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Conformational Study of Lysergic Acid Derivatives in Relation to their Hallucinogenic and Antiserotonin Activities

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Conformational analysis of five lysergates in six different solvents has been carried out by an empirical method. The energy maps are developed for all molecules in all solvents. Further, the receptor site conformations are identified for both hallucinogenic and antiserotonin activities. It appears that all the molecules do not act on the same site. Effect of solvent is examined by comparing the solvated conformation with that of vacuum and it can be concluded that this effect definitely exists, but depends on both solute and solvent. Various properties such as free energy, entropy, percent population, dipole moment, translational and rotational diffusion coefficients, and relaxation time are obtained for receptor site conformations and correlated with the observed activities. It is concluded that the mode of action in eliciting the hallucinogenic response is different from that of antiserotonin response.

INTRODUCTION

The ergot alkaloids have always been a fascinating class of drug molecules due to their diversified effects and unusual structure activity relationships. There have been numerous investigations regarding the pharmacological actions of LSD (d-lysergic acid diethylamide) and other similar compounds. Among all the pharmacological actions, the hallucinogenic (H) action has drawn most of the attention (Sankar 1975). The main interest lies in understanding the mechanism of hallucinogenic and/or antiserotonin (S) actions in terms of molecular structure under existing physiological conditions. Earlier molecular orbital studies (Karreman et al. 1959; Snyder and Merrill 1965; Kang and Green 1970) have indicated a charge transfer reaction for the hallucinogenic activity of LSD (being a donor) due to high degree of correlation between the activity and the highest occupied molecular orbital energy which was later found to be not true (Johnson et al. 1975; Kumbar and Sankar 1973; Sankar and Kumbar 1974). In recent years, however, attention has been turned to utilize the concept of "structural resemblance" in explaining the activities of various hallucinogens other than LSD. This concept has been examined by

using molecular models (Snyder 1970), x-ray crystallography (Baker et al. 1973), and molecular orbital methods (Kier 1971; Green et al. 1974; Pullman et al. 1974). All these studies, however, have been confined to congeners of LSD, but not to the derivatives of d-lysergic acid.

The quantitative values of hallucinogenic and antiserotonin effects are known for about 20 lysergates (Cerletti and Doepfner 1958). These include mono and disubstituted amides, cycle and 1, 2, and 8 substituted derivatives of LSD. In the present study, only five lysergates (figure 1) have been selected due to their structural differences in side chains which might help to assess the role of the side chain in producing the pharmacological response. Any change in the drug molecule and in the medium in which the molecule exists can dramatically effect the active (receptor site) conformations. Therefore, these molecules are studied in different solvents varying in physiochemical properties to see how the conformational behavior changes from solvent to solvent. In the course of this action, the empirical method in conjunction with reaction field theory (Sinanoglu and Abdulnur 1965) has been used. Within the framework of reaction field theory, an approach to solvation effect involves the computation of the interaction energy of solute with its surrounding, making use of a continuum model for solvent. However, considerable doubt exists (Linder 1967) about the applicability of this continuum model, because of its treatment of the solvent as a uniform medium inside and outside the cavity of the molecule. In reality, the dielectric constant inside and outside of the cavity may be different. Previously (Kumbar 1976), it was pointed out that the effective dielectric constant (inside the cavity) is about one half of the bulk dielectric constant (outside the cavity). With this in mind, a conformational analysis is carried out and properties such as free energy, entropy, percent population, dipole moment, translational and rotational diffusion coefficients, and relaxation times are deduced for active conformations, with the hope of obtaining a quantitative relation between structure and activity.

The translational diffusion coefficient describes how the molecule travels in a given medium, while the rotational diffusion coefficient gives an indication of how the molecule orients itself at the receptor site. When an interaction between the drug molecule and the receptor site begins, the molecule that is present in a random state in a solution near the receptor site must come to an order state (specific orientation) at the receptor site for a proper interaction. Therefore the relaxation time may be defined as the time required for the molecule to relax itself from an ordered state into a random state. In other words, the relaxation time may be considered as the time spent by the drug molecule at the receptor site.

METHOD OF CALCULATION

(a) Conformational energy: The total energy of a molecule for a particular geometry under the influence of a solvent is calculated as

$$E_{total} = E_{solute} + E_{solvation} \quad (1)$$

where E_{solute} is the total energy of a solute molecule in the free space approximation and $E_{solvation}$ is the energy of solute solvent interaction. E_{solute} is computed as the sum of various contributions as given in the following equation:

$$E_{solute}(\phi, \psi, \tau_i) = E_{nonbonded} + E_{torsional} + E_{electrostatic} \quad (2)$$

where ϕ, ψ, and τ_i are the dihedral angles defined in figure 1. The nonbonded interaction energy between the pair of interacting atoms is calculated by means of the Lennard-Jones 6-12 potential function, which is,

$$E_{nonbonded} = \sum_{i,j} d_{ij} r_{ij}^{-12} - e_{ij} r_{ij}^{-6} \quad (3)$$

The first term in this equation represents the repulsive forces and the second term describes the attractive forces. The term r_{ij} is the distance between the ith and the jth interacting atoms, and e_{ij} and d_{ij} are coefficients which have been determined according to the method described previously (Scheraga 1968; Kumbar 1975) The torsional potential energy about C-C single bonds and the C-N single bond is added via the following equation

$$E_{torsional} = (E^{o}_{\phi}/2)(1+\cos 3\phi) + E^{o}_{\psi}/2)(1+\cos 2\psi) + \sum_{i} (E^{o}_{\tau i}/2)(1+\cos 3\tau_i) \quad (4)$$

where E^{o}_{ϕ}, E^{o}_{ψ}, and $E^{o}_{\tau i}$ are the energy barriers which are respectively set equal to 1.0 kcal mole^{-1}, 1.9 kcal mole^{-1}, and 0.58 kcal mole^{-1} (Volkenstein 1963; Flory 1969; Scheraga 1968). In recent years, various crystallographic studies (Cody et al. 1973) and theoretical investigations (Renugopalkrishnan and Rein 1976) have indicated that the peptide bond deviates from its planar structure. Besides, the assumption of the planar structure in d-lysergic acid diethylamide introduces considerable steric interaction between the side chain and the ring portion. In order to understand how the side chain behaves if this constraint is relaxed, and how this effects the orientation of -C=O bond, the peptide bond is treated as a single bond. In addition, the potential barrier is lowered to about one tenth of its true value. Therefore, the results obtained here should be used cautiously, due to hypothetical nature of the present model. The electrostatic energy is evaluated using the formula

$$E_{electrostatic} = 332\, e_i e_j / \varepsilon' r_{ij} \quad (5)$$

where ε' is the effective dielectric constant that is applicable inside the cavity and e_i is the charge on the ith atom, which is the sum of π and σ charges. The π and σ charges are computed respectively by the Hückel method (Pullman and Pullman 1963) and the procedure suggested by Del Re (1958).

$E_{solvation}$ energy is the sum of three contributions, namely,

$$E_{solvation} = E_{es} + E_{dis} + E_{cav} \tag{6}$$

where E_{es} is the electrostatic solute solvent interaction, E_{dis} is the solute solvent interaction energy due to dispersion forces, and E_{cav} is the energy required to create a solvent cavity. The E_{es} is computed by treating the solute as a sphere of radius a with a point dipolar ion of charge q and the total dipole moment μ positioned at the center. The solute sphere is imbedded in a cavity of identical size, making the dielectric constant of the medium inside and outside the cavity different. According to Onsager's reaction field theory (Onsager 1936), the electrostatic energy is given by

$$E_{es} = -(\mu^2 L\, \bar{a}^3)(1 - \bar{\alpha}\, \bar{a}^3/L)^{-1} \tag{7}$$

$$\text{with } L = 2(\varepsilon-1)/(2\varepsilon+1) \tag{8}$$

where ε is the bulk dielectric constant of the solvent outside the cavity and $\bar{\alpha}$ is the average polarizability of the medium, which is $\bar{\alpha} = 1/3\ (\alpha_{\parallel} + 2\alpha_{\perp})$. The solute-solvent interaction energy due to dispersion forces is

$$E_{dis} = \frac{4\pi\rho}{2} \int_0^{\infty} V_{AB}^{eff}(r)\, g^2(r)\, r^2 dr \tag{9}$$

where ρ is the number density of the solvent, $g^{(2)}(r)$ is the radial distribution function for solvent molecule about a central solute, which is taken as zero for $r<a$ and unity for $r \geq a$. The effective pair potential between a solute A and a solvent B at a separation r is

$$V_{AB}^{eff} = V_{AB}(r)\, B'_{AB}(r) \tag{10}$$

where $V_{AB}(r)$ and $B'_{AB}(r)$ are pairwise interaction potentials for a molecule in a gas phase and a liquid phase correction factor (Sinanoglu 1967) respectively. The $V_{AB}(r)$ is taken in the form of a Kihara potential (Kihara 1953), assuming each molecule as a spherical core of diameter 1. This potential function is

$$V_{AB} = C_{AB}\, (\sigma_{AB}^{6}\ P_{AB}^{-12} - P_{AB}^{-6}) \tag{11}$$

In the above equation, C_{AB} is the London dispersion coefficient, P_{AB} is the intercore distance, and σ_{AB} is the collision diameter.

The intercore distance is given by

$$P_{AB} = r_{AB} - l_{AB} \tag{12}$$

with $l_{AB} = \frac{1}{2}(l_A + l_B)$

and $\sigma_{AB} = \frac{1}{2}(\sigma_A + \sigma_B)$

These core size parameters are evaluated from the semiempirical relations

$$l_A = a\,\beta^{-1}(3.24 + 7\omega_A)^{-1} \tag{15}$$

$$\sigma_A = 2^{-1/6} a\,\beta^{-1}\,(2.24 + 7\omega_A)(3.24 + 7\omega_A)^{-1} \tag{16}$$

where ω_A is Pitzer's "accentric factor" (Dannon and Pitzer 1962), $\beta \approx 1.15$, and a is an effective solute cavity radius which is taken as (Amos and Burrows 1973)

$$a^3 = r'^3_A\,(1+r')^4\,(\pi r')^{-1};\ r' = r'_A/r'_B \tag{17}$$

The r'_A is generated from the radius of gyration for a particular conformation and r'_B is determined from the critical densities of solvents. The liquid phase correction factor for the gas phase potential in equation (10) (Sinanoglu 1967) is

$$B'_{AB} = 1 - \frac{1}{2}\,\frac{\Delta'_{AB}\,D'_B\,L'_{AB}}{1 - \{\sigma_{AB}/(r - l_{AB})\}^6} \tag{18}$$

where Δ'_{AB} is a function of ionization energies I_A and I_B, as shown in the following equations:

$$\Delta'_{AB} = (I_A + 2I_B)/\{2(I_A + I_B)\} \tag{19}$$

and $D'_B = D_B/(1 + D_B)$ (20)

with $D_B = (n_B^2 - 1)/(n_B^2 + 2)$ (21)

where n_B is the refractive index of the solvent. The London dispersion coefficient C_{AB} is set equal to

$$C_{AB} = (3/2)(1.35)\,\bar{\alpha}_A\bar{\alpha}_B\,I_A I_B/(I_A + I_B) \tag{22}$$

Finally, the energy required to create a solvent cavity to accomodate a spherical solute of volume v is expressed as

$$E_{cav} = M\,v_A^{2/3}\,(1 + N\,v_A^{-2/3}) \tag{23}$$

with $M = 6.96 \times 10^{-3} \gamma_B \left(1 - \frac{\partial \ell n \gamma_B}{\partial \ell n T} - \frac{2T}{3}\right)$ (24)

and $N = v_B^{2/3}(\kappa_B(1)-1)$ (25)

where κ_B is the constant dependent of the volume fraction, v_B/v_A, T is the thermal expansion of the solvent, γ_B is the surface tension of the solvent, and T is the absolute temperature of the system which is set equal to 310°, a physiological temperature.

(b) Conformational properties: The Helmholtz free energy is calculated by

$$A = E-TS \tag{26}$$

where E is the conformational energy in a particular solvent, and S is the entropy, which is computed by the following set of equations:

$$S = R \ln z + \langle E \rangle / T \tag{27}$$

$$\langle E \rangle = z^{-1} \Sigma_i E_i \exp(-E_i/RT) \tag{28}$$

$$\text{and } z = \Sigma \exp(-E_i/RT) \tag{29}$$

The dipole moment, on the other hand, is predicted by using the equation, $\mu = \Sigma q_i r_i$, where q_i is the charge on the ith atom and r_i is the distance of the ith atom from the origin of the chosen reference coordinate system. The translation and rotational diffusion coefficients are obtained from the well known equations applicable to spherical molecules in an unbounded fluid of viscosity η. These equations are

$$D_t = kT/6\pi\eta r \qquad \text{and} \qquad D_r = kT/8\pi\eta r \tag{30}$$

Here, k is the Boltzmann constant. Further, the rotational diffusion coefficient is related to the relaxation time (τ) through the equation, $\tau = 1/2\, D_r$. The percent population of the nth minimum is estimated according to the equation:

$$Pn = \Sigma_i \exp(-E_i^n/RT) / \frac{\Sigma\Sigma}{ni} \exp(-E_i^n/RT) \tag{31}$$

where E_i^n is the energy of the ith conformation in the vicinity of the nth minimum. The most probable properties associated with a given energy valley are determined by

$$\langle p \rangle = z^{-1} \Sigma P_i \exp(-E_i/RT) \tag{32}$$

In addition, the most probable properties averaged over various solvents are computed through the following equation:

$$\langle\langle p \rangle\rangle = z'^{-1} \Sigma \Sigma P_i \exp(-E_i/RT) \tag{33}$$

with $z' = \Sigma \Sigma \exp(-E_i/RT)$. (34)

RESULTS AND DISCUSSION

Energy maps were obtained for all five molecules (figure 1) in six different solvents: heptane, carbon tetrachloride, aniline, ethanol, methanol, and water which have a wide range of dielectric constants. The LSD molecule has a bulky side chain with six degrees of freedom. It is difficult (see figure 1) to rotate all six dihedral angles simultaneously, due to computer time. Hence, a different approach was taken. Firstly, the angles τ_3 and τ_4 in all the molecules were fixed at 60° in a staggered position with the preceding group (minimum interactions). Secondly, the angles τ_1 and τ_2 were rotated in 10° interval to determine the most stable values by considering only the interactions in the side chain. The energy maps produced as a result of rotations of τ_1 and τ_2 contained two minima centered around $\tau_1 = \tau_2 = 90^\circ$, and $\tau_1 = 70^\circ$ and $\tau_2 = 250^\circ$. The minimum energy conformations may not represent the energy valley in which they exist. Therefore, most probable conformations were determined as indicated in equation (32). It happened that the most probable values did not deviate considerably from their respective minimum values. So these values were used in further computations in LSD and dimethylamide. The same strategy was also adopted for ethylamide and found that τ_2 had three different most probable values, namely 60°, 90°, and 180°. Similarly, the most probable value of τ_2 in methylamide was determined to be 180°. Using these values, the rotations around ϕ and ψ were carried out in 10° increment in various solvents mentioned above. The most probable conformations for each molecule in all six solvents are shown in figures 2(a) to 2(e).

Effect of solvation

In order to understand the influence of the solvent medium or to gain some information about the conformational behavior in presence of external forces (solvent medium), the vacuum (gaseous phase) conformations were also generated by setting $\varepsilon' = 1.0$ in E_{solute} equation (2). The most probable conformations are also indicated in figures 2(a) to 2(e). These vacuum conformations may be considered as the most 'ideal situation' conformations (ideal conformations). Some of the properties of ideal and solvated conformations are compared in figure 3. It is apparent that the solvated conformation is quite different from an ideal conformation. The degree of influence of the solvent medium depends on the nature of the solute as well as the nature of the solvent. In all cases, the conformational energies of ideal conformations are lower than the corresponding solvated conformations. The conformational entropy decreases when molecule is solvated, due to a loss of conformational freedom. A further decrease in entropy is observed when the dielectric constant of the medium is increased. The dipole moment is higher when the molecule is solvated except for dimethylamide, where it is lower. This property

slightly varies as the dielectric constant of the medium changes. The volumes of all the molecules except dimethylamide are smaller in a given solvent and also to some extent depend on the dielectric constant of the medium. Therefore, it is clear that the solvent definitely influences the conformational behavior of the solute, depending upon the nature of the solute as well as that of the solvent.

Solvated conformations

For a given molecule, number of minima appearing in energy maps depends on the nature of the solvent. As the dielectric constant of the medium increases, some of the minima disappear due to an increased interaction between the solute and the solvent that favors certain conformational regions. As a result, the conformational entropy decreases. Even though the most probable values of the dihedral angles ϕ and ψ have altered to some extent from solvent to solvent, they have grouped together into a small region as shown by the circles in figures 2(a) to 2(e). This behavior is observed in spite of the fact that τ_1 and τ_2 have been set at different values. This might be an indication that these subsidiary angles have less influence on the main two dihedral angles, ϕ and ψ. On the whole, the LSD has eight conformational regions, dimethylamide has four, ethylamide has four, methylamide has two, and an amide has four. In reality, the LSD should have only 4 conformational regions, the dimethylamide should have only 2, and the amide should have only 2 due to the symmetry nature of the side chain over the dihedral angle ψ. The asymmetry over the angle ψ is due to fixing of τ_1 and τ_2 at certain values when ϕ and ψ were rotated.

Free energy, entropy, dipole moment, percent population, translational and rotational diffusion coefficients, and relaxation times are important aspects of drug receptor interactions. All these properties truly depend on the nature of the solvent medium. Some of these properties of each molecule as a whole, without differentiating various minima, are considered in figure 3. It is obvious that these properties are functions of the nature of the medium and the molecule. For a given property, all molecules except dimethylamide have behavior similar to the dielectric constant of the medium increases. These changes in properties point out that the solvent medium that exists around the receptor site(s) may play an important role. The effect of the solvent depends on the nature of the energy valley. If the valley is deeper, for example, IV(VIII) in LSD, the effect is smaller. On the other hand, if the valley is shallow like I or III or IV in ethylamide, the effect is greater. The shallowness, however, is dictated by the conformational flexibility. It means that a molecule with a considerable flexibility might experience a greater effect of the solvent.

Receptor site conformations

Among the five molecules studied here, the LSD is highly

potent in terms of hallucinogenic and antiserotonin activities. The magnitudes of these activities are also shown in figure 1. The differences in the activities of these molecules may be attributed to differences in behaviors of side chains. The structural differences, together with differences in various physiochemical factors, might account for the variability of their activities. Therefore, it is essential to identify those conformations which are believed to be present at the receptor site(s). This is, of course, a difficult task. To get around this problem, the following approach is taken. Since the LSD possesses the maximum activities (H=100 and S=100), it is assumed that all four conformations (figure 2(a)) are involved in producing these activities. However, it is difficult to assess their degree of contribution towards the total activity. When a drug molecule binds to the receptor site, the molecular conformation might be complementary to the receptor site(s). On this basis, it is assumed that the LSD binds to four different sites corresponding to four sterically different conformations labelled as I to VIII in figure 2(a). Region III(VII) appears only in high dielectric constant medium as a result of disappearance of region II(VI). It means that there are only three sites in low dielectric medium and three in high dielectric medium. If there is a continuous fluctuation in dielectric constant, or if the receptor site region exists in an inhomogeneous medium, then all four sites might be activated simultaneously as shown below:

site	I(V)	II(VI)	III(VII)	IV(VIII)
low ε	O	O		O
high ε	O		O	O
fluctuation in ε	O	O	O	O

In order to obtain the receptor site conformations for other molecules, the conformational regions of each molecule are compared with those of the LSD in figures 4(a) to 4(d). It is clear that some of the regions lie close to those of the LSD. Thus it appears that there exists a conformational resemblance between LSD and other molecules. Therefore, it is conceivable to assume that these molecules elicit their pharmacological response by resembling the conformations of LSD. However, in methylamide the resemblance is found only for regions II and IV, and in amide only for I and IV. In addition, all molecules do not act on the same site (table I). To have some kind of overall representation of each region shown in figure 2(a) to 2(e), a further averaging over all solvents is carried out and resulting dihedral angles, together with various properties, are tabulated in table II. These overall conformations are presented in figures 5(a) to 5(e).

A close look at the LSD molecule reveals that it contains various centers for interactions as schematically shown in figure 6. Various intracenter distances for all the overall conformations are listed in table III. These distances might be complementary

to the interacting centers existing in receptor site(s). Since the ring portion of the LSD is common to all molecules, the interactions in this portion are retained in all molecules. Therefore, the variation in antiserotonin and hallucinogenic activities might be explained in terms of the variability that exists in side chain interactions such as the hydrogen bonding, hydrophobicity, free energy, etc. The hydrophobicities for these molecules have been calculated by Dunn and Bederka (1974) which are 2.16, 1.16, 1.16, 0.66 and 0.16 respectively for LSD, dimethylamide, ethylamide, methylamide, and amide. This property decreases as the activities decrease. In addition to hydrophobicity, other factors might also influence the drug receptor interaction. We have looked into the possibility of hydrogen bonding by the carbonyl oxygen of the side chain and the receptor site. Since the LSD molecule has the maximum activities among the molecules considered here, it is assumed that the oxygen atom in all the receptor site conformations (I ... IV, table II) of LSD is situated in an optimum position. The deviations of this atom from the optimum positions (measured in terms of the angle, θ, figure 6) for only receptor site conformations (shown in figures 4(a) to 4(e)) are also tabulated in table III. This angle increases as activities decrease, suggesting that the strength of hydrogen bonding is also an important factor. This strength decreases as activities decrease. Further, it is possible to distinguish the conformations responsible for hallucinogenic and antiserotonin activities using the angle θ. The antiserotonin activity is always higher than the hallucinogenic activity for a given molecule, which might be due to a close congruity between the molecule and the receptor site(s). It means that a stronger hydrogen bonding is necessary for antiserotonin activity compared to hallucinogenic activity. Thus, the conformations with smaller θ values might be responsible for antiserotonin activity while larger θ for the hallucinogenic activity. This distinction is noted in table III by the letters S and H. This is further supported by a good correlation obtained between the θ and the differences in activities (table IV).

In order to investigate the role of other properties in drug receptor interaction, a correlation is also carried out between these properties and the activities. From the correlation coefficients, few conclusions may be drawn. Entropy and percent population do not seem to play any role. On the contrary, the free energy, rotational diffusion (relaxation times), hydrophobicity, and the strength of the hydrogen bonding appear to be an important determinants. The dipole moment and translational diffusion coefficients to some degree are also important factors only in hallucinogenic activity. The amide has no hallucinogenic activity. Therefore, we assume that the conformations falling in region II(IV) are responsible (figure 2(e)) for this activity. Hence, the properties of this region are used in correlating the hallucinogenic activity. From the correlation coefficients, one can see that even among the correlated properties, the degree of correlation is not the same for both activities. Besides, the dipole moment is better correlated in hallucinogenic activity. Therefore, it is concluded that the mode of action in eliciting the hallucinogenic action is quite different from that of antiserotonin activity.

TABLE I

Receptor site conformations.
The Roman numerals indicate the conformational regions shown in figures 2(a) to 2(e) and 4(a) to 4(d)

Molecule	LSD Sites			
	I(V)	II(VI)	III(VII)	IV(VIII)
d-lysergic acid dimethylamide				II(IV)
d-lysergic acid ethylamide	I	III	II	IV
d-lysergic acid methylamide			I	II
d-lysergic acid amide		I(III)		II(IV)

TABLE II

Over all conformations (averaged over all solvents) with their various properties

Site	$\langle\langle\phi\rangle\rangle$ deg	$\langle\langle\psi\rangle\rangle$ deg	$\langle\langle A\rangle\rangle$ kcal mole^{-1}	$\langle S\rangle$ cal deg^{-1} mole	$\langle\langle v\rangle\rangle$ A^{o3}	$\langle\langle\mu\rangle\rangle$ D	%P	$\langle\langle D_t\rangle\rangle \times 10^5$ cm^2 sec^{-1}	$\langle\langle D_r\rangle\rangle \times 10^{-9}$ sec^{-1}	$\langle\langle\tau\rangle\rangle \times 10^{11}$ sec
					LSD					
I	140	82	-11.651	4.922	292	9.450	66	1.421	6.287	8.009
II	201	94	-10.627	4.635	263	9.062	13	1.459	6.927	7.348
III	257	60	-6.446	2.808	233	10.460	1	1.004	5.165	10.200
IV	333	86	-8.270	2.393	252	9.316	1	1.448	7.076	7.379
V	127	260	-9.078	6.193	315	5.669	1	1.389	5.847	8.584
VI	201	274	-10.627	4.635	263	9.062	13	1.459	6.927	7.348
VII	268	257	-9.852	4.832	258	11.938	4	1.043	5.013	10.009
VIII	333	266	-8.270	2.393	252	9.316	1	1.448	7.076	7.379
					dimethylamide					
I	62	85	-17.739	8.235	263	5.554	35	1.479	7.021	7.125
II	326	99	-17.300	6.198	220	12.606	17	1.570	8.395	5.957
III	60	265	-17.735	8.051	262	5.678	35	1.481	7.046	7.100
IV	330	281	-17.151	5.876	222	12.335	13	1.565	8.320	6.012
					ethylamide					
I	149	81	-39.379	6.340	256	5.850	2	1.494	7.237	6.923
II	259	77	-41.295	6.327	213	7.822	31	1.587	8.669	5.769
III	182	279	-41.314	5.998	243	8.854	37	1.519	7.602	6.585
IV	317	273	-41.082	5.576	208	7.398	30	1.600	8.896	5.629

Table II. Continued

						methylamide				
I	275	87	-47.262	7.019	196	13.714	32	1.632	9.424	5.306
II	307	275	-47.733	6.917	193	14.027	68	1.640	9.570	5.225
						amide				
I	170	94	-45.651	9.507	190	7.102	39	1.649	9.722	5.143
II	289	91	-44.839	8.930	181	8.220	11	1.675	10.205	4.900
III	170	274	-45.051	9.507	190	7.102	39	1.049	9.722	5.143
IV	289	271	-44.839	8.930	181	8.220	11	1.675	10.205	4.900

TABLE III

Various intracenter distances and the angle θ (see Fig. 6) for various sites.

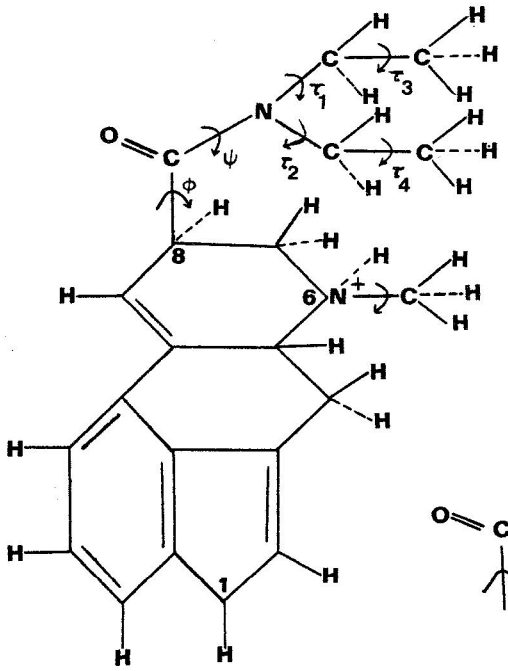
Site	b A^{o}	c A^{o}	d A^{o}	θ deg	Site	b A^{o}	c A^{o}	d A^{o}	θ deg
			LSD					ethylamide	
I	4.215	3.145	5.681		I	4.193	2.813	5.487	8(S)
II	4.236	3.173	5.580		II	4.531	2.789	4.785	5(S)
III	4.519	2.985	4.618		III	4.187	2.812	5.505	16(H)
IV	4.830	3.174	4.663		IV	4.798	2.846	4.563	14(H)
V	4.259	3.130	5.587						
VI	4.236	3.174	5.580					methylamide	
VII	4.583	3.107	4.700						
VIII	4.830	3.174	4.663		I	4.621	2.846	4.670	16(S)
					II	4.766	2.834	4.599	22(H)
		dimethyl						amide	
I	4.605	3.158	4.925		I	4.176	2.840	5.502	27(S)
II	4.818	3.136	4.834	6(H)	II	4.692	2.858	4.614	38(H)
III	4.616	3.165	4.912		III	4.176	2.840	5.502	27(S)
IV	4.826	3.121	4.751	3(S)	IV	4.692	2.858	4.614	38(H)

TABLE IV

Summary of the properties of the receptor site conformations for both activities along with correlation coefficients

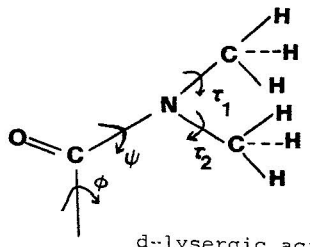
Molecule	ΔA kcal mole^{-1}	ΔS kcal mole^{-1} deg	$\|\Delta\mu\|$ D	$\|\Delta D_t\| \times 10^5$ cm^2 sec^{-1}	$\|\Delta D_r\| \times 10^{-9}$ sec^{-1}	Δ Hydrophobicity	$\|\Delta\%P\|$	θ deg	Δ Activity
				antiserotonin activity					
dimethylamide	8.881	-3.483	3.019	0.119	1.244	1.0	12.67	3	76.80
ethylamide	27.728	-1.418	3.600	0.073	0.950	1.0	66.74	8	88.10
	34.849	-3.519	2.638	0.583	3.504	1.0	30.98	5	88.10
methylamide	40.816	-4.20	3.254	0.628	4.259	1.50	31.98	16	93.70
amide	35.024	-4.872	1.960	0.190	2.795	2.0	26.10	27	95.70
corr. coeff.	0.93	-0.38	-0.35	0.38	0.62	0.75	0.29	0.82	
				hallucinogenic activity					
dimethylamide	9.03	-3.805	3.29	0.122	1.319	1.0	16.68	6	90
ethylamide	30.687	-1.363	0.208	0.06	0.675	1.0	24.10	16	96
	32.862	-3.189	1.918	0.152	1.820	1.0	29.67	14	96
amide	36.569	-6.537	1.098	0.227	3.129	2.0	10.0	38	100
corr. coeff.	0.96	-0.41	-0.75	0.53	0.63	0.73	-0.19	0.90	

FIGURE 1



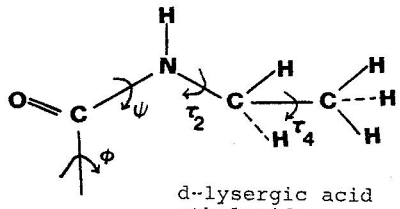
d-lysergic acid diethylamide

H=100 S=100



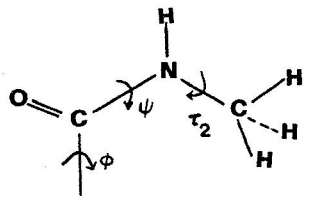
d-lysergic acid dimethylamide

H=10 S=23.2



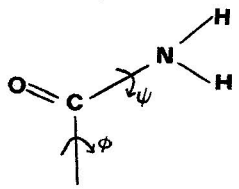
d-lysergic acid ethylamide

H=3.4,5 S=12



d-lysergic acid methylamide

H= - S=6.3



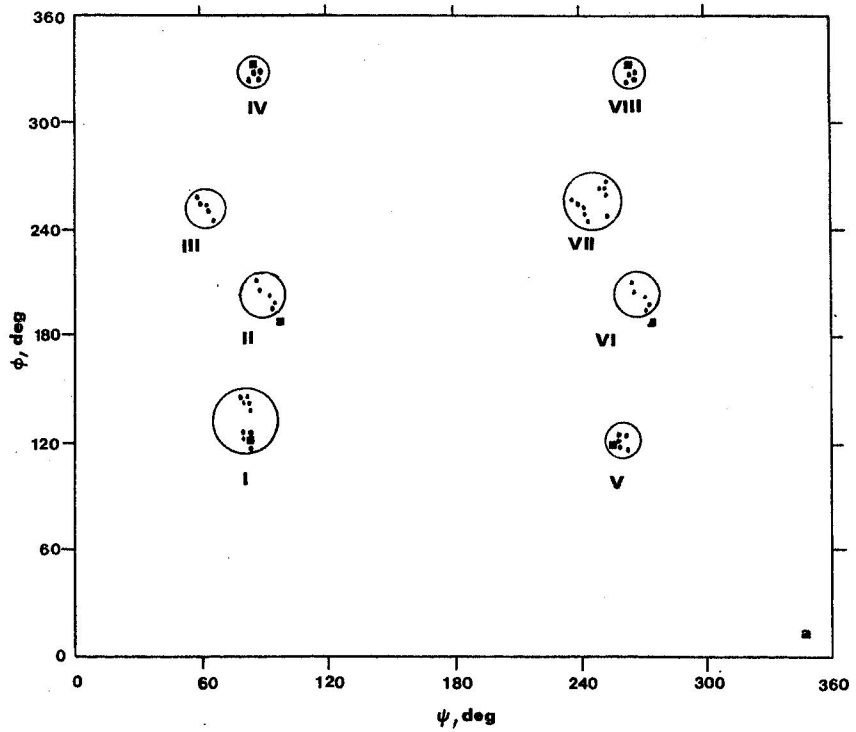
d-lysergic acid amide

H= 0 S=4.3

Definition of dihedral angles. ϕ=0 when C_7-C_8 bond is in planar cis position with C-N bond, ψ=0 when C_8-C bond is in planar cis position with N-C bond. $\tau_1(\tau_2)$ =0 when C-N bond is in planar cis position with C-C bond, $\tau_3(\tau_4)$=0 when N-C bond is in planar cis position with C-H bond. The calculations were performed for $\tau_3 = \tau_4 = \omega = 60^0$. The magnitude of the hallucinogenic (H) and antiserotonin (S) activities is also indicated.

FIGURE 2

(a) d-lysergic acid diethylamide (•)



The most probable conformations in all six solvents. Each minimum is identified by Roman numeral. The vacuum conformation is shown by: ■ (a) d-lysergic acid diethylamide, (b) d-lysergic acid dimethylamide (c) d-lysergic acid ethylamide, (d) d-lysergic acid methylamide, and (e) d-lysergic acid amide.

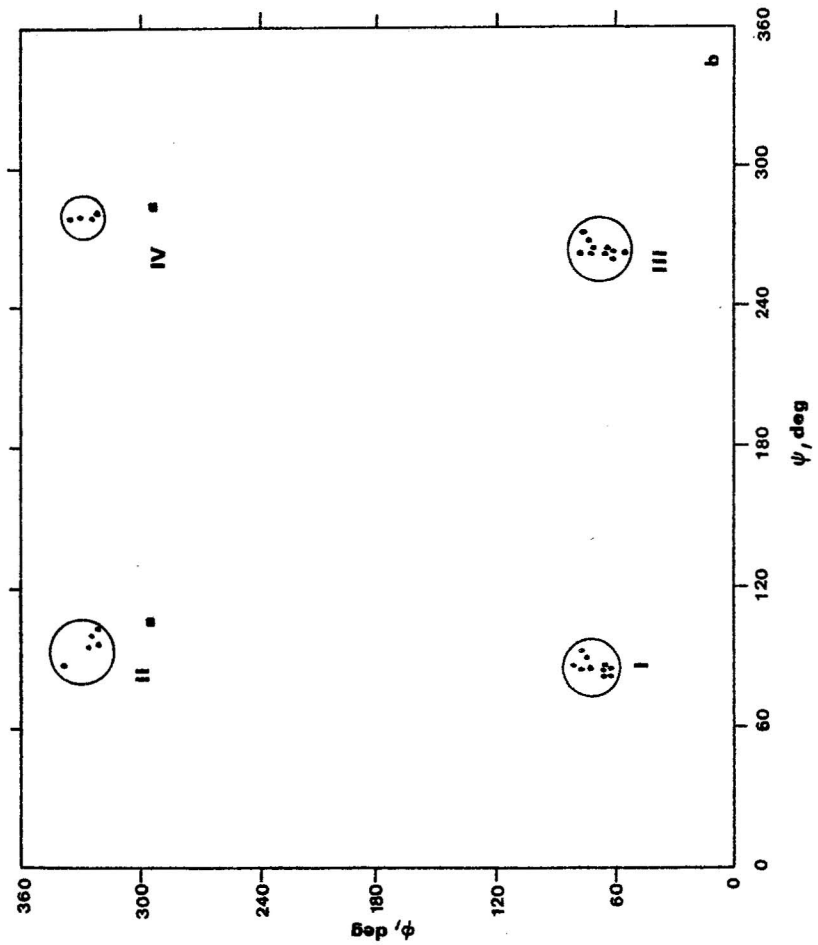


FIGURE 2
(b) d-lysergic acid dimethylamide (•)

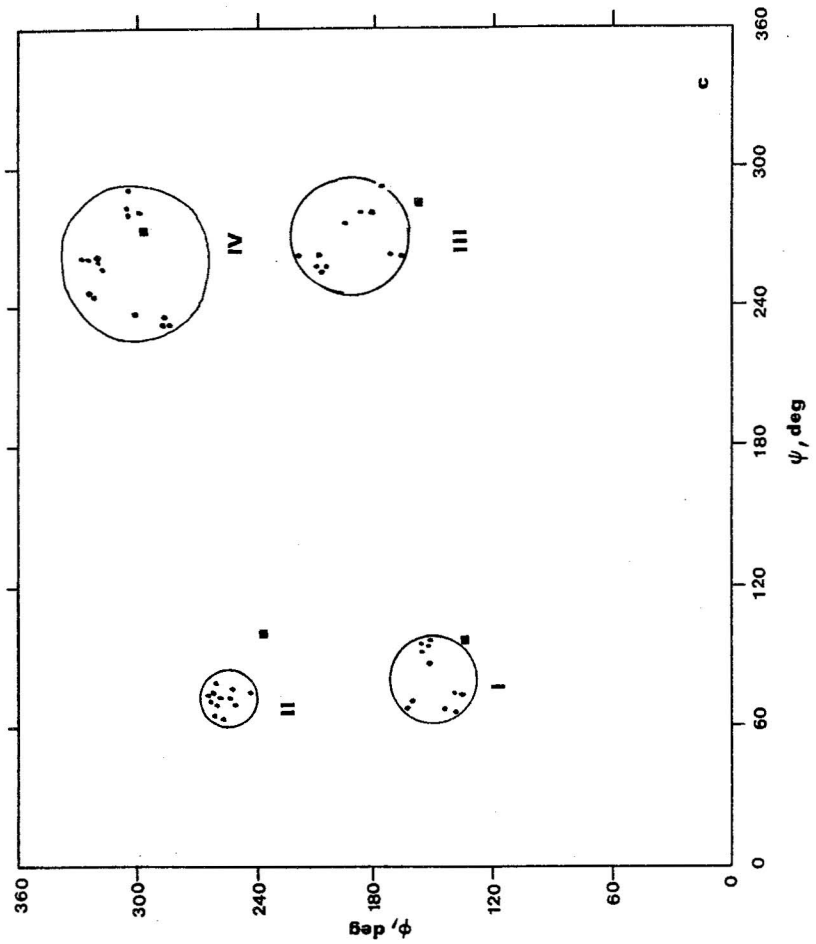


FIGURE 2
(c) d-lysergic acid ethylamide (•)

FIGURE 2
(d) d-lysergic acid methylamide (•)

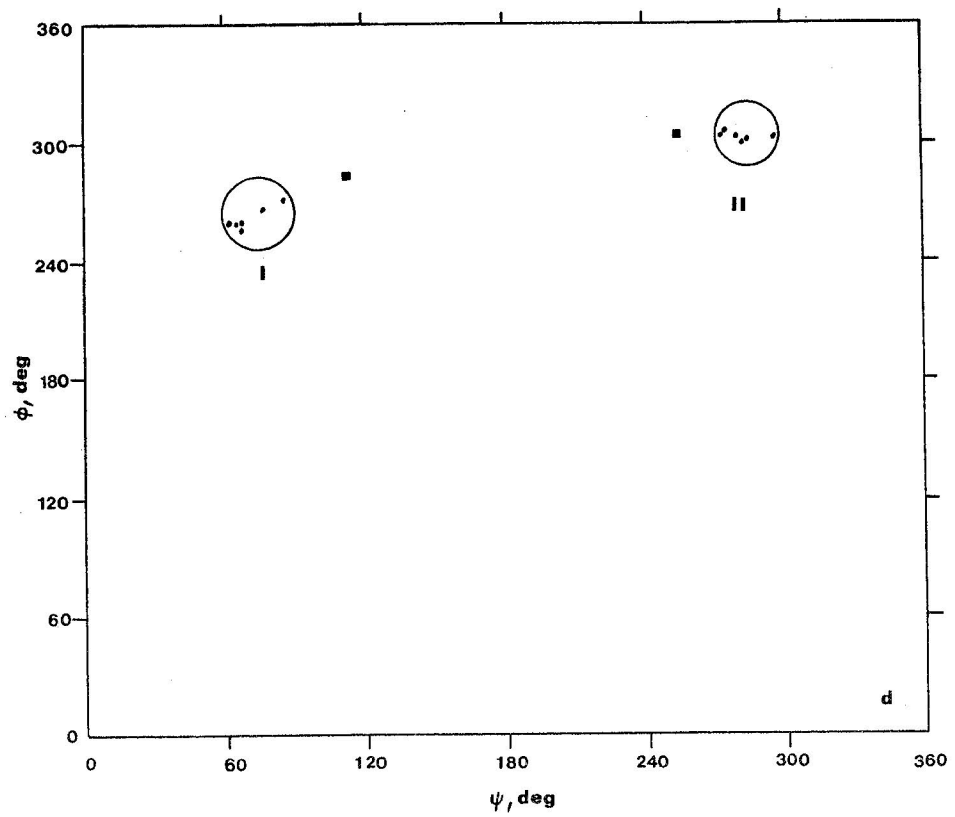


FIGURE 2
(e) d-lysergic acid amide (•)

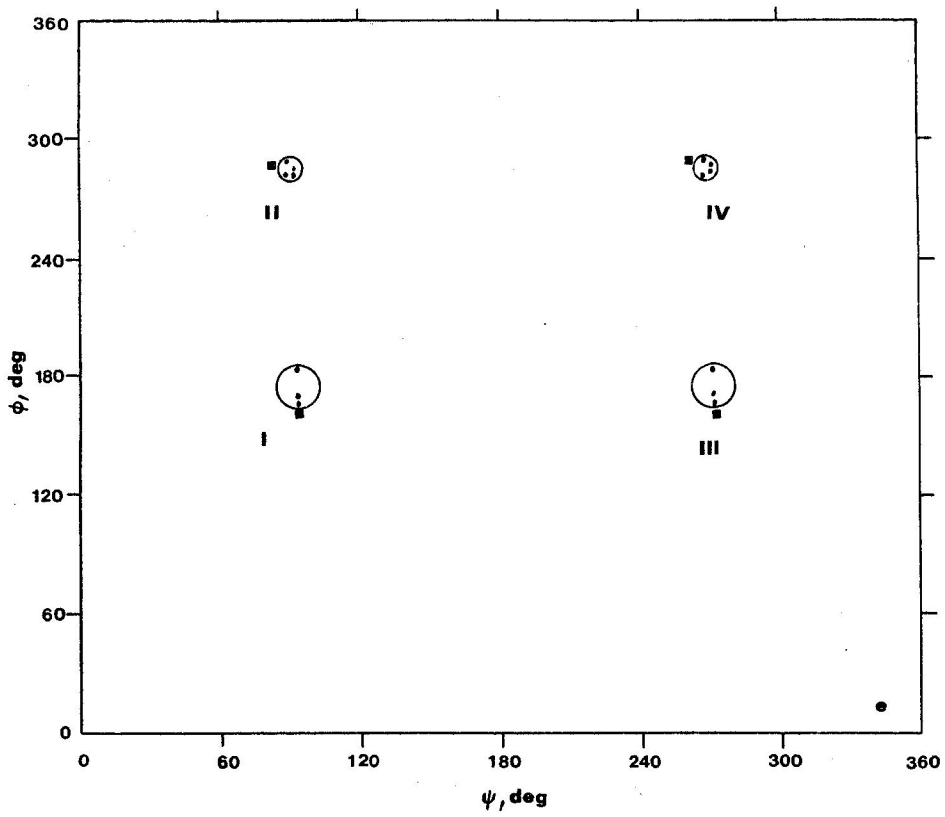
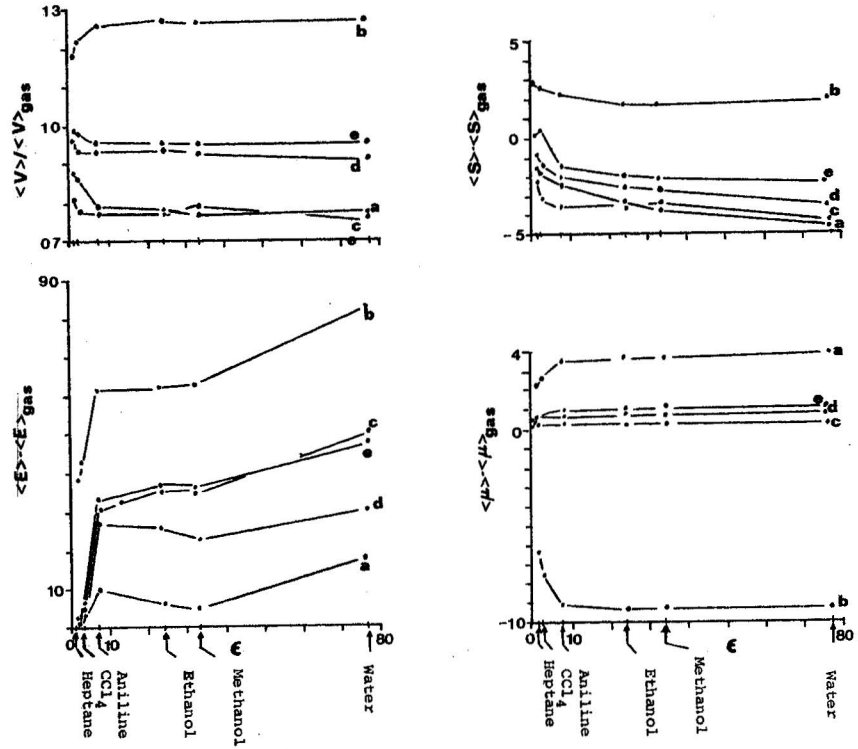


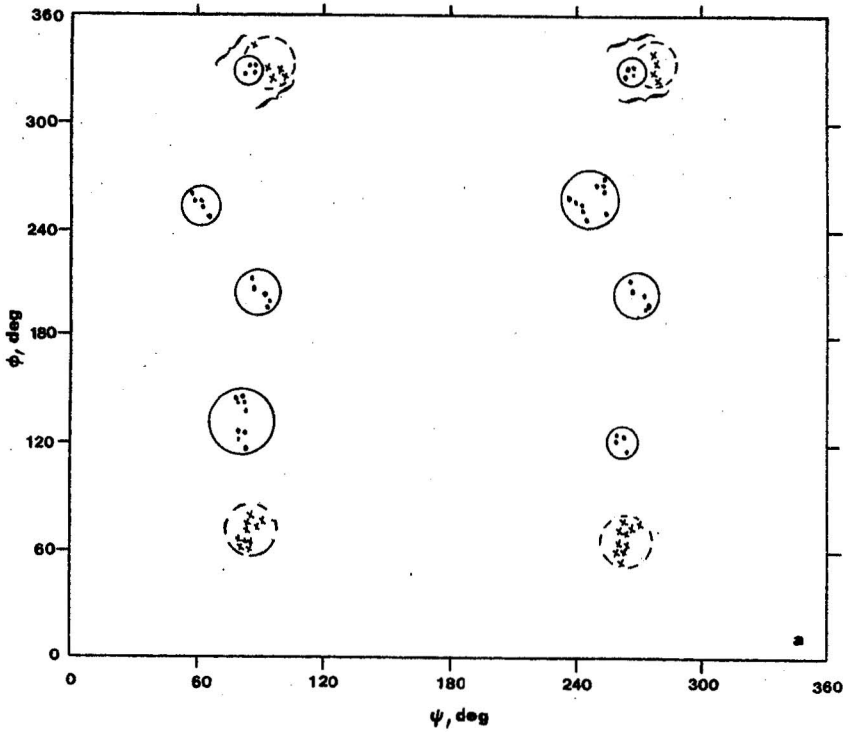
FIGURE 3



Comparison of various properties in various solvents relative to the vacuum conformations: (a) LSD, (b) dimethylamide, (c) ethylamide, (d) methylamide, and (e) amide.

FIGURE 4

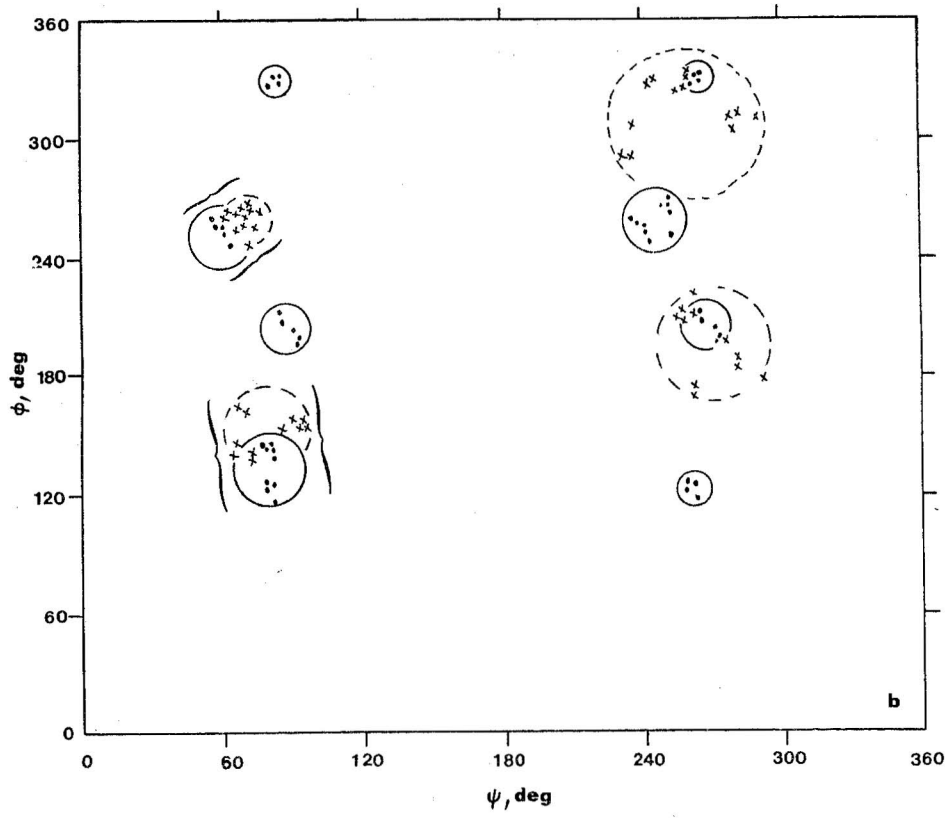
(a) LSD (•) and dimethylamide (x)



Comparison of various most probable conformational regions of a given molecule with those of LSD. •- LSD and x - a given molecule: (a) LSD and dimethylamide, (b) LSD and ethylamide, (c) LSD and methylamide, and (d) LSD and amide.

FIGURE 4

(b) LSD (•) and ethylamide (x)



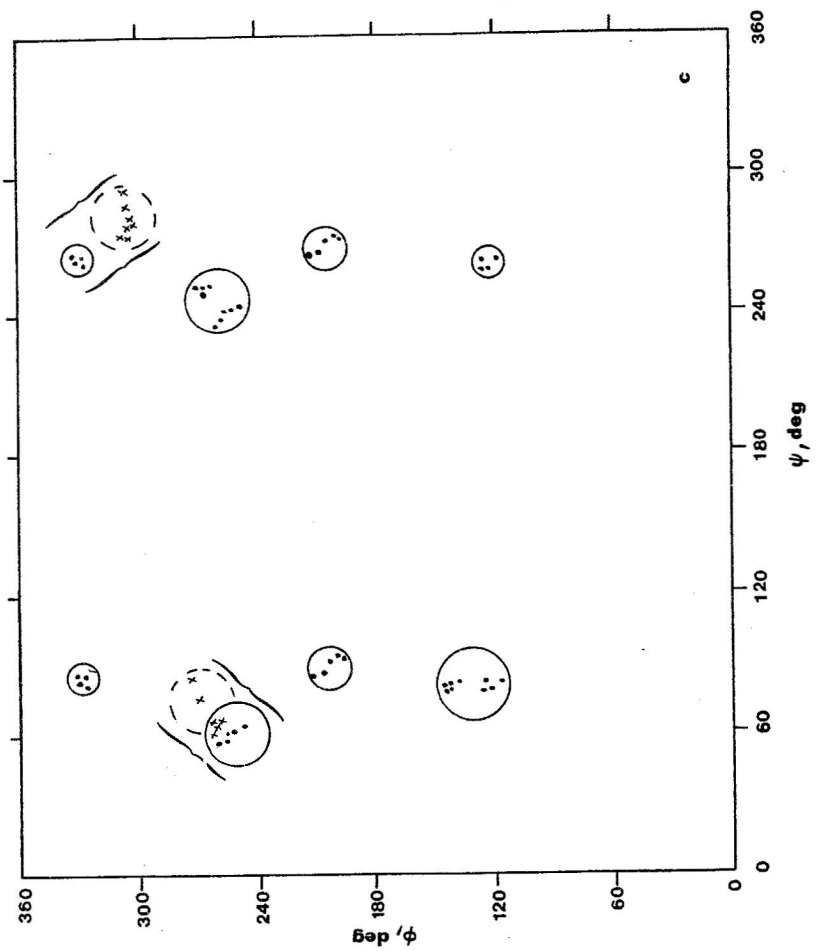


FIGURE 4
(c) LSD (•) and methylamide (x)

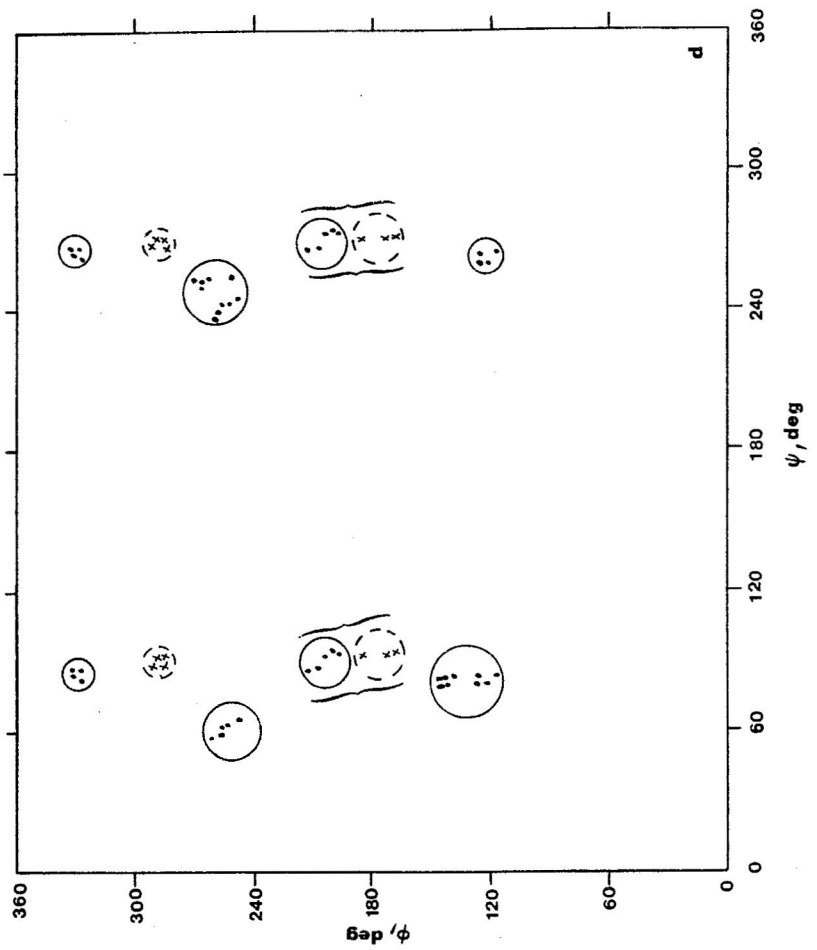
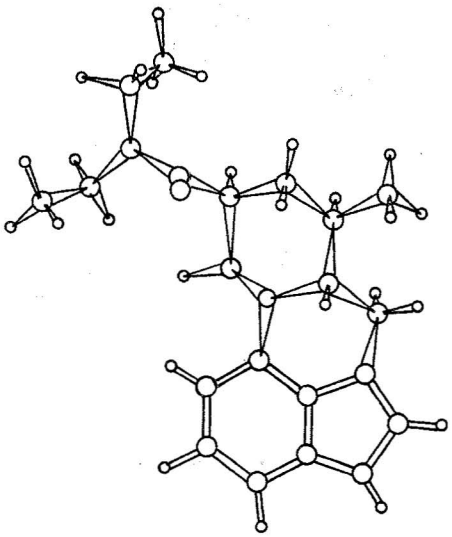


FIGURE 4
(d) LSD (•) and amide (x)

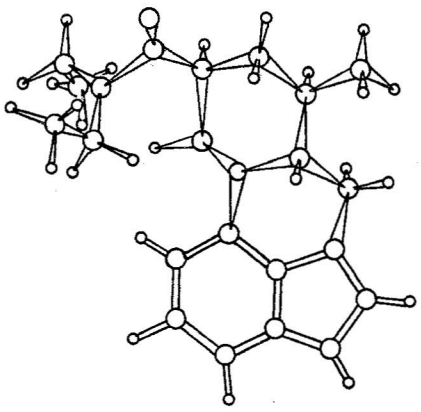
FIGURE 5

Over all conformations (see text and also table III) of molecules studied here. The conformation(s) responsible for each activity (both activities) is (are) indicated by S and/or H: (a) LSD, (b) dimethylamide, (c) ethylamide, (d) methylamide, and (e) amide.

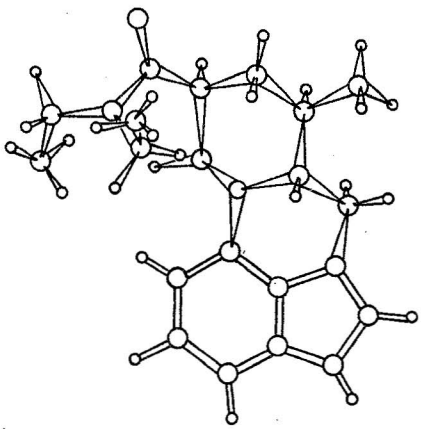
(a) LSD



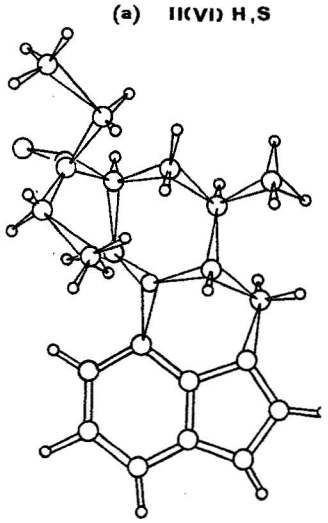
(a) I(V) S



(a) II(VI) H,S

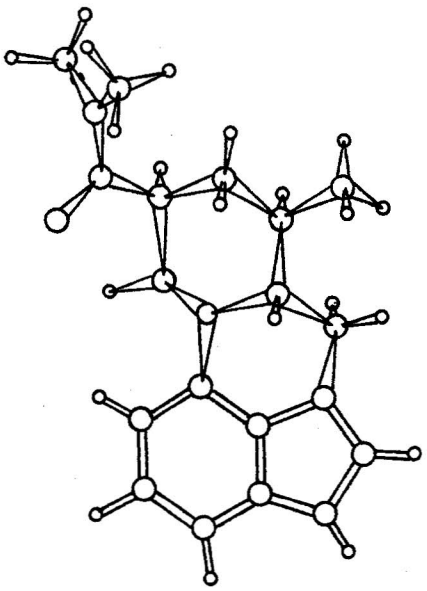


(a) III(VII) S

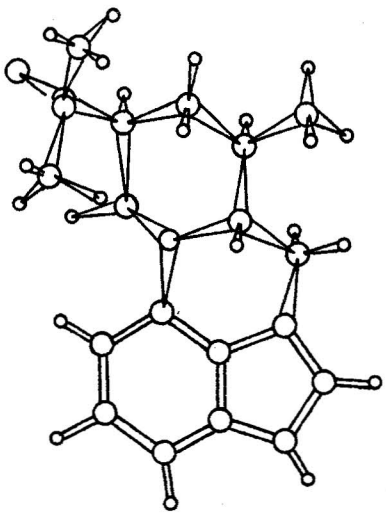


(a) IV(VIII) H,S

FIGURE 5
(b) dimethylamide



(b) K(III)



(b) K(IV) H,S

FIGURE 5
(c) ethylamide

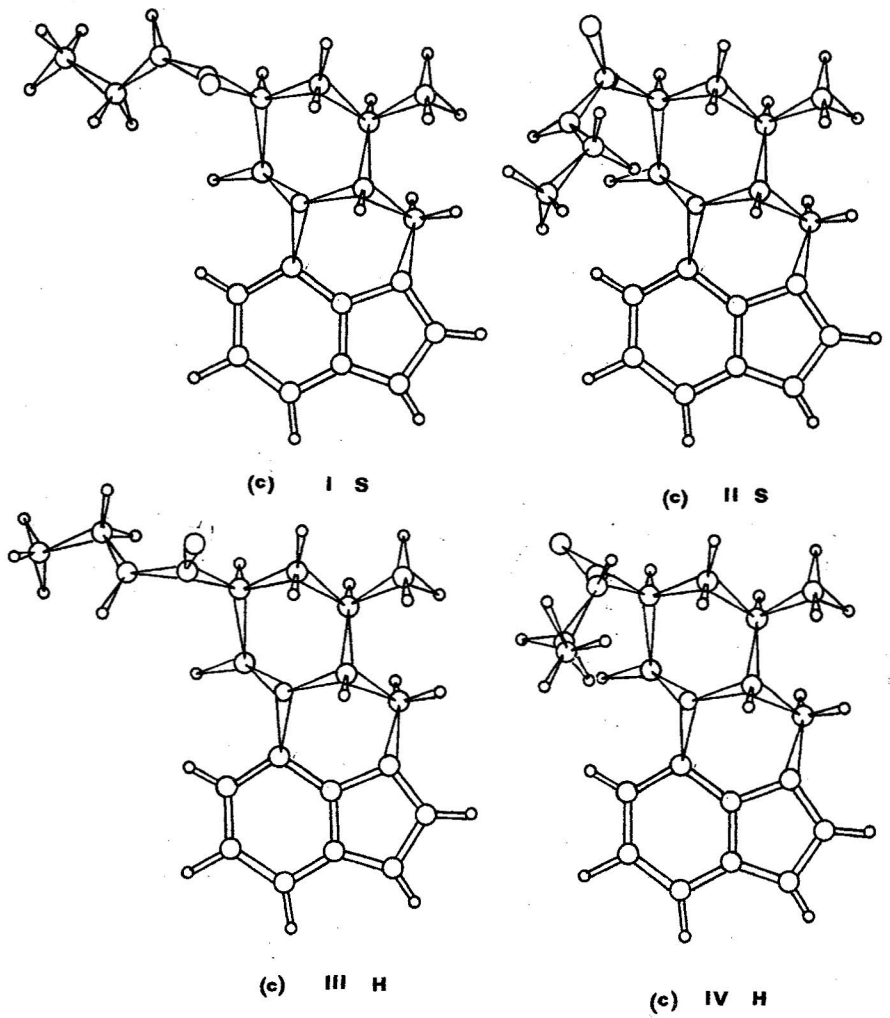
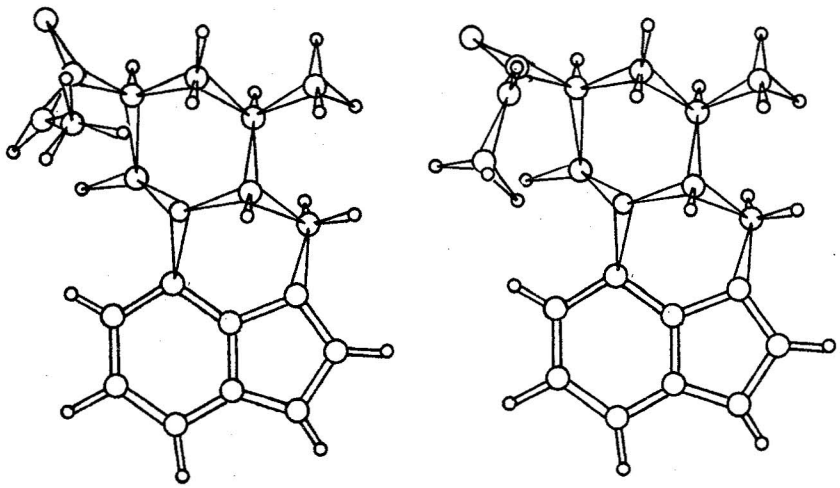


FIGURE 5

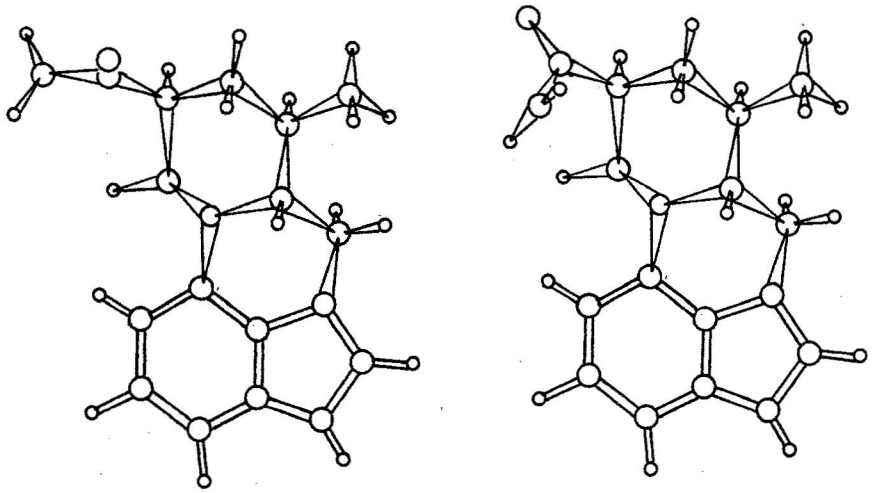
(d) methylamide



(d) I S

(d) II H

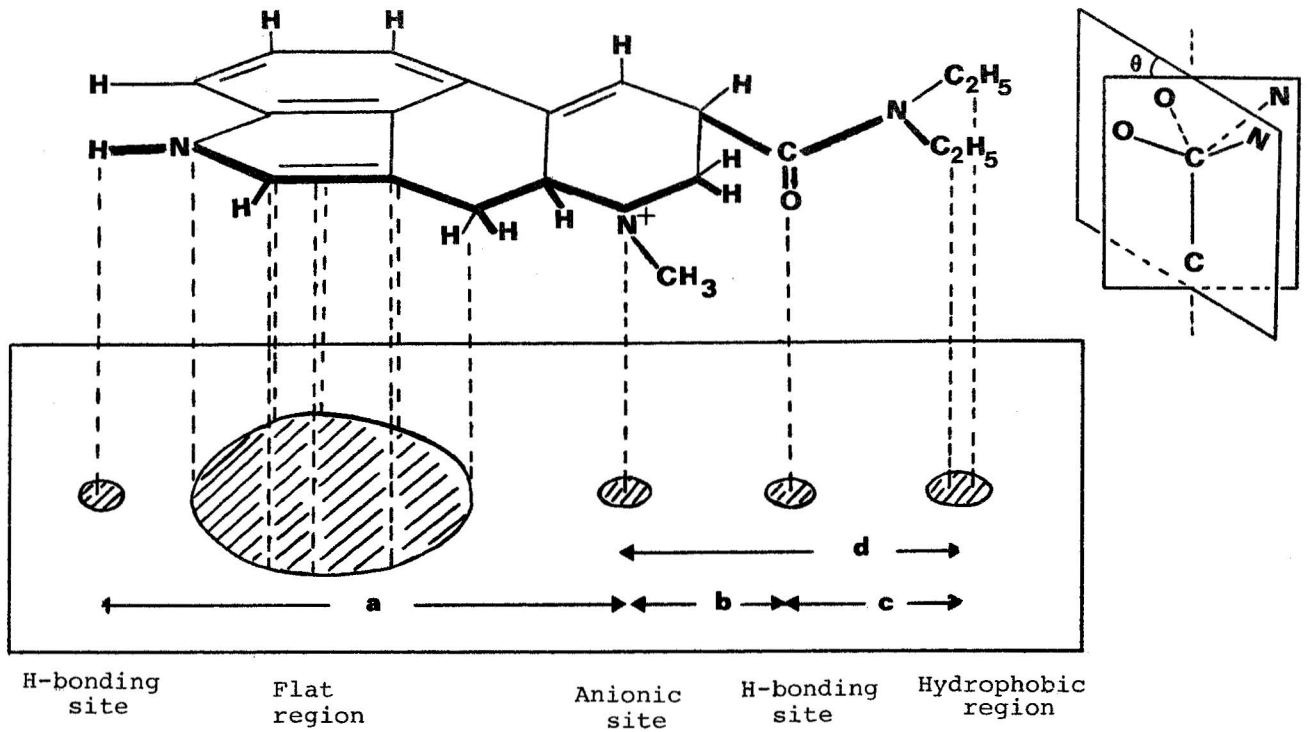
(e) amide



(e) I S

(e) II H

FIGURE 6



Schematic representation of various centers for interaction in LSD. The intracenter distances are listed in Table III. The angle θ measures the deviation of -C=O bond in receptor site conformations (see figures 4(a) to 4(d)). It is zero for LSD conformations. The values may be found in table III.

ACKNOWLEDGMENT

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