Lysergamides Revisited

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INTRODUCTION

In discussions of hallucinogens in past years, most of the focus has been on phenethylamines and phenylisopropylamines, with a modest amount on tryptamines. A large gap always has been the lack of discussion of lysergamides. Lysergic acid diethylamide (LSD) is one' of the classic hallucinogenic agents, but substituted lysergamides always have seemed to be largely ignored. The lysergamides have been investigated on several historical occasions, but the late 1950s witnessed most of the recent work (Abrahamson 1959; Cerletti and Doepfner 1958; Gogerty and Dille 1957; Isbell et al. 1959). Within the past 8 years, there has been an attempt to fill in some obvious gaps that exist in the understanding of lysergamide-type hallucinogens.

The lysergamides are derived from the ergot fungus, well known throughout history as a source of various types of medications. Extracts of ergot have been recognized as legitimate pharmaceutical preparations since at least the Middle Ages. Lysergic acid is derived from hydrolysis of the ergot alkaloids. Although present-day methods of ergot production utilize submerged culture fermentation rather than cultivation on rye or other cereal grains, *Claviceps* is the ultimate alkaloid source.

It is also known that lysergamides have been employed as psychoactive preparations, with some of these uses stretching back to antiquity. For example, arguments have been made that the Greek mysteries at Eleusis were related to the ingestion of a preparation that contained lysergamides derived from an ergot fungus that infested the grass in that region. Another example is ololiuqui, a South American Indian and Mexican psychoactive preparation that was prepared from the seeds of certain morning glories, *Rivea corymbosa.* Ergine, or lysergic acid amide (figure 1), is the primary psychoactive component of morning glory seeds. In 1943, Hofmann discovered the unusual properties of LSD, the diethyl amide or lysergic acid.

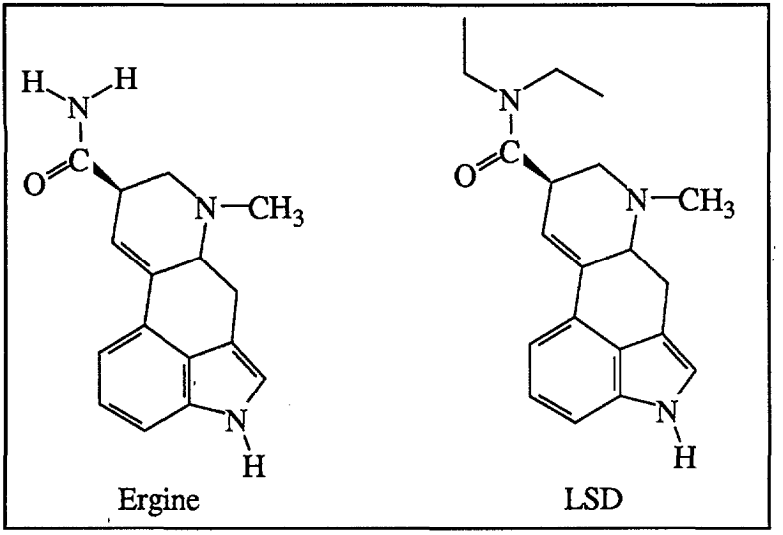

FIGURE 1. *Structural representations of ergine and LSD*

OVERVIEW OF THE ERGOLINES

All ergolines have a tetracyclic framework based on the aromatic two-ring indole nucleus. Lysergic acid has a carboxy function at the 8-position. Because of their structural complexity, lysergamides have several locations that can be modified for structure-activity studies of these hallucinogens. These are shown in figure 2.

Substitution at the N(1) position generally attenuates or abolishes hallucinogenic activity (Brimblecombe and Pinder 1975). Substitution at the C(2) position, particularly with a halogen such as bromine (e.g., BOL) or iodine, leads to compounds that not only are inactive as hallucinogens but also can antagonize the effect of a subsequently administered dose of LSD (Brimblecombe and Pinder 1975).

The stereochemistry is critical for the lysergic acid molecule. The *R* stereochemistries at both the C(5) and C(8) positions are essential. Inversion of either stereocenter abolishes hallucinogenic activity (Brimblecombe and Pinder 1975). C(5) inversion gives *l*-lysergic acid derivatives, as compared with the natural *d*-lysergic acid. Epimerization at the C(8) position gives the isolysergic acid or iso-LSD derivatives.

Reduction of the 9, 10-double bond also abolishes hallucinogenic activity (Brimblecombe and Pinder 1975). Ring substitution at the C(12) or

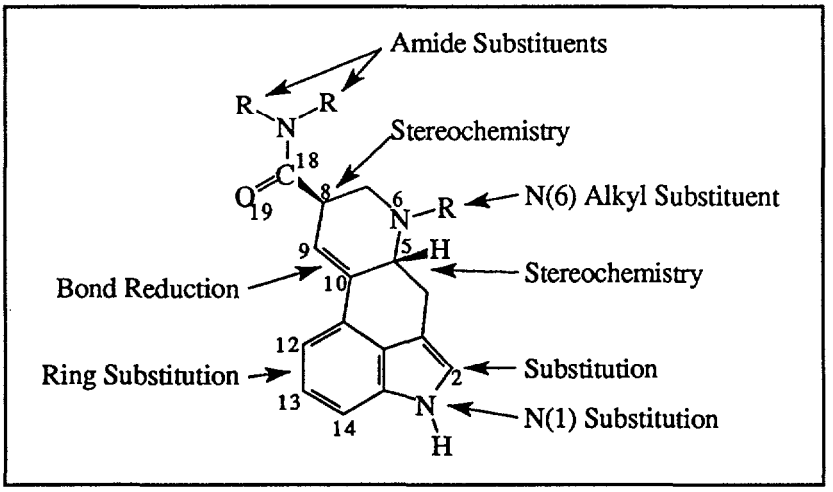

FIGURE 2. *Locations and types of structural modifications studied for lysergamides*

C(13) positions is fairly difficult. Because entire doctoral theses have been written about the total synthesis of lysergic acid, it is apparent that the synthesis of derivatives modified at the 12-, 13-, or 14-position would be quite a formidable task. Nevertheless, the 12-hydroxy compound was prepared years ago. The authors obtained a sample of this and performed drug discrimination (DD) studies in LSD-trained rats. It had unremarkable properties, with only about 20 percent of the potency of LSD (Pffaf et al., unpublished observations).

It also has been postulated that hydroxylation in vivo occurs at the 13-position. This occurrence would correspond to the 6-hydroxy-tryptamines that Szára (this volume) discusses. There is evidence in the literature that hydroxylation at this position confers high dopaminergic potency on ergolines, but it is not clear whether this could be related to the hallucinogenic properties of LSD.

These ring modifications are generally the only ones that have been studied, primarily because of the difficulty in carrying out chemistry on a complex molecule like an ergoline.

EFFECTS OF N(6) SUBSTITUTION

One major gap in the literature that the authors looked at some years ago was substitution on the basic N(6) nitrogen atom. Recently, the authors have examined substitutions on the amide nitrogen. Dopaminergic compounds had been studied for many years, and it was known that if the alkyl group on the N(6) nitrogen was extended from methyl to ethyl to propyl, the dopaminergic effects of the ergolines were maximal. About 10 years ago, the authors envisioned that a propyl group placed on the N(6) nitrogen of LSD might optimize its dopaminergic effects. Consequently, it might be possible to determine, in some way, the importance of that pharmacological component to the overall action of the drug. It was decided to make a series of N(6)-alkyl substituted compounds. At about the same time, Niwaguchi and colleagues (Nakahara and Niwaguchi 1971; Niwaguchi et al. 1976) also prepared a small series of N(6)-alkyl substituted lysergamides and examined them in smooth muscle preparations; they reported high activity. Therefore, the authors synthesized several N(6)-alkyl derivatives in the laboratory. Testing data for these are summarized in table 1 (Hoffman 1987).

TABLE 1. *Drug discrimination ED_{50} values and receptor affinities of N(6)-alkyl-nor-LSD derivatives*

Compound	DD* (µmol/kg)	K_I(nM)		
N(6)-alkyl	ED_{50}	[^{3}H]-5-HT	[^{3}H]-ketanserin	[^{125}I]-*R*-DOI
Allyl	0.013	15.5	8.1	3.4
Ethyl	0.020	3.8	5.1	5.1
Propyl	0.037	4.9	5.6	
Methyl (LSD)	0.046	5.9	5.2	5.1
CH_2-c-C_3H_5	0.067	10.9	7.7	
i-Propyl	0.10	21.4	14.1	
n-Butyl	0.36	45.7	5.2	
Propargyl	0.62	91.2	100.0	
2-Phenethyl	NS†			
H (nor-LSD)	NS†	30.2	158.0	

* Rats (n = 8) were trained to discriminate 0.08 mg/kg (+) LSD from vehicle.

† No substitution occurred with these analogs.

KEY: DD = drug discrimination; nM = nanomolar; [^{125}I]-*R*-DOI = [^{125}I]-*R*-1-(2,5 dimethoxy-4-iodophenyl)-2-aminopropane

In the first column are DD data. Glennon (this volume) describes the DD paradigm, so it will be noted simply that LSD was used as the training drug at a dosage of 0.08 milligrams per kilogram (mg/kg) of the tartrate salt. The DD data are median effective dose (ED,) values for compounds that fully substituted. The ED, values are in micromolars (μmol)/kg, so direct potency comparisons can be made that take into account differences in molecular weight.

Displacement of tritiated serotonin in rat brain homogenate was investigated several years ago as a measure of affinity for serotonin receptors. This work was done prior to some of the differentiation of receptor subtypes; the data in column 2 probably closely represent inhibition constant (K_I) values at the 5-HT_{1B} receptor subtype (Pazos and Palacios 1985). Displacement of tritiated ketanserin from the serotonin 5-HT_2 receptor also has been investigated, and on a few compounds there exist data for displacement of [^{125}I]-*R*-DOI from the agonist state of the 5-HT_2 receptor.

The DD data indicate that the *n*-propyl is slightly more active than LSD, although not significantly so, but the ethyl and allyl compounds were significantly more potent than LSD. From the serotonin displacement data alone, there is no obvious basis for these results, although perhaps the ethyl and propyl compounds have slightly higher affinity. The cyclopropylmethyl compound is somewhat less active, but the isopropyl is even less so, indicating that branching adjacent to the nitrogen atom is not well tolerated. The data for the isopropyl derivative can be compared with those for the *n*-propyl derivative. The *n*-butyl compound drops off about tenfold in potency. There is a medicinal chemist's adage that says something like "ethyl, propyl, butyl, futile." However, it more properly should be stated as "ethyl, propyl, butyl is futile," because in most cases when *N*-alkylated amines are extended beyond propyl, a marked drop in activity is seen.

The allyl compound, which was the most potent, differs from the propargyl in that the allyl has two sp^2 carbon atoms and a double bond, whereas the propargyl has two *sp* carbon atoms and a triple bond. There is a dramatic difference in the activity of the allyl versus the propargyl. In general, a decrease in receptor affinity is seen with the less active compounds. For example, the propargyl has about one-twentieth the affinity of most of the more active analogs at ketanserin sites.

The 2-phenethyl derivative was included because, in the opiates, this substituent often gives high activity. This compound did not substitute in LSD-trained animals, so there was no followup with binding studies. NorLSD did not substitute either, although it has modest affinity for 5-HT_1 sites.

This was an area of the structure-activity relationships (SAR) that had been unfilled, and there is now some knowledge of the effect of the N(6) alkyl group on activity of lysergamide hallucinogens. If the animal data are used as a criterion, it is known that LSD is, in fact, not the most potent LSD-like agent; the ethyl and allyl compounds are more potent. Clinical data presented by Jacob and Shulgin (this volume) seem to corroborate this observation.

Figure 3 shows wire-frame stereo-pair representations of the energy-minimized structures of the N(6)-allyl, -ethyl, and -propargyl compounds viewed from the top, or ß, face. The authors attempted to determine whether there was any basis for the fact that the propargyl is not very active, whereas the allyl is potent. The N(6)-ethyl has a fair amount of flexibility; it tends to lie with the terminal methyl below the ring plane as shown in the figure. The allyl adopts a similar orientation but with the terminal CH_2 of the double bond projected further toward the back face of the molecule. The N(6)-propargyl also is projected in a similar orientation. Looking at these molecules from the edge (figure 4) shows that the CH_2 of the allyl group is projected toward the lower face.

The terminal alkyne of the propargyl is rigid and has a linear geometry; it may be that it is not flexible enough and is unable to get out of the way, preventing the molecule from interacting favorably with the receptor. Otherwise, there seems no obvious reason the allyl compound should be so potent whereas the propargyl has such low activity.

EFFECTS OF AMIDE SUBSTITUTION

The other major area now being examined is substitution on the amide function. Most lysergamides that have been subjected to clinical studies were reported in the mid- to late-1950s. Table 2 lists relative potency in humans for most of the amides that were studied. The amides were not studied systematically, and their characterization in clinical studies was rudimentary. The data for the compounds that were studied do not give any insight as to why the diethyl substitution of LSD should be so potent.

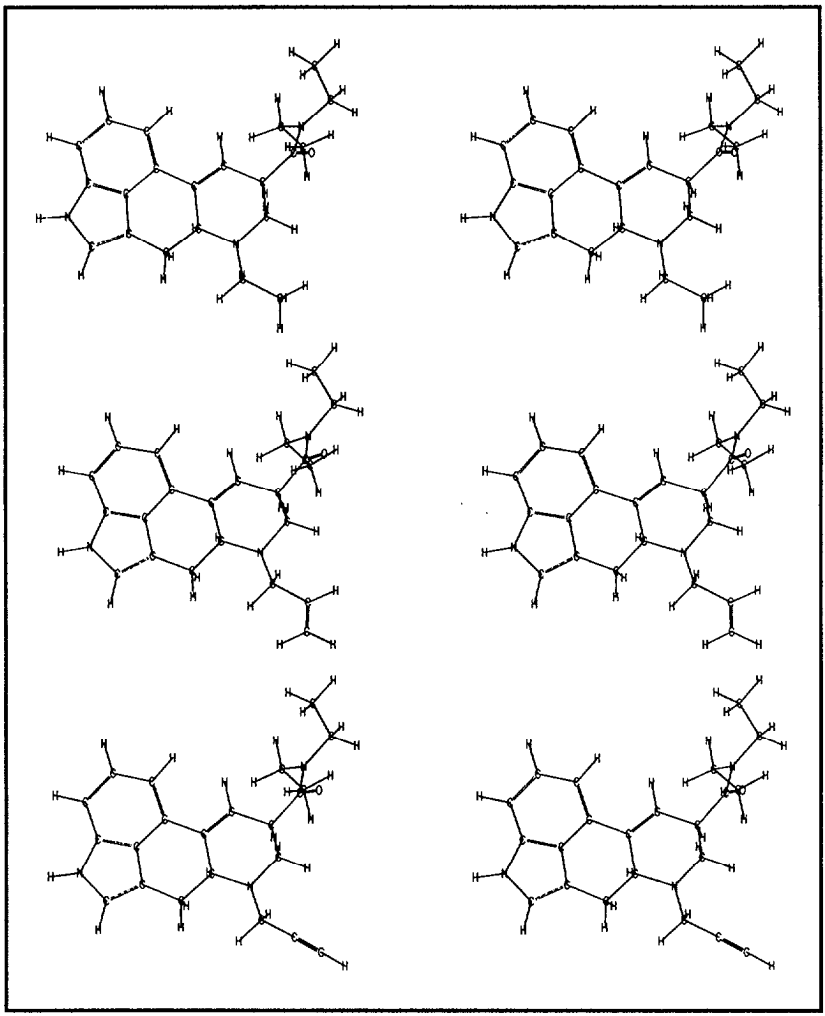

FIGURE 3. *Facial stereo views of the N(6)-alkyl LSD derivatives. Top: ethyl: center: allyl; bottom: propargyl*

It should be noted in table 2 that none of the compounds has more than about 30 percent of the activity of LSD. This is something that has always perplexed researchers in this field: What is it about the diethyl group that may be unique in this molecule? Even a substitution with the same number of carbon atoms, such as the *N*-methyl-*N*-propyl derivative, shows only about one-thirtieth the potency of LSD. The *N*-methyl-*N*-propyl presumably would have similar pharmacokinetics, with

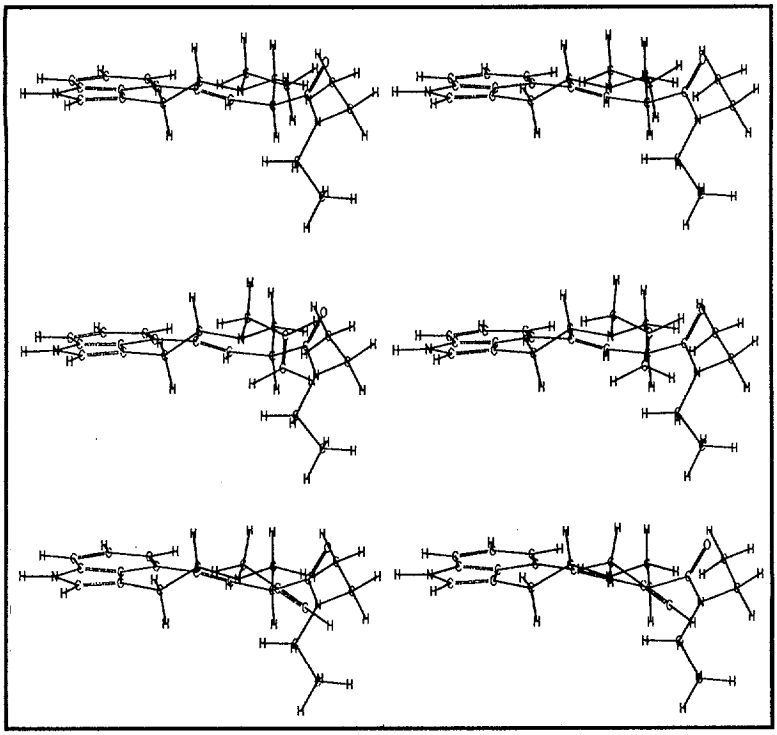

FIGURE 4. *Edge-on stereo views of the N(6)-alkyl LSD derivatives. Top: ethyl; center: allyl; bottom: propargyl*

comparable amounts of the drug expected to enter the brain, and yet this compound is only weakly active. Even the *N*-methyl-*N*-ethyl has low activity compared with LSD. With the *N,N*-diethyl (LSD) one sees optimum activity, but the *N*-ethyl-*N*-propyl is back to about one-third the potency of LSD, and *N,N*-dipropyl is down to one-tenth.

Compounds are being designed that might allow one to probe the dialkyl amide function and to try to understand what role it plays. If, in fact, the *N,N*-diethyl does have unique properties, why is this so? The authors' first attempt to address this problem was to "tie together" the two ethyl groups of LSD as a three-membered dimethylaziridine ring.

The target compounds are shown in figure 5. It was envisioned that the dimethylaziridines might resemble three possible conformations of the more flexible diethyl amide. There are three dimethylaziridines: a trans-

TABLE 2. *Relative human potency of lysergic acid amides**

R_1	R_2	Relative Potency
H	H (lysergamide, ergine)	3
H	CH_2CH_3	10
H	$CH(CH_2OH)CH_3$ (ergonovine)	3
CH_3	CH_3	10
CH_3	CH_2CH_3	3
CH_3	$CH_2CH_2CH_3$	3
CH_2CH_3	CH_2CH_3 (LSD)	100
CH_2CH_3	$CH_2CH_2CH_3$	32
$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	10
C_4H_8	(Cyclic pyrrolidide)	32
C_4H_8O	(Cyclic morpholide)	32

* Derivatives of ergine (figure 1) where the terminal amide -NH, has been replaced by $-NR_1R_2$

SOURCE: Data from Shulgin 1981

isomer with *R,R* stereochemistry, a transisomer with *S,S* stereochemistry, and a cis-meso compound in which both methyls are on the same side of the aziridine ring. These three molecules are isomeric probes that are similar in molecular weight to LSD. However, the methyls of what would be the corresponding ethyl groups in LSD are in different orientations. It was anticipated that evaluation of these compounds might offer insight into the role of the ethyl groups of LSD. Unfortunately, this was not to be. Acyl aziridines under acidic conditions are chemically labile. After condensation of the dimethylaziridines with lysergic acid—the amide protonates—the chloride then attacks the aziridine ring, which then opens to yield the chlorobutyl derivatives (Oberlender 1989) as shown in figure 6.

In the case of the trans-*R,R* enantiomer, chloride attack at either carbon 2 or 3 gives the same isomer, which has the 1*R*,2*S* configuration. Similarly, chloride attack at either of these positions in the trans-*S,S*. isomer gives the same diastereomer, the 1*S*,2*R* chlorobutyl. Depending on which center is attacked with the cis-meso compound, either the *R,R* or *S,S* diastereomer is obtained. When these four compounds (figure 7) were obtained, the authors carried out model reactions acylating the

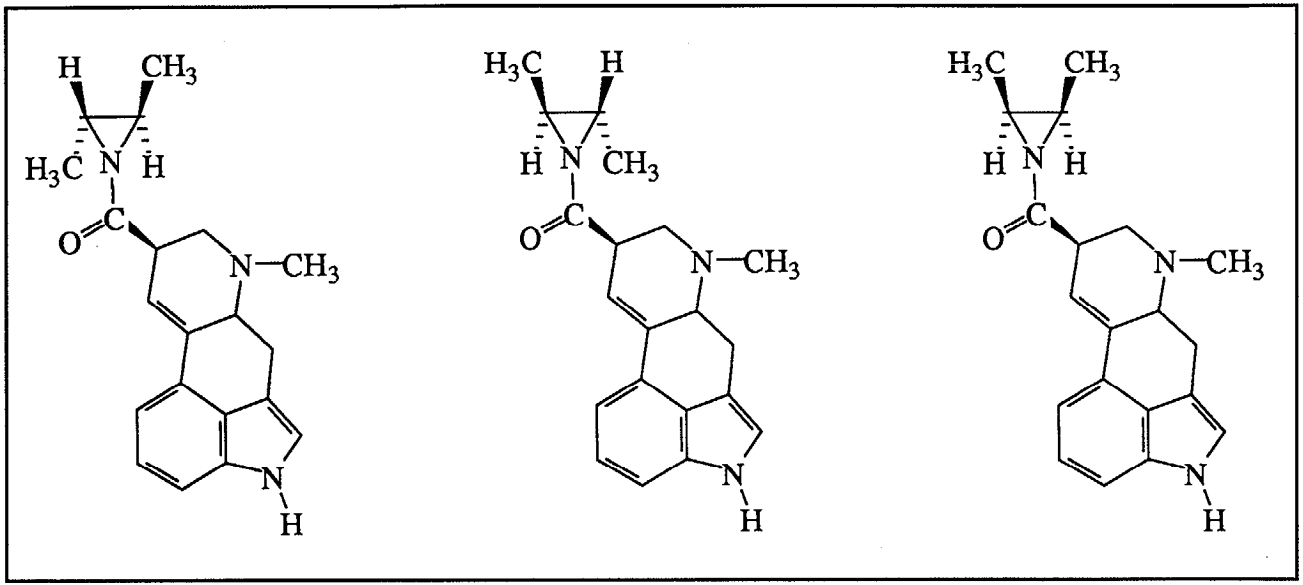

FIGURE 5. *The dimethylaziridinyl amides of lysergic acid. Left: R,R-dimethylaziridinyl; center: S,S-dimethylaziridinyl; right: cis-meso-dimethylaziridinyl*

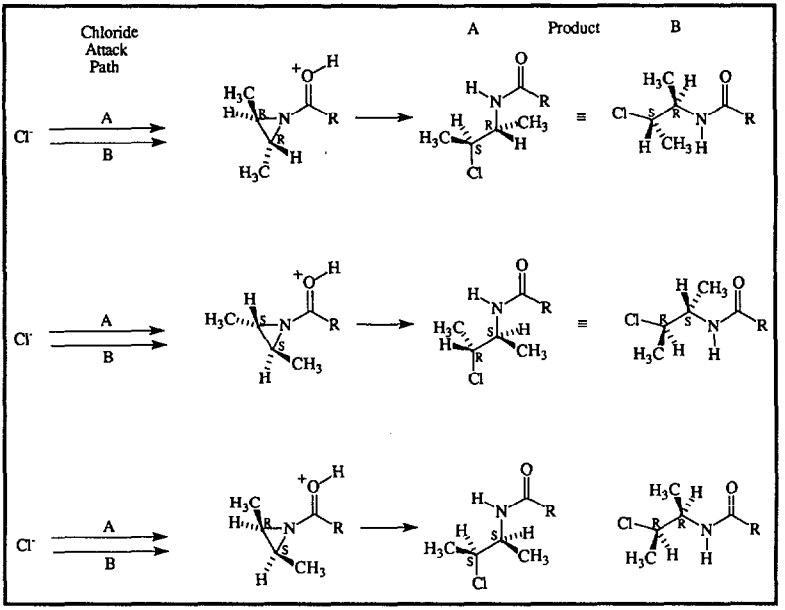

FIGURE 6. *Proposed mechanism of attack of chloride on the dimethylaziridinyl lysergamides*

dimethylaziridines with benzoyl chloride to prove that this occurred, and then chemically established that these were the products of the condensations between the dimethylaziridines and lysergic acid.

The four diastereomers were separated, purified, and tested in DD studies, and the data are summarized in table 3. It was found that one of the diastereomers was about 50 percent more potent than LSD. This was the first indication that something other than the diethyl amide might give high activity. Because this is a DD assay, it can give false positives, but it rarely, if ever, gives false negatives. So it seems probable that these compounds might have LSD-like activity. Yet, they are monoalkyl amides, not dialkyl amides. There is no precedent for a monoalkyl amide to have an activity approaching that of LSD. It should be noted that diastereomers 1 and 2 are obtained from racemic trans-dimethylaziridine, and diastereomers 3 and 4 are obtained from cis-dimethylaziridine. Diastereomers 1 and 3 are most potent, one derived from trans- and the other from cis-dimethylaziridine. Diastereomers 2 and 4 are much less potent. The pyrrolidide was included for comparison because it is known that in humans the pyrrolidide has about 10 to 15 percent of the potency

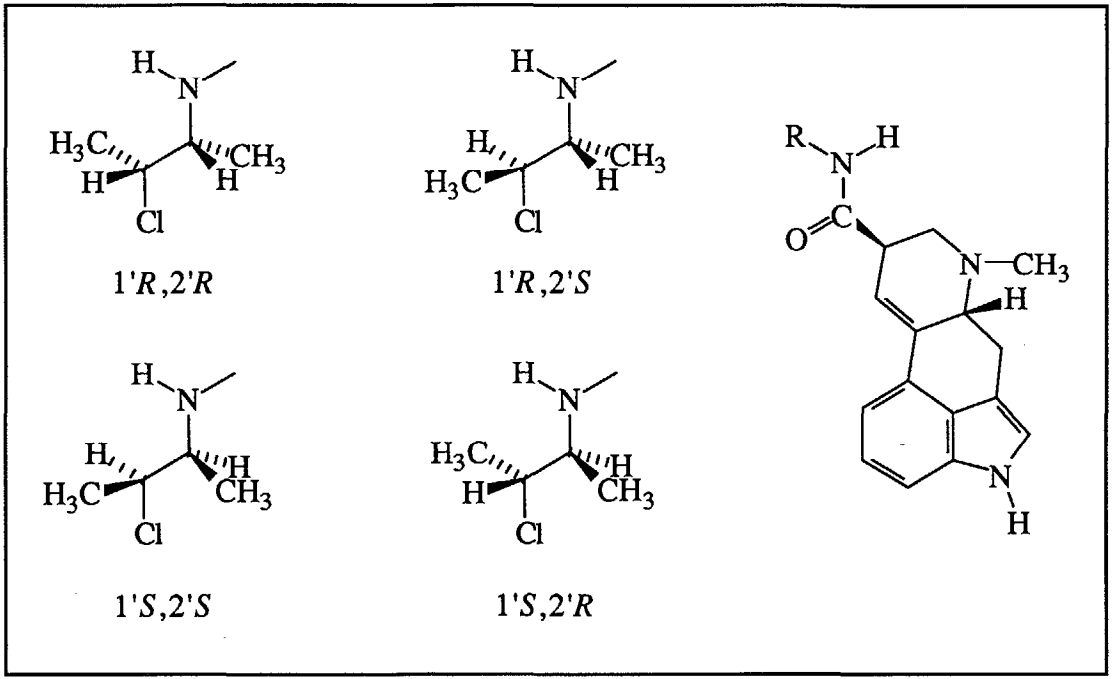

FIGURE 7. *The stereochemistries of the products of chloride attack on the dimethylaziridinyl lysergamides*

TABLE 3. *Potency of chlorobutyl and pyrrolidyl lysergamides in rats trained to discriminate 0.08 mg/kg of (+)LSD from vehicle*

Compound	ED_{50} (µmol/kg)	Relative Potency
Diastereomer 1	0.027	155
LSD	0.042	100
Diastereomer 3	0.156	27
Pyrrolidide	0.168	25
Diastereomer 4	0.387	11
Diastereomer 2	0.605	7

TABLE 4. *Radioligand-binding data for 2-butyl lysergamides*

Lysergic Acid Amide substituent	K_I (nM)		IC_{50} (nM)	
	5-HT_2 *	5-HT_{1A} †	D_1 ‡	D_2 §
N,*N*-diethyl (LSD)	6.31	5.05	60	13
R-2-butyl	2.63	2.01	44	15
S-2-butyl	7.76	4.61	70	37

KEY: Data are for the displacement of *[^{125}I]-*R*-DOI in rat frontal cortex homogenate, †[^{3}H]-8-OH-DPAT in rat frontal cortex homogenate (Oberlender et al. 1992), ‡[^{3}H]-SCH23390 in rat striatal homogenate, and §[^{3}H]-spiperone in rat striatal homogenate (unpublished results).

of LSD (Nichols et al. 1991). In DD trials, pyrrolidide shows considerably lower potency than LSD.

To simplify things, it was decided to prepare lysergamides from the enantiomers of 2-aminobutane, shown in figure 8. These were commercially available with either the *R* or *S* stereochemistry at the α-carbon (C-α).

The 2-aminobutane amide derivatives of lysergic acid were viewed as analogous to the chlorobutyl compounds but dechlorinated to remove the second stereocenter. Table 4 shows binding affinity data using

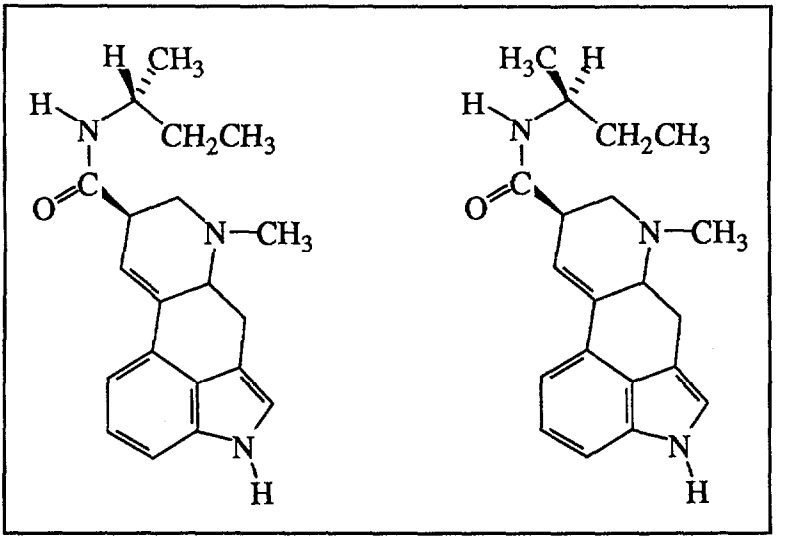

FIGURE 8. *The secbutyl lysergamides. Left: the diastereomer from the R-isomer; right: the diastereomer from the S-isomer*

[^{125}I]-*R*-DOI as a label for the 5-HT_2 receptor; [^{3}H]-8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT) as a label for the 5-HT_{1A} receptor; and [^{3}H]-SCH23390 and [^{3}H]-spiperone in rat caudate as labels for the dopamine (DA) type 1 (D_1) and type 2 (D_2) receptors, respectively. Some of the data were recently published (Oberlender et al. 1992).

As is already known, LSD has high affinity for the 5-HT_2 and the 5-HT_{1A} receptors (Nichols et al. 1991). Interestingly, 60 nM is a respectable affinity for the D_1 receptor, and 13 nM is certainly a high affinity for the D_2 receptor. It should be noted that the dopaminergic component of LSD has not been examined in any detail. Therefore, it can be seen that LSD has high affinity at these four possible recognition sites, and it is known also to have high affinity for other sites. Note that of the two secbutyl diastereomers, with *R* and *S* stereochemistry in the side chain, the *R* isomer has significantly higher affinity than LSD at both serotonin recognition sites and comparable affinity at the D_1 and D_2 sites. This compound, at least from the receptor-binding profile, looks more potent than LSD. Even the diastereomer from the *S* isomer has affinities similar to LSD.

One interesting aspect that has not been studied is the significance of these high affinities for the D_1 receptor. This may be the first report of

the D_1 receptor affinity for LSD. Presently, there is great interest in the D_1 receptor, in part related to its functional interactions with D_2 receptors and in part because of the possibility that D_1 receptor activation is necessary for expressing the biological activity of compounds that have a D_2 dopaminergic effect. With affinities of this magnitude, the D_2 effect of LSD must be considerable, and it could be anticipated that the D_1 receptor also might play a role in the overall action of lysergamides. It never before has been recognized that these compounds have such high affinity for the D_1 receptor.

Functional measures seem to parallel the serotonin receptor-binding data. Sanders-Bush (personal communication. 1992) has examined the ability of the 2-butyl lysergamides to stimulate phosphoinositide turnover in a cloned cell line transfected with 5-HT_2 receptor carrier deoxyribonucleic acid (cDNA). Both diastereomers were partial agonists, giving 75 to 80 percent of the response produced by 1 µM 5-HT. The diastereomer from the *R*-2-butyl enantiomer had approximately twice the potency of that from the *S* enantiomer. However, these diastereomers had only about 5 to 10 percent of the potency of LSD despite their comparable receptor affinity. Similarly, at the rat choroid plexus 5-HT_{1C} receptor, both diastereomers were partial agonists, with the diastereomer from the *R* enantiomer of 2-butylamine again having approximately twice the potency of that from the *S* enantiomer.

Mayaani (personal communication. 1992) also has examined these diastereomers for their ability to inhibit forskolin-stimulated adenylate cyclase in rat hippocampal homogenate. Both diastereomers were full agonists, comparable to 8-OH-DPAT. Again, the diastereomer from the *R* enantiomer of 2-butylamine was more potent than that from the *S* enantiomer.

Figures 9 and 10 illustrate edge-on and top views of the fully energy-minimized structures of LSD (top), the diastereomeric lysergamides of *R*-2-aminobutane (center), and *S*-2-aminobutane (bottom) as wire-frame stereo-pairs. Nothing is readily obvious from the structures, but it is possible to make an empirical observation that in the low-energy conformation of the diastereomer of the *R* enantiomer, the amide group "looks" a bit more like LSD. The amide of the diastereomer from the *S* enantiomer looks quite different in that all the bulk of the 2-butyl alkyl group is projected to the left of the molecule.

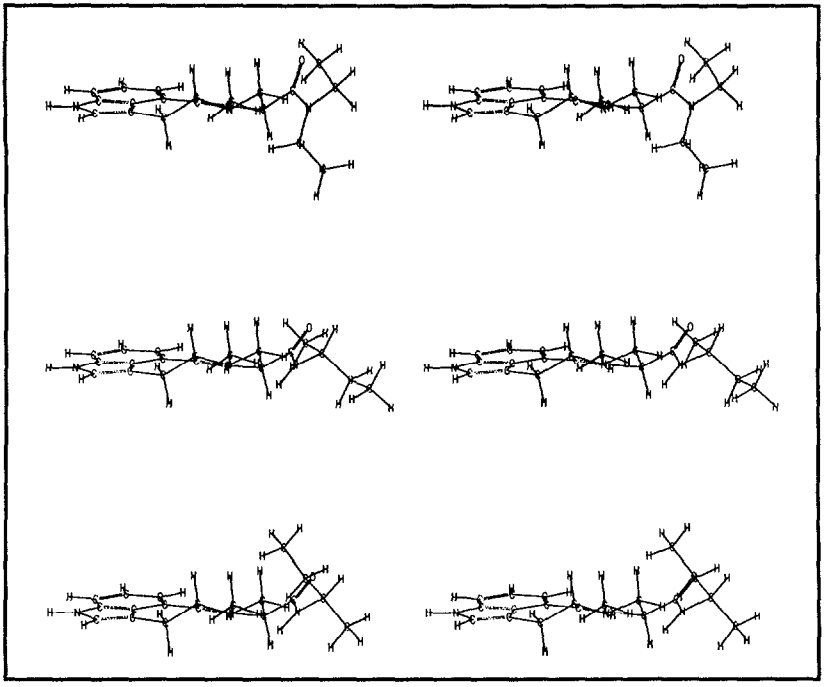

FIGURE 9. *Edge-on stereo views of LSD and the secbutyl lysergamides: Top: LSD: center: R-secbutyl lysergamide; bottom: S-secbutyl lysergamide*

These are flexible molecules, so no firm conclusions can be drawn. However, looking at the low-energy conformations, perhaps it can be said that the *R* isomer looks more like LSD than the *S* isomer. That begs the question and does not explain why LSD is active, but it is an interesting observation.

DISCUSSION

Much more work is needed on these amides. A series of compounds with a range of biological potencies is required to develop SARs. The authors now are trying to develop systematic series of amide-substituted compounds. Combining conformational analysis with biological activity data, some appreciation may be gained of the role of the amide in the lysergamides.

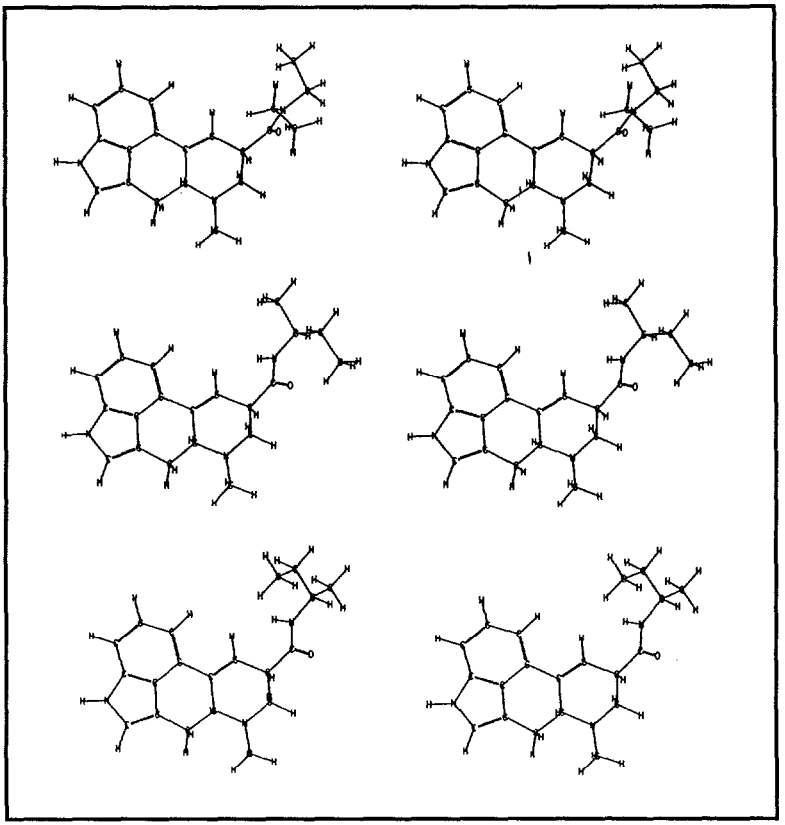

FIGURE 10. *Facial stereo views of LSD and the secbutyl lysergamides: Top: LSD; center: R-secbutyl lysergamide; bottom: S-secbutyl lysergamide*

Another compound to be studied is the methylisopropyl amide of lysergic acid (figure 11). This is an isomer of LSD where a methyl has been "removed" from one ethyl group and placed onto the α-position of the other. Receptor-binding data for that compound are compared with LSD in table 5. The affinity profile looks virtually identical to LSD for these four receptor types.

DD studies also have shown that this compound fully substitutes in animals trained to discriminate saline from LSD. Thus, it can be anticipated from the receptor-binding and behavioral data that this compound might be LSD-like.

The authors have been collaborating with Dr. Wilfred Dimpfel of the ProScience Private Research Institute in Germany, who employs a

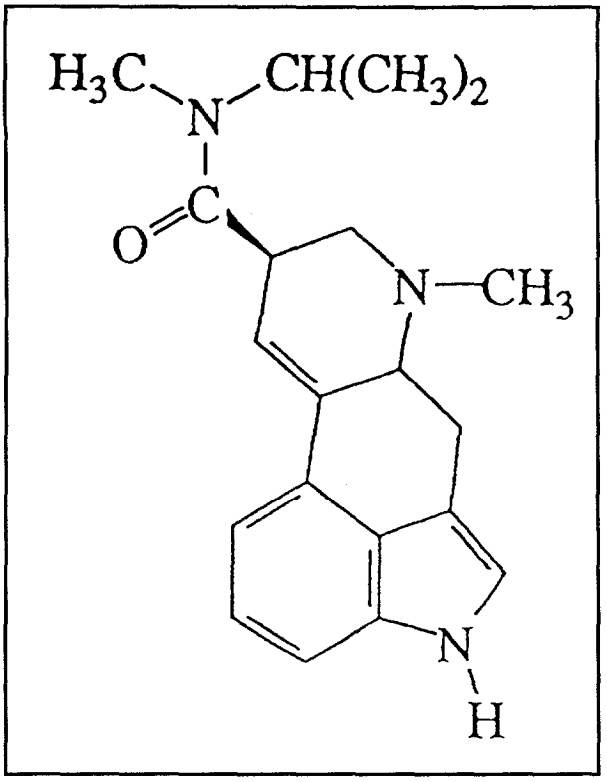

FIGURE 11. *The isopropyl amide of lysergic acid*

TABLE 5. *Radioligand-binding data for N-methyl-N-isopropyl lysergamide*

Lysergic Acid	K_I (nM)		IC_{50} (nM)	
Amide substituent	5-HT_2 *	5-HT_{1A} †	D_1 ‡	D_2 §
N,*N*-diethyl (LSD)	6.31	5.05	60	13
N-methyl-*N*-isopropyl	3.93	4.72	50	20

KEY: Data are for the displacement of *[^{125}I]-*R*-DOI in rat frontal cortex homogenate, [^{3}H]-8-OH-DPAT in rat frontal cortex homogenate (Oberlender et al. 1992), [^{3}H]-SCH23390 in rat striatal homogenate, §[^{3}H]-spiperone in rat striatal homogenate (unpublished results).

technique known as Tele-Stereo-EEG. Four bipolar stainless steel electrodes are chronically implanted into rat frontal cortex, caudate, hippocampus, and reticular formation. Field potentials in freely moving rats are recorded, processed by fast-Fourier transform, and filtered to generate dose- and time-dependent power spectra that give "EEG fingerprints" characteristic of the particular type of drug administered. LSD tartrate (0.01 to 0.05 mg/kg) has been compared by Dimpfel (personal communication 1992) with the *N*-methyl-*N*-isopropylamide tartrate (0.025 to 0.1 mg/kg) in this paradigm. In spite of the biochemical and DD data, the rat EEG studies give a surprising result. Although doses can be selected for the two drugs that have some similarities, the EEG fingerprint of the *N*-methyl-*N*-isopropylamide gives a best fit to the EEG fingerprint for dopamine D_1 agonists. This was totally unexpected and seems inexplicable. Perhaps when clinical trials are carried out with dopamine D_1 agonists, the result may be more understandable, but at the present time and in the absence of human data it is perplexing.

The series of isopropyl amides has recently been completed with the synthesis of the *N*-isopropyl, in addition to the *N*-methyl-*N*-isopropyl, *N*-ethyl-*N*-isopropyl, and the *N*,*N*-diisopropyl, as shown in figure 12.

With the exception of the *N*,*N*-diisopropylamide, all compounds completely substitute in the DD paradigm in rats trained to discriminate LSD from saline. In table 6, the receptor-binding data for displacement of [^{3}H]-ketanserin from rat cortical homogenate are shown. Although all *N*-isopropyl homologs have only 25 to 30 percent affinity of LSD for this site, it is interesting to note that the N-methyl-N-isopropyl compound discussed earlier has nearly equal affinity to LSD for the 5-HT_2 site labeled with the agonist ligand [^{125}I]-*R*-DOI. This illustrates the importance of determining the relative efficacy of these compounds rather than just receptor affinity.

The authors are continuing these studies with the *N*-alkyl-*N*-isopropylamides and also are expanding the studies with chiral alkyl groups in the amide function. Through a systematic approach utilizing modification of the amide alkyl combined with conformational and pharmacological analysis, the authors hope to identify correlations between activity and structure. Success in this endeavor might finally, after so many years, explain why LSD is such a potent compound and what actions at which monoamine receptors are the essential ones for expression of hallucinogenic effects.

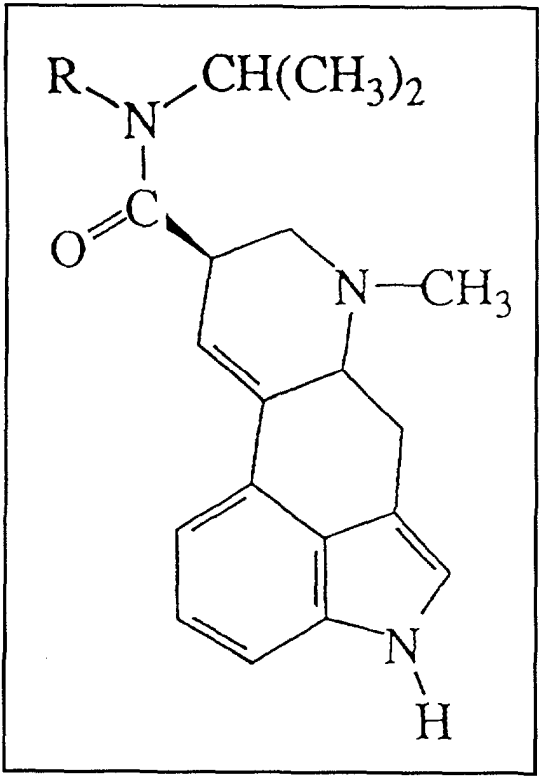

FIGURE 12. *The alkyl-isopropyl amides of lysergic acid*

TABLE 6. *Radioligand binding data for N-methyl-N-isopropyl lysergamides: [^{3}H]-ketanserin displacement (unpublished results)*

Compound	K_i (nM)	Hill Coefficient	N
LSD	4.8±0.5	0.94	3
N-isopropyl	26.2±2.2	0.89	4
N-methyl-*N*-isopropyl	28.1±4.5	0.89	4
N-ethyl-*N*-isopropyl	19.8±2.4	0.94	4
N,N-diisopropyl	20.2±2.4	0.90	3

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