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Studies of the Relationship Between Molecular Structure and Hallucinogenic Activity

DAVID E NICHOLS

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences Purdue University, West Lafayette, IN 47907

NICHOLS, D E *Studies of the relationship between molecular structure and hallucinogenic activity* PHARMACOL BIOCHEM BEHAV **24**(2) 335–340, 1986 —The nature of the stereochemistry and aromatic ring substituents and their importance to biological activity for phenethylamine-type hallucinogens is presented The possibility of a hydrophobic site to bind to the 4-substituent and its likely geometry is described A brief discussion of the structure-activity relationships for tryptamines such as psilocin and DMT is also given, with comments about the stereochemistry of alpha-methyltryptamines Evaluation of a series of N(6)-alkyl-nor-LSD derivatives indicated that selected members such as N(6)-ethyl, allyl and propyl were as potent as, if not more potent than LSD, both in a two-lever drug discrimination assay in rats, and in man N(6)-alkyl groups longer than n-propyl, such as n-butyl or 2-phenethyl, gave compounds that were greatly reduced in activity

Hallucinogen Lysergamides Nor-LSD derivatives Phenethylamines Psilocin Structure-activity relationships Tryptamines

WITH the many reviews that have appeared in recent years on the relationship between structure and activity for hallucinogenic agents, and with so few investigators now working in this area, relatively little new information is available However, modest gains are being made in our understanding of this area The net result is that we have a fairly good knowledge of the types of structural changes that can be made within all the classes of LSD-like hallucinogens On the other hand, it is not known why activity varies in the way it does for these structural modifications For most there is little understanding of why a particular structure change affects activity

As one of the first presentations in this symposium, an attempt will be made to briefly summarize what is known about the structure-activity relationships of hallucinogens In addition, some new findings will be noted, especially with regard to recent work in our laboratory with N-substituted nor-LSD derivatives

It is easiest to summarize structure-activity relationships based on compound type, considering in order the phenethylamines, tryptamines and the ergolines There is no particular reason for coverage in this particular order except that the phenethylamines have been the most synthetically accessible and have therefore been studied in greater detail, at least from the medicinal chemist's point of view

PHENETHYLAMINES

This large class of hallucinogenic compounds has evolved out of the prototype structure of mescaline (Fig 1), a naturally occurring substance that had been synthesized as early as 1919 [29] The evolution of the substituted phenethylamines from mescaline has focused on four major areas that include, (a) orientation of aromatic ring substituents, (b) alkylation of the side chain, (c) alkylation of the amino group, and (d) character of the aromatic substituents

The effects of mescaline are very similar to those of LSD, but it is a compound of very low potency, and requires a dosage in the hundreds of milligrams to produce an "effective" intoxication However, within a historical context, mescaline must be viewed as one of the more important of the "classical" hallucinogens

The phenethylamines can be considered to fall into two general classes, those with the 3,4,5-trisubstitution pattern seen in mescaline, and those with a 2,4,5-trisubstitution pattern The potency of some of the compounds in the latter category has in some cases exceeded that of mescaline by nearly three orders of magnitude Although these are the two major types of biologically interesting hallucinogenic phenethylamines, certain mono and disubstituted analogues are also active

Within both classes, N-alkylation or N,N-dialkylation, with only a few exceptions, dramatically attenuates activity Likewise, the side chain is sensitive to modification, although one finds that the most potent compounds all possess a methyl attached to the alpha side chain carbon The side chain can also be incorporated into a cyclopropyl ring to give ring-substituted trans-2-phenylcyclopropylamines Stereoselectivity for both types of transformations is observed That is, for alpha methyl group introduction, the more active enantiomer possesses the *R*-(−) absolute configuration (Fig 2) [26,28] For the one example where a trans-2-

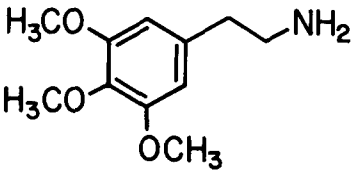
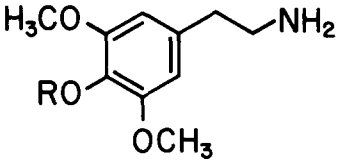


FIG 1 The structure of mescaline



R=Et ESCALINE
R=Pr PROSCALINE
R=iPr ISOPROSCALINE

FIG 3 The structures of escaline, proscaline and isoproscaline, three homologues of mescaline that have been modified at the 4-position to yield compounds that are more potent than mescaline

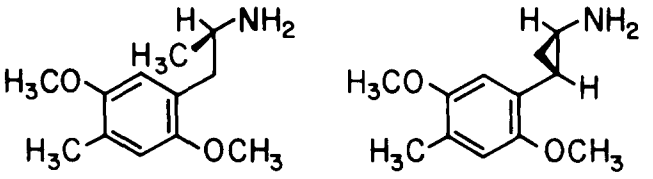


FIG 2 The more active enantiomers of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) (left structure) and 2-(2,5-dimethoxy-4-methylphenyl)cyclopropyl amine (right structure) have the *R* and *1R,2S* absolute configurations, respectively, as shown

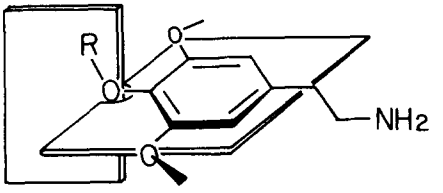


FIG 4 Based on the out of plane geometry of the 4-methoxy of mescaline, and the increased potency of escaline and proscaline, it is suggested that any hydrophobic site on the receptor at this position may have a geometry which is "normal" to the plane of the aromatic ring binding site

phenylcyclopropylamine was studied as its enantiomers, the *1R,2S*-(−) compound also proved to be more active (Fig 2) [18,22] However, the addition of methyl groups to the cyclopropane ring abolished activity in animal models [13], as did expansion of the ring to a cyclobutane [19] Alkylation of the side chain at the beta position, or alkylation at the alpha position with a group larger than methyl (i e , ethyl, propyl, etc) also abolished activity [1, 25, 30]

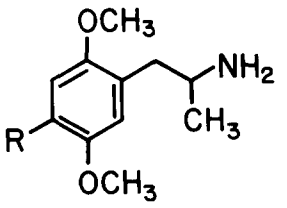
Furthermore, a fact noted but not satisfactorily explained, addition of an alpha methyl to 3,4,5-trisubstituted compounds increases activity only about two-fold from the parent phenethylamine, while a similar addition to 2,4,5-trisubstituted compounds can transform an inactive compound into one with about twenty times the potency of mescaline [27] The alpha methyl clearly has greater importance in the 2,4,5-trisubstituted series than in the 3,4,5-series

It is now also fairly well established that optimum activity resides in compounds with 2,5- or 3,5-dimethoxy substituents Replacement of methoxy by ethoxy at these positions abolishes or dramtically attenuates activity In 2,5-disubstituted compounds, an ethoxy or methylthio group is better tolerated (i e , less loss of activity occurs) at the 5-position than at the 2-position [15] In 3,4,5-trisubstituted compounds an ethoxy or alkylthio can be tolerated either at the 3- or the 5-position, but not both, with some retention of activity [14]

The unique feature of all the phenethylamines is the dependence of activity on the type of substituent at the 4-position For example, replacement of the 4-methoxy of mescaline with an ethoxy (Escaline, Fig 3) results in nearly an order of magnitude increase in oral activity It seems doubtful that this is simply due to more favorable biodistribution, since the 4-n-propoxy homologue (Proscaline, Fig 3) is slightly less active than escaline The 4-isopropoxy derivative has potency comparable to escaline or proscaline All of these, however, have octanol-water partition coefficients lower than the most active compounds in the 2,4,5-trisubstituted series It has been proposed that this enhanced activity may be due to a favorable interaction with a hydrophobic region of the receptor [21] Based on the out-of-plane geometry for the alkoxy substituent in mescaline [4], this potential hydrophobic site has been illustrated as coincident with a plane normal to the plane of the aromatic ring, as shown below in Fig 4 [18]

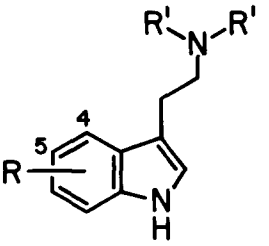
An interesting variation of this occurs with 2,4,5-trisubstituted compounds Clear increases in activity occur as the 4-substituent is varied from H, to OCH_3, to CH_3 or longer alkyl groups or to alkylthio or halogen (Fig 5) However, one does not see an increase in activity when the 4-substituent is an alkoxy larger than methoxy It has been argued that this may be due to the tendency of the oxygen to overlap its n-electrons with the aromatic pi system, which forces the alkoxy group to lie coplanar with the aromatic ring [2] This, in turn, might force the alkyl portion of the alkoxy to protrude into a sterically restricted region of the receptor, whereas ideally it must be twisted out of plane, as noted above

The 4-substituent can probably fill several roles First, it can enhance general hydrophobicity and lead to a more favorable penetration of the central nervous system [3] Second, this location is a site for oxidative metabolism such as aromatic hydroxylation, O-dealkylation, etc The presence of a slowly metabolized group, for example ethyl or halogen, will retard clearance of the compound from the body and prolong biological half-life A third role is that of giving the molecule a hydrophobic "appendage" which is suitably placed for interaction with a postulated hydrophobic region of the receptor [21] There may even be a more critical functional aspect than these, since it appears that the simple presence of a 4-substituent enhances activity in a noncon-



R = H	2,5-DMA
R = OCH_3	TMA-2
R = CH_3	DOM
R = Br	DOB
R = iBu	DOIB
R = sec Bu	DOSB

FIG 5 The structures of a series of 4-substituted 2,5-dimethoxyamphetamine homologues With the exception of the last compound in the series (DOSB) all of these have been found to be active as hallucinogens in man



R	R'	
H	H	TRYPTAMINE
5-OH	H	SEROTONIN
H	CH_3	DMT
H	C_2H_5	DET
4-OH	CH_3	PSILOCIN
$4\text{-}OPO_3H$	CH_3	PSILOCYBIN

FIG 6 A comparison of the structures of several hallucinogenic tryptamine derivatives with tryptamine and serotonin

tinuous way [7] One final point to note is that the 4-substituent cannot be bulky or branched Among alkyl substituents, an n-propyl gives optimum activity, but an isopropyl is considerably less active, while a tertiary butyl group seems to abolish activity [18] Branching or bulk is most deleterious when it is directly adjacent to the aromatic ring For example, when the 4-substituent is an isobutyl group (Fig 5), activity is largely retained, but with the isomeric sec-butyl, activity is found to drop dramatically [24]

Thus, one can see that quite a lot is known about the structure-activity requirements of phenethylamine hallucinogens Why some of these exist is not entirely clear One can imagine an empirically developed receptor model that would be complementary to these findings, but it is difficult to envision how such a model would apply to a particular receptor system Although there is speculation as to how phenethylamines and tryptamines can bind to the same receptor [18] there is no hard evidence to support these ideas A major problem for medicinal chemists studying hallucinogenic phenethylamines has been the lack of well-characterized *in vitro* systems for assay It is difficult, if not impossible, to clearly define molecular requirements for receptor interactions when the best available models are behavioral paradigms in whole animals One has great difficulty dissecting out the contribution that each molecular modification makes to intrinsic activity, efficacy, pharmacokinetics, etc , when the whole animal is used, and used in a way where the response to be measured is ill-defined at best

To complicate matters further, it is clear that phenethylamines may interact with a variety of neurotransmitter systems, having effects on transmitter uptake, storage, and release

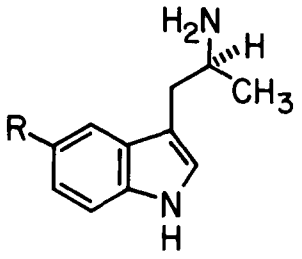
TRYPTAMINES

Hallucinogenic tryptamines are also naturally occurring substances that have a long folkloric use by native populations Tryptamine itself (Fig 6) serves as the basic structural unit for the neurotransmitter serotonin (Fig 6) The hallucinogenic activity of a variety of substituted tryptamines has reinforced the idea that interaction with serotonin receptors is a major and important component of the mechanism of action

Generally, N,N-dialkyltryptamines, such as N,N-dimethyltryptamine (DMT), N,N-diethyltryptamine (DET) or 5-methoxy-N,N-dimethyltryptamine, lack activity when administered by the oral route, These materials are more generally smoked or, in native societies, inhaled as snuffs The lack of oral activity has been attributed to rapid oxidative metabolism, presumably in the liver An interesting exception, and one of classical importance, is the oral activity of psilocin and psilocybin It is known that the latter compound is hydrolyzed *in vivo* to generate psilocin [11,12], the active species These compounds occur together as the active components of a number of species of psychoactive mushrooms They were first isolated by Hofmann from *Psilocybe mexicana* [10], one of a variety of "sacred mushrooms" (Teonanacatl, or flesh of the gods) used by Indians in South America, principally the Aztecs

In vitro receptor binding assays have revealed that psilocin has lower affinity than certain tryptamines that are oxygenated at the 5-position [31] However, psilocin has some unique physico-chemical properties which confer it with good potency and activity when administered orally First, for some reason it resists the type of metabolism that degrades other N,N-dialkylated tryptamines Second, it seems to have some type of intramolecular interaction between the 4-hydroxy and the side chain amino that lowers its basicity and increases lipid solubility so that passive entry in the central nervous system is facilitated [17]

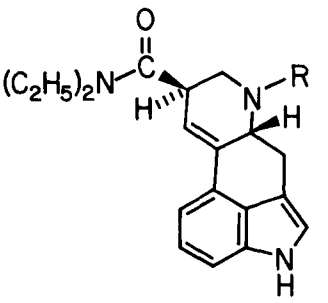
Aromatic ring substitution in the tryptamines has not



R=H S-(+)-α-METHYLTRYPTAMINE

R=OCH3 (+)-5-OMeAMT

FIG 7 The biologically more potent enantiomer of alpha-methyltryptamine and 5-methoxy-alpha-methyltryptamine has the *S*-(+) absolute configuration



R=Me	LSD
R=Et	ETHLAD
R=n-Pr	PROLAD
R=Allyl	ALLYLAD

FIG 8 A comparison of the structures of some N(6)-alkyl-nor-LSD derivatives The propyl derivative is at least as potent as LSD in a rat assay, with the ethyl and allyl compounds being slightly more active than LSD

been nearly as rewarding as the work with the phenethylamines With the exception of ring-unsubstituted compounds, and the 5-methoxy and 4-hydroxy (or phosphoryloxy as in psilocybin) substituents, no other ring-substituted compounds have been found active in humans, although only a few have been studied The receptor appears very sensitive to the nature and location of substituents in the aromatic ring

A second structural feature that lends oral activity to tryptamines is the addition of an alpha-methyl Alpha-methyltryptamine (Fig 7) is an inhibitor of monoamine oxidase and is not a substrate for this enzyme [16] Therefore, this ploy effectively prevents the metabolism which is so characteristic of non-alpha-methylated tryptamines, and allows distribution to the sites(s) of action Animal studies have shown that it is the (+) enantiomer of both alpha-methyltryptamine and 5-methoxy-alpha-methyltryptamine that is most active [5,6] In humans, a recent double blind study showed that the (+) isomer of 5-methoxy-alpha-methyltryptamine was about 2–3 times more potent than the (−) enantiomer The (+) isomer had about twice the potency of the racemic material (A T Shulgin, personal communication) Based on work with an asymmetric synthesis of these compounds, both (+) enantiomers possess the *S* absolute configuration, with stereochemistry identical to that of S-(+)-amphetamine [20]

Not surprisingly, since the alpha-methyltryptamines are not readily metabolized, they have a relatively long duration of action The N,N-dialkyl tryptamines, such as DMT or psilocin, have a rapid onset and a relatively brief action, with the effects of the former lasting no more than one hour while the effects of psilocin last 4–6 hours By contrast, the effects of 5-methoxy-alpha-methyltryptamine can last 18–24 hours, while mescaline and LSD typically have a 10–12 hour duration of action

ERGOLINES

The ergolines can be viewed as rigid tetracyclic tryptamines Within this class of compound is found the semi-synthetic d-lysergic acid diethylamide (Fig 8) (d-LSD), the most potent of the hallucinogenic drugs Since the discovery of its biological activity in 1943, thousands of studies have been reported in the literature Of the many structural modifications which have been made to the LSD structure, none had yielded a compound more potent than LSD itself This report will briefly describe some derivatives of LSD which do appear to have somewhat higher potency than LSD Generally however, one of the unique features of LSD is that its biological activity is so highly dependent on the complete, intact structure In the prior literature only one compound had been reported to be equipotent to LSD, the N(1)-acetyl derivative [27], a molecule so labile to hydrolysis that it is cleaved to yield LSD and acetate by treatment with hot water Present evidence indicates that cleavage of the N-acetyl occurs *in vivo* This compound is probably equipotent to LSD on a molar basis simply because it serves as a prodrug to LSD Other structural modifications, such as replacement of the diethylamide function with a variety of N-monoalkyl, N,N-dialkyl, or N,N-cycloalkylamides has led only to compounds with reduced activity [27]

Parallel interest in our laboratory in the structure-activity relationships of dopamine agonists led us to work on modification of the N(6)-alkyl substituent in the lysergamides At about the time we began this work, Niwaguchi *et al* [23] published the synthesis of several N(6)-alkyl-nor-LSD derivatives Subsequently, papers appeared which reported studies in the rat uterus and in the rabbit for some of these compounds [8,9] N(6)-n-propyl-nor-LSD appeared particularly interesting in view of the general enhancement of activity that occurs when dopamine agonists possess an n-propyl group attached to the basic nitrogen It was further desired to explore the limits of steric tolerance of the receptor(s) for the alkyl substituent of lysergamides

Using rats trained to discriminate saline injections from 0 08 mg/kg of LSD tartrate, the two-lever drug discrimination paradigm was used to evaluate the stimulus properties of these drugs and the similarity of their cue to LSD The ED_{50} values for LSD, N-ethyl-nor-LSD (ETHLAD), N(6)-n-

propyl-nor-LSD (PROLAD), and N(6)-allyl-nor-LSD (ALLYLAD) were 30 8, 10 7, 28 4 and 9 5 nM/kg, respectively Activity dropped dramatically when the alkyl was an isopropyl, n-butyl, or 2-phenethyl group Further, nor-LSD was nearly two orders of magnitude less active in this assay than was LSD itself The sharp drop in activity in going from an n-propyl to an n-butyl suggests that the receptor cannot accomodate an alkyl longer than three carbon atoms The medicinal chemist's adage "ethyl, propyl, butyl, futile" should perhaps instead be "ethyl, propyl, butyl is futile! "

The observation of potency comparable to, or greater than LSD was of great interest It seemed likely, based on the generalization in the drug discrimination assay and the high potencies of several of the derivatives, that these might well be more potent hallucinogens in man than LSD Very recently, preliminary studies were carried out (A T Shulgin, personal communication) which indicated that indeed, the N(6)-ethyl and the N(6)-allyl-nor-LSD derivatives are somewhat more potent than LSD, by perhaps a factor of 2–3 Early results also indicated that N(6)-propyl-nor-LSD retains activity comparable to LSD, but with perhaps less visual distortion These preliminary results were obtained after only a few experiments with each compound and further evaluation to define the potency and character of these lysergamides is underway

SUMMARY

We now have a general grasp of the types of structural changes that can be made within the various classes of hallucinogens In a few cases we believe we know why these structure-activity relationships exist, in most we do not However, the foregoing discussion has ignored one important question, that is, in what way do various structure changes modify the *qualitative* aspects of the biological effect? When discussing potency of hallucinogens it has been common to speak of "effective levels" or "intoxication," with little regard as to whether this was a severe disruption of all sensory modalities, was selective for one or only a few, and to what degree emotion and affect were involved More recently, attention has been paid to the need to characterize fully how a change in chemical structure may bring about a subtle change in the psychopharmacology of these substances It is certainly clear that if any of these compounds are eventually to find their way into medical practice, for example as adjuncts to psychotherapy, they will necessarily have fairly specific actions on mood and affect, and should not disrupt normal sensory processing

As exemplified by the N(6)-alkyl-nor-LSD derivatives reported here, it is possible to find interesting biological activity in still unexplored areas of the structure-activity relationships of some classes of hallucinogens However, in spite of this, it seems that major efforts need to be directed toward the pharmacology, and gaining a better basic understanding of the mechanism of action of these substances

It is to be hoped that the potential importance of these substances as tools to aid in understanding brain function will attract increasing research interest among neuroscientists It is a narrow view indeed to assume that no compound derived from the hallucinogens will ever become medically valuable Although this seems to have been the prevailing attitude over the past decade or so, perhaps this will begin to change now that compounds such as LSD have largely 'faded' from public view

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