Use of chemical approaches to probe serotonin receptor topography

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As extensions of continuing work on structure-activity relationships of hallucinogenic agents, the relevance was considered of a variety of structural features to serotonin agonist activity. A number of conclusions have been developed as a result of this work, which relate to conformational and molecular features of agonists.

Of particular interest were the following:

1. The location and orientation of a possible electrophilic site on serotonin receptors to accomodate the 5-hydroxy group of serotonin, and the influence on binding for tryptamine and phenethylamine type agonists.
2. The active, or binding conformation of the side chain of tryptamine derivatives, particularly 4-substituted derivatives, and the possibility that different binding conformations could be adopted, depending on the location of ring substituents.
3. The effect of N-alkylation on ergolines, and in particular N(6)-alkyl nor-LSD derivatives.

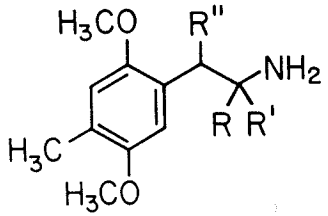
Electrophilic binding site for the 5-hydroxy of serotonin

A number of studies utilizing both receptor binding techniques and behavioral methods have shown that tryptamines have highest serotonin receptor affinity and greatest in vivo potency when substituted with a 5-oxygen, either as a hydroxy or, as in 5-methoxytryptamine, as a methoxy function [1]. A 4-hydroxy group is less effective, at least in binding to receptor preparations [1, 2]. Psilocin, which has a 4-hydroxy, is a potent hallucinogen. However, it is a weaker serotonin agonist *in vitro* than bufotenin, and its *in vivo* activity is related in large part to some unusual effects on pKa and partitioning behavior which probably allow it to penetrate the central nervous system readily [3].

Although one might expect that O-methylation of psilocin would give a compound with properties similar to 5-methoxy-N,N-dimethyltryptamine, 4-methoxy-N,N-dimethyltryptamine has several-fold decreased potency in monkeys and

Table 1

A comparison of the behavioral effects of 5-methoxy-6-methyl-N,N-dimethyltryptamine with 5-methoxy DMT and LSD.



Drug (Dose, mg/kg)	n	Limb Flicks	Abortive Grooms (Mean Frequency/Hour)	Grooms	Body Shakes
Saline		0.2±0.2	0.0	13.0±3.6	9.2±3.1
5-methoxy DMT (100)	6	11.7±6.5	3.7±2.7	12.3±7.1	12.2±4.5
5-methoxy-6-methyl DMT (106)	5	4.6±1.6	0.2±0.2	18.4±3.2	23.6±9.0
LSD (50)	5	46.8±5.9	4.0±3.3	11.8±5.2	25.2±5.5

mice relative to psilocybin [4, 5] even though 4-methoxy-DMT produces a discriminative stimulus in rats similar to 5-methoxy-DMT [6].

Before discussing the possible reason for the drop in activity for 4-methoxy substituted tryptamines, there is another finding which may be related to this discussion. It was reported by Glennon et al. [7] that 5-methoxy-6-methyl-N,N-dimethyltryptamine produced only saline-like responding in rats that had been trained to discriminate saline from 5-methoxy-DMT (1.5 mg/kg). The following data also indicate that 5-methoxy-6-methyl-DMT does not elicit a significant increase in the cat limb flick [8], another model for hallucinogens.

These indications of a lack of hallucinogenic activity, and probably lack of serotonin agonist action, may be explained in one of at least two ways. First, it is known that the 6-position of tryptamines is a site for metabolism. It seems possible that the serotonin receptor may simply have evolved in such a way that no tryptamine with a 6-substituent can be accomodated readily by the receptor. This idea is supported by Szara's early work with 6-fluoro-N,N-diethyltryptamine, which was apparently inactive as an hallucinogen [9] and also by Glennon's studies in the rat fundus, where 6-methyl-DMT did not bind to serotonin receptors in the fundus in a competitive manner [7].

On the other hand, it is also possible that the presence of the 6-methyl substituent forces the 5-methoxy to adopt an unfavorable conformation for binding. Suppose for example, that the serotonin receptor possesses an electrophilic binding site located to interact with the 5-hydroxy function. It may be assumed that this is not a nucleophilic, or hydrogen bond *acceptor* site, since both 5-hydroxy and 5-methoxytryptamines have similar *in vitro* receptor affinity. As an electrophilic site, the likely interaction is with the unbonded n electrons of the

5-oxygen function. Such an interaction will be highly conformation-dependent, with the orientation of the electrons playing a crucial role. Assume, for the moment, that this electrophilic site is located adjacent to the 5-indole position, but with sufficient mobility to interact, perhaps somewhat less well, with an oxygen at the indole 4 position. This site could therefore be suitably positioned to interact with an oxygen either at the 4- or the 5-position. Consider however, the situation that occurs if a) there is a 4-*methoxy* or, b) there is a substituent located at the 6-position. Due to the geometry of the indole ring, there is fairly severe nonbonded interaction between substituents attached to the 3 and 4 positions. The magnitude of this interaction is similar, or a little greater than that for a similarly 1,2-disubstituted benzene. Thus, for a 4-methoxy tryptamine derivative, the methoxy group is forced to adopt a conformation where the methyl group is directed away from the side chain, and where the oxygen n electrons are directed away from the postulated electrophilic site.

A similar situation applies when there is a 6-substituent attached to a 5-methoxytryptamine. The nonbonded interaction between the methoxy and the methyl group directs the 5-methoxy to a conformation where the oxygen n electrons are now also directed *away* from the proposed electrophilic binding site.

In the following figures are presented conformational energy profiles to illustrate these arguments. These profiles were generated using the CAMSEQ/M software [10], as implemented on a Tektronix 4052 microcomputer with dual disk drives and 64K RAM. Conformation energies were calculated using only the steric term, implemented in this program as pairwise Leonard-Jones 6–12 potentials [11, 12]. Major rotation angles were scanned at 10 or 20 degree resolution. Terminal methyl and ammonium groups were incremented through 120° at 30°

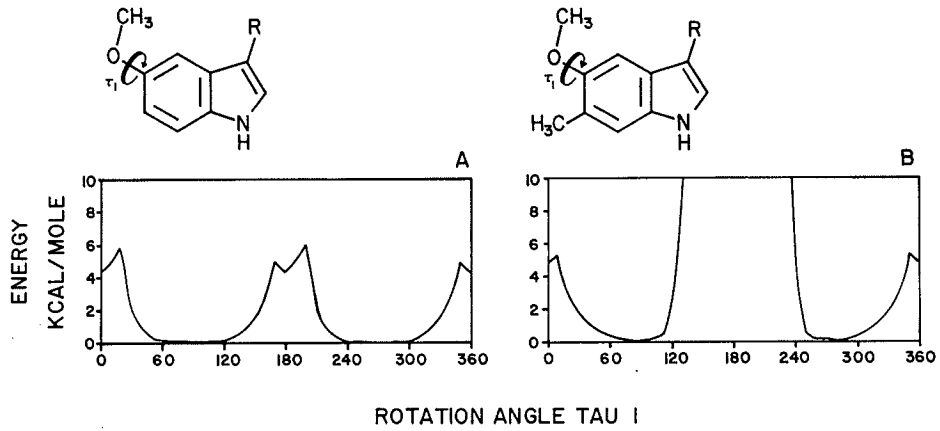


Fig. 1. Conformational energy rotational profile for the C–O bond of 5-methoxytryptamine and 5-methoxy-6-methyltryptamine. The starting (0°) conformation is shown, with the direction of positive rotation indicated as clockwise, when looking from the aromatic ring toward the ether oxygen atom. Energies are expressed relative to the global minimum.

resolution to locate minima. Starting conformations (0°) are illustrated. Energies are plotted as linear maps as a function of one major rotation angle, with all other interactions minimized.

Figure 1A and 1B show the effect on conformational energy of adding the 6-methyl to 5-methoxy-DMT. Energies where the methoxy is "syn" to the methyl exceed 100 kcal/mole above the global energy minimum. Even allowing for the assumption of rigid bonds, and no steric effect of electron pairs, the methyl will have a clear directing effect on the conformation of the methoxy.

Figures 2A and 2B illustrate an analogous situation for psilocin and 4-methoxy-DMT, where O-methylation of psilocin prevents conformations where the methoxy collides with the ethylamine side chain. One should keep in mind that these are steric profiles, and do not take into account stabilizing effects of resonance or orbital overlap. Nevertheless, the magnitude of the interaction clearly indicates that O-methylation of psilocin dramatically limits conformational mobility of the ring-oxygen bond.

This situation seems fairly evident for tryptamines, which are structurally similar to serotonin, the natural substrate for serotonin receptors. However, one might ask whether phenethylamines present any similar analogies. Although a suitable population of serotonin receptors has not been identified for assay of phenethylamine type hallucinogens and serotonin agonists, it seems generally accepted that compounds such as 1-(2,5-dimethoxy-4-methylphenyl)-2-amino-propane, DOM, Figure 3A, and similar 2,5-dimethoxy substituted phenethylamines do elicit their hallucinogenic effects by an agonist effect at serotonin receptors [13].

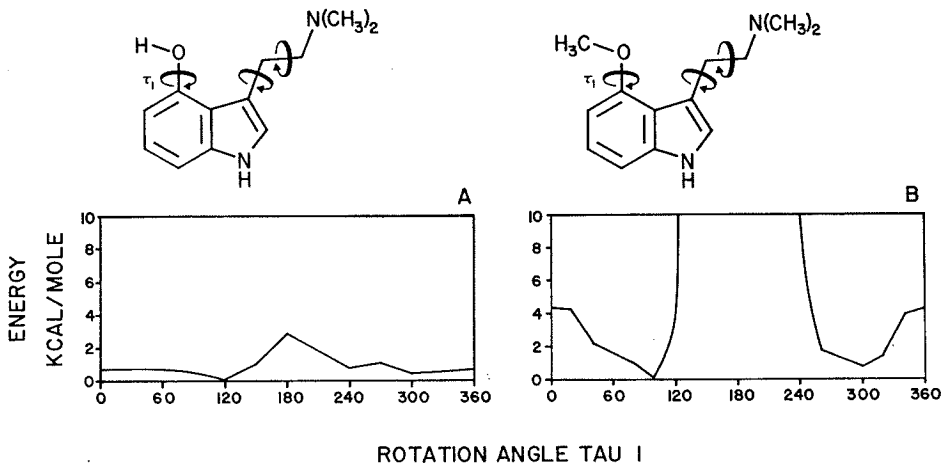


Fig. 2. A comparison of the conformational energy rotational profile for the C-O bond of psilocin and O-methylated psilocin. The side chain torsional angles were scanned to locate minima and the energies plotted in the above figure represent C-O angles with all other interactions minimized. The O-methyl bond was scanned through 120° at 30° resolution.

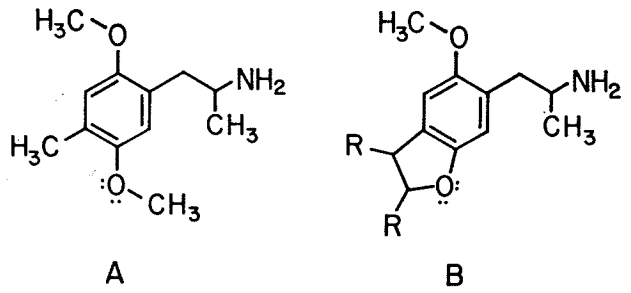


Fig. 3. A comparison of the structures of DOM (A) and certain 2 or 3 substituted 2,3-dihydrobenzofuran analogues of DOM. Note that the electron pair orientation for the 5-methoxy group of DOM, shown in its lowest energy conformation (see Figure 1 for an analogous situation), is rotated about 180° from that required by the geometry of the dihydrobenzofuran derivative.

A report communicated to our laboratory several years ago by a worker in Prague, Czechoslovakia, was particularly interesting. Trampota (personal communication) reported that a series of 1,2-dihydrobenzofurans of the general structure illustrated in Figure 3B possessed potent hallucinogenic activity in man.

Resynthesis in our laboratory allowed retesting of two of these in the two-lever drug discrimination assay, in rats trained to discriminate saline from LSD tartrate (0.08 mg/kg). In neither case did any generalization occur to the dihydrobenzofurans. Further, no significant disruption of performance occurred with either compound at doses up to 16 mg/kg. Perhaps more interesting was the finding by Shulgin (personal communication) that the compound where R=H, as the hydrochloride, produced no effects in humans when administered in an acute oral dose up to 20 mg. This finding was surprising in view of the fact that this molecule can be viewed as an analogue of DOM, where the 4-methyl and 5-methoxy groups have been "tied" together.

Although many explanations for this are plausible, the conformational energy profile for the 5-methoxy group of DOM is virtually identical to that for the 5-methoxy of 5-methoxy-6-methyl-DMT, indicating that the 5-methoxy of DOM will necessarily be directed away from the 4-methyl group. A conformation will not be favored where the 5-methoxy is directed toward the 4-methyl, yet this is precisely the situation found in the 2,3-dihydrobenzofurans shown above. If overlap between the pi system and the oxygen unshared electron pairs is important, it would seem that the dihydrobenzofurans could fulfill this requirement. On the other hand, if arguments about oxygen lone pair directionality are valid, this would indicate that a potential electrophilic site on the serotonin receptor may have strict requirements for electron pair directionality in substituted phenethylamines. As has been noted by Glennon et al. [14], a similar situation applies to phenethylamines with a 2-methoxy group, that have been also substituted at the 3-position. In that case however, the methoxy group cannot lie coplanar with the aromatic ring, but is twisted out of plane. This will have severe consequences for

the resonance energy of the ring, and it is not quite so clear that electron pair directionality for binding of the 2-methoxy can be invoked.

Active conformation of the tryptamine side chain

In previous work from our laboratory, it had been argued that the hallucinogenic alpha-methylphenethylamines ("amphetamines") bind to the receptor so that the alpha methyl projects away from the interacting surface of the receptor. Similar arguments could be offered to suggest that alpha-methyl-tryptamines also bind so as to project the alpha methyl group toward the non-interacting face of the agonist molecule. However, Glennon [15] has reported that it is the *S*-(+) enantiomer of alpha-methyltryptamine which has highest affinity for the serotonin receptor in the rat fundus. He has further proposed a binding conformation for S-(+) alpha methyltryptamine that resembles the tryptamine fragment within LSD. In considering this fact, which would seem to negate the argument of the alpha methyl projecting toward the non-binding molecular face, it also occurred to us that too strict an adherence to the concept of making molecules "look" like LSD might be deceiving. As noted above, in tryptamines there is a nonbonded interaction between the side chain and substituents at the 4-position. Indeed, it appears from the data published by Pullman et al. [16] that the addition of a 4-hydroxy to DMT

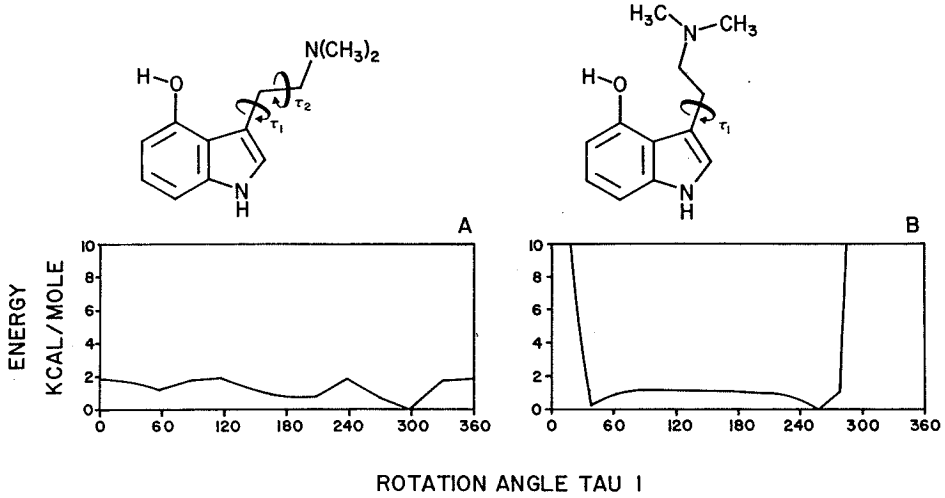


Fig. 4. A comparison of the conformational energies of psilocin when, in A above, bond tau$_2$ is also rotated to locate energy minima. A scan of energies for rotation about bond tau$_1$ indicates complete flexibility about this bond, but does not indicate whether LSD-like conformations are energetically favorable. By contrast, when the x-ray coordinates for LSD are used to generate the coordinates for the starting orientation of psilocin, and when tau$_2$ is kept fixed, it is clear that the interaction between the side chain and the 4-oxygen atom is severe in LSD-like conformations (when tau$_1$=0°). Strict correspondence between LSD and the active conformation of psilocin cannot therefore exist.

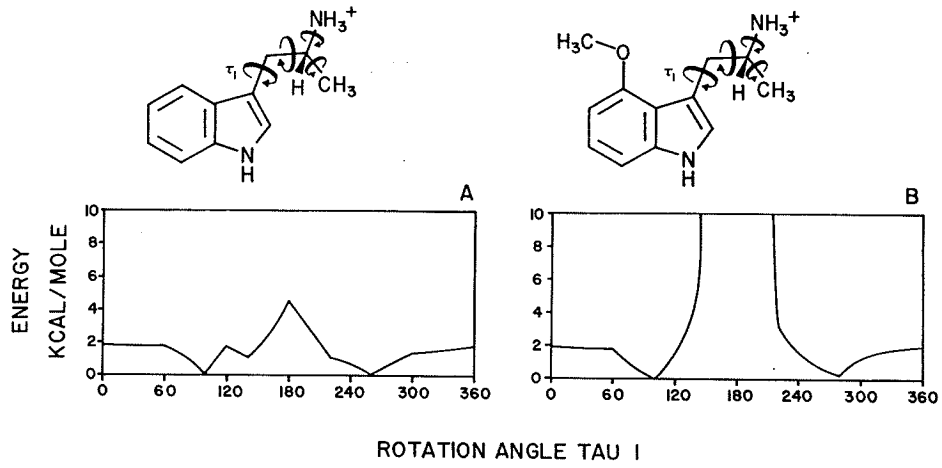
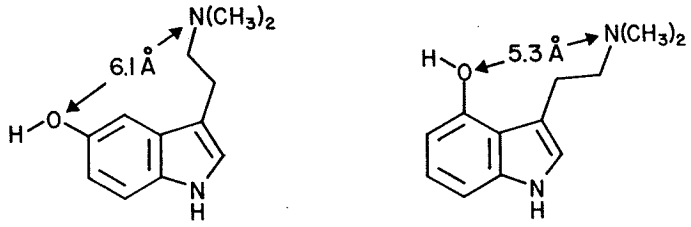


Fig. 5. An example of the effect of adding a 4-methoxy to the conformational energy of R-(−)-alpha-methyltryptamine. Even though all the indicated bonds are rotated to minimize interactions, the side chain cannot adopt conformations which closely resemble the tryptamine fragment within LSD.

to give psilocin dramatically reduces the probability of an LSD-like conformation. This interaction can be minimized by side chain rotations, but of course this deviates from the structure and planarity of LSD which was used as the original template to suggest such conformations. For example, in Figure 4A is the conformational energy profile for rotation of the C3-Cβ bond of 4-methoxy-DMT, allowing all other steric interactions to minimize (rotating about τ_2 and Cα-N), that is, for the side chain to adopt the minimum energy conformation for a given rotation angle of tau$_1$. Starting conformations (0°) are shown. On the other hand, if the side chain is fixed into the conformation that exists in the crystal structure of LSD, and angle tau$_1$ is now rotated, one can see that the presence of the 4-substituent clearly limits the ability of the side chain to adopt LSD-like conformations.

Using the rationale that the alpha methyl group might project away from the interacting surface of the receptor, for either enantiomer, it seemed possible that binding could occur in a non-LSD-like conformation. It was realized that the actual conformation which is so often drawn in the literature for psilocin and many of the tryptamines, and which is used to illustrate a similarity to LSD, is actually somewhat energetically unfavorable. Although this is apparently not serious in unsubstituted tryptamines, the presence of a 4-substituent (i.e. a hydroxy) greatly decreases the probability of LSD-like conformations. For example, Figures 5A and 5B represent the rotational energy as a function of rotation of the C3-Cβ bond for *R*-alpha-methyltryptamine and *R*-4-methoxy-alpha-methyltryptamine. The starting conformations (0°) are as shown and LSD-like conformations occur when the rotation angle is approximately 180°.



"alpha" Rotamer "beta" Rotamer

Fig. 6. An illustration of two possible binding conformations for tryptamines. On the left is illustrated an LSD-like conformation for bufotenin, which has been designated "alpha", and on the right is a non-LSD type conformer for psilocin, designated "beta". The alpha or beta conformer nomenclature is not associated with the presence or absence of ring substituents, but only reflects the type of side chain conformation. The oxygen atoms have been added to reflect the possible importance of the N to O distance. While this is set to a maximum in both examples, rotation of both side chain angles in bufotenin (left above) can bring the N to O distance to 5.3 Å.

An alternative which avoids this problem seems to have been overlooked in the literature. This may be the case since the structure of psilocin (or other tryptamines) can be easily manipulated to resemble LSD. Suppose that the amino nitrogen remains approximately in the aromatic ring plane, but in a conformation where the C3-Cβ bond is rotated 180° from an LSD-like conformation, that is, is set to the starting or 0° conformation shown in Figure 4A. This gives a low energy conformation that would involve the amino group binding at a site on the receptor translated about 2.5 Å away from its location in the LSD-like conformation. This conformation is indicated in Figure 6B as the "beta-rotameric" form and Figure 6A represents the standard LSD-like or "alpha-rotameric" form of a tryptamine.

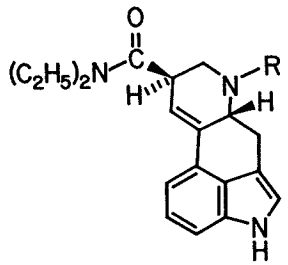
The alpha and beta rotamer terminology proposed here parallels that originally devised by Cannon [17] in his discussion of rigid conformers of dopamine. The distance between the amino group and meta-hydroxy of dopamine, when in an alpha-rotameric conformation compares favorably to the N to O distance in serotonin of 6.1 Å, when in an "alpha" rotameric conformation. There are a number of parallels that could be mentioned between certain dopamine receptors and serotonin receptors but perhaps for the present it will suffice to note that spiperone labels dopamine receptors in the striatum, while in the cortex it labels predominantly serotonin receptors [18].

A further consideration of interatomic distances reveals that, while psilocin has an N to O distance of 3.4 Å in an alpha rotameric conformation, in the beta rotamer this distance is 5.3 Å. For serotonin, the comparable N to O distances are 6.1 Å for the alpha rotamer and 7.9 Å for the beta rotamer. Clearly, the most similar distances between the amino and oxygen functions occur in the alpha rotamer of serotonin (6.1 Å) and the beta rotamer of psilocin (5.3 Å). Furthermore side chain rotations of approximately 30–40° for each of the major rotation angles give slightly distorted alpha rotamers for serotonin with N to O distances of 5.3–5.7 Å.

Thus, it is proposed that the N to O distance for oxygenated tryptamines plays a crucial role in determining serotonin receptor affinity. Dissimilar conformations of unlike molecules may fix this and such an approach may aid in understanding the functional similarities between different types of serotonin agonists. For example, in a series of N,N-di-n-propyl-2-aminotetralins, it is only when a hydroxy is located at the 8-position (8-OH-DPAT) that significant serotonin agonist activity occurs [19]; the N to O distance for this molecule is measured as 5.2 Å, very similar to the beta rotamer N to O distance for psilocin of 5.3 Å. However, the N to O distance for 7-hydroxy-2-aminotetralin is 7.6 Å. Clearly, if the amino to oxygen distance is important, this would seem to be in the range of about 5.3–6.1 Å.

Effects of N-alkylation on activity of lysergamides

Another area of importance is an examination of the effects of various N-alkyls on biological activity of lysergamides. Although this is well studied in phenethylamines and tryptamines, very little work has been done with the lysergamides. Within series of N-alkylated dopamine agonists it has been found that an n-propyl gives optimum activity. This is true for ergolines as well as for aporphines, simple phenethylamines, and tetralins. It was of some interest to determine whether an n-propyl at N(6) of LSD would also enhance serotonin agonist activity. Several N(6)-alkyl-nor-LSD derivatives had earlier been reported by Niwaguchi et al. [20] and brief pharmacology studies in the rat uterus and in the rabbit had subsequently been reported [21, 22]. Therefore, several N(6)-alkyl-nor-LSD analogues were prepared and evaluated for their discriminative stimulus properties in the two-lever drug discrimination assay, using rats trained to discriminate saline injections from 0.08 mg/kg of LSD. The compounds were synthesized by modifications of the methods of Niwaguchi et al. [20] and of Fehr et al. [23]. While studies of the pharmacology of these compounds is not yet complete, a sufficient number of animals have been tested to obtain reliable estimates of the ED_{50} values of these compounds in rats. Figure 7 illustrates the structures of the more active congeners, and Table 2 lists ED_{50} values [24]. Both the N(6)-ethyl and N(6)-allyl compounds appeared to be somewhat more active than was LSD itself in this assay, while the n-propyl appears nearly equipotent to LSD. In a preliminary study, Shulgin [A. T. Shulgin, personal communication] has found that the activities of the N(6)-ethyl, N(6)-allyl and N(6)-propyl compounds seem to parallel the results from the two-lever drug discrimination assay. That is, the ethyl and allyl compounds appear to be about 2–3 times more potent than LSD, while the n-propyl appears about equipotent, but with perhaps less visual disruption than with LSD. *In vivo* analysis cannot of course take into account effects of biodistribution and metabolism, so it is not clear to what extent these potencies reflect changes in serotonin receptor affinity or agonist activity. Receptor binding studies are now underway to examine the affinities of these compounds for serotonin and dopamine receptors.



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

Fig. 7. Structures of some N(6)-alkyl substituted nor-LSD derivatives.

Phenethylamines as serotonin agonists

One of the perplexing questions regarding hallucinogenic phenethylamines is whether they exert their effects by a direct serotonin agonist action, as has been proposed for the tryptamines. It is not entirely clear at the present time that phenethylamines do stimulate serotonin receptors in the CNS, *per se,* or whether they have an important action at the nerve terminal that involves release of stored transmitters. This latter could lead to an "indirect" action that ultimately results in the hallucinogenic effect. Certainly it seems probable that serotonin pathways are ultimately involved, but the issue is whether or not these compounds are direct serotonin agonists.

The concept of multiple serotonin receptors, at least in rat brain, seems well established [25] and this further complicates studies of phenethylamines. At least two populations of serotonin receptors, S_1 or 5-HT_1 and S_2 or 5-HT_2, can be

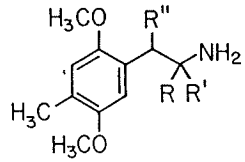
Table 2

Estimated ED_{50} values for generalization of the LSD training drug stimulus (0.08 mg/kg) to N(6)-alkyl-substituted-nor-LSD derivatives in the two-lever drug discrimination assay in rats. See Figure 7 for structures.

N(6)-Alkyl Group	ED_{50} (nM/kg)
Methyl (LSD)	30.8
Ethyl (ETHLAD)	10.7
n-Propyl (PROLAD)	28.4
n-Butyl	400.
Allyl (ALLYLAD)	9.5
H (norLSD)	2770.

Table 3

Competition, measured as IC_{50} values[a], of a series of side-chain substituted phenethylamine derivatives shown in the above structure, for the serotonin binding site (S_1 receptor) in calf striatal homogenate.



R	R′	R″	Enantiomer	IC_{50} (μM)
H	-CH_2-		1*R*,2*S*	0.5
H	-CH_2-		1*S*,2*R*	3.0
H	CH_3	H	*S*-(+)	6.2
H	CH_3	H	*R*-(−)	12
H	C_2H_5	H	*R*-(−)	25
H	C_2H_5	H	*S*-(+)	39
	-CH_2-CH_2-	H	–	78
CH_3	CH_3	H	–	280

[a] IC_{50} values for displacement of specifically bound [^{3}H]-5-HT (3.0 nM) from calf striatal homogenate (protein concentration 0.9 mg/mL). Specific binding was determined using 200 nM unlabelled serotonin. Tris buffer, 50 mM (pH 7.4) was used with a 45 min incubation at room temperature. IC_{50} values were extrapolated from adsorption isotherms using at least four test drug concentrations and 2 to 4 separate determinations at each concentration, each done in triplicate.

obtained from rat frontal cortex and can be distinguished by their preferential binding of [^{3}H]-5-HT and [^{3}H-]-ketanserin, respectively [26, 27]. Evidence has been presented that the S_1 receptor (possibly two S_1 receptor populations exist with low to high affinity for neroleptics [28]) is linked to adenylate cyclase. The S_2 receptor is not cyclase linked and appears to be responsible for the serotonin behavioural syndrome [26].

We have had some interest in locating a receptor population with high affinity for phenethylamine hallucinogens. It is clear that for a large series of phenethylamines, if a binding site could be identified that had affinity for phenethylamines that correlated well with *in vivo* activity, this site would be a candidate for the locus of action for this class of hallucinogen. Some present efforts involve studies of the effects of phenethylamines in a variety of *in vitro* preparations, including rat, bovine and brain homogenates. Initial studies of the S_1receptor, however, did not reveal a correlation between affinity for this receptor and activity. Affinities, measured as IC_{50} values were in the micromolar range, and the S_1 site did not display any apparent stereoselectivity for the more active enantiomers. A summary of these data is presented in Table 3 [29].

An examination of Table 3 clearly shows that one of the critical requirements for identifying the site of action, stereochemical preference for the more biologically active R-(−)-enantiomers is lacking, at least for 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane. Interestingly, the cyclopropylamine with the 1*R*,2*S* configuration does display about a six-fold greater affinity for the S_1 receptor, and this parallels biological activity in several models and in man. Still, even the more active enantiomer has only poor affinity for the S_1 site. Further-

more, the rank order of potencies does not generally correlate with the observed affinities. Thus, at least in the striatum, it does not appear that the S_1 receptor is a site of action for hallucinogenic phenethylamine derivatives.

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