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LITERATURE SURVEY

Structure–Activity Relationships of Phenethylamine Hallucinogens

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Keyphrases □ Phenethylamines—structure–activity relationships, compared with other hallucinogens, animal, human, and *in vitro* studies reviewed, literature survey □ Structure–activity relationships—phenethylamines, compared with other hallucinogens, animal, human, and *in vitro* studies reviewed, literature survey □ Hallucinogens—phenethylamines, structure–activity relationships, compared with other hallucinogens, animal, human, and *in vitro* studies reviewed, literature survey

The phenethylamine hallucinogens are simple 2-phenylethylamine derivatives of the general formula I, the majority of which are substituted with methoxy and alkyl or halogen groups. Where R is a methyl group, the compounds have been referred to as hallucinogenic "amphetamines." Although not strictly correct, this nomenclature is used throughout this discussion.

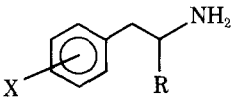
Although these drugs are not widely abused at present, several were prevalent on the illicit drug market during the 1960's. The more common ones were 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane ("STP," II) (1), 1-(3,4-methylenedioxyphenyl)-2-aminopropane (III) (2), and 1-(4-methoxyphenyl)-2-aminopropane (IV) (3). The latter two were responsible for several deaths. Their popularity was due to their relatively high potency, coupled with the economic attractiveness of starting materials such as anisaldehyde, piperonal, and methylhydroquinone. With the exception of lysergide (LSD), the "classical" hallucinogens psilocin or psilocybin and mescaline were seldom available (4). Thus, the amphetamines served as convenient substitutes.

Structure–activity studies have been carried out with several classes of hallucinogens. However, lysergamides, related to lysergide and the most potent series, have received only limited attention, chiefly due to the molecular complexity of lysergic acid and the problems inherent in modification of such a structure. The simple tryptamines have been investigated somewhat more extensively, but few novel compounds have emerged. In addition, many of the indoles necessary as starting materials are tedious to synthesize. Therefore, the tryptamines have probably not received the attention they deserve.

In contrast, the phenethylamines have been studied extensively. The commercial availability or ease of synthesis of numerous substituted benzaldehydes has led to the synthesis and evaluation of literally hundreds of analogs. Because the mechanism of action for phenethylamine hallucinogens appears to be identical or similar to that for lysergide and the tryptamines (5–10), studies with phenethylamines could be used to infer information about the action and binding features of indoles.

This class of agents was reviewed by Nieforth (11) in 1971 as "psychotomimetic" phenethylamines. It is not the intent of this author to delve into the significance and comparisons of such terms as psychotomimetic, hallucinogenic, and psychedelic. The controversy over appropriate terminology has been considered in the literature. Within this discussion, the terms hallucinogenic and psychotomimetic are used interchangeably. Psychedelic is another term that has been used to describe this class of compounds.

A word of caution about biological data is in order. Activity is discussed for several animal and *in vitro* models, as well as for humans, where available. However, the use of *in vitro* and animal data can be misleading. For example, compounds have been compared in rats for their ability to disrupt a conditioned avoidance response. In clinical terms, this approach is meaningless. In rabbits, many compounds have been compared for their ability to elicit hyperthermia.



I: R = H or CH_3, X = OR, alkyl, halogen
II: R = CH_3, X = 2,5-$(OCH_3)_2$-4-CH_3
III: R = CH_3, X = 3,4-OCH_2O
IV: R = CH_3, X = 4-OCH_3

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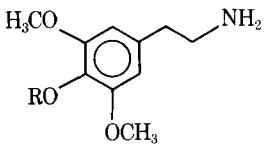
Again, these data have little clinical relevance. In general, however, such tests have been correlated with potency of the compounds in humans. Many of the animal tests were found to allow predictions, albeit approximate, of human potency. Thus, in cases where animal data are cited, some effective central component of action is indicated. Nevertheless, the reader should be aware that only those compounds that were assayed in humans can be truly categorized as hallucinogenic.

There is a good deal of flexibility in interpretation even in this situation, and much of this should be attributed to the multiplicity of actions possessed by the phenethylamines. These simple structures have direct actions on serotonin receptors, both as agonists (12–14) and as antagonists (15), are capable of releasing serotonin (16), norepinephrine, and dopamine (17), have direct actions at dopamine receptors, or can be metabolized to species that further influence qualitative mechanisms of action (18), all depending on the particular structure studied. The effect on monoamine oxidase for most structures also is unknown. These and other factors combine to varying degrees for each agent. Hence, a particular compound could be said to possess a unique profile of action all its own. That is, each substitution pattern could be expected to present a slightly different qualitative pattern of clinical activity that will be revealed only by tests in humans. Therefore, when one speaks of hallucinogenic activity, it is uncertain just exactly what is meant. Most often, in humans at least, the term refers to a subjective similarity to a standard agent such as lysergide or mescaline. In this light, one can see how inadequate any animal testing will be. Fortunately, Shulgin and his coworkers provided a wealth of quantitative human data for correlation and analysis.

Although elucidation of subtle qualitative structure–activity relationships must await more structured and well-designed clinical assays, legal strictures and public sentiment presently oppose such research. One is forced to rely largely on animal assays. Ignoring the work that has used animals and *in vitro* models leaves a serious gap in an understanding of structure–activity relationships. Such studies should be considered, but with the caveats discussed always in mind.

This paper briefly, but critically, reviews the advances made in understanding the structure–activity relationships of phenethylamine hallucinogens. It is hoped that a clearer picture will emerge of the probable requirements for receptor binding and some of the essential conformational and stereochemical features. Where possible, these requirements are related to human clinical activity.

Comprehensive reviews of hallucinogens were presented by Brawley and Duffield (6) and subsequently by Shulgin (19–21). Jacobs and Trulson (22) also recently presented a brief review of the mechanism of action for hallucinogens. However, none of these reports dealt in sufficient depth with the structure–activity requirements for the most widely studied class of hallucinogens, the phenethylamines. The excellent and comprehensive reviews by Shulgin come closest to this goal but tend to focus on active compounds and a description of structure–activity relationships as they apply to human clinical studies. These reviews understandably omit several studies where activity in animal models has not been confirmed by human testing.



V: R = CH_3
VI: R = CH_2CH_3

The present discussion attempts to pull together findings from many approaches, both *in vivo* and *in vitro*. The treatment begins with aromatic substitution patterns and proceeds to brief highlighting of what is known about the molecular mechanism of action. It is hoped that the reader will gain a better understanding of the structural features necessary for activity and, where possible, insight into the possible reasons for their importance.

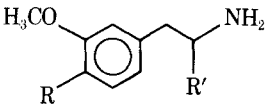
AROMATIC SUBSTITUENTS

Orientation—It has been concluded that a 2,4,5-trisubstitution pattern yields optimally active compounds (19, 23). Although this statement generally remains true, some interesting exceptions exist. For example, replacement of the 4-methoxy group in mescaline (V) with an ethoxy group gives escaline (VI), which is about six times more active than mescaline (24).

Within the 3,4,5-trisubstituted series, replacement of the 4-methoxy with a bromine, alkyl, or alkylthio group leads to compounds with high activity (24). Acute dosages in humans were reported to be in the 10–20-mg range (21). In an *in vitro* assay, several 3,4,5-trisubstituted compounds showed potency comparable to similarly substituted 2,4,5-substitution patterns (25). This point is important. Attention has been called to the possibility of quinone generation from 2,5-dimethoxy-substituted compounds as an explanation for their high potency (19, 21, 23, 26). Although di-*O*-demethylation and consequent oxidation to quinones were observed in liver microsomes, no such reactions were detected *in vivo* (27). However, the potential neurotoxicity of such reactive metabolites (28), even if produced only in miniscule amounts, should give cause for concern in the unlikely event that these drugs might be used on a chronic high dosage basis.

In general, the most active compounds studied to date possess 4,5-disubstitution with a methoxy group at either the 2-position (2,4,5-substitution) or the 3-position (3,4,5-substitution). However, 2,4,6-trimethoxyamphetamine possesses about 10 times the activity of mescaline in humans (21). Since little work has been reported with 2,4,6-substituted compounds, it is impossible to assess whether further substituent modification will give more potent compounds in this series.

Nature of Substituents—In any substitution series, the 4-substituent has been of unique importance. Although it probably contributes a general lipophilic effect that favors more effective central nervous system (CNS) penetration (29), it also may serve in at least two other specific roles. First, the most active compounds possess *para*-substituents that are resistant to oxidative metabolism. Increasing potency generally parallels increasing stability of this group. Second, a recent *in vitro* quantitative study indicated that serotonin receptors may possess a specific hydrophobic site that accommodates the *para*-substituent,



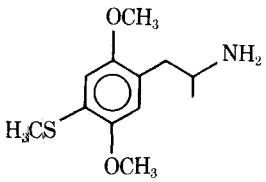
VII: R = OCH_3, R′ = H
VIII: R = OCH_2CH_3, R′ = H
IX: R = CH_3, R′ = H
X: R = Br, R′ = CH_3

providing it is <5–6 Å in length (30). These conclusions were supported by studies of molecular connectivity (31). Green *et al.* (32) also proposed a specific hydrophobic site approximately at this region of the serotonin receptor.

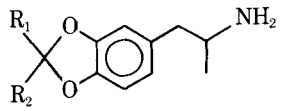
The unique importance of the *para*-substituent can be best illustrated with several examples. Anderson *et al.* (33, 34) evaluated a series of isomeric 2,4,5-trisubstituted dimethoxymethylamphetamines. Substantial activity in the rabbit hyperthermia model was observed only when the substituents were in the 2,5-dimethoxy-4-methyl configuration. A similar finding occurred for a series of 2,4,5-substituted dimethoxymethylthioamphetamines. Significant activity occurred only with the 2,5-dimethoxy-4-methylthio orientation (35).

The *para*-substituent is even more critical for compounds lacking an *o*-methoxy group. For example, 3,4-dimethoxyamphetamine (VII) may be orally active in humans but only at acute doses of >1 g (36). However, simple replacement of the 4-methoxy in VII with an ethoxy group gives VIII, leading to some retention of central activity. In humans, VIII possessed mood-elevating properties in the 0.1–0.2-g range (36). In an assay in mice, 3-methoxy-4-methylamphetamine (IX) was just as potent and long lasting as 2,5-dimethoxy-4-methylamphetamine (II) (37). In a series of bromomethoxyamphetamines, the 3-methoxy-4-bromo group (X), but not the isomeric 3-bromo-4-methoxy group, elicited a mescaline-like effect in rats (38). Thus, for hallucinogen-like activity in rodent models, the *o*-methoxy group may not be required. However, it was found that IX, despite its reported activity in mice, is totally inactive in humans at doses 10-fold greater than the threshold for II (36).

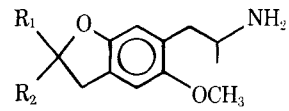
An interesting variation in activity is encountered where the *para*-substituent is an alkylthio group. It was speculated initially that the metabolic lability of sulfur might provide interesting biological properties, in contrast to more oxidation-resistant groups (39). Clinical studies of the first compound in this series, 1-(2,5-dimethoxy-4-methylthiophenyl)-2-aminopropane (XI), proved it to be highly active (26). Its duration of action was reduced somewhat from that observed with more metabolically stable compounds. However, this drug appears to produce a unique enhancement of intellectual function while lacking other features of the hallucinogens such as severe visual sensory distortion. Shulgin and his colleagues (21, 40) described this "aleph" effect and expanded on this lead. Alkylthio-substituted compounds in both the 2,4,5- and 3,4,5-series have been examined for activity. Several



XI



XII: $R_1 = R_2 = H$
XIII: $R_1 = H$, $R_2 = CH_3$
XIV: $R_1 = R_2 = CH_3$



XV: $R_1 = R_2 = H$
XVI: $R_1 = H$, $R_2 = CH_3$
XVII: $R_1 = R_2 = CH_3$

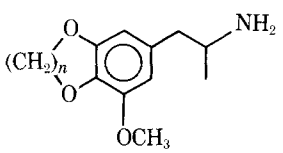
are quite potent and retain the specific intellectual-enhancing properties of XI. The more interesting of these compounds contain the alkylthio group in an orientation *para* to the side chain.

Replacement of a 2-, 3-, or 5-methoxy with a larger alkoxy, methyl, or halogen usually resulted in inactive compounds (34, 41, 42), although some activity was retained in a few cases. Within the 2,5-dimethoxy series, replacement of one methoxy with a hydroxy group increased *in vitro* serotonin receptor affinity (43, 44). Substitution at the 5-position with hydroxy had a greater enhancing effect on affinity than at the 2-position.

Steric Effects—Recent studies are beginning to answer questions about the bulk properties of the aromatic ring substituents. Although there may be a hydrophobic region on the receptor that accommodates the *para*-substituent, bulky hydrocarbon groups are not tolerated, as illustrated by the series of 2,5-dimethoxy-4-alkyl-substituted amphetamines. Activity can be ordered in the following sequence for the 4-alkyl group: propyl > ethyl > methyl and also propyl > isopropyl > *tert*-butyl (45–47). The clinical activity of the *p*-isopropyl and *p*-*tert*-butyl homologs has not been established, and potencies are based on animal studies (46, 48). However, the *tert*-butyl homolog was inactive in humans at acute dosages up to 10 mg, far above the effective amount for a *p*-methyl group (20).

It has been proposed that the receptor that interacts with hallucinogens can be modeled as a planar surface which can tolerate little, if any, steric bulk projecting from the binding face of the hallucinogen molecule (49, 50). Nonbonded interactions between the 4-alkyl and an adjacent methoxy group certainly play a role in the allowed conformational states of the alkyl group. One can envision the type of steric profile presented to the receptor by an isopropyl or *tert*-butyl group. In the latter case, it would be impossible to rotate the *tert*-butyl group to remove bulk completely from one face of the molecule. With an isopropyl group, this would not be so severe.

Evidence to support the idea of a deleterious effect of bulky substituents comes from studies on two series of homologs. Structures XII, XIII, XV, and XVI were shown to possess clinical activity (36, 51). Compound XIV has not been tested in humans, but was inactive in animal models (52). The *gem*-dimethyl compound (XVII) is inactive in humans (20). This pattern of activity is in agreement with the suggestion that one face of the molecule must remain unhindered. This explanation may apply to the inactivity of the ethylenedioxy (XVIII*a*) and trimethylenedioxy (XVIII*b*) compounds (53).



XVIII*a*: $n = 2$
XVIII*b*: $n = 3$

In addition to interactions between substituents and the receptor, interaction between the substituents themselves probably plays an important role in determining activity. X-ray crystallographic studies established that the 4-methoxy group of mescaline is twisted nearly perpendicular to the ring plane (54). It is unlikely that a more bulky group such as ethoxy can rotate from a perpendicular conformation. In view of the substantial potency, not only of escaline (VI) but of its 4-isopropoxy homolog, isoproscaline (36), it seems doubtful that the 4-oxygen plays any crucial role with respect to resonance overlap of its n electrons with the π system of the aromatic ring. This concept is reinforced by the fact that the 4-substituent can be replaced by alkyl or halogen with an increase in activity.

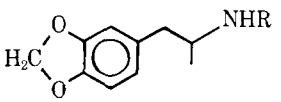
On the other hand, twisting of the 2- or 5-methoxy functions seems to abolish activity. Such twisting has been invoked to explain the inactivity of certain 2,3-dimethoxy-substituted compounds (55) since a 2,3-methylenedioxy group usually gives active compounds (23). One may speculate that the 2- and 5- or the 3- and 5-methoxy groups, depending on the substitution pattern, must lie coplanar with the aromatic ring. One obvious effect of this arrangement is to maximize overlap between the oxygen n electrons and the ring π system. However, this explanation seems weakened by the observation that 2,3,5- and 2,3,6-trimethoxyamphetamines are clinically active as hallucinogens (19). The picture here is not very clear, and one wonders to what extent qualitative differences in mechanism of action may be responsible.

Snyder and Richelson (56) suggested that intramolecular hydrogen bonding between the o-methoxy and side-chain amino groups could be important for activity. However, no evidence for such hydrogen bonding has been obtained from X-ray crystallographic studies (57, 58).

Although theoretical (59) and experimental gas-phase (60) studies indicated a noncoplanarity when two methoxy groups are adjacent, NMR solution studies found such methoxy groups to be equivalent (61). Furthermore, the high activity of the dihydrobenzofuran derivative (XV) suggests that the orientation of the 5-methoxy group is not critical if it remains coplanar with the ring. Steric effects seem to indicate that a 5-methoxy group should be directed away from the 4-alkyl group. In XV, the alkoxy function is directed toward the 4-alkyl group.

SIDE-CHAIN MODIFICATION

N-Substitution—It has been demonstrated with several compounds that N-alkylation abolishes or dramatically attenuates *in vivo* activity (26, 47, 62–64) and *in vitro* receptor affinity (65). Only in the case of 3,4-methylenedioxy ring substitution has N-alkylation afforded active compounds, the N-methyl (XIX) and N-ethyl (XX) analogs. These analogs retain potency comparable to the primary amine (III), although qualitative aspects of the intoxication are altered (66). In III, the (R)-enantiomer possesses activity; upon N-methylation, the isomer with the (S)-configuration has proven to be active.



XIX: R = CH_3
XX: R = CH_2CH_3

These results have been interpreted to mean that the actions of (R)-III and N-methyl-(S)-III are mediated by different mechanisms. This idea is reinforced by the finding that there is no cross-tolerance between III and XIX (62). This result is not too surprising since III was shown to possess both a lysergide-like and an amphetamine-like component of action (67–70). Thus, it was speculated that III exerts its effects by direct action on serotonin receptors, similar to explanations for the action of (R)-II. By contrast, N-methyl-(S)-III was suggested to work by release of endogenous transmitter (62). Unfortunately, studies of III and its derivatives are complicated by its multiplicity of actions on various monoaminergic systems.

Although it has been concluded that N-methylation generally destroys activity, this conclusion may be premature since few N-methylated amphetamines have been examined. Cheng *et al.* (17) studied a series of substituted amphetamines and found that substitution patterns other than 2,5-dimethoxy have a significant indirect component of action. If the arguments relating to III are valid, many of these derivatives may retain or possess enhanced activity upon methylation. Furthermore, as with amphetamine, the (S)-isomer is expected to be the more potent releaser and thus possess activity.

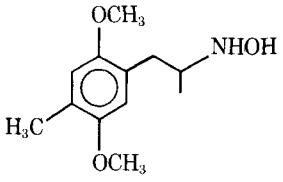
Further extension of the N-alkyl group to higher homologs generally abolishes activity (66). N,N-Dialkylation does not give active compounds, even with the 3,4-methylenedioxy substitution (36).

In an analogy to the opiate antagonists, DeSantis and Nieforth (71) prepared the N-propyl, N-cyclopropylmethyl, and N-allyl derivatives of mescaline. In mice, the propyl and allyl derivatives produced a slight antagonism of mescaline-induced disruption of swimming behavior.

One other active substitution on nitrogen is the N-hydroxy group. N-Hydroxylation of III gives a compound possessing clinical activity (66). Coutts and Malicky (72) evaluated several congeners of II. One, the N-hydroxy derivative (XXI), elicited behavioral effects in rats but at about six times the dosage required for II.

Side-Chain Alkylation—The addition of a methyl group to the α-side-chain position dramatically enhances the *in vivo* activity of 2,4,5-trisubstituted compounds. For example, 2,4,5-trimethoxy-β-phenethylamine is inactive (73), but addition of an α-methyl group gives the corresponding amphetamine, which is 17 times more potent than mescaline (23). This potency increase also is observed in compounds with a hydrophobic *para*-substituent such as methyl or bromine but is less dramatic. 2,5-Dimethoxy-4-methylphenethylamine is clinically active at doses of ~15–20 mg (74); addition of an α-methyl group to give II increases potency about fourfold.

The potency increase with α-methylation is very small in 3,4,5-substituted compounds. Addition of an α-methyl group to mescaline gives 3,4,5-trimethoxyamphetamine, a compound only about twice as active as mescaline (23). This slight increase is maintained in this series where the 4-substituent is a hydrophobic group. This finding probably reflects an effect on metabolism since addition of the α-methyl group has little effect on *in vitro* receptor affinity in either series (30, 65). Thus, it is tempting to speculate



XXI

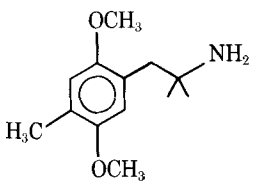
that 2,4,5-substituted compounds are more susceptible to amine oxidation than are 3,4,5-substituted analogs. However, Clark *et al.* (75) reported that 2,4,5-trimethoxyphenethylamine is deaminated less extensively than mescaline by a soluble rabbit liver amine oxidase preparation. In any case, with either substitution pattern, the simple addition of the α-methyl group increases hydrophobicity and at least facilitates passive diffusion into the CNS.

Extension of the α-methyl group to ethyl or higher homologs abolishes activity (76). This result was observed in 3,4,5-trimethoxy compounds and in several 2,5-dimethoxy-4-substituted analogs (77). The addition of an α-ethyl group, while abolishing hallucinogenic action, leads to potential antidepressant compounds (77–80). At present, there is no explanation as to why this occurs.

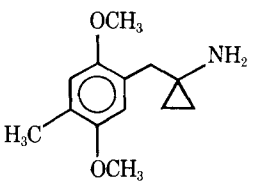
In vitro, the α-ethyl group shows mixed agonist–antagonist action at the serotonin receptor whereas the α-methyl group is a pure agonist (81). The conformational properties, as determined by solution NMR studies, for α-methyl and α-ethyl compounds do not differ significantly (82). Their dynamic behavior appears comparable, and it is difficult to ascribe the difference in action to a conformational effect. Theoretical calculations using empirical potential functions likewise have failed to reveal a conformational explanation for the difference (83). Some undefined steric effect seems the most plausible answer.

Dialkyl substitution on the α-carbon also destroys activity. This effect is evident as a loss of *in vitro* activity and a lack of behavioral effect in cats for XXII (84). Surprisingly, linking these two methyl groups in the form of a cyclopropyl ring (XXIII) restores some activity. The original report suggested that this result might be due to enhanced distribution into lipid for the cyclopropyl group but not the *gem*-dimethyl group. More recently, the difference in activity was attributed to the lack of conformational flexibility for the dimethyl compound and its inability to assume the active conformation (85). These conclusions were supported by theoretical calculations and carbon 13 spin-lattice relaxation times from solution NMR studies. The data support the idea that the active conformation is one where the side chain must be in an antiperiplanar arrangement with the aromatic ring.

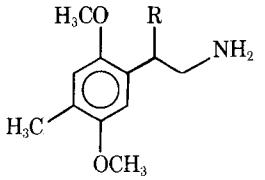
On the other hand, adding a second α-methyl group to III to give the α,α-dimethylphenethylamine led to an active compound (36). Again, the 3,4-methylenedioxy substitution presents an anomalous case. This analog can be



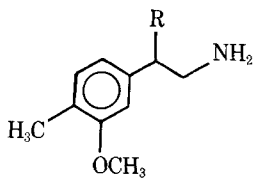
XXII



XXIII



XXIV: R = H
XXV: R = CH_3



XXVI: R = H
XXVII: R = CH_3

viewed as a substituted phentermine derivative, and its activity also may prove to be due to the release of endogenous neurotransmitter.

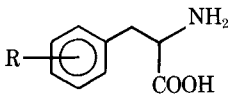
The addition of a β-methyl group to the side chain dramatically attenuates *in vivo* activity in animals (47). This effect also was observed for β-hydroxy or β-keto analogs in an *in vitro* receptor affinity assay (55). In the latter instance, the beta substituent was most deleterious when an *o*-methoxy group also was present. This may be due to an unfavorable steric interaction between the beta and *ortho*-substituents. However, in the ear-scratch response in mice (48) for XXIV–XXVII, only XXV retained any activity, and it was very weak (86). This finding again emphasizes the importance of the α-methyl and *o*-methoxy groups for optimal activity.

The α,β- or β,β-dimethyl side-chain substitution abolishes hallucinogen-like activity in animal models (47). None of these substitutions has been tested yet in humans.

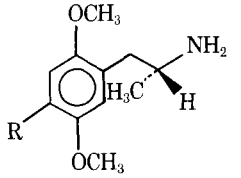
There are two reports of phenylalanine analogs of hallucinogens. The 2,5-dimethoxy-4-methyl analog (XXVIII*a*) and the mescaline congener [3-(3,4,5-trimethoxyphenyl)alanine (XXVIII*b*)] were examined for activity, although neither is expected to be a substrate for brain decarboxylases according to Ferrini and Glasser (87). Neither of these substituted phenylalanines showed biological activity (88–90).

Stereochemistry—It has been known for several years that in the substituted hallucinogenic amphetamines, the (*R*)-enantiomer is the most active (91–93). Although the (*S*)-enantiomers generally have not been studied at high dosage levels, the (*R*)-enantiomer subjectively and quantitatively reproduces the effect of twice its weight of racemate in humans. Both *in vitro* and animal models demonstrate stereoselectivity, with about a four- to 10-fold difference in potency between the (*R*)- and (*S*)-enantiomers (94–98). The classical approach to this observation has related the (*R*)-configuration of the amphetamines, shown in binding orientation A, to the (*R*)-configuration at C-5 of lysergide. With this view, the methyl group of the amphetamines corresponds to the C-4 methylene group of lysergide. However, the relatively small effect (30, 96) on receptor affinity in α-methyl compounds with the (*R*)-configuration, as compared with the α-unsubstituted phenethylamines, seems inconsistent with any interaction of the α-methyl group with the receptor.

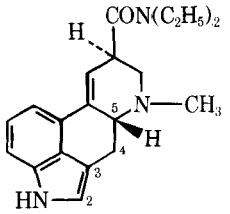
A newer hypothesis from these laboratories related this stereoselectivity to binding orientation B, where the



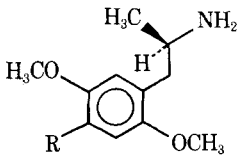
XXVIII*a*: R = 2,5-$(OCH_3)_2$-4-CH_3
XXVIII*b*: R = 3,4,5-$(OCH_3)_3$



binding orientation A



lysergide



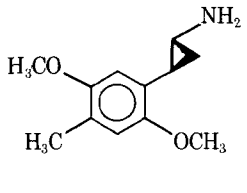
binding orientation B

α-methyl group is allowed to project away from the binding surface (49, 50). With either hypothesis, it was assumed that the receptor binds to the alpha face of the lysergide molecule since this surface presents the most unhindered access to the N-6 unshared electrons (58, 98). The phenethylamines were assumed to bind in a conformation where the side chain is relatively coplanar with the aromatic ring in an extended, or antiperiplanar, arrangement. This arrangement would give the closest similarity to lysergide. In conformation B, the α-methyl group is directed away from the binding surface. In this view, α-methylation has little effect on receptor binding when the configuration is *R*. In contrast, and consistent with experimental findings (14, 96), the methyl group of the (*S*)-enantiomer has a deleterious effect on affinity.

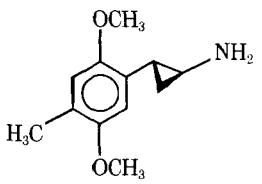
Of the two isomers of the 2-phenylcyclopropylamine analog of II, the (1*R*,2*S*)-enantiomer (XXIX*a*) is more active (99). The (1*S*,2*R*)-isomer (XXIX*b*) showed no activity at any dose tested. If the argument is valid that the steric bulk of the C-3 methylene must project away from the receptor, then activity for the (1*R*,2*S*)-isomer is only consistent with a binding conformation for flexible analogs similar to that shown for XXIX*a*. If strict structural congruences can be invoked, this hypothesis would correlate the 5-methoxy group of the phenethylamines with the 5-hydroxy group of serotonin. This is borne out by the greater enhancement of *in vitro* receptor affinity when the 5-methoxy group of the phenethylamines is replaced by hydroxy than when the 2-methoxy group is replaced by hydroxy (43).

Problems arise in considering stereochemistry for other substituted amphetamines. As discussed in the section on *N*-substitution, methylation of III reverses the stereoselectivity of activity and it is the (*S*)-enantiomer of *N*-methyl-III that is active. However, this latter derivative may possess different mechanisms of action (62).

Both the (*R*)- and (*S*)-enantiomers of 3,4-dimethoxyamphetamine were required to elicit a mescaline-like behavioral profile in rats (100). Furthermore, coadministration of the (*R*)-enantiomer of 3,4-dimethoxyamphetamine with (*S*)-amphetamine gave a response identical to that obtained with racemic 3,4-dimethoxyamphetamine. Cheng *et al.* (17) demonstrated that this compound possessed an indirect releasing component of action in an *in vitro* smooth muscle assay. Therefore, it is possible that the *in vivo* effects of racemic 3,4-dimethoxyamphetamine also may be partially ascribed to the releasing effects of the (*S*)-enantiomer.



XXIX*a*
(1*R*,2*S*)



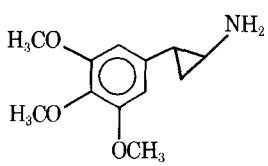
XXIX*b*
(1*S*,2*R*)

Although many additional studies are needed to elucidate such mechanisms definitively, the following conclusions would be generally consistent with previous work (17, 94, 96). For compounds possessing 2,5-dimethoxy substituents, the (*R*)-enantiomer has stereoselective *in vivo* activity. This action is correlated with *in vitro* direct agonist effects at serotonin receptors. For any other substitution patterns, a possible indirect component of action, such as a releaser of serotonin or catecholamines, must be considered. In this latter case, the (*S*)-enantiomer may contribute a significant component to *in vivo* activity. One may speculate that *N*-methylation allows retention of activity with these substitutions (62). For the 3,4,5-trisubstitution pattern of mescaline itself, *in vivo* activity appears to correlate with a direct effect at the serotonin receptor (30, 55).

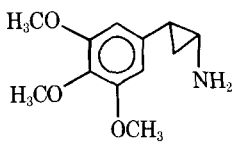
Rigid Analogs—Several rigid analogs of phenethylamine hallucinogens have been evaluated to elucidate the binding conformation of the side chain. To date, none has been particularly revealing, although some interesting findings have emerged. The simplest rigid analogs are the substituted 2-phenylcyclopropylamines. The 3,4,5-trimethoxy compounds (XXX and XXXI) first were prepared as mescaline analogs (101). Inactivity for the *cis*-isomer (XXXI) seems to establish conclusively the side-chain binding conformation as *trans* in the flexible phenethylamines. As discussed previously, the 2,5-dimethoxy-4-methyl-substituted analog (XXXIX) has been resolved into its enantiomers. Activity only for the (1*R*,2*S*)-enantiomer has provided evidence of the binding conformation for the (*R*)-enantiomer of the amphetamines.

Recently, Law and Borne (102) reported the synthesis and preliminary pharmacology for the substituted *exo*- and *endo*-2-azabicyclo[2.2.2]octanes (XXXII and XXXIII, respectively). Examination of spontaneous activity in mice indicated that the *endo*-isomer (XXXIII) was about two times more active than the *exo*-isomer. This finding provides further evidence for an antiperiplanar side-chain conformation as important for activity.

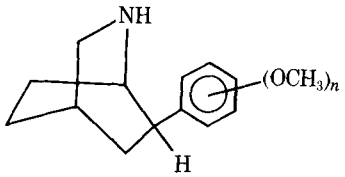
Additional studies of the side-chain conformation and stereochemistry have been carried out utilizing rigid analogs. In particular, 2-amino-1,2,3,4-tetrahydronaphthalenes (2-aminotetralins) have received attention. Kang and Green (103) pointed out the possibility that these compounds could be compared to lysergide. The unsub-



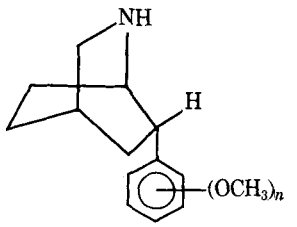
XXX



XXXI



XXXII



XXXIII

n = 2 (3,4-substituted)
n = 3 (3,4,5-substituted)

stituted parent (XXXIV), as the racemate, shows some similarity to the hallucinogens in rat models (104). The (*S*)-(−)-enantiomer seems to possess biological activity (105). This stereochemistry is inverted from that observed for lysergide. This observation was used in arguments presented earlier against orientation A as the active binding orientation for the phenethylamines (49).

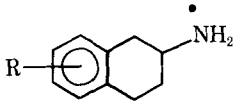
Green *et al.* (106) also examined a series of methoxy- and hydroxy-substituted 2-aminotetralins. They reported that XXXV possessed electroencephalographic effects in rats that were similar to those evoked by mescaline.

In a series more closely approximating active hallucinogens, the dimethoxymethyl-substituted compounds (XXXVI–XXXVIII) were examined. Although *in vivo* activity was indicated for the aminoindan (XXXVIII) at high doses (107), other studies proved that XXXVIII was much less active than the tetralin (XXXVII) both *in vivo* (108) and *in vitro* (109). Neither compound produced a mescaline-like response in the conditioned avoidance response in rats. The dimethoxy compound (XXXVI) possessed a sedative effect in mice (104). Although none of the tetralins had clearcut hallucinogen-like action in any animal models, XXXVII produces hyperthermia in rabbits and evokes a rage response in cats (49).

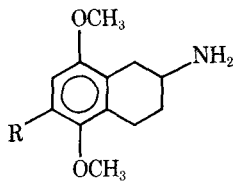
Violland *et al.* (110) also examined several methoxy-substituted 2-aminotetralins as analogs of hallucinogens. In mice and dogs, these compounds possessed pharmacological activity characterized by ataxia, sedation and, in some cases, analgesia. *N*-Alkylated derivatives of 2-amino-2,3-dihydrophenalene also were prepared. Although possessing pharmacology similar to the aminotetralins, they were much more potent. Again, no clinical studies have been carried out with any of the aminotetralins or phenalenes, and there is no evidence to suggest that they possess hallucinogenic action in humans.

Numerous other investigators have explored the 2-aminotetralins as congeners of lysergic acid, with particular reference to identification of the oxytocic pharmacophore of the ergot alkaloids. Such studies are not reviewed here.

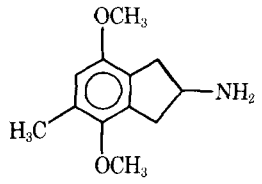
Additional rigid analogs have been prepared where the phenethylamine side chain is incorporated into a heterocyclic ring (XXXIX–XLII). Compound XXXIX could be viewed as possessing the structural features of both mescaline and methylphenidate (111), although it possessed no mescaline-like action in animal models. The morpholino



XXXIV: R = H
XXXV: R = 7-OH



XXXVI: R = H
XXXVII: R = CH_3



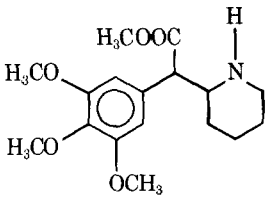
XXXVIII

analog (XL) was reported to possess more mescaline-like tendency in animals than XLI or XLII (112). It is unknown whether any of these compounds possess hallucinogenic action in humans. However, none had appreciable potency in animal models.

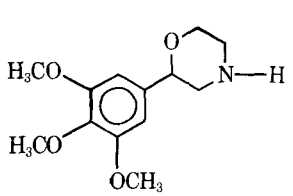
EFFECTS OF DISTRIBUTION AND METABOLISM

The ability of the compounds to penetrate the CNS is a requisite for activity. As pointed out by Vogel and Evans (113), when one considers the actual levels of drug detected in the brain rather than the systemically administered dose, dramatic differences in structure–activity relationships may appear. That is, some compounds that appear to possess little activity upon peripheral adminstration are highly potent if actually administered into the CNS. For compounds with a more favorable distribution, only small doses may be needed to achieve the same brain levels. These distribution differences are independent of actual efficacy at the receptor(s). Vogel and Evans (113) argued further that structure–activity relationships should be based on minimal effective brain levels rather than on dosage measures that reflect a quantity necessary for peripheral administration. Although this approach has merit, most investigators probably will not carry out the additional studies required to establish minimal effective brain level values.

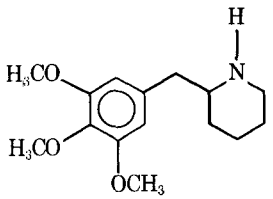
The importance of passive partitioning was noted in a study where 1-octanol–water partition coefficients were measured and correlated with human clinical activity (29). As expected, the regression obtained was parabolic, with an optimum log P value of 3.14. Although R^2 for the regression was only 0.62, there was large variability in the human data. Furthermore, the study included numerous compounds that undoubtedly possess several components of action, as is the case for III. Coincidentally, the optimum log P value from this study was nearly identical, within statistical limits, to the optimum determined in an *in vitro*



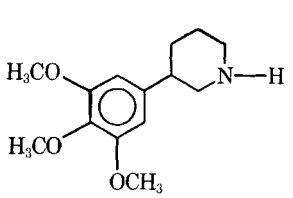
XXXIX



XL



XLI



XLII

assay (30). In the latter study, this value reflected, in part, a specific hydrophobic interaction with the receptor.

The CNS distribution of [^{3}H]mescaline and the isomeric 2,3,4-trimethoxyphenethylamine was studied using autoradiography (114). The latter compound is inactive and gave weak and homogeneous labeling in the brain. By contrast, mescaline was selectively accumulated in the hippocampus and amygdala. The findings of this study are in agreement with similar results obtained for the distribution of ^{3}H-labeled II (115). However, the 2,3,4-trimethoxy isomer also is metabolized more rapidly than mescaline (116). Mitoma (117) compared 2,4,5-trimethoxyamphetamine with the isomeric 2,3,4-substitution. The latter is inactive clinically while 2,4,5-trimethoxyamphetamine is 17–20 times more active than mescaline. Surprisingly, the brain levels of the inactive 2,3,4-isomer were higher than those attained with the active 2,4,5-substitution pattern in rats.

No studies of differential brain distribution for enantiomers of active amphetamines have been published. However, the (*S*)-(+)-enantiomer of II is metabolized more rapidly than the (*R*)-(−)-isomer when the drug is administered as the racemate (118, 119).

Some distinction should be made between metabolic processes that essentially "detoxify" the hallucinogenic phenethylamines and those that may be involved in the mechanism of action, *i.e.*, may be responsible for generating active species. For a discussion of the former processes, the review by Castagnoli (120) is excellent. The latter type of metabolism is of major interest here. Also of interest are processes that metabolize compounds possessing high *in vitro* potency but that lack whole animal or clinical activity.

It was once believed that phenethylamines, particularly mescaline, might be active due to the formation of a metabolite (121). A recent study (122) indicated that this is not the case, at least for mescaline. Zweig and Castagnoli (27, 123) also suggested that di-*O*-demethylation of II may generate an active metabolite that contributes to activity. The inability to generate significant amounts of these metabolites, coupled with the high observed *in vitro* activity for II, argues against this possibility. Furthermore, Ho *et al.* (124, 125) showed that II is oxidized primarily at the methyl group in the *para* position, leading to the *p*-hydroxymethyl and *p*-carboxy species. Weinkam *et al.* (126) confirmed that the *p*-hydroxymethyl derivative is the major metabolite in rabbit liver microsome preparations. Thus, if *O*-demethylation does occur, it is very minor. Unfortunately, no definitive experiments have been carried out that would settle the issue. It is this reviewer's opinion, however, that this process is not important in the intoxication mechanism. This seems to be the only instance where controversy presently exists regarding the role of an active metabolite in the activity of the phenethylamines.

There are examples to suggest that some compounds possessing high affinity for *in vitro* receptors may lack *in vivo* activity due to rapid metabolic inactivation. Such effects must be considered when developing receptor structure–activity relationships. Lack of *in vivo* or clinical activity may camouflage the fact that a particular compound actually possesses high intrinsic activity at a receptor site.

Charalampous *et al.* (127) showed that the half-life of mescaline in humans is ~6 hr. By contrast, the inactive 3,4-dimethoxyphenethylamine is metabolized extensively, with a half-life of <1 hr (128). This result is consistent with the other findings (75) that phenethylamines with more than three methoxy groups are not deaminated *in vivo*.

As was mentioned under *Aromatic Substituents*, functions in the *para* position that are resistant to metabolism give more potent compounds. Since deamination is a minor metabolic pathway in humans, increased resistance of the aromatic ring and its substituents to metabolism will certainly affect activity. The most obvious result will be an increased biological half-life and consequent duration of action.

In 3,4-dimethoxyamphetamine, the 4-methoxy group is about 15 times more extensively *O*-demethylated than the 3-methoxy group (129). Likewise, in 2,4,5-trimethoxyamphetamine, *O*-demethylation at the 4-position is about twice that at the 5-position and nearly three times that of the 2-methoxy group (130). With a *p*-alkyl, Ho *et al.* (125) found that the *p*-methyl group of II is oxidized progressively to the carboxy group. Tansey *et al.* (131) studied the metabolism of the *p*-ethyl homolog of II and reported that the benzylic carbon of the *p*-ethyl group was hydroxylated but much more slowly than the methyl of II. Finally, with a halogen in the *para* position, such as in the bromine homolog of II, no organic bromide was detectable in the urine following administration to humans (132). The stability of the *p*-halogen group, either as bromine or iodine, led to investigation of the utility of these compounds as brain-imaging radiopharmaceuticals (133).

ACTION AT MOLECULAR LEVEL

Little is known of the mechanism of receptor interaction for hallucinogenic phenethylamines. However, circumstantial evidence indicates that one event that occurs may be electron donation to the receptor to form a charge transfer complex. This initially was suggested by Karreman *et al.* (134) in 1959, based on extended Hückel molecular orbital calculations for lysergide. Subsequent quantum chemical studies by several groups led to development of correlations between activity and energy of the highest occupied molecular orbital (135, 136).

Experimentally, the possible requirement for a high energy aromatic system was indicated by correlations between activity and: (*a*) the degree of native fluorescence (137), (*b*) the excitation wavelength and molar absorptivity (138), and (*c*) the strength of the charge transfer complex between substituted phenethylamines and 1,4-dinitrobenzene (139). Furthermore, Domelsmith and Houk (140) observed good correlation between human activity and experimentally measured energy of the first aromatic ionization potential in the gas phase. Ionization potentials are well correlated with the highest occupied molecular orbital.

Dipaolo *et al.* (141) carried out model interaction calculations for phenethylamines using 3-methylindole as the interacting species. Using CNDO calculations, they reported a correlation between human activity and interaction energy. However, this study only included interactions between the aromatic ring of the phenethylamines and the six-membered ring of indole.

Green *et al.* (142), using a more rigorous theoretical approach, calculated several electronic parameters for tryptamines. High frontier electron density at the 4- and 5-positions of the tryptamines appears to be well correlated with activity. Assuming that tryptamines and phenethylamines possess a similar mechanism of action implies that charge transfer complexation may be a possible receptor interaction for hallucinogens in general.

The biological activities for XII–XVII were discussed under *Steric Effects*. Decreased activity (or inactivity) of compounds with steric bulk protruding toward both faces of the molecule also is consistent with the formation of an electron donor–acceptor complex as a component of the molecular mechanism of action. Charton (143) pointed out the importance of such effects in model systems where bulky groups were attached to the donor molecule.

However, Glennon *et al.* (44) recently suggested that, depending on the aromatic substitution pattern, phenethylamines may orient differently upon binding to the receptor. That is, depending on the particular substituents possessed by the phenethylamine, it may bind in either binding orientation A or binding orientation B. If so, interpretation of structure–activity relationships at the molecular level may be very difficult.

Although all of the hallucinogens possess a basic nitrogen atom, there is little apparent dependence on basicity. Whereas lysergide or substituted phenylcyclopropylamines have pKa values of ~8–8.3, the phenethylamines or substituted amphetamines have higher pKa values, at ~9.4–9.8. Weinstein *et al.* (144) suggested that the amine undergoes deprotonation upon binding and that quantum chemical calculations of the bound species are carried out more properly when the amino is considered to be nonprotonated. Although this concept has not been verified experimentally, lower pKa values would facilitate deprotonation. Of course, one should also be aware that less basic amines also are less highly ionized at physiological pH. This fact normally will lead to brain levels that are higher than for a more basic amine.

At present, little else in the way of a molecular mechanism of action can be safely concluded. This situation is certainly not unique to the hallucinogens. Nevertheless, the multiplicity of pharmacological actions and the subjective nature of the effects they produce make studies difficult at the molecular level. Experiments aimed at defining these receptor interactions must be carefully designed and cautiously interpreted.

CONCLUSIONS

The preceding sections dealt with various aspects of the nature and conformation of aromatic ring substituents and the side chain in the hallucinogenic phenethylamines. Although these empirical structure–activity relationships can be described, there is at present no clear rationale for many of them. Certainly the mechanisms at the receptor level are unknown. The multiplicity of actions these compounds have on monoaminergic systems have made their study very difficult. Furthermore, structure–activity relationships that define these multiple actions have not been approached.

Some may question whether it is realistic to expect any structural congruence between phenethylamines and tryptamines to emerge. However, this hypothesis has been the guiding principle of much of the recent work with phenethylamines. If a clear structural–functional relationship between the phenethylamines and the tryptamines could be identified, one would have the molecular pharmacology equivalent of a series of simultaneous equations. Reactive and functional sites in the two series could be studied in parallel. Quantum chemical comparisons would be most interesting. It may be justified to speculate that such findings would lead to important insights into fundamental receptor activation mechanisms.

The reality is that we are still some distance from such a unified theory. Nevertheless, significant progress has been made in the past 10 years in defining the importance to activity of various structural and physicochemical parameters within the phenethylamines. It is perhaps unfortunate that research interest in this fascinating class of compounds is limited to so few laboratories.

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