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Medicinal Chemistry and Structure-Activity Relationships of Hallucinogens

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Elucidation of the mechanism of action for virtually all biologically active substances has been a collaborative effort between scientists in a variety of disciplines. In the area of drug research, medicinal chemists have played important roles by providing series of homologs and congeners of prototype compounds. The development of potency series, where the *in vivo* action can be correlated with *in vitro* or biochemical effects, has often played a pivotal role in formulating hypotheses about mechanism of drug action at the molecular level.

Hallucinogens present a unique challenge to medicinal chemists who attempt the development of useful potency series, primarily because of limitations on the ability to gather clinical or meaningful *in vivo* data. Second, even when clinical results are available, problems are presented because the mental state produced by hallucinogens is extremely difficult to quantitate. Nevertheless, for several years, we have been involved in attempts to elucidate structure-activity relationships and mechanism of action for hallucinogens. These efforts have been directed toward the synthesis and evaluation of structural congeners and novel analogs of known hallucinogenic drugs. The development of correlations between *in vitro* and *in vivo* data, based on such series, can play an important role in identifying neuronal and receptor systems involved in the process of hallucinogenesis.

Compounds in these series may also prove to be useful pharmacologic tools in the study of normal sensory processing. For example, there are a number of phenethylamine and tryptamine derivatives that have been categorized as hallucinogens but which do not produce severe sensory disruption and intoxication at moderate doses; rather, they alter consciousness in subtle ways. Some of these compounds have been described as amplifying empathy, facilitating intellectual function and the flow of ideas, and promoting access to subconscious material and long-term memory. Indeed, one compound has even been reported which

seems to selectively lower the perceived pitch of musical tones (202)! Considering the broad range of pharmacologic effects that the hallucinogens are capable of producing, it is possible that careful and systematic structural modification will lead to compounds that have a specific or selective effect only on one sensory modality. In such cases, following a complete characterization of the human psychopharmacology, studies of the pharmacology in animals and *in vitro,* as well as examination of regional brain distribution and receptor binding characteristics, should lead to a greater understanding of the role of the various neural substrates in the processing of those particular sensory data.

At the outset, the reader should be cautioned regarding the nature of the biologic data used in this chapter. It will be apparent after reading other chapters in this book, that hallucinogenic drugs represent a unique pharmacologic classification. If one wishes to develop useful therapeutic agents, models are generally available that have easily measured quantitative endpoints. This is true for virtually all drug classes. Hallucinogens, however, produce a unique state of human consciousness that cannot be adequately modeled in nonhuman species. Ethical considerations and legal proscription have largely prevented the assay of hallucinogenic drugs in man. Furthermore, complete dose-response studies have not always been conducted when human subjects have been employed. With the exception of the extensive work reported by Dr. A. T. Shulgin and his co-workers, much of which is cited in this chapter, few recent clinical data are available for hallucinogens. This is unfortunate, since all models thus far developed depend for validation on the degree to which activity in the model can be correlated with human potency.

The paucity of clinical data reflects the expense and difficulty of obtaining permission to carry out clinical studies with a class of drugs that presents little or no recognized therapeutic value. Hence the apparent benefit-to-risk ratio is infinitesimally small. It is, perhaps, unfortunate that therapeutic reality must ignore some of the most basic processes that occur in the human brain. For these reasons, a number of animal models have been used, not through choice but by necessity. Our reliance on animal and *in vitro* models has been essential to the development of structure-activity relationships for hallucinogens. In general, conclusions from animal models are accepted as valid. We have attempted to place these approaches in perspective, however, by referring to the particular animal model that was used. When a particular compound has been tested in man, it is stated. If one assumes that the models employed are appropriate and can be expected to reflect human potency, the knowledge of structure-activity relationships can be viewed as considerably expanded in recent years. Nevertheless, unless a particular compound has been tested in humans, one cannot be certain that all the structure-activity relationships described in this chapter will apply in the clinical situation. Based on our collective experience, it is likely that the most common error found in animal models is the identification of "false positives." That is, the models may indicate a compound to be active, whereas actual testing in humans reveals inactivity. It is clear that no present animal models correlate with the qualitative differences between hallucinogens observed in humans.

Examples of common animal models that have been used over the last decade include the following: (a) disruption of the conditioned avoidance response in rats (27), (b) mouse head twitch (43), (c) rabbit hyperthermia (1), (d) cat rage response (244) and cat limb flick (121), (e) mouse ear scratch (135,251), (f) flexor and stepping reflex in chronic spinal dog (140,143), (g) serotonin syndrome in rats (118), (h) tactile startle response in rats (68), and (i) two-lever drug discrimination in rats (84).

The variety in the above examples is illustrative of the long and frustrating search for valid animal models to correlate with clinical findings. While none of the listed models is ideal, perhaps the last, two-lever drug discrimination, is the best. The drug discrimination procedure, in fact, is a drug "detection" method that employs a subtle behavioral paradigm, as one intuitively feels that such an assay should be, and is, exquisitely sensitive (38). Furthermore, within limits, by choice of appropriate training drug, one can obtain certain qualitative and quantitative data (82). The rapid and increasing acceptance of this model for the study of a variety of behaviorally active drug classes attests to its usefulness and power (39). The reader is referred to the chapter in this book by Appel and Rosecrans for further information regarding this method.

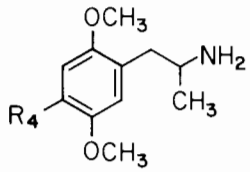
The application of the drug discrimination method to the study of hallucinogenic agents has been recently reviewed (84). Using this paradigm with DOM (see Table 1) as the training drug, Glennon and co-workers (84,88,91) have demonstrated that certain members of each of the classes of agents discussed herein, the phenylalkylamines, N,N-dialkyltryptamines, alpha-methyltryptamines, beta-carbolines, and lysergic acid diethylamide (LSD), are capable of producing similar stimulus properties in rats. Animals apparently recognize these agents at a particular dose as producing a common interoceptive cue. Although the nature of this cue is unknown, there is an excellent correlation between the ED_{50} values of a group of 33 such agents in the drug discrimination study and their overall human hallucinogenic potencies (84). Thus the use of the drug discrimination paradigm should prove to be a useful tool for studying the structure-activity relationships and mechanism of action of hallucinogenic agents. Specific and more detailed comments on some of the above assays can be found in chapters on conditioned and unconditioned behavior elsewhere in this volume.

For the purposes of this chapter, hallucinogens are divided into two separate categories. The first section covers the substituted phenylalkylamines, with the prototype for these structures being mescaline. The second category includes indole-based compounds, including various substituted tryptamines, beta-carbolines, and LSD.

Most of the structure-activity work that has been done lends itself to such a division. Within each category, one can make meaningful comparisons. At present, the possible functional and pharmacologic relationship between these

TABLE 1. *Human hallucinogenic potencies of 2,5-dimethoxy-4-substituted phenylisopropylamines*[a]

4-Substituent	Trivial designation	Potency (MU)[b]
H	2,5-DMA	8
OCH_3	TMA-2	20
OCH_2CH_3	MEM	20
SCH_3	paraDOT (aleph-1)	40
$SCH(CH_3)_2$	Aleph-4	40
F	DOF	—[c]
Cl	DOC	—[c]
Br	DOB	400
I	DOI	400
CH_3	DOM (STP)	80
C_2H_5	DOET	100
C_3H_7	DOPR	80
$isoC_3H_7$	DOIPR	—[d]
C_4H_9	DOBU	40
$sec\text{-}C_4H_9$	DOSB	—[d]
$iso\text{-}C_4H_9$	DOIB	20
$tert\text{-}C_4H_9$	DOTB	—[d]
$n\text{-}C_5H_{11}$	DOAM	10



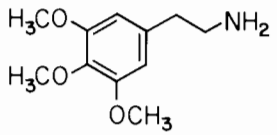
[a] See refs. 194, 196, and 197 for extensive listings.
[b] Human activity expressed in mescaline units (MUs) (205). An approximate effective oral dose in milligrams can be obtained by dividing 400 mg by the MU value.
[c] Not tested in humans.
[d] Not active at acute oral dosages of the hydrochloride salt up to 10 mg.

two general categories remains speculative. However, some general comments are presented, which concern the potential structural and/or functional similarities between the phenethylamines and the tryptamines.

Our goal in this discussion is to present the types of structural variations that have been studied in the various classes of hallucinogens and to explain how these changes affect biologic activity. Where possible, reasonable explanations for these differences are offered. Since we are just beginning to scratch the surface in our search for useful structure-activity relationships, the reader will soon note that most of the correlations are empirical, with no readily apparent biochemical or pharmacologic rationale.

PHENYLALKYLAMINES

The natural prototype for the phenylalkylamines is mescaline (Structure **1**), isolated from the peyote cactus (*Lophophora williamsii*) by Heffter in 1896 (100) and subsequently obtained synthetically by Spath in 1919 (218). Used for many centuries in the form of peyote by Indians in Mexico and the American Southwest (3), it is often referred to as one of the classic hallucinogens, along with psilocybin, psilocin, and LSD. Little structure-activity work was directed toward mescaline or its congeners until 1955, when Peretz et al. (174) reported that α-methyl mescaline (TMA) (8), which represented a "hybrid" of the structure



Structure 1. Mescaline.

of mescaline and amphetamine, possessed approximately twice the potency of mescaline in humans.

A great deal of structural modification work has ensued in the subsequent years. At present, however, the level of effort and number of laboratories involved in this area are small compared to that during the 1960s and 1970s, when hallucinogens were a popular topic in the lay media. It will be easiest to describe this work by focusing on specific types of molecular modifications and how they affect activity.

Orientation of Aromatic Substituents

The most potent compounds thus far studied invariably possess a 2,4,5-trisubstitution pattern. The second most common orientation is 3,4,5-trisubstitution, as seen in mescaline. Selected compounds with other substituent orientations (e.g., 2,4,6-) are active; but the 2,4,5- and 3,4,5-trisubstituted analogs are the most numerous and comprise the bulk of active compounds reported to date. Numerous reviews are available covering work through about 1980 (1,24,172,193,194,196,197,205).

It has been suggested that compounds with 2,5-dimethoxy substituents may be O-demethylated to generate reactive quinone species, and that this may play a role in their high activity (193,197,205). However, this substitution also leads to high-energy molecular orbitals. Furthermore, transposing the 4-methyl of 2,5-dimethoxy-4-methylamphetamine (DOM) (see Table 1) or the 4-bromine of 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB) to the 3-position results in a 100-fold decrease in receptor affinity, as well as a loss of behavioral activity in animals (78,82). This structural modification would lead to a twisting out of plane for the 2-methoxy and a consequent loss of the resonance overlap between the pi system and the *n* electrons of the oxygen. The result of this would be a decrease in the energy of the molecular orbitals, one possible explanation for the observed loss of biologic activity. Domelsmith et al. (52–54) have demonstrated correlations between human potency and the ionization potentials of substituted phenethylamines. These findings are in agreement with many suggestions that hallucinogens may form a charge-transfer complex with an electron acceptor at the receptor (125,212,220). Furthermore, *in vivo* activity generally parallels *in vitro* assays, where metabolism is not a factor. Thus the 2,5-dioxygenation pattern serves in an electronic capacity to confer optimal molecular orbital properties to the molecule (53). This appears to be the best explanation, based on the available data.

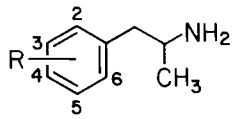
Substituent orientation is largely responsible for determining the relative importance of various possible qualitative components of action. For example, the effects of 3,4,5- or 2,4,5-substituted compounds typify what is more commonly thought of as "hallucinogenic action." On the other hand, those that are 4-monosubstituted, or others with certain disubstitution patterns, may possess striking qualitative differences in man. Often, these have a powerful amphetamine-like stimulant effect. Several workers have commented on the fact that "hallucinogens" actually fall into a broad pharmacologic spectrum, ranging in action from amphetamine-like to LSD-like (1,88,143,155). A recent study by Glennon et al. (82) suggests that it may be possible to study certain of these qualitative differences using the two-lever drug discrimination assay in rats, based on the stimulus generalization that occurs to the training drug selected. It is unlikely, however, that any nonhuman model will be developed which can reliably predict these properties in advance. This is simply due to the large number of possible component processes involved, including not only direct receptor effects but also the release of various endogenous neurotransmitters (31,32,160,233,234) and blockade of their reuptake (139). Each of these component processes will have its own structure-activity relationships. The net result of the administration of a given drug will depend on the degree to which its particular substitution pattern allows it to interact with each possible component in the biologic system.

The agents of major interest that have been evaluated in man are listed in Tables 1 and 2. Although the potencies of these are given relative to mescaline, the foregoing discussion should make it clear that the intoxication at the effective dose for each of these may vary widely in its qualitative aspects.

Nature of Substituents

It has become clear that there are severe limitations on the type of substituents that may be present at the 2- and 5-, or 3- and 5-positions of the phenethylamines. For 2,4,5-substituted compounds, no substituent at the 2-position, other than methoxy, has demonstrated significant clinical activity. The replacement of the 2-methoxy with a methyl (5), methylthio (115), ethoxy (191), or bromine (11,188) destroys or dramatically attenuates activity. Replacement of the 2-methoxy by hydrogen in 2,4,5-trimethoxyphenylisopropylamine gives 3,4-dimethoxyphenylisopropylamine (3,4-DMA) (Table 2), which is inactive. Replacement of the 2-methoxy of DOM (see Table 1) with a hydrogen gives a compound that retains activity in mice (104), but which has lost its activity in other animal models (1) and which is clinically inactive at doses up to 25 mg, acutely (199). It appears that a methoxy precisely fulfills critical steric and electronic requirements. A recent study using the discriminative stimulus paradigm has further emphasized the importance of the 2-methoxy (87). *In vitro* and animal behavioral data suggest that a 2-hydroxy may also lead to active compounds (79), but no clinical trials confirm this. Only one important exception exists: 3,4-methylenedi-

TABLE 2. *Hallucinogenic potencies in humans for selected alkoxy-substituted phenylisopropylamines*[a]



Trivial designation	Substituent at position 2	3	4	5	6	Potency (MU)[b]
PMA	H	H	OCH_3	H	H	6
3,4-DMA	H	OCH_3	OCH_3	H	H	1
2,4-DMA	OCH_3	H	OCH_3	H	H	6
TMA-3	OCH_3	OCH_3	OCH_3	H	H	2
TMA-4	OCH_3	OCH_3	H	OCH_3	H	4
TMA-5	OCH_3	OCH_3	H	H	OCH_3	10
TMA-6	OCH_3	H	OCH_3	H	OCH_3	10
MMDA	H	OCH_3	$O\text{-}CH_2\text{-}O$		H	3
MMDA-2	OCH_3	H	$O\text{-}CH_2\text{-}O$		H	10
MMDA-3a	OCH_3	$O\text{-}CH_2\text{-}O$		H	OCH_3	10
MMDA-3b	$O\text{-}CH_2\text{-}O$		OCH_3	H	H	3
MMDA-5	$O\text{-}CH_2\text{-}O$		H	H	OCH_3	10
DMMDA	OCH_3	$O\text{-}CH_2\text{-}O$		OCH_3	H	12
DMMDA-2	OCH_3	OCH_3	$O\text{-}CH_2\text{-}O$		H	5

[a] Taken from ref. 197.
[b] Human activity expressed in mescaline units (MUs) (205). An approximate effective oral dosage in milligrams can be obtain by dividing 400 mg by the MU value.

oxyamphetamine (MDA; Structure **3a**). This compound has approximately twice the potency of mescaline in humans (205). The subjective effects produced by MDA and other methylenedioxy-substituted compounds are considerably different than those with 2,5-dimethoxy substituents (190,207). This illustrates the problem of clinical potency assessment; on a weight basis, MDA is more potent than mescaline, but at effective dosages, it produces a qualitatively different intoxication state.

The 5-methoxy seems less critical; its replacement by methylthio or ethylthio groups, especially in 3,4,5-substituted compounds, has recently been explored by Jacob and Shulgin (116). Activity in this series is not reduced. Recently, the authors (117) prepared the 2- and 5-thio isosteres of DOM and DOET. With a 2-thiomethyl, activity was retained but was attenuated to about 1/20 to 1/25 of the oxygen isosteres. The 5-thiomethyl isomers possessed two to four times the activity of the thiomethyls at the 2-position. When both the 2- and 5-methoxys were replaced by thiomethyl groups, activity was essentially abolished.

The most interesting and fruitful area of structural modification is at the 4-position, i.e., para to the side chain. Virtually every type of substituent tried has yielded active compounds in one series or another. Some of the more important compounds are listed in Table 1.

Specific data are discussed later; but the 4-substituent has potential importance in one or more of the following ways: (a) to increase general lipophilicity, facilitating passive diffusion into the CNS (13); (b) to confer metabolic stability on the molecule by simultaneously blocking aromatic hydroxylation at this site and by providing a group that is relatively resistant to oxidative metabolism (194); and (c) by possibly providing a group to interact with a hydrophobic region which is proposed to be located at a complementary site on the serotonin receptor (54,80,131,158,164). Much of the recent structure-activity work on phenethylamine hallucinogens has focused on manipulation of the para substituent.

The types of para substituents that have been examined include halogen, alkyl, and alkoxy or alkylthio. The halogens Br and I have both yielded highly active compounds in human trials. The 4-bromo homolog of DOM, DOB, is the most potent hallucinogenic amphetamine yet prepared. It has an oral threshold dose of about 0.2 mg and is approximately 400 times more potent than mescaline (206). Its ease of synthesis and high potency have led to illicit manufacture and abuse (48,198). Unfortunately, cases have been reported where chronic high dosages of DOB have led to gangrene due to peripheral vasoconstriction, and at least one death has been attributed to DOB abuse (198). It has been previously shown that DOB is a potent peripheral vasoconstrictor (32,56). This vasoconstriction is probably mediated by the serotonin-like agonist action of DOB, which has been demonstrated in vascular smooth muscle from dog and sheep and in the rat stomach fundus (32,56,72). Although at high doses DOB apparently has an LSD-like quality, the initial clinical report, at relatively low dosages, described central nervous system (CNS) effects that were relatively mild and involved primarily changes in mood and affect similar to those elicited by MDA. The iodine homolog DOI is quite potent and apparently presents a clinical picture similar to that of DOB (see Table 1) (197). The chlorine homolog DOC is about equipotent to DOB in rabbit and cat models (1) but has not been tested in man. The fluorine homolog DOF has been evaluated in rats in a two-lever drug discrimination assay (88). It has relatively high potency in this model and might be expected to be clinically active, but no human studies have been reported. In this study by Glennon et al. (88), the (−) isomers of DOB, DOI, and the nitro homolog DON all proved to be more potent than their racemates in stimulus generalization tests in rats trained to discriminate DOM from saline. Previously, the racemates of DON and DOC had been tested in a general rat behavioral screen and had been found to be equipotent to DOM (44).

In the 2,5-dimethoxy substituted series, when the 4-substituent is alkoxy, a methoxy group gives optimum activity. (Compare, for example, TMA-2 and MEM in Table 1.) The 4-ethoxy group does not lead to an increase in activity, despite increased lipophilicity. This is in sharp contrast to 3,4,5-substituted compounds (discussed below), where an analogous transformation leads to an activity increase of nearly an order of magnitude.

An alkylthio substituent at the 4-position increases activity and also brings

about a qualitative change in the intoxication. The first member of the series "para-DOT" was synthesized in 1976 (163) using the rationale that the sulfur atom might prove labile to oxidative metabolism. This was contrasted with the metabolic stability of a group such as bromine. Shulgin and his co-workers (116,197,204) have characterized the clinical effects of para-DOT as well as several other 4-alkylthio substituted compounds. At low dosages, these compounds are described as having the ability to enhance intellectual function and promote the flow of ideas without otherwise impairing sobriety. These workers have termed this the "aleph" effect.

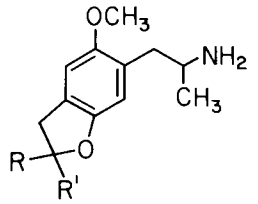
Once again, clinical studies reveal a divergence between potency and qualitative effect. No *in vitro* or animal model studies have yet indicated any major difference between oxygen at the 4-position and its sulfur isostere, although there are changes in their experimentally measured ionization potentials (54).

Compounds with a 4-alkyl seem to produce the most severe sensory disruption. The prototype of these is DOM (Table 1), which received notoriety following its introduction into the illicit market in 1967. Extension of the alkyl to ethyl (DOET) and *n*-propyl (DOPR) gives further potency increases (203). In early reports, the low dosage effect of DOET was characterized as nonhallucinogenic (211,215); it is clear, however, that this is dose dependent.

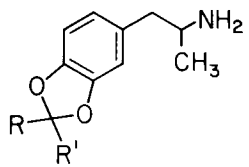
The variation of human or whole animal potency as the para-alkyl is modified may be due in part to metabolic or pharmacokinetic factors. Simply substituting a para-alkyl enhances affinity for serotonin receptors in the rat fundus preparation (78). Extension of a methyl to ethyl or higher homologs, however, or branching of the alkyl apparently has little further effect on affinity (77). For the series of 2,5-dimethoxy-4-alkyl substituted phenylisopropylamine derivatives, human activity does not seem to parallel *in vitro* assays (77), and whole animal models provide better correlations (88,149). In the two-lever drug discrimination paradigm, with rats trained to discriminate 5-methoxy-N,N-dimethyltryptamine from saline, the training stimulus only generalizes completely to the 4-methyl compound (DOM). The other 4-alkyl homologs do not completely generalize, suggesting that a complete exploration of the human psychopharmacology of the active members of this series might reveal qualitative differences. On the other hand, if DOM is used as the training drug, stimulus generalization occurs with DOET and DOPR but not with DOTB or DOAM.

Branching in the 4-alkyl group is deleterious, at least if the branch is adjacent to the aromatic ring, as in such compounds as DOIPR, DOTB, and DOSB. Branching in the alkyl, if it is more distal from the ring, may lead to compounds that retain high activity (e.g., DOIB). These observations may be related to a possible requirement for the aromatic ring of the phenethylamines to closely approach the receptor surface, presumably to form a charge-transfer complex, as noted earlier. Bulky, branched alkyls attached to the ring would hinder this interaction (165). By contrast, branching further removed from the ring would not be expected to have as severe an effect.

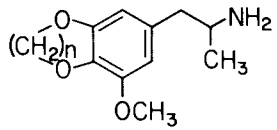
It has been suggested that the receptor that interacts with hallucinogenic



Structure 2. a: R=R′=H, **b:** R=H, R′=CH_3, **c:** R=R′=CH_3.



Structure 3. a: R=R′=H, **b:** R=H, R′=CH_3, **c:** R=R′=CH_3.

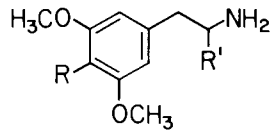


Structure 4. a: n = 2, **b:** n = 3.

phenethylamines can be modeled as a planar surface (162,166). This would be consistent with the above arguments. There are additional data to support this idea. For example, in the homologous series **2a,b,c** and **3a,b,c** the latter compound in each (Structures **2c** and **3c**) is inactive.

In the case of **2c,** no activity was apparent in human experiments (24), while **3c** was inactive in mice (159). Both **3a** (MDA) and **3b** possess human activity, although **3b** is apparently much reduced in potency (199). Clinical activity for compounds **2a** and **2b** has not been confirmed, although it was communicated several years ago that both were quite potent in man (231). The lack of activity for **4a** and **4b** (190) may also be explained by considering the steric effects introduced by puckering in the heterocyclic ring.

These results suggest that one face of the aromatic ring must be relatively free of steric bulk. This would be consistent with a requirement for close approach of the ring face to an electron acceptor moiety at the receptor, assuming that charge-transfer complex formation is an important receptor event. Similar reasoning has been advanced recently by Knittel and Makriyannis (133) to explain the lack of activity for TMA-3 (Table 2), where the methoxy groups are perpendicular to the ring plane but staggered 180° apart. The resulting projection of methoxy groups toward each face of the molecule would thus hinder access to the receptor surface. However, other arguments may be equally valid. For example, if the receptor geometry can be represented as a groove or slot in the membrane, one edge of this groove may simply be able to accommodate protruding steric bulk more easily than the other. In any case, it is likely that the receptor does discriminate between the two faces of the aromatic ring.



Structure 5. a: R=H, R′=CH_3, **b:** R=OCH_2CH_3, R′=H, **c:** R=OC_3H_7 R′=H, **d:** O-i-C_3H_7 R′=H.

One of the interesting features in 3,4,5-substituted series is the dramatic enhancement of activity that occurs on modification of the 4-substituent (21). The absence of a 4-substituent (3,5-DMA; Structure **5a**) leads to little change in receptor affinity from that of 3,4,5-TMA (8), as measured in the rat fundus preparation (78). However, DOM-stimulus generalization to 3,5-DMA does not occur in rats (87). No human data have been reported for 3,5-DMA.

Homologation of mescaline to the 4-ethoxy (escaline; **5b**) increases potency about sixfold (21). The 4-propoxy (proscaline; **5c**) is nearly as active, as is the isopropoxy, **5d.** A 4-butoxy at this position, while less active than ethoxy or propoxy, is still more potent than mescaline, although the qualitative aspect of the intoxication has not yet been fully characterized. In these series, it is clear that the 4-substituent must be twisted to a conformation where the alkyl-oxygen bond is nearly perpendicular to the aromatic ring (58). Certainly large alkoxy groups, such as isopropoxy, will be even more severely constrained. This would seem to negate the possibility of significant resonance overlap between the pi system and the unshared electrons of the 4-oxygen atom. Thus, while a methoxy may be optimal or even a requirement in the 2-, 3-, or 5-position of some series, there is no such requirement at the 4-position. Indeed, in 3,4,5-substituted compounds, hydrophobic groups, such as alkyl, alkylthio, or halogen, greatly increase potency (21).

It is interesting that alkoxy groups larger than methoxy at the 4-position in 2,4,5-substituted compounds do not increase potency in the way they do in the 3,4,5 series. Based on the out-of-plane conformation of the 4-substituent in 3,4,5-substituted series, it is tempting to speculate that any hydrophobic site or accommodating region on the receptor at this position does not lie in the plane of the aromatic ring, but rather might be visualized as a surface that is more nearly perpendicular to the aromatic ring plane. This could be visualized schematically in Fig. 1. By contrast, a 4-alkoxy in the 2,4,5-substitution series will prefer to lie coplanar with the aromatic ring in order to maximize overlap of the *n* electrons with the pi system (6). The alkyl of the alkoxy, therefore, would not be favorably oriented to interact with a region of the receptor having such geometry. Furthermore, the bulk of the larger alkyl, now attempting to reside in the plane of the ring, may direct unfavorable steric interactions toward other portions of the receptor.

The preferred conformations of methoxy groups attached to aromatic rings in the phenethylamines have recently been investigated using theoretical approaches, gas phase experimental methods, and nuclear magnetic resonance (NMR) techniques for the molecules in aqueous solution. *Ab initio* theoretical calculations and experimental gas phase results have indicated that when two

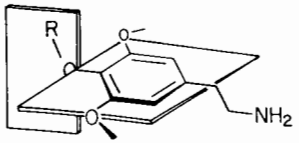
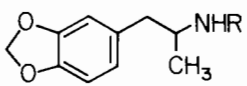


FIG. 1. Illustration of a proposed hydrophobic surface, normal to the plane of the aromatic ring, which can accommodate lipophilic 4-substitutents in 3,4,5-trisubstituted phenethylamine derivatives.

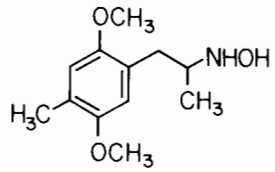
methoxy groups are adjacent to each other, one prefers to twist out of plane (5,6). However, solution NMR measurements have indicated that both methoxy groups prefer to remain coplanar with the aromatic ring (133,145).

N-Substituents

In contrast to the *in vivo* action of the tryptamines, N-alkylation of the phenethylamines abolishes or greatly attenuates biologic activity (105,197). Two noteworthy exceptions are the 3,4-methylenedioxy-substituted compounds Structures **6a** (204) and **6b** (22). These retain potency nearly comparable to the parent **3a** (MDA) but present a different qualitative picture. Their duration of action is reduced to about $1\frac{1}{2}$ to 2 hours, and they produce only minor disruption of normal sensory processing. They apparently amplify empathy and would seem to be ideal candidates as adjuncts to psychotherapy (psycholytic therapy) (197). The mechanism of action for **6a** also seems to be different than that of the nonmethylated parent **3a.** The evidence for this comes primarily from studies of the *R* and *S* enantiomers of **6a** and **3a** (4). In the nonmethylated parent **3a,** it is the *R* enantiomer that shows highest biologic activity. In contrast, it is the *S* enantiomer of **6a** that is most active. Furthermore, there is no cross tolerance between **6a** and **3a.** This is also a good case to use to illustrate the utility of the drug discrimination assay. Recently, using rats trained to discriminate DOM from saline, it was found that the DOM stimulus generalized to racemic **3a** or its clinically active *R*-(−) enantiomer (92). However, DOM stimulus generalization was not observed to the *S* enantiomer of **6a.** Thus the results of this animal model also are in agreement with the clinical findings. The fact that the *S* enantiomer of **6a** has the same absolute configuration as (+)-amphetamine has led to speculation that **6a** may owe its activity to the ability to induce release of endogenous transmitter (4). It has been shown that the *S* enantiomer of **6a** is in fact more potent in inducing release of ^{3}H-serotonin from prelabeled rat whole brain synaptosomes (160). It seems likely that other monoamines may also be involved, since Marquardt et al. (139) have shown that the *S* enantiomer of **3a** is more potent in inhibiting the uptake of norepinephrine into rat brain synaptosomes. The possibility of multiple components of action for hallucinogenic phenethylamine derivatives must be kept in mind.



Structure 6. a: R=CH_3, **b:** R=CH_2CH_3, **c:** R=OH.



Structure 7.

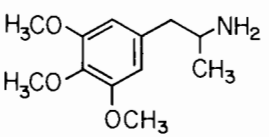
Homologation of the N-substituent beyond ethyl generally abolishes activity (22). N,N-dialkylation does not lead to active compounds, even with 3,4-methylenedioxy substitution (197). It should be noted, however, that only a few N,N-dialkyl compounds have been clinically evaluated. N-alkylation also decreases *in vitro* serotonin receptor affinity (80). Certain N-propyl, N-cyclopropylmethyl, and N-allyl derivatives show weak antagonism against mescaline-induced disruption of swimming behavior in mice (50).

Two reports have appeared for compounds with an N-hydroxy. Compound **6c** retains clinical activity nearly comparable to that of **6a** (22), while Structure **7** shows weak activity in rats (44).

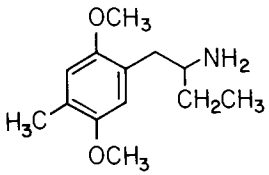
Side Chain Modifications

While mescaline is a simple 2-phenethylamine derivative, the addition of an alpha-methyl group to the side chain yields Structure **8** (TMA). This simple hybrid of the structures of mescaline and amphetamine retains the hallucinogenic effects of mescaline but possesses about twice the potency of the latter (174,200). Addition of the alpha-methyl to other 3,4,5-substituted compounds generally brings about an approximately twofold increase in potency. The addition of an alpha-methyl to 2,4,5-substituted compounds, however, may dramatically increase activity. For example, 2-(2,4,5-trimethoxyphenyl) ethylamine apparently is clinically inactive (195). Addition of an alpha-methyl gives TMA-2 (Table 1), with 20 times the potency of mescaline. However, the addition of an alpha-methyl does not significantly increase *in vitro* receptor affinity in either 3,4,5- or 2,4,5-series (72,78). Thus it is probable that the alpha-methyl may confer metabolic stability *in vivo.* It could also be speculated that this protection is more important in the 2,4,5-substituted series than in 3,4,5-substituted compounds.

Little work has been done in this area. Clark et al. (36), however, reported that mescaline is more extensively deaminated by a soluble rabbit liver amine oxidase preparation than is 2,4,5-trimethoxyphenethylamine. One should also note that the addition of the alpha-methyl will increase the octanol-water partition



Structure 8.



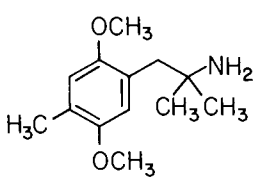
Structure 9.

coefficient by a factor of about 3. In most cases, this increase in lipid solubility will lead to higher drug concentrations in the CNS. This is especially true of mescaline, which has poor lipid solubility. The small increase in *in vivo* activity for alpha-methylated 3,4,5-substituted compounds may be due largely to increased lipid solubility. On the other hand, Cooper (40) has suggested that the potentiating effect of the alpha-methyl on potency may be due to the preferential stabilization of one of the two possible staggered conformations of the side chain. Nevertheless, several compounds that possess substantial activity do not have the alpha-methyl group. Most noteworthy are the nonalpha-methylated homologs of DOM and DOB. Although neither is as potent as the alpha-methyl congener, both possess relatively high activity (201).

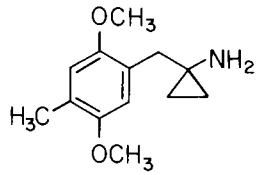
The introduction of a methyl, or other alkyl, into the side chain also introduces asymmetry into the molecule. Numerous studies of the resulting (+) and (−) enantiomers have now been reported. These will be discussed in detail later.

Extension of the alpha-methyl to an ethyl or longer alkyl homolog completely abolishes activity in both 3,4,5- and 2,4,5-substituted compounds (189,219). The most thoroughly studied example is the alpha-ethyl homolog of DOM, Structure **9** (BL-3912A). This compound was evaluated for potential mood elevating properties (219) and facilitation of learning (42,230). In sheep umbilical artery smooth muscle, it showed mixed serotonin agonist/antagonist activity, whereas DOM was a pure agonist (55). The dynamic behavior of DOM and its alpha-ethyl homolog **9** do not appear to differ, either as studied in solution using NMR techniques (47,144) or as calculated using empirical potential functions (246). The lack of activity for **9** almost certainly must be due to a steric effect, presumably an interaction between the alpha-ethyl group and some feature of the receptor.

Dialkyl substitution on the alpha-carbon also abolishes activity. the α,α-dimethyl analog of DOM, Structure **10,** is inactive in a variety of assays (10). Linking the two alpha-methyls to give the cyclopropyl analog Structure **11** restores activity in a cat behavioral model (10). The difference in activity between **10** and **11** has been ascribed to the inability of **10** to adopt an antiperiplanar



Structure 10.



Structure 11.

conformation, which is presumably a requirement for receptor binding (247). Bond angle distortion in the cyclopropane ring reduces this problem in **11** and restores conformational mobility.

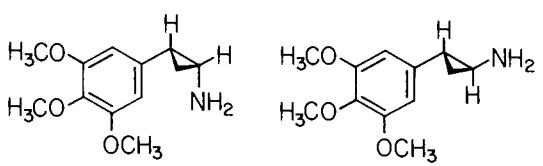
Adding the second alpha-methyl to MDA gives a compound that apparently is only weakly active in man (199). Again, the 3,4-methylenedioxy substitution seems anomalous. This may also be due to an indirect effect, such as release of endogenous neurotransmitter from nerve terminals. However, neither this α,α-dimethylated MDA analog nor α,α-dimethyl-4-methoxy-β-phenethylamine had any ability to induce the release of ^{3}H-serotonin from rat whole brain synaptosomes (160).

The addition of a beta-methyl to the side chain dramatically attenuates activity in animal models (1,155). An α,β- or β,β-dimethyl substitution also abolished hallucinogen-like activity in animal models (1).

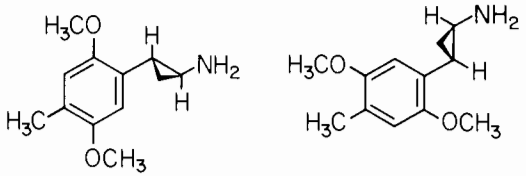
Phenylalanine derivatives, substituted either with 3,4,5-trimethoxy or 2,5-dimethoxy-4-methyl substituents did not show activity (46). Although these would yield potentially active phenethylamines if decarboxylated *in vivo,* neither is likely to be a substrate for decarboxylases in the CNS (62). Several additional side chain alkylated compounds are discussed in the next section as rigid analogs.

Rigid Analogs

Since the phenethylamines are flexible molecules, it has been natural to speculate on the conformation that they adopt at the receptor. Such studies have been based on crystallographic observations (35) or calculated preferred conformations (128). There is now general recognition that the active conformation need not be of lowest energy, nor need it be that observed in the solid state. Since no methodology presently exists to study the active binding conformation of the phenethylamines at receptor sites, a number of workers have designed rigid analogs in order to fix the side chain into a particular conformation (166). Activity for several of these has led to inferences about the binding conformation of the nonrigid prototypes. Perhaps the simplest rigid analogs are the 2-phen-



Structure 12. Cis, **left;** trans, **right.**



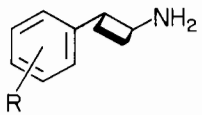
Structures 13 (left) and 13R (right).

ylcyclopropylamines. The first of these were the mescaline analog Structures *cis* and *trans* **12.** These were prepared and tested in rats by Cooper and Walters (40,41). Mescaline-like activity only for the *trans* isomer seems to clearly indicate that mescaline binds to the appropriate receptors with the side chain in a *trans* extended conformation. This finding negated any possibility that hallucinogenic phenethylamines could mimic an indole at the receptor by adopting a cisoid conformation where the side chain amino group corresponded to the indole N(1) atom (213). Aldous et al. (1) prepared the racemic *trans*-2-(2,5-dimethoxy-4-methylphenyl) cyclopropylamine Structure **13.** In three animal models (cat, rat, and rabbit), the racemate showed potent hallucinogen-like effects. This DOM homolog was resolved into its enantiomers (−)-1*R*,2*S*-(**13***R*) and (+)-1*S*,2*R*-(**13***S*). Assays in mice, cats, and rabbits revealed the (−) enantiomer **13***R* to be selectively active (162,167). Subsequently, racemic **13** hydrochloride was found to be a potent hallucinogen in man, with an effective acute oral dosage in the range of 15 to 20 mg (199). As predicted from the animal models, it is the (−) isomer that possesses clinical activity.

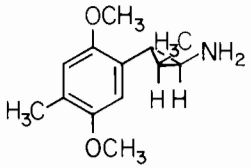
The 2-phenylcyclobutylamines Structures **14** and **15** have also been prepared (161). In contrast to the cyclopropylamine, however, **15** showed no clinical activity following oral administration of a dose up to 25 mg of the racemic hydrochloride (199). The trimethoxy congener **14** has not been tested. The appropriately ring-substituted *trans*-2-phenylcyclopentyl or cyclohexylamines have not been reported. Based on the apparent lack of activity for **15,** as well as the lack of activity for alpha-ethyl phenethylamine derivatives, however, these might be predicted to be inactive.

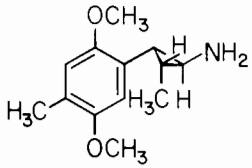
In view of the activity of **13,** but the lack of activity for the alpha-ethyl homolog of DOM, the two isomeric ring-methylated derivatives Structures **16a** and **16b** were recently prepared (114). Neither isomer showed significant activity, either as an agonist in the rat fundus preparation or in a mouse assay, when compared with **13.** It would appear that little bulk can be tolerated near the alpha-carbon, other than a methyl or methylene.

Another series of rigid analogs that have been examined to some degree are the aminotetralins with the general formula of Structure **17.** If, as might be

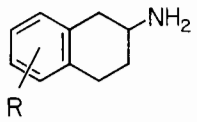


Structures 14: R=2,3,5-$(OCH_3)_3$ and **15:** R=2,5-$(OCH_3)_2$-4-CH_3.





Structure 16a (left) and 16b (right).

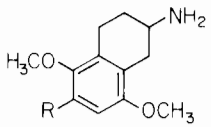


Structure 17. R=OCH_3, R, OH.

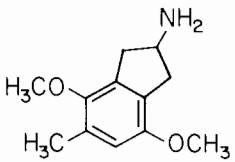
inferred from the data on the 2-phenylcyclopropylamines, the phenethylamine side chain binds in an antiperiplanar conformation, then one might expect to see high activity in such compounds as tetrahydronaphthalenes. The side chain is nearly locked into a conformation that should resemble closely that of the phenethylamines in proposed active binding conformations. Surprisingly, aminotetralins produce sedation in rodents (14,241) and do not elicit behavioral effects that resemble their flexible phenethylamine counterparts.

The aminotetralins have been suggested to represent the A and C rings of LSD as the possible pharmacophoric element, as shown in Fig. 2. Kang and Green (126) noted this possible relationship, which is similar to analogies presented earlier by other workers concerning the oxytocic activity of ergot alkaloids. This view was utilized by several groups (45,156,241). Aminotetralins closely related in structure to highly potent phenethylamines have been prepared (e.g., Structures **18a, 18b,** and **19**).

The tetralins **18a** and **18b** were potent serotonin agonists in dog vascular smooth muscle (33) but did not elicit hallucinogen-like action in a conditioned avoidance response model in rats (156). However, **18b** is a potent pyretic agent in rabbits and produces a rage response in cats (166). Addition of a double bond into the 3,4-position of the tetralins led to decreased serotonin-like action



Structure 18a: R=H, and **18b:** R=CH_3.



Structure 19.

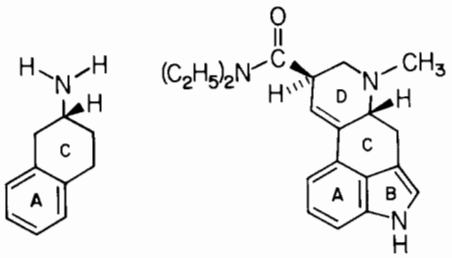


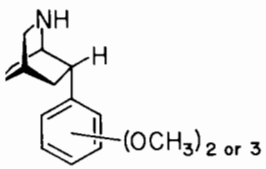
FIG. 2. Possible structural correspondence between aminotetralius and LSD.

in the rat fundus and further attenuation of the *in vivo* activity in the rat serotonin syndrome model (134). Contraction of the six-membered ring of **18b** to the five-membered indan **19** analog did not restore activity (156). Coutts and Malicky (45) did report that high doses of the indan derivative produced a DOM-like effect in a general screen in rats.

Violland et al. (241) examined several methoxy-substituted 2-aminotetralins as hallucinogen analogs. Characterized in mice and dogs, these produced ataxia, sedation, and analgesia.

The lack of clear-cut hallucinogen-type activity for the 2-aminotetralins could be explained in several ways. The known deleterious effect of molecular bulk in the alpha-position would seem to direct attention to the steric effect of the reduced ring of the tetralins as detrimental to activity. In **18b,** however, it has been noted (156) that the 5-methoxy group is forced out of plane by the adjacent 6-methyl and 4-methylene groups. The importance to activity of maintaining the methoxy groups coplanar with the aromatic ring has been emphasized earlier. Both substituent orientation and N-alkylation must also be important to activity, and it may not be realistic to make direct comparisons between the phenethylamines and the 2-aminotetralins.

Several additional analogs that incorporate the side chain into a heterocyclic ring have been prepared and evaluated. Generally, these have been hybrids between the structure of mescaline and phenmetrazine or methylphenidate. Based on the finding that both N-alkylation and α-alkyl groups larger than a methyl are detrimental to activity, it is not surprising to find that none possessed significant activity in animal models (249,250). However, Law and Borne (136) prepared endo and exo isomers of substituted azabicyclooctanes. A screen for



Structure 20.

effects on motor activity in mice revealed the endo isomer Structure **20** to be more active, demonstrating again that structures that incorporate the phenethylamine moiety in an extended *trans* conformation are more active than those with cisoid conformations. This is consistent with the discussions above regarding the cyclopropyl analogs.

Stereochemical Considerations

It has been known for many years that only the 5*R*,8*R*-(+) isomer of LSD is biologically active. Based on ability to produce cross tolerance and similarity of pharmacologic and subjective clinical effects, it has often been suggested that LSD, other hallucinogenic tryptamines, and the phenethylamine hallucinogens share a common or similar component of action. It is possible that this could involve interaction of all these structures at a particular receptor type. Such a possible functional similarity between the tryptamines and the phenethylamines has led to attempts to relate the stereochemistry of the phenethylamines to that of LSD. This relationship was noted by Kang and Green (126) and emphasized by Barfknecht and Nichols (12,157). This analogy, illustrated in Fig. 3 for *R*-(−)-DOM and LSD, correctly predicted that the illustrated *R* isomer of the hallucinogenic phenylisopropylamines would possess highest activity when compared with its *S* enantiomer. This was first confirmed in human assays of the enantiomers of DOM (192) and has been shown to be true for all substituted derivatives that are primary amines, both *in vitro* and *in vivo* (1,15,56,72,88,162,214,251). There is generally a four- to 10-fold difference in potency between the enantiomers.

In Fig. 3, the two molecular faces of LSD can be designated as "beta," in this case the side of the molecule facing the reader, and "alpha," the face of the molecule hidden from the viewer (181). Based on X-ray crystallographic (9) and solution NMR studies (8), the molecule is nearly planar, and the unshared electron pair on N(6) is directed toward the alpha face of the molecule. It is typically assumed that the basic nitrogen atom is an important site for interaction with the receptor. It has also been assumed that the solid state and solution conformation of LSD is the same as the binding conformation at the receptor. That is, there is no present evidence to suggest that the D ring of LSD undergoes a conformational flip which would reorient the N(6) electron pair. It may be inferred, therefore, that the receptor interacts with the alpha face of LSD. Using the analogy presented above, and assuming that LSD and DOM can bind to the same receptor system(s), would lead one to the conclusion that DOM and similarly substituted phenethylamine derivatives also bind to the receptor with their alpha face, the surface of the molecule hidden from the reader. Binding to the alpha face of the more active *R*-(−) enantiomer of DOM in this case would force the alpha-methyl of the side chain into the proposed receptor surface. Similarly, binding of the cyclopropylamine analogue **13R** would direct the C3 methylene of the cyclopropane ring into the binding surface. One could argue that such an interaction may be necessary to elicit the receptor response induced

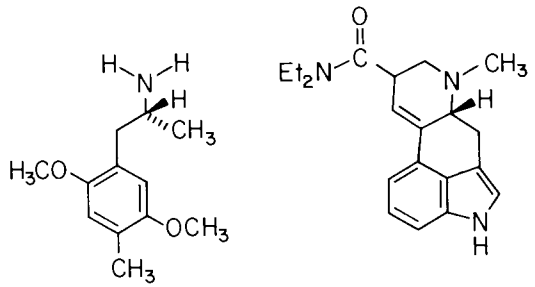


FIG. 3. Possible structural similarity between *R*-(−)-DOM and LSD.

by hallucinogens. An appealing feature of this model is that it might explain the lack of activity for the alpha-ethylphenethylamines. It has been suggested that the alpha-ethyl homologs are inactive as a result of some steric effect at the receptor (47,144,246). If the alpha-alkyl projects into the receptor surface, it seems natural to assume that the receptor would be sensitive to the nature and size of this group. This type of orientation would also be consistent with the observation that it is the *S* enantiomer of alpha-methyltryptamine and the (+)-isomer of 5-methoxy-alpha-methyltryptamine (which presumably has the *S* absolute configuration) which are the most active (72,76).

It is also possible that the beta face of the phenethylamines is the one that is more important for receptor binding. That is, the surface of the molecule that is visible to the reader in Fig. 3 may be the one involved in receptor binding. Thus the binding orientations for *R*-(−)-DOM and **13R** would be as shown in Fig. 4, with the receptor binding to the face of the molecule that is now hidden from the reader. In this orientation, the alpha-methyl in the *R* enantiomer of the amphetamines, or the C3 methylene of the cyclopropylamine with the 1*R*,2*S* configuration, projects away from the binding surface. The inactivity of alpha-ethyl homologs would still be explained as a steric effect. In this case, however, the alpha-alkyl would probably limit access to the receptor. For example, using enzyme active site geometry as a model, the receptor may be more accurately visualized as a groove or cavity in the membrane surface. Although such a receptor might tolerate only limited steric bulk directed toward the alpha face, the beta face of the molecule might be the one that actually interacts with the functional portion of the receptor.

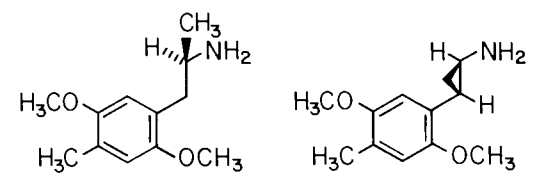


FIG. 4. Binding orientations for *R*-(−)-DOM and **13R**.

This view offers an explanation for the stereoselectivity of the phenylisopropylamines, i.e., the isomer that is more active is the one that presents least interference to the drug-receptor interaction. This idea would be consistent with the observation that the *R* enantiomers of the phenylisopropylamines have receptor affinity similar to their nonalpha-methylated homologs, and that the alpha-methyl of the *S* enantiomer of the amphetamines has a deleterious effect on affinity (72,78). There is no strongly compelling evidence in favor of either of the above hypotheses, however, and either is tenable.

It undoubtedly will be some time before this situation is completely clarified. It may prove to be the case, as suggested by Glennon et al. (79), that the phenethylamines can adopt different binding orientations at the receptor, depending on the nature and orientation of the aromatic substituents.

Pharmacokinetic and Metabolic Effects

Thus far, there has been considerable discussion of structure-activity relationships at the molecular level, or at some hypothetical receptor(s). However, *in vivo* activity must depend on ability to penetrate into the CNS. Furthermore, the duration of action, as well as the overall potency, also must depend on how readily a particular compound is metabolized and removed from the body by excretion. For example, 2,4,5-trimethoxy-β-phenethylamine lacks hallucinogenic activity. Cohen et al. (37) could not detect this material in brain, following administration to rats. The lack of penetration into the CNS could be the reason for the inactivity of this compound, in contrast to mescaline, the 3,4,5-substituted isomer. As these workers emphasize, parameters, such as absorption, metabolism, distribution, excretion, and penetration through the blood-brain barrier, will all be important when considering the potency of the drug in the intact organism. Vogel and Evans (243) have argued that structure-activity relationships should be based on effective drug concentrations in the brain rather than on total administered dose. They have proposed that minimal effective brain levels (MEBLs) be used as the measurement. This suggestion clearly has merit, but no subsequent studies using MEBL have been reported.

Partitioning into the CNS will be important for hallucinogens, as for any drug that acts centrally. Correlation between 1-octanol/water partition coefficients and human activity has been reported (13). Regression analysis of log human activity on log P yielded a parabolic fit with an optimum at log P 3.14. The derived equation accounted for only 62% of the variance but included compounds with a variety of substitution patterns and, presumably, qualitative differences in activity.

No importance of metabolic processes to the mechanism of action has yet been demonstrated. The phenethylamines generally are not good inhibitors of monoamine oxidase (MAO), although more active compounds may not be good substrates for this enzyme (MAO) (36). However, no extensive studies of phenethylamines have been reported, as either inhibitors or substrates of MAO. For

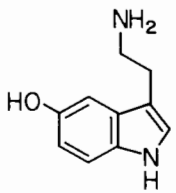
a more detailed discussion of the metabolic fate of phenethylamine hallucinogens, the reader is directed to the recent review by Castagnoli (28).

INDOLEALKYLAMINES

Indolealkylamines constitute a large class of compounds, of which the best known and most studied derivative is the neurotransmitter serotonin (5-hydroxytryptamine; Structure **21**). A number of indolealkylamines are hallucinogenic, and these can be conveniently divided into three basic groups: (a) tryptamine derivatives, (b) beta-carbolines, and (c) lysergic acid derivatives. The pharmacology and structure-activity relationships of hallucinogenic indolealkylamines have been previously reviewed (24,81,106,196,208). As noted above, because clinical evaluation of hallucinogenic agents is relatively restricted, few new human data have been reported since these reviews were published. Nevertheless, this discussion presents an overview of major findings with respect to human activity and attempts to highlight (a) compounds that have previously received limited attention, and (b) the more recent literature. Key references to classic *in vitro* and *in vivo* animal pharmacology are cited. The interested reader is referred to the above reviews and/or to the primary literature for more detailed discussions.

It should be pointed out that much of the data to be discussed is derived from animal studies. Using animals as subjects, greater numbers of compounds and structural modifications can be studied. The reader should be reminded, however, that the relationship between behavioral activity and potency in animals versus man is not yet fully understood or well defined. Furthermore, although many different activities have been measured in animals, these studies have rarely included large series of compounds, making it difficult to formulate structure-activity relationships. Thus an attempt is made to sift through the data and to discuss structure-activity relationships derived from studies employing relatively large numbers of compounds where comparisons can be made with somewhat more confidence. Conversely, studies involving only small numbers of compounds are given less emphasis.

The conformational and quantum chemical properties of indolealkylamines have been investigated (see, e.g., refs. 9,35,61,94–96,112,126–130, and 177), but, to date, such studies have had a limited impact on the understanding of structure-activity relationships. Evidence suggests that the indolealkylamine side



Structure 21.

chain can exist in any of several preferred conformations. These may only be separated by small energy barriers, and one of them roughly corresponds to the indolealkylamine nucleus within LSD. Thus it does not appear to be energetically impossible for indolealkylamines to mimic the aminoethylindole portion of the LSD structure. With respect to electronic properties, no significant relationship to hallucinogenic activity has been demonstrated for an extended series of compounds; however, work in this area continues.

The neurotransmitter serotonin (**21**) has been implicated as playing a role in the mechanism of action of the hallucinogenic indolealkylamines; however, the importance of other neurotransmitters cannot be ruled out at this time. Studies targeted specifically toward the elucidation of the mechanism of action of indolealkylamines are considered in other chapters, and this review is limited to a discussion of structure-activity relationships.

For convenience, the structures discussed in the following sections are listed in Table 3. In many cases, the compounds do not have common or trivial names and are referred to in the text by number.

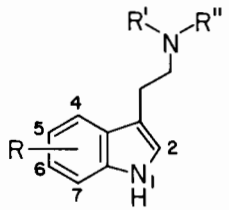
Tryptamines

Primary Amine and Monoalkyl Derivatives

The simplest member of this structural family is tryptamine (**22**). In man, tryptamine increases blood pressure and produces some perceptual distortion (141) but is not generally considered to be hallucinogenic. In animal studies, derivatives of tryptamine have received only scant attention. The 5-hydroxy derivative of tryptamine, serotonin, has not been demonstrated to be hallucinogenic in man or behaviorally active in animals. Comparative clinical evaluations of the isomeric hydroxytryptamines have not been reported. Various tryptamines, including the methoxy derivatives **23–26** (see Table 3), display serotonin agonist (or partial agonist) activity in the isolated rat fundus preparation, guinea pig ileum, or rat uterus (17,63,96,239). 5-Methoxytryptamine has been shown to be more potent than tryptamine or the 6- and 7-monomethoxy isomers **25** and **26,** respectively, in displacing ^{3}H-LSD from rat brain homogenates (95). However, none of these compounds has shown any significant behavioral activity in animal models.

Martin and co-workers (142,143) have found that, in animals, tryptamine produced many of the physiologic effects characteristic of LSD; however, it does not appear to elicit behavioral effects similar to those of LSD. At relatively high doses, 5-methoxytryptamine (**24**) does produce some behavioral effects in rats (66,242) and in nonhuman primates (101). Vogel (242) has suggested that the disruptive effects of 5-methoxytryptamine might be due to the peripheral actions of this agent. Tryptamine had no effect on acquisition of avoidance behavior, whereas 5-methoxytryptamine slightly decreased such behavior (240). Both tryptamine and 5-methoxytryptamine produced discriminative effects in rats

TABLE 3. *Structures of tryptamine derivatives which have been studied for potential hallucinogenic activity*



Structure no.	Designation	R	R′	R″
22	Tryptamine	H	H	H
23		4-OCH_3	H	H
24		5-OCH_3	H	H
25		6-OCH_3	H	H
26		7-OCH_3	H	H
27	N-MeT	H	CH_3	H
28	N-EtT	H	C_2H_5	H
29		H	n-C_3H_7	H
30		H	i-C_3H_7	H
31		H	n-C_4H_9	H
32		H	i-C_4H_9	H
33		H	$CH_2C_6H_5$	H
34	4-OH-N-MeT	4-OH	CH_3	H
35	4-OH-N-EtT	4-OH	C_2H_5	H
36	5-OMe-N-MeT	5-OCH_3	CH_3	H
37	DMT	H	CH_3	CH_3
38	DET	H	C_2H_5	C_2H_5
39	DPT	H	n-C_3H_7	n-C_3H_7
40	DIPT	H	i-C_3H_7	i-C_3H_7
41	DBT	H	n-C_4H_9	n-C_4H_9
42	DHT	H	n-C_6H_{13}	n-C_6H_{13}
43		H	-CH_2CH_2-	
44		H	-$CH_2(CH_2)_2CH_2$-	
45	5-TMT	5-CH_3	CH_3	CH_3
46	6-TMT	6-CH_3	CH_3	CH_3
47	7-TMT	7-CH_3	CH_3	CH_3
48		4-CH_3	CH_3	CH_3
49	Psilocin	4-OH	CH_3	CH_3
50	4-OH-DET	4-OH	C_2H_5	C_2H_5
51		4-OH	CH_3	i-C_3H_7
52	4-OH-DIPT	4-OH	i-C_3H_7	i-C_3H_7
53	Bufotenin	5-OH	CH_3	CH_3
54	5-OAc-DMT	5-$OCOCH_3$	CH_3	CH_3
55	6-OH-DMT	6-OH	CH_3	CH_3
56	6-OH-DET	6-OH	C_2H_5	C_2H_5
57	7-OH-DMT	7-OH	CH_3	CH_3
58	4-OMe-DMT	4-OCH_3	CH_3	CH_3
59	5-OMe-DMT	5-OCH_3	CH_3	CH_3
60	5-OMe-MET	5-OCH_3	CH_3	C_2H_5
61	5-OMe-DET	5-OCH_3	C_2H_5	C_2H_5
62	5-OMe-DPT	5-OCH_3	n-C_3H_7	n-C_3H_7
63	5-OMe-DIPT	5-OCH_3	i-C_3H_7	i-C_3H_7
64		4,5-OCH_2O-	CH_3	CH_3

TABLE 3. (*continued*)

Structure no.	Designation	R	R′	R″
65		4,5-OCH_2O-	i-C_3H_7	i-C_3H_7
66		5,6-OCH_2O-	CH_3	CH_3
67		5,6-OCH_2O-	i-C_3H_7	i-C_3H_7
68	4-SMe-DMT	4-SCH_3	CH_3	CH_3
69	5-SMe-DMT	5-SCH_3	CH_3	CH_3
70	6-SMe-DMT	6-SCH_3	CH_3	CH_3
71	6-OMe-DMT	6-OCH_3	CH_3	CH_3
72	7-OMe-DMT	7-OCH_3	CH_3	CH_3
73		5,7-$(OCH_3)_2$	CH_3	CH_3
74		4,5,6-$(OCH_3)_2$	CH_3	CH_3
75		5,6,7-$(OCH_3)_2$	CH_3	CH_3

that were dissimilar to those of the hallucinogen 5-methoxy-N,N-dimethyltryptamine (5-OMeDMT; **59**). Administration of either **22** or **24** to rats trained to discriminate 5-OMeDMT from saline did not result in stimulus generalization (84). 7-Methoxytryptamine displayed weak behavioral activity in animals (124).

Tryptamines that are unsubstituted on the terminal amine are good substrates for oxidative deamination by MAO. Furthermore, it has been demonstrated that tryptamine and 5-methoxytryptamine cross the blood-brain barrier with great difficulty; administration of 50 mg/kg 5-methoxytryptamine to rats results in a low brain/plasma ratio when measured 15 min postadministration (242).

N-Monoalkyltryptamines are another group of agents that have not received much attention. N-Methyltryptamine (**27**) and its 5-methoxy derivative **36** have been detected as constituents of plant materials used by certain South American Indians as hallucinogenic snuffs (109). Because these plant materials are also known to possess the established hallucinogens N,N-dimethyltryptamine (DMT; **37**) and 5-OMeDMT and since neither N-methyltryptamine (**27**) nor 5-methoxy-N-methyltryptamine (**36**) has been studied in the pure form, the effect of these latter two agents in man is presently unknown.

Like tryptamine, N-methyltryptamine (**27**) had some serotonin agonist activity, as measured using the isolated rat uterus preparation (227); in the rat fundus preparation, however, it possessed one-half the serotonin receptor affinity of tryptamine (75). DeMontigny and Aghajanian (49) compared the effects of microiontophoretic application of 5-methoxytryptamine and 5-OMeDMT (**59**) on the firing of serotonin-containing neurons of the midbrain raphe nucleus and on two postsynaptic brain areas that receive serotonin input from the raphe. Certain similarities were found in that both agents tended to exert more of an effect on the presynaptic neurons. The authors discussed the behavioral implications of these findings.

N-Methyltryptamine (**27**) was found to have no effect on the acquisition of avoidance behavior (240). Brimblecombe (23) compared the behavioral effects of a series of N-monoalkyltryptamines and N,N-dialkyltryptamines using Hall's open-field test. Although there was no clear-cut structure-activity relationship,

the dialkyl derivatives tended to be more active than their monoalkyl counterparts when the alkyl group was small. That is, the monomethyl, ethyl, propyl, and isopropyl derivatives **27–30** were less active than DMT (**37**), DET (**38**), DPT (**39**), and DIPT (**40**), respectively. The opposite was true for N-butyltryptamine (**31**) and N-benzyltryptamine (**33**). In cats, N-benzyltryptamine (**33**) was less active than either DMT or DET in disrupting operant behavior, while administration of N-ethyltryptamine (**28**) produced aggressive behavior (25). Many of the above agents also produced hyperthermia in animals (23). Cerletti and co-workers (29) found that tryptamine inhibited the knee-jerk reflex in spinal cats, while N-methyltryptamine had no effect; 4-hydroxy-N-methyltryptamine (**34**) also inhibited the reflex, while 4-hydroxy-N-ethyltryptamine (**35**), like psilocin (**49**), augmented the reflex response. There was no indication of behavioral disturbance with the 4-hydroxy-N-monoalkyl derivatives.

Misztal (148) prepared 5-methoxy-N-methyltryptamine (5-OMeN-MeT; **36**) for the purpose of pharmacologic evaluation, but no data were reported. Smythies and co-workers (210) reported that 5-OMeN-MeT was much less active than either DMT or 5-OMeDMT in disrupting the conditioned avoidance response in rats. Taborsky and McIsaac (229) also found 5-OMeN-MeT to be less active than 5-OMeDMT. These latter authors further demonstrated that 5-OMeN-MeT was rapidly and nearly quantitatively metabolized by MAO to 5-methoxyindole acetic acid. Julia and Manoury (123) investigated 5-methoxy and 6-methoxy derivatives of N-monoalkyl-substituted tryptamines. Both 5-OMeN-MeT and 5-methoxy-N-isopropyltryptamine (**30**) produced a significant hyperthermic effect in rabbits. N-Cyclopropyltryptamine and its 5-methoxy (248), 7-methoxy (248), 5,6-dimethoxy (34), and 6,7-dimethoxy (34) derivatives have been reported to be inhibitors of MAO, but none of these agents has been evaluated for behavioral activity.

In summary, primary amine and monoalkyl derivatives of tryptamine have not yet been demonstrated to produce hallucinogenic effects in man or to consistently produce profound behavioral effects in animals. Admittedly, relatively few compounds have been examined, and few studies have been conducted. Nevertheless, present evidence suggests that these derivatives, by virtue of their inability to penetrate the blood-brain barrier and/or their rapid metabolism, may not be able to achieve adequate brain levels to elicit effects. In some cases, these factors may lead to masking of potential central effects by peripheral actions of the compounds or their metabolites.

N,N-Dialkyl Derivatives

One of the best studied tryptamine derivatives is DMT (**37**). DMT and 5-OMeDMT (**59**) are probably the active constituents of a variety of South American hallucinogenic snuffs. These and related indolealkylamines have been detected in members of at least five different plant families: Agaricaceae, Leguminosae, Malpighiaceae, Myristicaceae and Rubiaceae (107,109,110,187). In

man, DMT is hallucinogenic at total intramuscular doses of 50 to 100 mg, with the normal dose being approximately 1 mg/kg. Gillin et al. (70) have reviewed human studies with DMT up to 1976; their review included results of trials on more than 150 subjects. While active by parenteral administration or by inhalation (i.e., by smoking or as a snuff), DMT was without activity at a total oral dose of 350 mg (235). The onset of effects after intramuscular administration is usually quite rapid (2–5 min), and the duration of action is relatively brief (about 1 hr). This time course closely follows the blood levels of DMT, with a 50 mg dose resulting in a maximal concentration of 100 ng/ml whole blood (69). There appears to be some question with respect to the minimal effective dose of DMT. Turner and Merlis (235) noted that inhalation of 5 to 20 mg DMT powder was essentially without behavioral effect, and that intravenous administration of 5 to 25 mg led to anxiety and restlessness but not (except for one subject) to disorientation or visual disturbances. On the other hand, Bickel et al. (18) reported that intramuscular doses of less than 20 mg (i.e., 0.25 mg/kg) were capable of producing altered states of consciousness, including hallucinogenic episodes; and Meltzer et al. (147) have recently reported that 50 mg DMT produced psychotomimetic effects. Thus the threshold dose of DMT in man is probably between 20 and 50 mg.

Szara and co-workers (221,223,225) noted psychotomimetic activity for N,N-diethyltryptamine (DET; **38**) at a dose of 1 mg/kg. In at least one study (223), the effects of DET were found to be unpleasant. In a study involving 71 subjects, DET produced behavioral effects at intramuscular doses of approximately 50 mg (0.65 to 0.85 mg/kg) (19). The duration of action of DET was somewhat longer (about 3 hr) than that of DMT. Interestingly, some subjects in the latter study reported, in contrast to Szara's findings, that DET produced a euphoric effect. Szara has suggested that this might be a dose-related phenomenon.

N,N-Dipropyltryptamine (DPT; **39**) is also hallucinogenic in man at 1 mg/kg (222). It has been employed as an adjunct to psychotherapy (97,179,216,217), and, therefore, more information is available concerning dose-effect relationships. The threshold dose for the induction of psychologic effects is in the 10 to 15 mg range, parenterally. There is loss of reality contact with doses greater than 30 mg, although doses of up to 165 mg have been used in psychotherapy (97,217). The onset of effects (5–20 min) is slightly longer than that for DMT, and the duration of action of DPT is dose dependent (1.5–6 hr) (97).

Branching of the propyl groups results in N,N-diisopropyltryptamine (DIPT; **40**), which is orally active at 20 to 50 mg (202). N,N-Dibutyltryptamine (DBT; **41**) and N,N-dihexyltryptamine (DHT; **42**) have been examined only briefly. At 1 mg/kg, DBT produced only slight perceptual, emotional, and thinking disturbances in man, while DHT at the same dose was completely inactive (222).

Although DMT, DET, and DPT are relatively similar in potency, insufficient dose-effect data make it difficult to draw structure-activity conclusions. Additional information can be obtained from animal studies. Szara and co-workers (224)

found that with respect to increasing spontaneous locomotor activity in mice, DPT was slightly more active than DET, which was, in turn, somewhat more active than DMT. Both DBT (**41**) and DHT (**42**) decreased locomotor activity. In producing hyperthermia in rabbits, DPT was more active than DMT or DET, and DBT was the least active of the four compounds.

The compound DMT is capable of producing a hyperactivity syndrome in animals, the head-twitch response in mice (44), limb-flick behavior in cats (119,120), and the "serotonin syndrome" in rats (211). In such assays, tryptamine (**22**) was found to be inactive (119), while DET was approximately twice as active as DMT (210). In a recent drug discrimination study, the effects of DMT, DET, DPT, and DIPT were directly compared in rats. The order of potency was DPT > DIPT > DET > DMT, with ED_{50} values of 7.8, 9.2, 9.6, and 20.2 μmoles/kg, respectively (83,91). Numerous other reports concerning the activity of these agents have not lent themselves to interagent comparisons, or different routes of administration have been employed within a series. Nevertheless, the above results suggest that, with respect to simple dialkyl substitution, the order of potency (on a molar basis), at least in various animal studies, is DPT > DET > DMT. There is probably no more than a two- or threefold difference in potency among this series. As the size of the alkyl groups is increased beyond propyl, activity decreases. Branching of the alkyl groups does not abolish activity and, in the case of DIPT (**40**), may even increase potency. The effect of branching has not been well studied, however, and too few data are available to make any definitive statements.

Cyclic analogs of DMT and DET, i.e., **43** and **44,** respectively, have been synthesized; the aziridine **43** appears to possess activity as a CNS depressant (171), while the pyrrolidine **44** displays some behavioral activity. Compound **44** was active in Hall's open-field test but was less active than DET (**38**) (23). In attempts to measure hyperthermic activity, **44** was found to be rather toxic in rabbits (111). Oddly enough, no cyclic analog has ever shown activity/potency comparable to its acyclic counterpart. Thus, based only on scant animal data, cyclization of the lower dialkyl homologs apparently does not lead to marked behavioral activity.

The complete role of N,N-dialkyl substitution is not fully understood, although it serves to enhance blood-brain barrier permeability and to hinder metabolic inactivation.

Ring-Substituted N,N-Dialkyl Derivatives

N,N-Dialkyltryptamines bearing an alkyl substituent on the aromatic nucleus have not been evaluated in man, and only data from animal studies are available. Taborsky et al. (228) found 1-methylation to have variable effects on behavioral activity. This might reflect blood-brain barrier permeability. Methylation at the N1 position of DMT (**37**), to give 1,N,N-trimethyltryptamine (1-TMT), had

little effect on serotonin receptor affinity, as measured in the rat fundus preparation, but decreased its behavioral activity in rats (73,93). Similarly, 1-methylation of 5-OMeDMT (**59**) also led to decreased behavioral potency (16).

Methylation at the 2-position of a variety of unsubstituted and 5-substituted N,N-dialkyltryptamines afforded agents with weak *in vitro* activity as serotonin antagonists (30), but behavioral activity was not studied. Methylation of the 2-position of DET (**38**) decreased its behavioral activity (20). Both the 5-methyl and 7-methyl derivatives of DMT, i.e., 5-TMT (**45**) and 7-TMT (**47**), respectively, were somewhat more potent than DMT in tests of discriminative control of responding in rats, using 5-OMeDMT as the training drug (93); 6-TMT (**46**) produced saline-like effects at comparable doses (86). Using DOM as the training drug, the order of potency was DET = 4-TMT (**48**) > 7-TMT (**47**) > DMT; 7-methylation of 5-OMeDMT did not adversely affect potency (91,252).

Hydroxylation of N,N-dialkyltryptamines can either increase or decrease hallucinogenic potency, depending on the position of the hydroxyl group. Psilocin (**49**), 4-hydroxy-N,N-dimethyltryptamine, is the best studied of the hydroxylated N,N-dialkyltryptamines. Psilocin and its phosphate ester psilocybin are the active components of several species of hallucinogenic mushrooms. Evidence suggests that Aztec and other Indians may have used such mushrooms (*teonanacatl*) in various ceremonial rituals as long as 3,000 years ago (see refs. 24, 106, 154, and 176 for detailed discussions on psilocin). Psilocin and psilocybin are active in man at oral doses of approximately 8 to 12 mg, with psilocin being somewhat more active than its ester on a weight basis. As such, psilocin is about eight times more potent than DMT. Homologation of psilocin to 4-hydroxy-N,N-diethyltryptamine (4-OH DET; **50**) has little effect on human potency, as does replacement of one of the methyl groups by an isopropyl group (i.e., 4-hydroxy-N-methyl-N-isopropyltryptamine, **51**) (196). Replacement of both methyl groups by isopropyl groups (i.e., 4-hydroxy-N,N-diisopropyltryptamine, **52**) apparently halves activity (196).

Psilocin has also been the object of considerable investigation using animals as subjects. Much of the initial work with psilocin, as well as other 4-hydroxytryptamine derivatives with alterations in the side chain and/or terminal amine, was performed at Sandoz Laboratories in Switzerland (29,245). Subsequent investigations have shown that psilocin produces hyperthermia in rabbits (113), induces the head-twitch in mice (43), disrupts acquisition of avoidance behavior in rats (240), increases startle response magnitudes in rats (68), increases limb-flick behavior in cats (120), and produces discriminative stimulus effects in rats similar to those of 5-OMeDMT (**59**) (93).

The 5-hydroxy derivative of DMT, bufotenine, or N,N-dimethyl-serotonin, is another naturally occurring tryptamine found to occur in South American snuffs. Intravenous administration of bufotenine (**53**) was reported by Fabing and co-workers (59,60) to be hallucinogenic in man. This finding is in conflict with a later report by Turner and Merlis (235). Apparently, due to its low lipid

solubility (65), bufotenine does not readily cross the blood-brain barrier (64,183). The initial observations made by Fabing et al. (59,60) may be the result of peripheral toxic manifestations.

Bufotenine has been found to be behaviorally inactive, or only weakly active, in most animal studies, although at 15 mg/kg, it did produce the head-twitch resonse in mice (43). It was also behaviorally active in experiments in which the blood-brain barrier was bypassed (78). Acylation of the polar hydroxy group of bufotenine increases its lipid solubility (65,74) and apparently enhances its ability to cross the blood-brain barrier (64). For example, 0-acetylbufotenine (5-acetoxy-N,N-dimethyltryptamine; **54**) disrupted conditioned avoidance behavior in rodents (65) and produced tremorigenic activity similar to that elicited by DMT (**37**) or 5-OMeDMT (**59**) when administered to mice (64). In this latter study, a comparison of brain levels of bufotenine after administration of 0-acetylbufotenine with those of DMT and 5-OMeDMT revealed bufotenine to be the most active of the three agents, based on brain concentration. The pivaloyl ester of bufotenine also appears to possess behavioral activity, since stimulus generalization was observed when this agent was administered to animals trained to discriminate 5-OMeDMT from saline (74).

There are only two reports of the human evaluation of a 6-hydroxylated N,N-dialkyltryptamine. Szara and Hearst (223) studied the effects of 6-hydroxy-N,N-diethyltryptamine (6-OH-DET; **56**) in a single subject. Doses of 1 and 2 mg were inactive; a 5-mg dose produced a short-lasting perceptual disturbance; and a 10-mg dose, after 1 hr, produced some psychotomimetic disturbances. Rosenberg et al. (182) compared the activity of DMT with that of 6-OH-DMT (**55**) in five human subjects. While DMT was active, the 6-hydroxy derivative was found to be inactive at intramuscular doses of approximately 50 to 75 mg. At a dose of 10 mg/kg, 6-OH-DMT (**55**) increased spontaneous activity in mice more so than a comparable dose of DMT; 6-OH-DET (**36**) was essentially equiactive with DET in this respect (224). In most other animal studies, however, 6-hydroxylation of DMT has been observed to result in a decrease or complete loss of behavioral activity (228,236–238). The behavioral potency of 5-OMeDMT (**59**) was also reduced by 6-hydroxylation (226). 7-Hydroxy-N,N-dimethyltryptamine (7-OH-DMT; **57**) has not been evaluated in man. At an intraperitoneal dose of 33 μM/kg, 7-OH-DMT displayed no behavioral effects in rats (228). The pharmacologic effects of all four hydroxylated derivatives of DMT, psilocin (**49**), bufotenine (**53**), 6-OH-DMT (**55**), and 7-OH-DMT (**57**) have been compared in studies by Taborsky et al. (228) and by Cerletti et al. (29).

4-Methoxy-N,N-dimethyltryptamine (4-OMeDMT; **58**) has been examined only in animal studies and has shown behavioral activity roughly comparable to that of DMT (65,236,238). It also produced discriminative stimulus effects similar to those of 5-OMeDMT with a potency somewhat less than that of DMT but greater than that of either 6-OMeDMT (**71**) or 7-OMeDMT (**72**) (93). In drug discrimination studies using DOM as the training drug, 4-OMeDMT was more active than DMT but less active than DET (91).

5-Methoxy-N,N-dimethyltryptamine (0-methylbufotenine; **59**) is hallucinogenic in man at a parenteral dose of approximately 6 mg (204). Numerous animal studies have shown that 5-OMeDMT is behaviorally quite active (16,65–67,71,178,184). This compound also produced limb-flick behavior in cats (119) and the "serotonin syndrome" in rats (209). Glennon et al. (85) demonstrated that 5-OMeDMT serves as a discriminative stimulus in rats and have employed rats trained to discriminate 5-OMeDMT from saline to investigate the structure-activity relationships of various substituted N,N-dialkyltryptamine derivatives. The results of these studies have recently been reviewed (84).

In man, 5-methoxy-N,N-diisopropyltryptamine (5-OMeDIPT; **63**) appears to be equipotent with 5-OMeDMT (**59**) and is orally active (202). With the exception of these two agents, no other 5-methoxy-N,N-dialkyltryptamines have been studied in man. Several derivatives, including compounds **60–63,** possess behavioral activity in animals (25,65,93,111). In a drug discrimination study using DOM as the training drug, the following order of potency was reported: 5-OMeDET (**61**) > 5-OMeDIPT (**63**) > 5-OMeDMT (**69**) (91).

Kline et al. (132) have recently prepared the 4,5-methylenedioxy derivatives of DMT and DIPT, **64** and **65,** respectively, as well as the isomeric 5,6-methylenedioxy compounds **66** and **67.** The diisopropyl derivatives **65** and **67** were more active in disruption of behavior than their corresponding dimethyl derivatives. The 4,5-methylenedioxy group conferred higher activity than did the 5,6-methylenedioxy. Kline et al. (132) also evaluated the 4-, 5-, and 6-methylthio derivatives of DMT, **68, 69,** and **70,** respectively, and found 5-SMeDMT (**69**) to be the most active of the three. In a drug discrimination study, Glennon et al. (89) compared 4- and 5-methoxy DMT with their methylthio counterparts and obtained the following ranking of potency: 5-OMeDMT (**59**) > 5-SMeDMT (**69**) > 4-OMeDMT (**58**) > 4-SMeDMT (**68**).

The 6- and 7-methoxy derivatives of DMT, **71** and **72,** respectively, display a low order of behavioral activity in animals (65,86,91,93,124). 5,7-Dimethoxy-N,N-dimethyltryptamine (**73**) was much less active than 5-OMeDMT (**59**) in tests of discriminative control of behavior in rats (86). Nir et al. (170) have reported that 4,5,6- and 5,6,7-trimethoxy DMT, **74** and **75,** respectively, produced unique and long-lasting behavioral effects in rodents.

Side Chain-Altered N,N-Dialkyl Derivatives

Four alterations of the side chain of N,N-dialkyltryptamines have been studied: (a) hydroxylation, (b) shortening, (c) lengthening, and (d) branching. Hydroxylation of the side chain of N,N-dialkyltryptamines ordinarily leads to a decrease in potency (228), as does shortening the chain to one carbon to give the gramines **76** (R = H, n = 1 and R = OMe, n = 1). While these compounds appear to possess some central activity (103), their effects are probably different than those of N,N-dimethyltryptamines. In a recent drug discrimination study, 5-meth-

oxygramine was found to produce effects that were dissimilar to those produced by its homolog 5-OMeDMT (91).

Lengthening of the side chain of DMT by a single methylene group produces N,N-dimethylhomotryptamine (DMHT; **76,** R = H, n = 3), which produced hyperthermia when administered to rabbits (7,232) but was found to be inactive in man (235). Intravenous administration of 5 and 10 mg and intramuscular injection of 20 to 70 mg DMHT was without psychologic effect in 10 human subjects (235). Additional studies on DMHT homologs (i.e., **76,** n = 4–10) did not show any interesting activity (7,232).

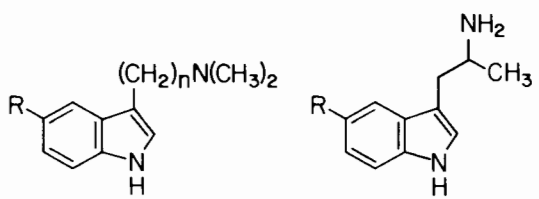
Alpha-methylation of DMT reduced its behavioral activity in animals, while alpha-methylation of N-methyltryptamine (**27**) resulted in an agent with stimulant properties (137,228). Alpha-methyltryptamine (α-MeT; structure **77**), however, is hallucinogenic in man at doses of about 30 mg. Thus it is two to three times more active than DMT (for review see refs. 24, 81, and 196). 5-Methoxy-α-methyltryptamine (5-OMe-α-MeT; **78**) was also determined to be twice as active in man as its dialkyl counterpart, 5-OMeDMT. In human trials, 5-OMe-α-MeT produced behavioral effects at about 3 mg (204). A comparison of the activities of the individual isomers of **78** in man has not been reported. However, Glennon and co-workers (76,83,90) found that the (+)-isomers of both α-MeT and 5-OMe-α-MeT are more active than their racemates in tests of discriminative control of behavior in rats. Although (+)-5-OMe-α-MeT was four times more active than its enantiomer, (−)-α-MeT did not produce effects similar to either racemic α-MeT or 5-OMeDMT.

Homologation of the α-methyl group of α-MeT results in compounds with central activity but activity that may be different from that of α-MeT. Alpha-ethyltryptamine, for example, has been used in man as an inhibitor of MAO. However, hallucinogenic activity was not evident (see refs. 24 and 106 for more details).

Structure-Activity Relationship Summary

Based on the foregoing discussion, it is possible to formulate some structure-activity relationships with respect to the behavioral properties of various tryptamine derivatives. It should be noted that these structure-activity relationships are derived from the results of both human and animal studies.

Tryptamine and its N-monoalkyl derivatives are behaviorally inactive, or, at



Structures 76, left; right 77: R=H; **78:** R=OCH_3.

best, only weakly active. This is probably a consequence of their rapid metabolism and/or their inability to penetrate the blood-brain barrier. N,N-dialkyltryptamine derivatives, where the alkyl groups vary from methyl to propyl, are active, with the dipropyl derivative being slightly more active than the dimethyl compound. Branching of the dipropyl groups (i.e., diisopropyl) appears to allow retention of activity. Dialkyl substituents larger than propyl tend to reduce activity.

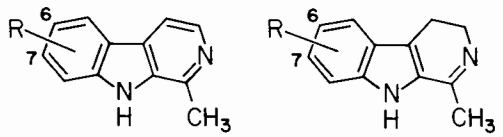
Methylation of N,N-dimethyltryptamines at either the 1-, 2-, or 6-position decreases potency, while methylation at the 5- or 7-position seems to have relatively little effect on activity. The 4-hydroxy derivatives of DMT appear to be the only hydroxy compound to show appreciable activity. The 5-, 6-, and 7-hydroxy isomers are either less active or inactive. Methylation of these hydroxy groups to yield the corresponding methoxy derivatives has different effects, depending on the position of the substituent. Methylation of the 4-hydroxy group decreases potency, while methylation of the 5-hydroxy group increases activity dramatically. The 6- and 7-methoxy derivatives are less active than either the 4- or 5-methoxy isomers.

Both shortening and lengthening of the alkyl side chain result in decreased activity. While alpha-methylation of N,N-dialkyltryptamines reduces activity, alpha-methylation of the primary amines results in agents that are more active than their corresponding N,N-dimethyl counterparts. Further homologation of the alpha-methyl group decreases activity.

Beta-Carbolines

Most discussions of hallucinogens have paid little attention to the beta-carbolines. There are several reasons for this, not the least of which is their relative difficulty of synthesis and consequent general unavailability for detailed study. Furthermore, the effects of the beta-carbolines in man seem to differ qualitatively from that of LSD or mescaline. Nevertheless, a great deal of attention has recently been directed toward beta-carbolines. While most of this renewed interest has been centered on their potential anxiogenic or anxiolytic activity, recent reports have indicated possible pharmacologic similarities between certain beta-carbolines and LSD (38,91,168). Since the pharmacology of hallucinogenic beta-carbolines has not been well characterized, it seemed appropriate to review this class of compounds, which has a long and rich folkloric history.

The beta-carbolines are structurally related to the tryptamines, except that the aminoethyl side chain has been cyclized to form a tricyclic structure. Here again, several members of this class of compounds are naturally occurring. Certain South American Indian tribes prepare a hallucinogenic beverage, variously known as Ayahuasca, Caapi, and Yage, from, principally, the malpighiaceous vine *Banistereopsis caapi* (186). Closely related plants and admixtures have also been employed (2,51,57,108,109,152,153,180,185). Numerous beta-carboline derivatives have been detected and/or isolated from these plants, including harmine (**79**), harmaline (**80**), and tetrahydroharmine (**81**)



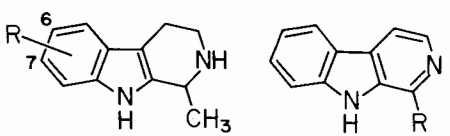
Structure 23. Left: 79: R=7-OCH_3, **84:** R=6-OCH_3; **Right: 80:** R=7-OCH_3; **85:** R=6-OCH_3.

(5,11,109,152,180,185) Structures **23, 24.** Harman (**82**) and norharman (**83**) have been isolated from cigarette smoke (175), and Janiger and deRios (122) have suggested that some of the tobacco-induced altered states reported by South American Indians might be related to the cumulative effects of these beta-carbolines.

A series of early pharmacologic studies on beta-carboline derivatives employing both human and nonhuman subjects was reported by Gunn (99) in 1935. Ho (102) has reviewed the general pharmacology of beta-carbolines, and Buckholtz and Boggan (26) have reviewed their structure-activity relationships as inhibitors of MAO. More recently, Muller et al. (150) have investigated the binding of various beta-carbolines to serotonin, dopamine, opiate, cholinergic, and benzodiazepine binding sites, and Ninan and co-workers (169) have reported that the ethyl ester of beta-carboline-3-carboxylic acid has a high affinity for benzodiazepine receptors in the brain and produces a behavioral syndrome in monkeys that may provide a useful animal model of human anxiety.

A positional isomer of harmaline, 6-methoxyharmalan (**85**), was found to be slightly more active than harmaline in disrupting conditioned avoidance behavior in rats (146). Gryglewski and co-workers (98) found that replacement of the 1-methyl group of 6-methoxytetrahydroharman (**86**) by aryl substituents diminished excitatory behavior and resulted in a series of agents that produced a generalized depressant effect.

In tests of discriminative control of behavior in rats using DOM (1.0 mg/kg) as the training drug, Glennon et al. (83,91) found that administration of harmaline and 6-methoxyharmalan, but not harmine, resulted in stimulus generalization. 6-Methoxyharmalan was somewhat more potent than either its positional isomer **80** or DMT (**37**). The ED_{50} values determined for **85, 80,** and **37** were 5.13, 6.19, and 5.80 mg/kg, respectively. In a similar study using animals trained to discriminate LSD (0.1 mg/kg) from saline, Nielsen et al. (168) found that harman produced saline-like effects at 3 mg/kg, while tetrahydro-beta-carboline (7.1 mg/kg), 6-methoxytetrahydro-beta-carboline (approximately 10 mg/kg), and harmaline (8 mg/kg) produced 69, 70, and 54% LSD-appropriate responding, respectively. The effect of higher doses was not explored.



Structure 24. Left: 81: R=7-OCH_3; **86:** R=6-OCH_3; **Right: 82:** R=CH_3; **83:** R=H.

In a single trial with one human subject, 200 mg harmine (**79**) produced a mild hallucinogenic response that included auditory buzzing and visual distortion (138). In a study employing a larger number of human subjects, it was determined that intravenous administration of harmine produced hallucinogenic effects in five of 11 subjects. The threshold dose was estimated as being 150 to 200 mg (173). Higher doses were not investigated because of the incidence of bradycardia and hypotension. Harmine was inactive when administered orally (up to 960 mg) or subcutaneously (40–70 mg) (173).

Harmaline (**80**) appears to be about twice as active as its fully saturated counterpart harmine (152). Naranjo (151,152) determined that harmaline was effective at intravenous doses of 1 mg/kg and at total oral doses of 300 to 400 mg. In a limited study, tetrahydroharmine (**81**) was found to be approximately one-third as active as harmaline, with an oral dose of 300 mg producing an effect similar to that of 100 mg harmaline (152). Repositioning of the 7-methoxy group of harmaline to the 6-position gives 6-methoxyharmalan (**85**). This compound was active at oral doses of approximately 100 mg (1.5 mg/kg). Reduction to the tetrahydro counterpart, 6-methoxytetrahydroharman (**86**), resulted in a compound with about one-third the potency of the parent 6-methoxyharmalan (152). Rivier and Lindgren (180) have estimated that a 200 ml portion of Ayahuasca contains 30 mg harmine, 10 mg tetrahydroharmine, and 25 mg DMT. Based on the potencies of **79** and **81,** together with the finding that beta-carbolines are inhibitors of MAO, it may be that the effects of such concoctions are due to the presence of DMT as a result of its decreased metabolism by the beta-carbolines. The effects produced by hallucinogenic beverages that contain harmaline may be a direct result of the presence of harmaline. This interesting class of agents certainly warrants additional study.

In summary, based on the results of relatively limited studies, the dihydro beta-carboline, harmaline (**80**), is more active than either its fully unsaturated derivative harmine (**79**) or its reduced derivative tetrahydroharmine (**81**). The positional isomer of harmine, 6-methoxyharmalan (**85**), is slightly more potent than harmaline. Reduction to the tetrahydro derivative **86** reduces potency. Although thorough dose-effect studies have not yet been performed, none of the beta-carboline derivatives has been found to be significantly more potent than DMT (**37**).

Lysergic Acid Derivatives

The most potent of the known hallucinogenic agents is LSD. It is orally active in man at doses of about 0.1 mg (0.05 to 0.25 mg). The vast majority of human studies involving LSD and its structural variants were performed in the 1950s and 1960s and have been reviewed in great detail (24,154,196,208). Therefore, some of the key structure-activity relationships are briefly highlighted here only for the sake of completeness.

Lysergic acid diethylamide possesses two asymmetric centers, one at the 5-position and the other at the 8-position; its absolute configuration is 5*R*, 8*R*. Inversion of the configuration at either of these centers essentially abolishes hallucinogenic activity. From a potency standpoint, LSD can withstand almost no structural variation without at least reduction, if not total loss, of activity. The 1-acetyl derivative of LSD is reportedly equivalent in activity to the parent compound but evidently is readily hydrolyzed *in vivo* to yield LSD. Shortening of the diethylamide to a dimethyl, methyl, ethyl, or monoethyl amide reduces potency by at least 10-fold; lengthening has a similar effect. Cyclization of the diethylamide to a pyrrolidine diminishes activity by an order of magnitude. Reduction of the 2,3-double bond also reduces activity by almost an order of magnitude, while reduction of the 9,10-double bond abolishes activity. The bromination of LSD yields 2-bromo-LSD (BOL). This compound not only lacks hallucinogenic activity but can block the effects of a subsequently administered dose of LSD.

It is surprising that the most potent of all the hallucingens should possess such a rigid structural requirement. Conversely, it may be this rigid requirement that accounts for its unique potency. Relatively little has been reported on the structure-activity relationships of LSD derivatives. This is probably a direct consequence of the difficult task of preparing such compounds.

CONCLUSION

Attempts to discuss the structure-activity relationships of phenylalkylamine and indolealkylamine hallucinogens are stymied by the paucity of human hallucinogenic data. This is further complicated by the subjective nature of the response being measured and by the general lack of good dose-effect studies. On the other hand, discussions of structure-activity relationships may resort to including the results of animal studies, where larger numbers of structural modifications have been examined and where dose-response data are usually collected. However, here exists another problem: Is there any relationship between human hallucinogenic activity/potency and any measure of activity using animals as subjects? Surprisingly enough, there can be considerable qualitative, if not quantitative, agreement between the human data and certain recent animal studies (84). Nevertheless, caution is advised in interpreting structure-activity relationships derived from limited human studies or from animal data.

Taken together, the data presented here show that many phenyl- and indolealkylamines are hallucinogenic in man and behaviorally active in animals. In both series, primary amines penetrate the blood-brain barrier with difficulty, although this seems to be more of a problem with tryptamines (and even N-monoalkyltryptamines) than with phenethylamines. This situation is somewhat alleviated in the presence of an alpha-methyl substituent. The primary amines are also prone to rapid metabolism by oxidative deamination. Metabolism, however, can be impeded by the presence of an alpha-methyl or N-alkyl function.

Compounds such as LSD or the beta-carbolines do not possess a primary amino group, are not rapidly metabolized in comparison to, for example, tryptamine, and enter the brain readily; certain substituent groups can alter this situation. Members of the phenylalkylamine and indolealkylamine families of hallucinogens can produce similar effects in animals but may be capable of producing distinctive effects in man. As yet, there is no satisfactory and comprehensive structure-activity relationship that encompasses both major classes of compounds. This may be due in part to unique metabolic and distributional characteristics associated with the individual ring systems.

From the foregoing discussion, it is apparent that progress is being made in our understanding of these compounds. Nevertheless, a great deal of work remains to be done. While there appear to be correlations between hallucinogenic activity and the ability of tryptamine derivatives to displace [^{3}H]-LSD or serotonin in receptor binding assays, this is not true for phenethylamines. Phenethylamine derivatives generally have low affinity for these sites. Electrophysiologic studies have also failed to identify an anatomic or physiologic basis for the action of phenethylamine-type hallucinogens. Although it is generally believed that the phenethylamines act through a serotonergic mechanism, and this is supported by neurochemical and *in vitro* studies, their locus of action remains obscure. Therefore, continuation of structure-activity studies remains of high importance, particularly for the phenethylamines. Well-designed series of congeners, when the human psychopharmacology is also well defined, will be extremely useful. Such compounds can be studied and their neurochemical effects compared. Their receptor binding properties can be evaluated, and physicochemical and pharmacokinetic parameters can be measured. This information could lead to a much clearer understanding of the relative importance of all these factors and the significance of the various possible component processes in the overall drug effect.

Furthermore, additional work must be done with enantiomers and diastereoisomers in order to completely characterize the stereochemical requirements of the receptor(s) involved. Comparisons between the biologic activities of such isomers, where physicochemical and pharmacokinetic factors are nearly equal, can lead to important insights. Consider, for example, how the knowledge that it is the *R* enantiomer of the hallucinogenic amphetamines that is most active has affected our approach to comparing the structures of the phenethylamines to that of LSD. Furthermore, labeling of such isomers with radionuclides may well help to identify anatomic sites involved in hallucinogenic drug action. One might note that, as of this writing, the simple experiment of comparing the regional brain distribution of the *R* and *S* [^{3}H]-labeled enantiomers of DOM has not even been carried out.

We are still confronted by a list of interesting and important questions that have not been answered. To what extent are dopamine pathways involved in hallucinogenic drug action? What is the relative importance of presynaptic versus postsynaptic serotonergic action? Is the release of endogenous neurotransmitters

an important factor? If so, which transmitters are involved? Given the similarity in structure between mescaline and the catecholamines, is there an as yet unidentified role for norepinephrine receptors in the action of mescaline? With the more sophisticated tools and methods now becoming available to neuropharmacologists, these questions become more amenable to detailed study.

These and many other questions are best answered when one has in hand a series of compounds that differ not only in potency but also in qualitative effect. Only in this way can statistical, theoretical, and modern quantitative and qualitative analytic methods be applied to offer the most meaningful interpretation of the results and to appreciate fully the subtle relationships between molecular structure and biologic effect. Indeed, in this case, we need these compounds to define what is even meant by "biologic effect."

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Common Neurochemical Correlates to the Action of Hallucinogens

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Hallucinogens are defined by their ability to induce distorted auditory, visual, and tactile sensations and hallucinations, i.e., dreamlike episodes in the awake state in humans. In many respects, the symptoms produced by hallucinogens are qualitatively similar to those seen in certain types of psychotic illness, notably schizophrenia. This leads most authors to the postulate that the functional disorders triggered by these drugs are closely related to those occurring in the central nervous system (CNS) of schizophrenic patients. On this basis, investigations on the central biochemical alterations produced by hallucinogens have two main goals: (a) to understand the cellular and molecular mechanisms of action of these drugs and to design appropriate pharmacologic treatments to counteract hallucinogen intoxication in addicts, and (b) to obtain some information regarding the possible functional disorders in the brain of psychotic patients. Limitations to these ambitious goals are obvious, however, since experimental studies concern exclusively animal species, mainly the rat, in which hallucinations are only hypothesized in light of the behavioral disturbances produced by the drugs causing true hallucinations in man. Nevertheless, biochemical investigations in the cerebrospinal fluid (CSF) of schizophrenic patients undergoing hallucinatory episodes and postmortem studies on the brain of psychotic patients support the theory, since the alterations in monoaminergic neurotransmission in these patients are apparently similar to those induced by the administration of hallucinogenic drugs to animals. Such observations confirm that studies on neurotransmitter metabolism in animals treated with these drugs might be a valuable approach to understand the etiology of hallucinations associated with mental illness in man.

Hallucinogens comprise a heterogeneous family of drugs, including indoles [*d*-lysergic acid diethylamide (LSD), 5-methoxy-N,N-dimethyltryptamine (DMT), bufotenine, psilocybin, and derivatives], phenylethylamines [mescaline, 2,5-dimethoxy-4-methylamphetamine (DOM or STP), and other methoxyamphetamines], anticholinergic agents [scopolamine and the glycolate esters ditran and N-methylpiperidyldiphenyl glycolate hydrochloride (A 1111)], opiates interacting with the sigma type of receptors [mainly benzomorphans, such as N-