iboga* plant, with the bark scrapings being the richest source. The ritual may last for two or three days with a continuous feeding of the sacrament to the initiate, at the maximum tolerated rate.

3.3.3 AYAHUASCA

This is an ancient decoction made from one or more South American plants. Originally the drink, Ayahuasca (Vine of the Soul) or Yaje, was prepared by the prolonged boiling of the fleshy parts of a Western Amazon liana known as *Banisteriopsis caapi*. The major alkaloids present are harmaline and harmine, both known to be with psychoactive properties. Both of these materials are classified as beta-carbolines. (See Figure 3.15.)

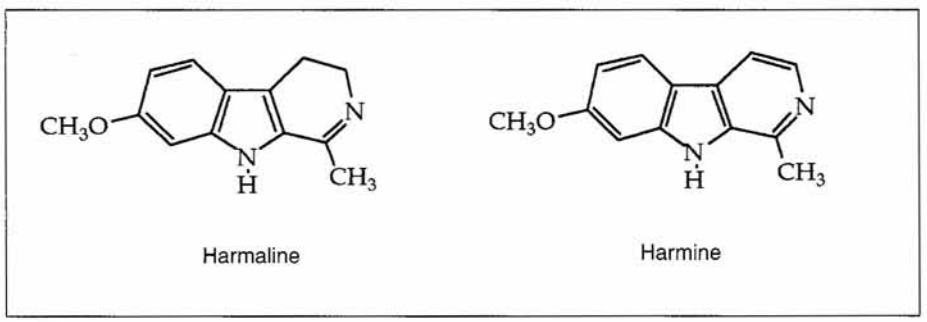


Figure 3.15
Chemical structures of the beta-carboline alkaloids of ayahuasca

Harmaline is 7-methoxy-1-methyl-3,4-dihydro-β-carboline and harmine is the totally aromatic 7-methoxy-1-methyl-β-carboline. Their action in humans is one of intoxication with a visual component, but with a considerable burden of nausea and related toxic symptoms. But both compounds are effective monoamine oxidase inhibitors (MAOI) which explains their role in the more complex forms of ayahuasca. Many native tribes have, over the years, developed a pattern of adding additional plant materials to the ayahuasca brew. One of the most fascinating has been the addition of the material chacruna, the leaves of another plant *Psychotria viridis*. This addition greatly enhances the visual and sacramental impact of ayahuasca, without doubt because this latter plant has, as its major alkaloidal constituent, N,N-dimethyltryptamine (DMT). This is the ubiquitous tryptamine base that is not active orally because it is destroyed by the deamination enzymes in the gut. But in the mixture of these two plants, the beta-carboline alkaloids are effective inhibitors of the enzyme system that destroys the DMT. Neither component of the ayahuasca mixture works well alone; in combination they become an effective hallucinogenic agent.

Over the last decade the term "ayahuasca" has come to represent, in the popular jargon of the drug-oriented scene, a mixture of any two things that are, in combination, psychoactive. The choice of each of the two components has became increasingly loose. The caapi component is often replaced by the seeds of the Syrian rue plant, *Peganum harmala*. They contain the harmala alkaloid inventory similar to *Banisteriopsis caapi*, with the addition of several quinazoline alkaloids that may contribute to psychopharmacological differences. Also, both harmine and harmaline are available commercially as fine chemicals, and they have been reported as the components in the inhibitory side of the drink being called ayahuasca. The chacruna side of this combination has been supplied by any of the many botanical individuals, from grasses to bamboos to acacia trees, any of which can provide the DMT component. And there are totally different tryptamines that can serve this role. The base 5-methoxytryptamine (5-MeO-DMT) can be gotten from many sources such as the secreted toxins of the desert toad *Bufo alvarius*, to the catalogs offering fine chemicals from any of several chemical supply houses. I have analyzed one street sample that showed, by GCMS, only two components. It was a mixture of pure harmine and pure 5-MeO-DMT. As neither of these two chemicals is included in the Scheduled Drug listings, this combination is completely legal. The term "ayahuasca" has now come to describe any two individual things that, in combination, evoke a psychotropic state.

3.3.4 TETRAHYDROCANNABINOL

The final two compounds illustrated here are unusual in that they do not contain the nitrogen atom, an unusual property for a centrally active drug.

Tetrahydrocannabinol is the major active component of *Cannabis sativa*, or marijuana, and is psychoactive in the area of 10mg. It is the major active component within the tissues of the plant itself. The resinous material around the blossom area of the female plant is especially rich in THC, and the collection of this resin produces a potent form of marijuana known as hash, a term derived from the ancient term, hashish. Since THC cannot be isolated from the marijuana plant without considerable sophistication, the only practical source of it is through chemical synthesis. (See Figure 3.16.)

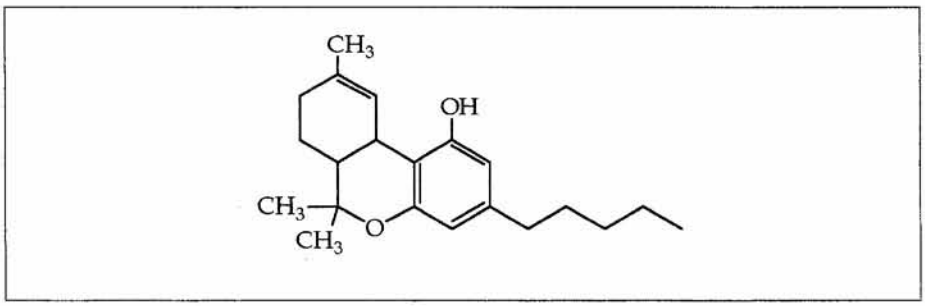


Figure 3.16
Chemical structure of tetrahydrocannabinol

This product is the prescription drug Marinol (l-Δ1-THC) which has been approved by the authorities for use as an anti-emetic. There are many dozens of related compounds in the plant itself, and all of them are potential pharmacological contributors to the action of the total plant. The single component THC is probably not the sole active component. Many structural variations of THC have been studied, some in the rabbit, some in the dog, and few in humans. Variations on the 5-pentyl group in the resorcinol half of the molecule have led to drugs of both legal and pharmacological interest. The 5-hexyl homologue is Parahexyl or Synhexyl, and it was brought into an illegal status because there was no evidence for its safety. The dimethyl-heptyl homologue is the most potent of these analogues, and was explored as a possible weapon in the military chemical warfare research studies.

There are a number of metabolic products known, but they have been used largely to confirm the illicit use of marijuana by urine tests. THC is an unusually lipophilic compound, and so tends to deposit in the fat tissues of the body. This removes it from availability for biological action, but it does provide a reservoir of "active" chemical that can only be excreted over a long time period. This means that there is a wait of several weeks for the clearance of sequestered THC from the body, long after all psychopharmacological effects have disappeared. In urine testing for drug impairment, there can well be a positive result from a person who is not under the influence of the drug at the time of the urine sampling. The psychological effect of THC spans a few hours. The presence of urinary THC spans a few weeks.

Hemp is the bulk fiber material of the plant *Cannabis sativa*, and has many

commercial uses. It is a fiber, it is a cloth. It is the primary material for our cigarette paper and our $20 bills; and for the paper upon which the US Constitution was written.

3.3.5 SALVINORIN-A

The Mazatec Indians in northern Oaxaca have used for centuries a mint plant as a healing medicine and a sacred sacrament. The plant has the botanical taxon *Salvia divinorum* (Hojas de la Pastora) and is apparently raised as a cultigen as it has never been observed in the wild. The major active component is a diterpene, a neoclerodane, and is usually absorbed from the tissues of the mouth. It is not orally active, but the dried leaves can be smoked. (See Figure 3.17.)

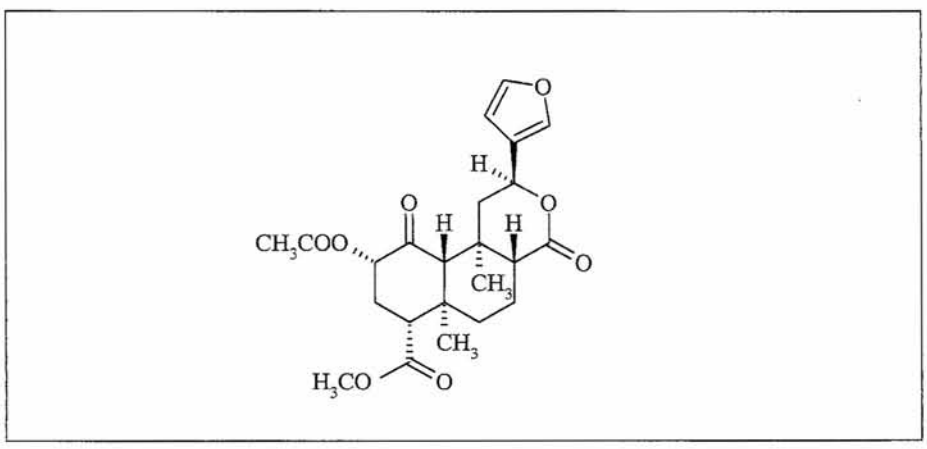


Figure 3.17
Chemical structure of salvinorin A

The pure, isolated active compound Salvinorin A is parentally active at a dose of less than a milligram. As of the present time, the mechanism of action and the metabolic fate in humans is totally unexplored. But with the commercial availability of the plants, the extracts, and the pure Salvinorin A itself, clinical research with this most potent of all natural hallucinogenic drugs will be done.

This has been little more than a touching of the surface of the world of the hallucinogens. There are many plants that have not yet received sufficient study to be included in any compilation such as this, plants that may be intoxicants or delusional agents, but which would be hallucinogenic in some people's definition. There are hallucinogenic components described in many synthetic analgesics or anesthetics. The pharmacological classification remains forever unsatisfactory as this particular property is one that demands the human animal for its identification.

3.4 FEDERAL US DRUG LAW

3.4.1 HISTORY

There have been two broad Federal drug laws, the Harrison Narcotics Act, enacted in 1914, which was succeeded by the Controlled Substances Act of 1970. The first drug that received Federal attention was opium. Along with the importation of tens of thousands of Chinese people as inexpensive labor for the construction of the trans-continental railroads, came the importation of smoking opium. Opium, and its major active alkaloid morphine, were medically approved and widely use in the United States, for pleasure as well as pain relief. It was available in over-the-counter medicines. But it was with the connection of the smoking custom, the opium dens, with the Chinese unemployment problem, that focused the legal attention more to a racial issue than to a drug issue. In the 1870s a number of cities passed ordinances, States passed laws forbidding the smoking of opium and outlawing opium dens. When these failed, the Federal Government passed a law prohibiting the importation of opium into the United States by any citizen of China. Importation from Canada was still allowed.

Over the next two decades, there was the formation of an Opium Commission (1903) to study the steadily increasing levels of opium and of coca leaves, and they recommended more legal action. A law was passed in 1909 prohibiting any importation of opium for other than medical purposes. A Hague Convention in 1912 concluded that controls should also be placed on domestic sales. This set the stage for the Harrison Narcotics Act.

In 1914, while the initial actions were taking place in Europe that exploded into World War I, the US Congress was arguing the wording of the Federal drug law. On 17 December 1914, President Wilson signed U.S.C. 4701, the Federal Narcotics Internal Revenue Regulations, commonly called the Harrison Narcotics Act. The measure was a tax and registration measure, not a prohibition one. It was carefully worded so as not to interfere with the practice of medicine. The goal was to register the dispensers of the narcotic drugs (mainly opium, morphine, heroin and cocaine) for the fee of $1 a year so as to allow orderly marketing. The law actually stated, "Nothing . . . in this section shall apply . . . to the dispensing and distribution of any of the aforesaid drugs to a patient by a physician, dentist, or veterinary surgeon registered under this Act in the course of his professional practice only."

There was a strange transition that occurred over the next six years that was intimately tied in with the proposal and passage of the Volstead Act and the ratification of the alcohol prohibition 18th Amendment, both in 1919. During

this period there was a national change in attitude towards drugs. The Supreme Court (in 1916, US *v.* Jin Fuey Moy) heard a case where the enforcement authorities claimed that addiction was not a disease and therefore a physician is violating the law by prescribing a drug to support that addiction. The court decision went against the Revenue police with the comment that such an interpretation of the Act would be unconstitutional. Just three years later, in an almost identical case (US *v.* Web) the same court found that a physician doing the same thing should, according to the law, be criminally prosecuted. The Volstead Act gave the Internal Revenue Service a Prohibition Unit, with a subunit that was called the Narcotics Division. Opium and cocaine prohibition fell under the purview of the IRS. In 1929, President Coolidge signed the Porter Bill which established the first Narcotics Farms for the confinement and treatment of Federal prisoners who were addicts.

In June 1930, Congress established the Bureau of Narcotics, still within the Department of Treasury, and Herbert Hoover appointed Henry J. Anslinger to head the Bureau. The reefer madness era began with claims that marijuana caused madness and criminal behavior, that all kids would start using it. President Roosevelt signed the Marihuana Tax Act of 1937. So by an act of Congress, marijuana had become a narcotic.

For the next 25 years, a number of minor laws were passed, all designed to curb illicit production, increase penalties and to broaden the strength and the scope of the Bureau of Narcotics' power.

In 1962, a landmark bill was passed into law. This was the Racketeering and Corrupt Organizations Act (RICO, 18 U.S.C. 1962). Its purpose was to eliminate the infiltration of organized crime into legitimate organizations. There was no indication that this law had been specifically intended to address criminal activities such as drug trafficking. In 1970, Congress modified the RICO law to insert criminal forfeiture provisions. Although there is a rich history of civil forfeiture involved in proceedings against property which has been involved in some criminal action, the act of criminal forfeiture involves seizure of property of a person convicted of a felony. It was a common penalty in historic England but it was specifically prohibited in 1790 by the first Congress of the United States. As a result, criminal forfeitures were unknown in the United States for 180 years. This amendment to the RICO statute, and the Continuing Criminal Enterprise section of the Controlled Substance Act (see below) are the first inclusions of this penalty, ever, in American history. The need of a conviction before seizure was dropped in 1978 (see below).

In the mid-1960s some new developments occurred in the social scene. There was an ever-increasing protest to the Vietnam War, there was a musical and philosophical rebellion characterized by the "Summer of Love," and there

were the hippies. And with them came a cascade of new drugs, stimulants and hallucinogens, certainly very little in the opium and cocaine narcotics world. Marijuana was everywhere, yes, but just about everything else was unknown to the law. The law-makers responded to this new crisis with the introduction of the Drug Abuse Control Amendments of 1965. These were approved by Congress and on 1 February 1966, there was established within the Food and Drug Administration, a Bureau of Drug Abuse Control (BDAC) under the direction of John H. Finlator. Suddenly the FDA was empowered to become a law enforcement police power. They put out a monthly newsletter called the *FDA Papers*. The flood of hallucinogens, as they were called, were being placed in the BDAC illegal drug listings. The rivalry became quite intense.

Territorial battles were routine. Some semblance of order came from a Presidential Order from Lyndon Johnson on 8 April 1968, dictating a plan to merge the BDAC group (in the FDA) with the BN group (still in the Department of the Treasury). This new group was named the Bureau of Narcotics and Dangerous Drugs (BNDD) and they were to answer to the Department of Justice.

In 1970, the passage of the Comprehensive Drug Abuse Prevention and Control Act, known as the Controlled Substances Act of 1970, effectively removed the Harrison Narcotics Act from the books, after a life of some 55 years. This new law, which is still current and in effect today, dictates that all illegal drugs are to be placed in one of five Schedules. These are to classify drugs with a high abuse potential to drugs with a low abuse potential. The definitions of the five Schedules follow from page 116.

Schedule I:
(a) The drug or other substance has a high potential for abuse,
(b) The drug or other substance has no currently accepted medical use in treatment in the United States,
(c) There is the lack of accepted safety for the use of the drug or other substance under medical supervision.

Schedule II:
(a) The drug or other substance has a high potential for abuse,
(b) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions,
(c) Abuse of the drug or other substance may lead to severe psychological or physical dependence.

Schedule III:
(a) The drug or other substance has a potential for abuse less than the drugs or other substances in Schedules I or II,
(b) The drug or other substance has a currently accepted medical use in treatment in the United States,
(c) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

Schedule IV:
(a) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III,
(b) The drug or other substance has a currently accepted medical use in treatment in the United States,
(c) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

Schedule V:
(a) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV,
(b) The drug or other substance has a currently accepted medical use in treatment in the United States.
(c) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule IV.

Note that there is no place to put a drug that has no currently accepted medical use but which has a low potential for abuse. There is a listing of all currently scheduled hallucinogenic drugs later in this section, along with a

tabulation of all listed chemicals that are legally associated with the manufacture of scheduled drugs.

There are two aspects of the Controlled Substances Act that deserve special mention, as they have become quite important in the last few years. The Continuing Criminal Enterprise (CCE) section was mentioned above, in the RICO discussion. A person is defined as engaging in a continuing criminal enterprise if he or she is the organizer or supervisor of a group of five or more persons who have obtained substantial income through a series of violations of this Act. He or she is not only subject to more severe penalties, but shall also forfeit both profits and properties associated with his or her felonious acts. A second aspect deals with the no-knock entry issue. Following the legal issuance of a search warrant, an authorized agent may enter, forcibly and without warning, if he or she feels that evidence might otherwise be disposed of, or if the warrant has allowed such action to be taken.

In March 1972, Congress passed the Drug Abuse Office and Treatment Act, which was dedicated to bringing about a reduction of the incidents of drug abuse within the shortest period of time. It called for the formation, within the Executive Office, of a Special Action Office for Drug Abuse Prevention (SAODAP). It also called for the establishment of a National Council for Drug Abuse Prevention which would provide for the creation of a National Drug Abuse Training Center. There would also be the creation of a National Institute on Drug Abuse (NIDA). The following year (1973), the Drug Enforcement Administration (DEA) was created by the merging of three groups: the Office of Drug Abuse Law Enforcement (ODALE, which was created in the Department of Justice in 1972), the Office of National Narcotics Intelligence (ONNI, also created in the Department of Justice in 1972) and the Bureau of Narcotics and Dangerous Drugs (BNDD, created from the merger of the Bureau of Narcotics, BN, and the Bureau of Drug Abuse Control, BDAC, in 1968). The drug enforcement and intelligence functions of the US Customs Service were also brought into the merger. The DEA answers to the Department of Justice.

Congress passed the Psychotropic Substance Act of 1978 as an amendment to the Controlled Substance Act, which dealt mainly with increased penalties for phencyclidine (PCP) and precursors such as piperidine. The very last section of the amendment is entitled "Forfeiture of Proceeds of Illegal Drug Transactions." This addition states, quite simply, that all proceeds from drug transactions may be seized as forfeiture. This has given the government immediate possession of boats, airplanes, real estate property and bank accounts. This asset seizure and forfeiture (before conviction) has been felt by many law enforcement groups to have proven itself to be an effective weapon in the area of drug use prevention.

The Posse Comitatus Act was passed into law just after the Civil War. It was a strategy to keep Federal soldiers from interacting with the civilians in the South, and the specific prohibition was that no military forces can be involved in the enforcement of civil law. The "Department of Defense Authorization Act of 1982" includes a provision that revises the Posse Comitatus statute. Prior to this law, any military involvement in civil law was prohibited unless authorized by the Constitution or by some specific action of Congress. With this law there was a clarification of the role of the military in civilian enforcement activities, and the assistance and support services which may be rendered by the military to law enforcement were defined. There was quick implementation in the formation of the President's Task Force South Florida in January, 1982. This operation was geared to the interdiction of narcotics being smuggled into Florida from the Caribbean and from Latin America. The military aid provided included complex logistic and vessel support, aviation and radar surveillance, and the loan of equipment and facilities. This "allowing" of military participation in drug law matters was further extended in 1986 and in 1989. On 8 April 1986, President Reagan signed a National Security Decision Directive stating that drug trafficking constituted a threat to the national security of the United States. This authorized the military to participate in all international law enforcement activity that was drug related, except for making seizures and arrests. These latter two restrictions were removed by an opinion published by the Department of Justice, on 3 November 1989.

The release of information concerning income tax returns and related financial records has been, at least up until 1982, severely restricted. In September of that year, the "Tax Equity and Fiscal Responsibility Act of 1982" opened everything up. Complex financial transactions are often associated with sophisticated criminal activity, and this information was not available to Federal law enforcement authorities. The new law included several provisions sought by the Department of Justice "to facilitate the appropriate disclosure of tax information to Federal law enforcement agencies for criminal investigative purposes while maintaining safeguards needed to protect the privacy of innocent citizens." Federal officials may now gain access to tax information which is a most valuable source of financial data necessary to prosecute narcotics trafficking and organized crime.

The "Comprehensive Crime Control Act of 1984" is commonly called the Emergency Scheduling Act. The conventional way for the DEA to place a new drug into the CSA has always been to publish an announcement of this intention in the Federal Register, and open a 60-day window, during which time all interested parties could request an input at public hearings. If there were no offended parties, the drug became scheduled in 60 days. If there were to be hearings and discussion, the delay would be longer. This new law is

designed to put an immediate legal control on a new drug, before the hearings are requested and scheduled. The window authorized is one year, extendible by another six months, and at the end of this time, the drug enters its appropriate scheduled position. But during this entire period, it has the status of a scheduled drug and is, of course, illegal. It achieved that "illegal" status immediately with the first announcement in the Federal Register.

An amendment was made to the Controlled Substance Act which was originally called the Scheduled Drug Analogue Bill, but which finally evolved as the "Designer Drug Enforcement Act of 1986." It was initially inspired by the appearance on the street of several analogues of the drug Fentanyl; in its final form it was considerably broader. One of the strengths of the CSA was that it was explicit. It stood apart from many drug laws of other countries in that the drugs to be considered as being covered by the law were precisely named. True, there was an occasional "all possible isomers" but when there can only be six, there is an exact and unambiguous definition of just what structures were covered by the law. This explicitness was lost in 1986 with the introduction of the Analogue Drug Bill. The process of scheduling drugs changed from a list format, which was cumbersome with respect to meeting new and evolving trends, to a structure and activity format which provides a catch-all whether or not a compound related to a scheduled one has any abuse liability. Here is an exact transcription of the text of the law:

PUBLIC LAW 99-570
CONTROLLED SUBSTANCE ANALOGUE ENFORCEMENT ACT OF 1986

(32) (A) Except as provided in subparagraph (B), the term "controlled substance analogue means a substance –

(i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in Schedule I or II;

(ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in Schedule I or II; or

(iii) with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant depressant, or hallucinogen effect on the central nervous system of a controlled substance in Schedule I or II.

(B) Such term does not include –

(i) a controlled substance;

(ii) any substance for which there is an approved new drug application;
(iii) with respect to a particular person any substance, if an exemption is in effect for investigational use, for that person, under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) to the extent conduct with respect to such substance is pursuant to such exemption; or
(iv) any substance to the extent not intended for human consumption before such an exemption takes effect with respect to that substance.

TREATMENT OF CONTROLLED SUBSTANCE ANALOGUES
SEC: 203. A controlled substance analogue shall, to the extent intended for human consumption, be treated for the purpose of this title and title III as a controlled substance in Schedule I.

Some comments are appropriate concerning this analogue drug law – points that may not be immediately apparent from the first reading. Let us assume that the drug in question is the correctly identified, but completely legal drug, ABC.

Many people, lawyers and defendants alike, come to the conclusion that if a drug fits the description of being an analogue, then that drug becomes a Schedule I drug. This is absolutely not so. If, in a situation where a case has gone to trial and the jury accepts that drug ABC is indeed an Controlled Substance Analogue of a Schedule I or II , then in that court case, ABC is treated as a Schedule I drug. But if, in an entirely separate situation, there is a criminal charge dealing with ABC and the Controlled Substance Analogue Enforcement Act is the basis of the prosecution's case, ABC is a virgin again. It is not a Controlled Substance Analogue because of the other trial. It is not a Schedule I drug. The establishment of it as a Controlled Substance Analogue must start all over from scratch. This law does not make drugs into Schedule I drugs; however, it does permit the control of "designer" compounds on a case-by-case basis.

Within the areas of chemical structure, "analogue" is a chemical term meaning, quite loosely, something that looks pretty much the same as something else. Unlike the rather exact chemical terms such as isomer (same weight), isotope (same atom different mass) or homologue (one carbon different), the chemical term analogue is quite loose and means similar. But the legal term "Controlled Substance Analogue" is rigidly defined by the criteria listed above and as such "Analogue" and "Controlled substance Analogue" are not interchangeable.

In general, a new drug law, usually as an amendment of the Controlled Substances Act, has been enacted every even-numbered year. Usually they add new drugs to the schedules and increase the penalties. In 1988, there was enacted

the Chemical Diversion and Trafficking Act which brought into the legal record a listing of precursor chemicals and of essential chemicals. These were reclassified as List I and List II a few years later, and the current status of both lists is detailed below. In the same Act, there was the Anti-Drug Abuse Act amendment to the CSA that broadly increased the civil penalties associated with drug-related convictions, including the withdrawal of Federal benefits, the cancellation of FHA mortgages and student loans, and the suspension of drivers' licenses. This law also led to the creation of the Office of National Drug Control Program (ONDCP) which is now best known as the office of the Drug Czar. The mission of ONDCP was to coordinate the anti-drug efforts of the various agencies and departments of the Federal government, to consult with States and local agencies and assist their anti-drug efforts, to conduct a national media campaign, and to annually promulgate the National Drug Control Strategy.

The intended goal of the Comprehensive Methamphetamine Control Act of 1996 was to increase the penalties for the manufacture and trafficking in methamphetamine and other Scheduled drugs, and to increase regulatory controls. In this latter area, there was the establishment of yet another list of industrial chemicals, called a Special Surveillance, intended to alert chemical suppliers of possible misuse of the products that they sell, and to suggest that they may be held responsible if these products are misused. This list is given below (p. 122).

3.4.2 LISTED CHEMICALS

This is the current inventory of listed chemical (as of October 2000). As several of them are precursors to illegal drugs other than the hallucinogens, the target drugs are listed under the comments. Also included there are incidental bits of information that may be of value to the forensic chemist.

Prior to this listing process that was called for by the Chemical Diversion and Trafficking Act of 1988, a number of known precursors were recognized and were entered into the CSA Schedules. Although these are not drugs *per se*, they have remained in the schedules under a drug status, rather than having been relocated to the List I collection. They are tallied here for reference purposes.

SCHEDULED PRECURSORS WITH ILLEGAL DRUG STATUS

Precursor	*Commentary*
Lysergic acid	This is listed as a Schedule III depressant. It is not pharmacologically active but it is the immediate hydrolysis product of most of the ergot alkaloids, and is an immediate starting material for the synthesis of LSD, a Schedule I hallucinogen.
Lysergic acid amide	This is listed as a Schedule III depressant. It has a sedative amide action in humans, and is a documented component of morning glory seeds. On hydrolysis it gives rise to lysergic acid, and is an immediate starting material for the synthesis of LSD, a Schedule I hallucinogen.
Phenylacetone	This is listed as a Schedule II immediate precursor. It is not pharmacologically active, but it is an immediate precursor for the synthesis of amphetamine and methamphetamine, both Schedule II stimulants.
1-Phenylcyclohexylamine	This is listed as a Schedule II immediate precursor. It is not pharmacologically active, but it is an immediate precursor for the synthesis of phencyclidine (PCP), a Schedule II depressant.
1-Piperidinocyclohexane carbonitrile (PCC)	This is listed as a Schedule II immediate precursor. It is not pharmacologically active, but it is an immediate precursor for the synthesis of phencyclidine (PCP), a Schedule II depressant.

In Sec. 1300.02 (18) of the CSA, is the legal definition of List I chemicals. "The term List I chemical means a chemical specifically designated by the Administrator in Sec. 1310.02(a) of this chapter that, in addition to legitimate uses, is used in manufacturing a controlled substance in violation of the Act and is important to the manufacture of a controlled substance." These are entered below, valid as of October, 2000, with appropriate commentary.

LISTED CHEMICALS: LIST I – CHEMICAL PRECURSORS

Precursor	*Commentary*
(A) Anthranilic acid, its esters, and its salts	This is a precursor to N-acetylantranilic acid (also a listed chemical) which is, in turn, a precursor to either mecloqualone (a Schedule I depressant) or methaqualone (also a Schedule I depressant.)
(B) Benzyl cyanide	This compound in several steps is a precursor to phenylacetone, a listed Schedule II immediate precursor. See above.
(C) Ephedrine, its salts, optical isomers, and salts of optical isomers	This compound is an immediate precursor to methamphetamine, a Schedule II stimulant, using hydroiodic acid as the reducing agent. Phosphorous can be used to regenerate the hydroiodic acid, and elemental iodine can be used to initially generate the hydroiodic acid.
(D) Ergonovine and its salts	This compound is an intermediate to lysergic acid, an immediate precursor to Lysergic acid, a Schedule III depressant and precursor to LSD.
(E) Ergotamine and its salts	This compound is an intermediate to lysergic acid, an immediate precursor to Lysergic acid, a Schedule III depressant and precursor to LSD.
(F) N-Acetyl anthranilic acid, its esters, and its salts	This compound is mentioned under anthranilic acid (A above) as an immediate precursor to either mecloqualone (a Schedule I depressant) or methaqualone (also a Schedule I depressant).
(G) Norpseudo-ephredine, its salts, optical isomers,	This compound is an immediate precursor to amphetamine, a Schedule II stimulant, using hydroiodic acid as the reducing agent. Phosphorous can be used to regenerate the hydriodic acid

and salts of optical isomers	and elemental iodine can be used to initially generate the hydroiodic acid.
(H) Phenylacetic acid, its esters and its salts	This compound is a precursor to phenylacetone, a listed Schedule II immediate precursor. See above.
(I) Phenylpropanolamine, its salts, optical isomers, and salts of optical isomers	This compound is an immediate precursor to amphetamine, a Schedule II stimulant, and to 4-methylaminorex, a Schedule I stimulant.
(J) Piperidine and its salts	This compound is in several steps a precursor to 1-piperidino cyclohexane carbonitrile, the Schedule II immediate precursor mentioned above, and itself an immediate precursor for the synthesis of phencyclidine (PCP), a Schedule II depressant.
(K) Pseudoephedrine, its salts, optical isomers, and salts of optical isomers	This compound is an immediate precursor to methamphetamine, a Schedule II stimulant, using hydroiodic acid as the reducing agent. Phosphorous can be used to regenerate the hydroiodic acid, and elemental iodine can be used to initially generate the hydroiodic acid.
(L) 3,4-Methylenedioxyphenyl-2-propanone	This compound is an immediate precursor to MDA, MDMA, MDE and N-hydroxy-MDA, all Scheduled I hallucinogens.
(M) Methylamine	This compound is an immediate precursor to methamphetamine (a Schedule II stimulant) and to MDMA (a Schedule I hallucinogen).
(N) Ethylamine	This compound is an immediate precursor to ethylamphetamine (a Schedule I stimulant) or MDE (a Schedule I hallucinogen).
(O) Propionic anhydride	This compound is an immediate precursor to fentanyl (a Schedule II opiate) and ketobemidone (a Schedule I opiate).

(P) Isosafrole	This compound is in several steps a precursor to 3,4-methylenedioxyphenyl-2-propanone (L, above) as an immediate precursor to MDA, MDMA, MDE or N-hydroxy-MDA, all Schedule I hallucinogens.
(Q) Safrole	This compound is in several steps a precursor to 3,4-methylenedioxyphenyl-2-propanone (L, above) as an immediate precursor to MDA, MDMA, MDE or N-hydroxy-MDA, all Schedule I hallucinogens.
(R) Piperonal	This compound is in several steps a precursor to 3,4-methylenedioxyphenyl-2-propanone (L, above) as an immediate precursor to MDA, MDMA, MDE or N-hydroxy-MDA, all Schedule I hallucinogens.
(S) N-Methylephedrine	This compound is an immediate precursor to N,N-dimethylamphetamine, a Schedule I stimulant.
(T) N-Methylpseudoephedrine	This compound is an immediate precursor to N,N-dimethylamphetamine, a Schedule I stimulant.
(U) Hydroiodic acid	This compound is a frequently employed reducing reagent used in the synthesis of methamphetamine, a Schedule II stimulant.
(V) Benzaldehyde	This compound is in several steps a precursor to phenylacetone, a Schedule II immediate precursor (see above) to methamphetamine (a Schedule II stimulant).
(W) Nitroethane	This compound is in several steps a precursor to phenylacetone, a Schedule II immediate precursor (see above) to methamphetamine (a Schedule II stimulant).
(X)	Any salt, optical isomer, or salt of an optical isomer of the chemicals listed in subparagraphs (M) through (U) of this paragraph.

In Sec. 1300.02 (19) of the CSA, is the legal definition of List II chemicals. "The term List II chemical means a chemical, other than List I chemical, specifically designated by the Administrator in Sec. 1310.02(b) of this chapter that, in addition to legitimate uses, is used in manufacturing a controlled substance in violation of the Act." These are entered below, valid as of October 2000, with

appropriate commentary. It must be noted that these compounds on List II are widely used in industry as solvents or reagents widely used in research. Their gathering here is due to the fact that they have been used in the manufacture of illegal drugs as well.

LISTED CHEMICALS: LIST II – ESSENTIAL CHEMICALS

Essential chemical	*Commentary*
(A) Acetic anhydride	This compound is used in the conversion of morphine (a Schedule II opiate) to heroin (a Schedule I opium derivative); of anthranilic acid to N-acetyl anthranilic acid (both List I compounds) and can be used in the conversion of phenylacetic acid (I, List I, see above) to phenyl-2-propanone (a Schedule II immediate precursor, see above). It is a common laboratory chemical.
(B) Acetone	This compound is used in the conversion of cocaine base to cocaine hydrochloride, and in the purification of morphine base. It is a common laboratory solvent.
(C) Benzyl chloride	This chemical is used in the synthesis of phenyl-2-propanone, a Schedule II immediate precursor, see above. It is a common laboratory chemical.
(D) Ethyl ether	This chemical is used in the conversion of cocaine to cocaine hydrochloride, a Schedule II substance of vegetable origin. It is a common laboratory solvent.
(E)	Originally hydriodic acid. Moved from List II to List I in 1990.
(F) Potassium permanganate	This chemical is used to purify cocaine, a Schedule II substance of vegetable origin, and to oxidize ephedrine (List I, C) to methcathinone, a Schedule I stimulant. This is a common laboratory chemical.
(G) 2-Butanone	This chemical is used in the conversion of cocaine base to cocaine hydrochloride, a Schedule II substances of vegetable origin. It is a common laboratory solvent.

(H) Toluene	This chemical is used in the conversion of cocaine base to cocaine hydrochloride, a Schedule II substances of vegetable origin. It is a common laboratory solvent.
(I) Iodine	This chemical is used as a source of hydroiodic acid, a List I chemical. It is a common laboratory chemical.
(J) Hydrochloric gas.	This chemical, more often referred to as hydrogen chloride gas, is used as a reagent in the conversion of organic bases to their water-soluble hydrochloride salts. It is a common laboratory chemical.

The present status of the Special Surveillance List authorized by the Comprehensive Methamphetamine Control Act of 1998 is given here. This Act provides for a civil penalty of not more than $250,000 for the distribution by a business of a chemical to anyone who uses, or tries to use it in synthesizing either a controlled drug or a Listed chemical. The penalties would apply if the seller showed a "reckless disregard" of the possible illegal uses that their product could be put to. A number of chemical supply houses now will not sell any of the following, even to industrial and academic institutions, simply because of the increased paper work required.

SPECIAL SURVEILLANCE LIST

Ammonia gas
Ammonium formate
Bromobenzene
1,1-Carbonyldiimidazole
Cyclohexanone
1,1-Dichloro-1-fluoroethane (e.g. Freon 141B)
Diethylamine and its salts
2,5-Dimethoxyphenethylamine and its salts
Formamide
Hypophosphorous acid
Lithium metal
Lithium aluminum hydride
Magnesium metal (turnings)
Mercuric chloride
N-Methylformamide
Organomagnesium halides (Grignard reagents) e.g. ethylmagnesium bromide and phenylmagnesium bromide

Phenylethanolamine and its salts
Phosphorus pentachloride
Potassium dichromate
Pyridine and its salts
Red phosphorus
Sodium dichromate
Sodium metal
Thionyl chloride
ortho-toluidine
Trichloromonofluoromethane (e.g. Freon-11, Carrene-2)
Trichlorotrifluoroethane (e.g. Freon 113)

There are four equipment items on this list; hydrogenators, tableting machines, encapsulating machines, and 22 liter heating mantels. A previous anti-methamphetamine law had already made the possession of a three-neck round bottom flask illegal, if there is the intent to manufacture methamphetamine in it.

3.4.3 SCHEDULE I HALLUCINOGENS

Here is listed the full Schedule I inventory of Hallucinogenic Drugs with the exact printed name or names given. The primary printed name is followed by the DEA Controlled Substance Code Number. After a few of the 31 entries there is added detail and commentary, that will help flesh out the definition of unusual words and give some of the associated history that is involved.

> Sec. 1308.11(d) Hallucinogenic substances. Unless specifically excepted or unless listed in another Schedule, any material, compound, mixture or preparation, which contains any quantity of the following hallucinogenic substances, or which contains any of its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible with the specific chemical designation (for purposes of this paragraph only, the term "isomer" includes the optical, position (sic) and geometric isomers):
>
> (1) Alpha-ethyltryptamine 7249 Some trade or other names: etryptamine; Monase, alpha-ethyl-1H-indole-3-ethanamine; alpha-ET; and AET.

Alpha-ethyltryptamine is a stimulant produced by the Upjohn Pharmaceutical Company. After it was discontinued by them, it was added to the Schedule I drug list on 12 September 1994 [59 FR 46757].

(2) 4-Bromo-2,5-dimethoxy-amphetamine 7391 Some trade or other names: 4-bromo-2,5-dimethoxy-[alpha]-methylphenethylamine; 4-bromo-2,5-DMA.

The positional isomer addition in the opening paragraph of this section dictates that the 15 additional isomers of DOB are all to be considered as Schedule I drugs. DOB was added to the Schedule I list on 21 September 1973 [38 FR 26447].

(3) 4-Bromo-2,5-dimethoxyphenethylamine 7392 Some trade or other names: 2-[4-bromo-2,5-dimethoxyphenyl]-1-aminoethane; alpha desmethyl DOB; 2C-B; Nexus.

The positional isomer addition in the opening paragraph of this section dictates that the 15 additional isomers of 2C-B are all to be considered as Schedule I drugs. 2C-B was added to the Schedule I list on 6 January 1994 [59 FR 671].

(4) 2,5-Dimethoxyamphetamine 7396 Some trade or other names: 2,5-dimethoxy-[alpha]-methylphenethylamine; 2,5-DMA.

The positional isomer addition in the opening paragraph of this section dictates that the five additional isomers of 2,5-DMA are all to be considered as Schedule I drugs. 2,5-DMA was added to the Schedule I list on 21 September 1973 [38 FR 26447]. There is a non-medical use for this compound in the photographic industry, which requires and received approval for the production of multi-ton quantities. Also, this chemical can serve as the immediate synthetic precursor of DOB (see above) or the unscheduled analogue, DOI.

(5) 2,5-Dimethoxy-4-ethylamphetamine 7399 Some trade or other names: DOET.

The positional isomer addition in the opening paragraph of this section dictates that the 15 additional isomers of DOET are all to be considered as Schedule I drugs. DOET was added to the Schedule I list on 16 February 1973 [58 FR 4316].

(6) 4-Methoxyamphetamine 7411 Some trade or other names: 4-methoxy-[alpha]-methylphenethylamine; paramethoxyamphetamine, PMA.

The positional isomer addition in the opening paragraph of this section dictates that both additional isomers of PMA are all to be considered as Schedule I drugs. PMA was added to the Schedule I list on 21 September 1973 [38 FR 26447]

(7) 5-Methoxy-3,4-methylenedioxyamphetamine 7401

The positional isomer addition in the opening paragraph of this section dictates that the five additional isomers of MMDA are all to be considered as Schedule I drugs. MMDA was #2 of the 17 hallucinogenic drugs placed in the CSA when it was written.

(8) 4-Methyl-2,5-dimethoxyamphetamine 7395 Some trade and other names: 4-methyl-2,5-dimethoxy-[alpha]-methylphenethylamine; "DOM"; "STP."

The positional isomer addition in the opening paragraph of this section dictates that the 15 additional isomers of DOM are all to be considered as Schedule I drugs. DOM was #7 of the 17 hallucinogenic drugs placed in the CSA when it was written.

(9) 3,4-Methylenedioxyamphetamine 7400

The positional isomer addition in the opening paragraph of this section dictates that there is one additional isomer of MDA which is to be considered as a Schedule I drug. MDA was #1 of the 17 hallucinogenic drugs placed in the CSA when it was written.

(10) 3,4-Methylenedioxymethamphetamine (MDMA) 7405

The positional isomer addition in the opening paragraph of this section dictates that there is one additional isomer of MDMA which is to be considered as a Schedule I drug. MDMA was temporarily placed in Schedule I on 1 July 1985 under the authority of the Emergency Scheduling Act [50 FR 23118]. After one year (on 17 June 1986), this placement was extended for six months [51 FR 21911] and the permanent placement in Schedule I occurred on 13 November 1986 [51 FR 36552]. Shortly thereafter an appeal was filed concerning this ruling which argued, amongst other points, that the method of deciding currently accepted medical use, a requirement for the assignment to Schedule I, was inappropriate. The United States Court of Appeals for the First Circuit agreed with the petitioner on this point and ordered the DEA to vacate this drug from Schedule I (18 September 1987). The drug was removed from Schedule I effective 27 January 1988 [53 FR 2225] and relocated back into Schedule I on 22 February 1988, effective 23 March 1988 [53 FR 5156]. The Controlled Substance Handbook of the Government Information Services makes no mention of any of the earlier dates or Federal Register citations, and only records the last entry above for the placement of MDMA into Schedule I.

It is possible that there could not have been any illegal activity involving MDMA until 23 March 1988, if indeed it was not until this date that it became officially a Schedule I drug.

> (11) 3,4-Methylenedioxy-N-ethylamphetamine 7404 (also known as N-ethyl-alpha-methyl-3,4(methylenedioxy)phenethylamine, N-ethyl-MDA, MDE, MDEA.

The positional isomer addition in the opening paragraph of this section dictates that there is one additional isomer of MDE which is to be considered as a Schedule I drug. MDE was added to the Schedule I list on 13 April 1989 [54 FR 14797].

> (12) N-Hydroxy-3,4-methylenedioxyamphetamine 7402 (also known as N-hydroxy-alpha-methyl-3,4(methylenedioxy)phenethylamine, and N-hydroxy-MDA.

The positional isomer addition in the opening paragraph of this section dictates that there is one additional isomer of MDOH which is to be considered as a Schedule I drug. MDOH was added to the Schedule I list on 13 October 1988 [53 FR 40061].

> (13) 3,4,5-Trimethoxy amphetamine 7390

The positional isomer addition in the opening paragraph of this section dictates that there are five additional isomers of TMA which are to be considered as a Schedule I drug. TMA was #3 of the 17 hallucinogenic drugs placed in the CSA when it was written.

> (14) Bufotenine 7433 Some trade and other names: 3-([beta]-dimethylaminoethyl)-5-hydroxyindole; 3-(2-dimethylaminoethyl-5-indolol; N,N-dimethylserotonin; 5-hydroxy-N,N-dimethyltryptamine; mappine.

The positional isomer addition in the opening paragraph of this section dictates that there are three additional isomer of bufotenine which are to be considered as a Schedule I drug. One of these is the schedule I drug psilocin which is #26, below. Bufotenine was #4 of the 17 hallucinogenic drugs placed in the CSA when it was written.

> (15) Diethyltryptamine 7434 Some trade and other names: N,N-diethyltryptamine, DET.

The positional isomer addition in the opening paragraph of this section does not apply to DET as there are no substituents. DET was #5 of the 17 hallucinogenic drugs placed in the CSA when it was written.

(16) Dimethyltryptamine 7435 Some trade and other names: DMT

The positional isomer addition in the opening paragraph of this section does not apply to DMT as there are no substituents. DMT was #6 of the 17 hallucinogenic drugs placed in the CSA when it was written.

(17) Ibogaine 7260 Some trade and other names: 7-ethyl-6,6b,7,8,9,10,12,13-octahydro-2-methoxy-6,9-methano-5H-pyrido [1',2':1,2] azepino [5,4-b] indole; Tabernanthe iboga.

The positional isomer addition in the opening paragraph of this section dictates that there are three additional isomers of ibogaine which are to be considered as a Schedule I drug. The botanical binomial may be improperly entered here into the law. Ibogaine was #8 of the 17 hallucinogenic drugs placed in the CSA when it was written, but in that initial listing, the trivial name ibogaine alone appeared. On the full printing of the revised list in 1971, the name *Tabernanthe iboga* appeared as a synonym. It is, however, the name of a plant and not the name of the compound. To make a new material illegal requires a formal process (postings, hearing, etc.) and there is no record of this having been done. The compound is soundly illegal. The plant is quite possibly not illegal.

(18) Lysergic acid diethylamide 7315

The positional isomer addition in the opening paragraph of this section does not apply to LSD as there are no substituents. LSD was #9 of the 17 hallucinogenic drugs placed in the CSA when it was written.

(19) Marihuana 7360

Marihuana was entry #10 of the 17 hallucinogenic drugs placed in the CSA when it was written. It is not given any trade or other names in the Code of Federal Regulation — it is just as presented here, as one word. In the definition section, however, the following appears: "The term "marihuana" means all parts of the plant *Cannabis sativa* L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin.

Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, and other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil or cake, or the sterilized seed of such plant which is incapable of germination." Entry #27 below deals with the synthetic equivalents of the tetrahydrocannabinols which are normally found in the resin of *Cannabis sativa.*

(20) Mescaline 7381

Mescaline is 3,4,5-trimethoxyphenethylamine. The positional isomer addition in the opening paragraph of this section dictates that there are five additional isomers of mescaline which are to be considered as a Schedule I drug. Mescaline was #11 of the 17 hallucinogenic drugs placed in the CSA when it was written. It is also the major active component of the cactus Peyote, which is entry #22 below.

(21) Parahexyl 7374 Some trade or other names: 3-hexyl-1-hydroxy-7,8,9,10-tetrahydro-6,6,9-trimethyl-6H-dibenzo [b,d] pyran; Synhexyl.

The positional isomer addition in the opening paragraph of this section dictates that there are eleven additional isomers of parahexyl and, with a cis-trans possibility about the existing double bond there may be some 23 isomers which are to be considered as Schedule I drugs. Parahexyl was added to the Schedule I list on 22 December 1982 [47 FR 52432] as a direct consequence of the United States becoming (in 1980) a party to the International Drug Control Treaty "Convention of Psychotropic Substances, 1971." See the initial proposal [47 FR 33986] for details for this required scheduling.

(22) Peyote 7415 Meaning all parts of the plant presently classified botanically as *Lophophora williamsii* Lemaire, whether growing or not, the seeds thereof, any extract from any part of such plant, and every compound, manufacture, salts, derivative, mixture, or preparation of such plant, its seeds or extracts (Interprets 21 USC 812(c), Schedule Ic(c) (12))

This is one of the four plants that are listed in the Federal Drug Law with probable correctness. The other three are *Cannabis sativa* (marihuana, Schedule I above), *Papaver somniferum* (opium) and *Erythroxylon coca* (coca). The *Tabernanthe iboga* (#17 above) and *Catha edulis* (associated with Cathinone, Schedule I stimulants) are controversial. As peyote is a plant, the positional isomer detail in the opening paragraph has no meaning. It was #12 of the 17

hallucinogenic drugs placed in the CSA when it was written. Peyote is also the sacrament of an approved religion. Sec. 1307.31 exempts peyote from control when used in *bona fide* religious activities by the Native American Church, which is primarily made up of American Indians. However, persons who manufacture or distribute peyote to the Native American Church must register with DEA and otherwise comply with the regulations.

(23) N-Ethyl-3-piperidyl benzilate 7482

Both this compound and its N-methyl quaternary salt, as well as the N-methyl compound mentioned below in #24, have been studied as potential intoxicating agents of use in chemical warfare. The Lakeside code for this is JB-318. The positional isomer addition in the opening paragraph of this section dictates that two positional additional isomers of JB-318 can be classified as Schedule I drugs. The quaternary salt was explicitly excluded from consideration as a scheduled drug (see [35 FR 7069]). The presence of this compound, and the N-methyl directly below, is due to the fact that they were known and talked about during the Haight Ashbury times as compounds with wild potential. There is no evidence that they were ever drugs of abuse. JB-318 was #13 of the 17 hallucinogenic drugs placed in the CSA when it was written.

(24) N-Methyl-3-piperidyl benzilate 7484

As mentioned above, this compound and its N-methyl quarternary salt have been studied as potential intoxicating agents of use in chemical warfare. The Lakeside code for this compound is JB-336. See the entry above, #23, for some of the history and absence of abuse record. JB-336 was #14 of the 17 hallucinogenic drugs placed in the CSA when it was written.

(25) Psilocybin 7437

Psilocybin is the phosphate ester of N,N-dimethyl-4-hydroxytryptamine. The positional isomer addition in the opening paragraph of this section dictates that there are three additional isomers of psilocybin which are to be considered as a Schedule I drug. Psilocybin was #15 of the 17 hallucinogenic drugs placed in the CSA when it was written. It is a major active component of some hundred psychoactive mushrooms, many of the *Psilocybe* Genus, but none of these plants are recognized in the Federal law.

(26) Psilocyn

Psilocyn is N,N-dimethyl-4-hydroxytryptamine, and is usually spelled psilocin in the scientific literature. The positional isomer addition in the opening paragraph of this section dictates that there are three additional isomers of psilocin which are to be considered as a Schedule I drug. One of these is the Schedule I compound bufotenine mentioned previously (#14). Psilocin was #16 of the 17 hallucinogenic drugs placed in the CSA when it was written. It is present in many of the psychoactive mushrooms mentioned under #25. But again, none of these mushrooms are recognized in the Federal law.

(27) Tetrahydrocannabinols 7370 Synthetic equivalents of the substances contained in the plant, or in the resinous extracts of Cannabis, sp. and/or synthetic substances, derivatives, and their isomers with similar chemical structures and pharmacological activity such as the following:

Δ 1 cis or trans tetrahydrocannabinol, and their optical isomers
Δ 6 cis or trans tetrahydrocannabinol, and their optical isomers
Δ 3,4 cis or trans tetrahydrocannabinol, and their optical isomers

(Since nomenclature of these substances is not internationally standardized, compounds of these structures, regardless of numerical designation of atomic positions covered.) (sic.)

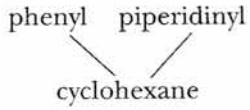
Tetrahydrocannabinol is one of the major components of cannabis resin. This entry covers all the major stereoisomers, but follows the synthetic approach. Tetrahydrocannabinol was #17 of the 17 hallucinogenic drugs placed in the CSA when it was written. The Δ 6 trans isomer, dronabinol or Marinol, in sesame oil in a soft gelatin capsule, is an FDA approved product, and was rescheduled on 13 May 1986, to Schedule II [51 FR 17576. It was rescheduled again on July 2, 1999, to Schedule III [64 FR 35928].

Some other names for dronabinol: (6a, 10a-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo [b,d]pyran-1-ol, or (-)-delta-9-(trans)-tetrahydrocannabinol. The other isomers remain, presumably, in Schedule I.

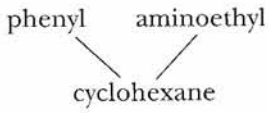
(28) Ethylamine analogue of phencyclidine 7455 Some trade or other names: N-ethyl-1-phenylcyclohexylamine, (1-phenyl-cyclohexyl)ethylamine, N-(1-phenylcyclohexyl) ethylamine, cyclohexamine, PCE.

This and the next three entries are all substitutional analogues of PCP. None of them have substitution, so there are no position isomers involved. All four of

these analogues have a structure that can be related directly to PCP, a Schedule II depressant. The parent PCP skeleton has a 1-phenyl-1-piperidinyl substitution pattern.



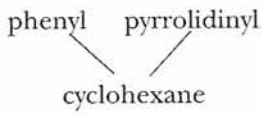
There are no ring substituents, thus there are no positional isomers. PCE has a 1-phenyl-1-aminoethyl substitution pattern. It can be symbolized as



It was entered into Schedule I on 25 October 1978 [43 FR 43295].

(29) Pyrrolidine analogue of phencyclidine 7458 Some trade or other names: 1-(1-phenylcyclohexyl)-pyrrolidine, PCPy, PHP.

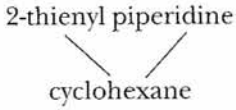
This is the second of the four most similar PCP analogues. The PCPy skeleton has a 1-phenyl-1-pyrrolidyl substitution pattern. It can be symbolized as:



It was entered into Schedule I on 25 October 1978 [43 FR 43295].

(30) Thiophene analogue of phencyclidine 7470 Some trade or other names: 1-[1-(2-thienyl)-cyclohexyl]-piperidine, 2-thienylanalogue of phencyclidine, TPCP, TCP.

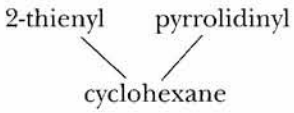
This the third of the four most similar PCP analogues. The TCP skeleton has a 1-(2-thienyl)-1-piperidyl cyclohexyl substitution pattern, and is known by the name of Tenocyclidine. It can be symbolized as:



It was entered into Schedule I on 11 August 1975 [40 FR 28611].

(31) 1-[1-(2-Thienyl)cyclohexyl]pyrrolidine 7473 Some other names: TPCP, TCPy

This is the fourth of the four most similar PCP analogues. The TCPy skeleton has a 1-(2-thienyl) 1-pyrrodinyl cyclohexyl substitution pattern. It can be symbolized as:



It was entered into Schedule I on 6 July 1989 [54 FR 28414].

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Rather than referencing a detailed bibliography, the reader wishing more detailed information is encouraged to seek out the citations included in the following reviews, which were called upon for this present chapter.

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