A Conformational Study of Lysergic Acid and *iso*-Lysergic Acid Dialkylamides by Proton Magnetic Resonance Spectroscopy

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The 220 MHz p.m.r. spectra of the dimethylamides of D-lysergic acid (**3**) and D-*iso*-lysergic acid (**4**) are reported. Extensive use of double resonance experiments and the presence of four long-range coupling constants provide an unambiguous assignment for the conformation of **3** in $CDCl_3$. Its D ring is shown to exist in a half-chair form in which the 8-β amide function is pseudo-equatorial. Its epimer essentially exists in the other half-chair form with a pseudo-equatorial 8-α amide function. Data from the p.m.r. spectra of a series of *N*,*N*-dialkylamides of these acids are also presented.

The spectrum of protonated **3** at 23 °C shows two forms of the 6-NCH_3 and 8-$CON(CH_3)_2$ groups but only one for the epimer **4**.

Les spectres de r.m.n. à 220 MHz des diméthylamides de l'acide D-lysergique (**3**) et de l'acide D-*iso*-lysergique (**4**) sont rapportés. L'usage extensif de la double résonance et la présence de quatre constantes de couplage à longue distance ont permis d'attribuer sans ambiguité la conformation de **3** dans le $CDCl_3$. On a montré que le cycle D de ce dernier existe sous la forme demi-chaise dans laquelle la fonction amide-8β est pseudoéquatoriale. Son épimère existe essentiellement sous l'autre forme demi-chaise avec la fonction amide-8α pseudo-équatoriale. Les données des spectres de r.m.n. d'une série de *N*,*N*-dialkylamides de ces acides sont également présentés. Le spectre de **3** sous forme protonée à 23 °C montre deux formes pour les groupes NCH_3-6 et $CON(CH_3)_2$-8 alors que l'épimère **4** n'en donne qu'une. [Traduit par le journal]

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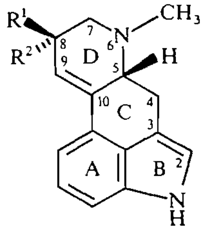
Introduction

Interest in possible similarities in the mode of action of LSD, tryptamines, and the hallucinogenic phenylethylamines (1–5) prompted us to study the solution conformation of LSD and other amides (**3**–**12**) of lysergic and *iso*-lysergic acids (**1** and **2**) (6) by p.m.r. spectroscopy (7). Stoll *et al.* (8) have presented evidence that ring D in both acids is in a ψ-chair form, the carboxyl function being equatorial in lysergic acid and axial in the *iso*-acid.

Experimental

The p.m.r. spectra of **3** and **4** were obtained on a Varian HR-220 spectrometer (Canadian 220 MHz n.m.r. centre, Ontario Research Foundation, Sheridan Park, Ontario). Double resonance experiments were carried out under track-field sweep decoupling conditions with a Wavetek, Model 101, voltage-controlled generator calibrated to the sweep widths of the spectrometer recorder. Other spectra were obtained on Varian A 60-A and XL-100 spectrometers.

The synthesis employed (9) gives a mixture of the isomeric amides of both acids, column chromatography on alumina readily separating the faster-running lysergamide from the *iso*-lysergamide (10). The p.m.r. spectral assignments in Table 1 are based primarily on chemical shift values and are supported by the decoupling experiments described below.



1 $R^1 = CO_2H$; $R^2 = H$
2 $R^1 = H$; $R^2 = CO_2H$
3 $R^1 = CON(CH_3)_2$; $R^2 = H$
4 $R^1 = H$; $R^2 = CON(CH_3)_2$
5 $R^1 = CONCH_3{\cdot}C_3H_7$; $R^2 = H$
6 $R^1 = H$; $R^2 = CONCH_3{\cdot}C_3H_7$
7 $R^1 = CONC_2H_5{\cdot}C_3H_7$; $R^2 = H$
8 $R^1 = H$; $R^2 = CONC_2H_5{\cdot}C_3H_7$
9 $R^1 = CON(C_3H_7)_2$; $R^2 = H$
10 $R^1 = H$; $R^2 = CON(C_3H_7)_2$
11 $R^1 = CONC_3H_7{\cdot}C_4H_9$; $R^2 = H$
12 $R^1 = H$; $R^2 = CONC_3H_7{\cdot}C_4H_9$

TABLE 1. P.m.r. data* for amides of D-lysergic and D-*iso*-lysergic acids

Compound, conditions†		$H_{12,13,14}$	H_2	H_9	H_8	N-CH_3
3	220	7.15	6.86	6.36	3.98	2.59
5	60	7.15	6.85	6.35	*ca.* 3.90	2.55
7	100	7.14	6.86	6.34	3.90	2.58
9	60	7.15	6.88	6.35	*ca.* 3.90	2.57
11	100	7.14	6.84	6.34	3.94	2.59
LSD‡	60	7.15	6.85	6.32	?	2.57
4	220	7.09	6.79	6.30	3.78	2.59
6	60	7.05	6.78	6.28	*ca.* 3.75	2.58
8	100	7.08	6.82	6.24	3.72	2.60
10	60	7.02	6.77	6.23	*ca.* 3.75	2.58
12	100	7.02	6.77	6.24	3.75	2.60

*δ-Values in p.p.m. downfield from internal TMS, solutions *ca.* 15% in $CDCl_3$; these signals are singlets or largely unresolved multiplets, H_8 is broad (*ca.* 20 Hz).
†Frequency of examination in MHz (see Acknowledgments).
‡Data made available by Dr. G. A. Neville, N.H. & W. laboratories.

TABLE 2. P.m.r. data* for D-lysergic acid *N,N*-dimethylamide (**3**)

δ ($CDCl_3$) (p.p.m.)	δ (C_6D_6) (p.p.m.)	Δ (p.p.m.)	J($CDCl_3$) (Hz)	Assignment	δ Irradiation ($CDCl_3$): observation
3.98	3.83	+0.15	10.5, 5.0, 3.5, *ca.* 2	$H_{8\alpha}$	6.36: Lose $J \approx 2$; 10.5, 5.0, 3.5 apparent 3.08: Lose $J \approx 5$ 2.89: Lose $J \approx 11$
3.54	3.40	+0.14	5.5, 14.8	$H_{4\beta}$	6.86: No change 6.36: No change
3.20	3.15	+0.05	11.5, 5.5, 3.8, 1.0	$H_{5\beta}$	6.36: Lose $J \approx 1.0$; 11.5, 5.5, 3.8 apparent
3.15	2.33	+0.82		$CONCH_3$	
3.08	*ca.* 2.97	$\approx +0.1$	11.2, 5.3, 1.0	$H_{7\alpha}$	6.36: Lose $J \approx 1.0$ 3.98: Lose $J \approx 5.5$
3.02	2.31	+0.71	singlet	$CONCH_3$	
2.89	*ca.* 2.97	≈ -0.1	11.2, 10.4	$H_{7\beta}$	3.98: Lose $J \approx 10$–11
2.68	2.84	−0.16	14.8, 11.5, 1.6	$H_{4\alpha}$	6.86: Lose $J \approx 1.5$
2.59	2.66	−0.07	singlet	N-CH_3	

*Measured at 220 MHz, with internal TMS, additional data in Table 1. J Values are first order, in Hz.

Results and Discussion

The assignment of signals other than those in Table 1 was not attempted with homologues higher than *N,N*-dimethyl, because the NCH_2-multiplets (doubled for every compound because of the partial double-bond character of the amide C—N link) extensively overlap multiplets derived from the basic ergoline system. The methyl resonances from compounds **3** and **4** provided the minimum interference and their spectra were determined at 220 MHz. The results are shown in Tables 2 and 3. Axial and equatorial positions are indicated parenthetically by a and e respectively and the designation α or β is made with respect to the proton at C-5 being termed β; see conformations **I–III**.

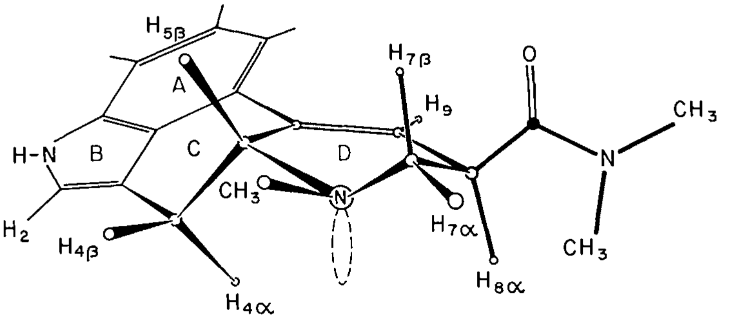
D-*Lysergic Acid Dimethylamide (3)*

The pertinent 220 MHz spectra are reproduced in Figs. 1 and 2. Double irradiation of the H_2 resonance at 6.86 p.p.m. (11) affected only the multiplet at 2.68 p.p.m. ($J = 1.6$ Hz). The magnitude of the coupling is typical of a *cisoid*-allylic coupling (12) and must involve H_2 and H_4 where the estimated dihedral angle $\theta_{2,4\alpha}$ between these hydrogens measures about 80°. The magnitude of geminal coupling constants adjacent to a π bond system is also known to be orientation dependent (12, 13). The observed − 14.8 Hz splitting in $H_{4\alpha}$ at 2.68 p.p.m. therefore is also consistent with an estimated $\theta_{2,4\alpha} = 80°$ where the indole π-bond lobes are more or less aligned with $H_{4\alpha}$ and are expected to exert

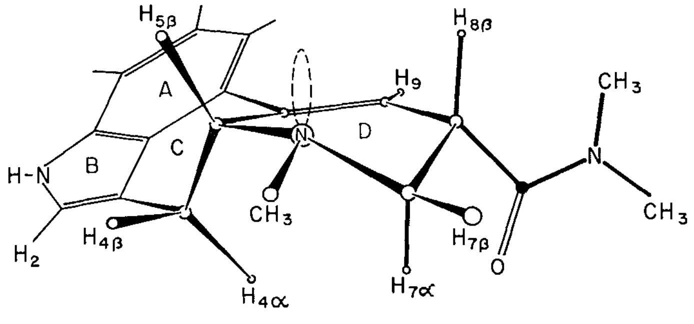
TABLE 3. P.m.r. data* for D-*iso*-lysergic acid *N*,*N*-dimethylamide (**4**)

δ (CDCl$_3$) (p.p.m.)	δ (C$_6$D$_6$) (p.p.m.)	Δ (p.p.m.)	J(CDCl$_3$) (Hz)	Assignment	δ Irradiation (CDCl$_3$): observation
3.78	3.48	+0.30	mult., W = 19 Hz	$H_{8\beta}$	6.30: Lose $J \approx 2$, complex multiplet remains
3.42	3.37	+0.05	11.5, 5.5, 2.5, *ca.* 1	$H_{5\beta}$	6.30: Lose $J \approx 1$; 11.5, 5.5, 2.5 apparent
3.25	3.14	+0.11	14.1, 5.5	$H_{4\beta}$	6.30, 6.70: No change
ca. 3.18	3.28	−0.10	12.0, 7.5	$H_{7\alpha}$	6.30, 6.70: No change apparent
3.19	2.36	+0.83	singlet	CONCH$_3$	
3.00	2.36	+0.64	singlet	CONCH$_3$	
2.86	2.69	+0.17	12.0, 5.2, *ca.* 1?	$H_{7\beta}$	6.30: Sharpening of peaks
2.82	2.83	−0.01	14.2, 12.0, 1.5	$H_{4\alpha}$	6.70: Lose $J \approx 1.5$; 14.2, 12.0 remain
2.59	2.65	−0.06	singlet	*N*-CH$_3$	

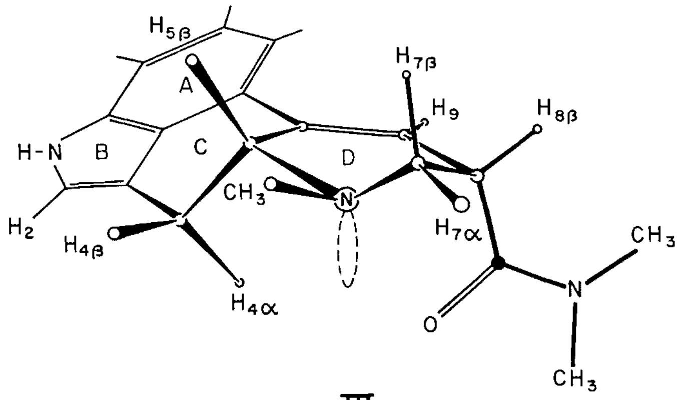
*See footnote Table 2; band-width (W) of multiplet (mult.) in Hz.



I



II



III

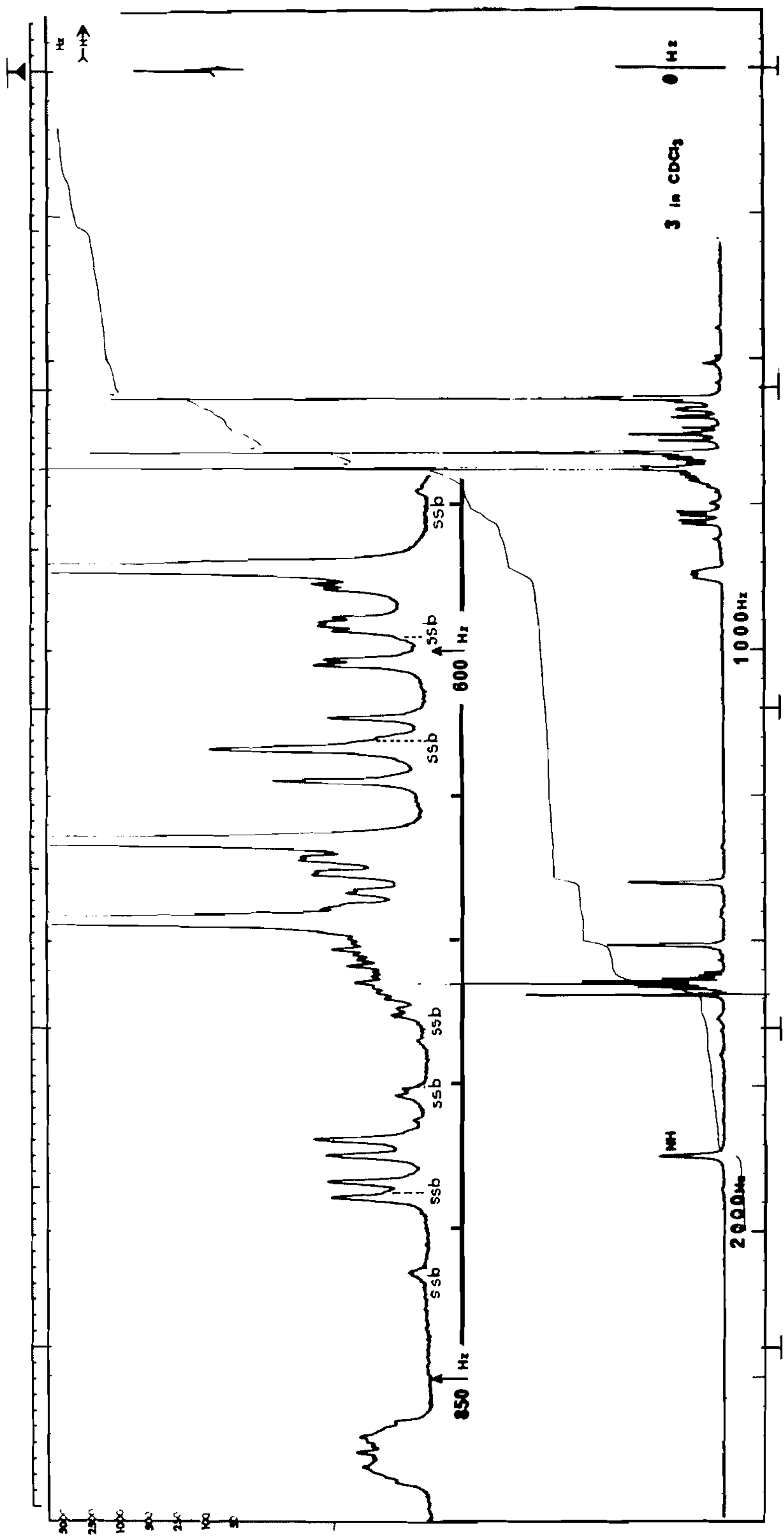


FIG. 1. 220 MHz spectrum of 3 in $CDCl_3$ solution. Lower trace: sweep width 2500 Hz. Insert: 5 × expansion of signals from δ 2.59–3.98 p.p.m., spinning side-bands are indicated by s.s.b.

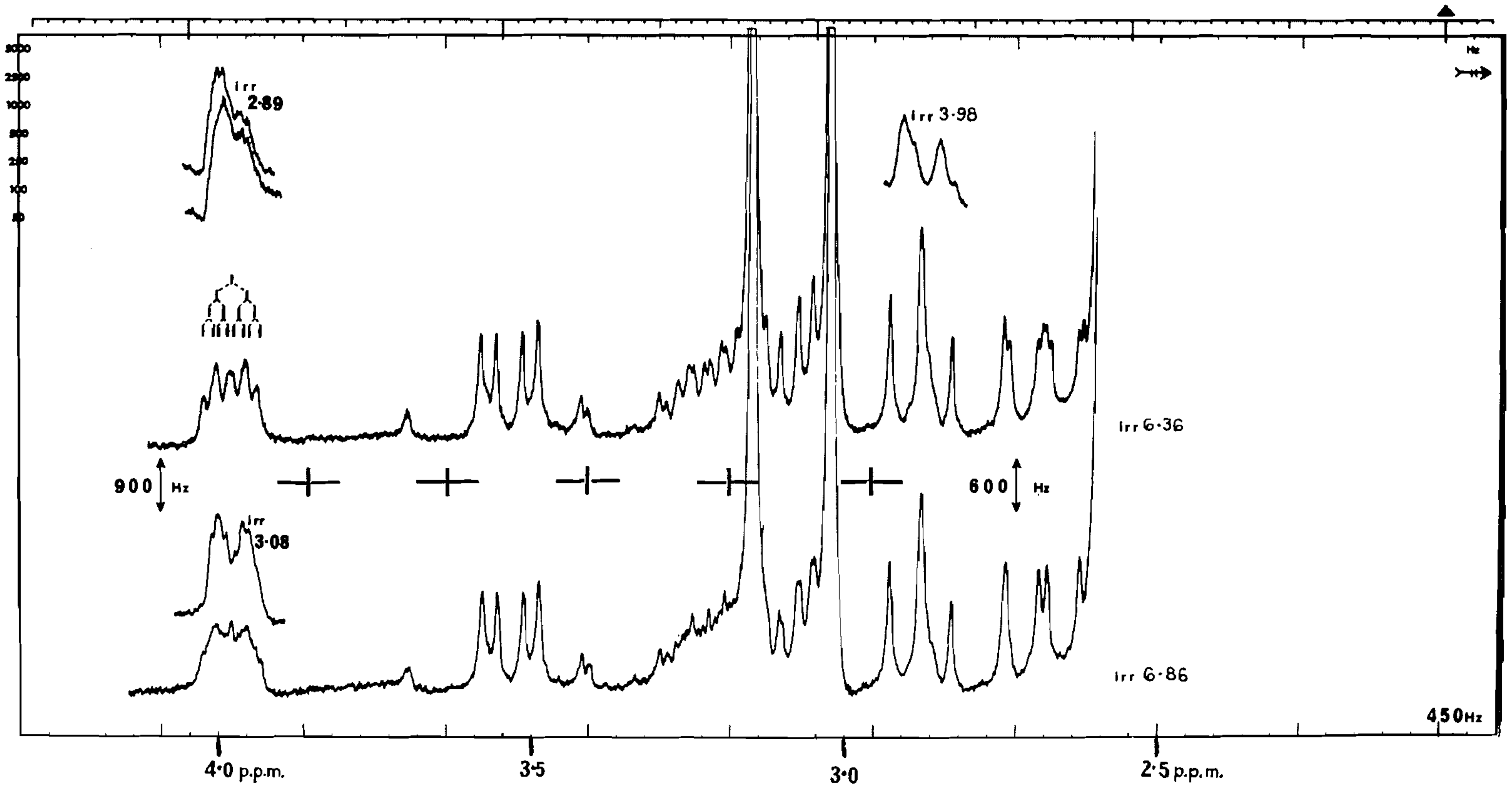


FIG. 2. 220 MHz spectrum of 3 in $CDCl_3$ solution, sweep width 500 Hz, signals from δ 2.59–3.98 p.p.m. Upper main trace with irradiation at δ 6.36 p.p.m.; lower trace with irradiation at δ 6.86 p.p.m. Inserts of signals demonstrate the effect upon them of irradiation of the signals indicated.

a near-maximum effect on J_{gem}. The well defined geometry for $H_{4\beta}$ necessitates that its resonance be deshielded relative to $H_{4\alpha}$ by virtue of its almost planar orientation with the aromatic B ring while showing a very small (0.5 Hz) $J_{2,4\beta}$ allylic coupling. Indeed, $H_{4\beta}$ is 0.86 p.p.m. to low field of $H_{4\alpha}$ and displays only two observable couplings of 5.5 and −14.8 Hz, the latter being $J_{4\alpha,4\beta}$.

Models indicate that the methine hydrogen $H_{5\beta}$ is rigidly fixed by virtue of its bridgehead position at C-5 which is at the puckered end of the half-chair ring C. This unique arrangement places H_5 above the aromatic ring plane of rings A and B with C_5—H_5 bond more or less perpendicular to these as well as to the olefinic double bond in ring D: an ideal position for allylic coupling with H_9. Double resonance experiments on H_9 at 6.36 p.p.m. clearly reduce the heavily coupled multiplet at 3.40 p.p.m. to an eight-line pattern with splittings of 11.4, 5.5, and 3.8 Hz. The former two are those observed in $H_{4\alpha}$ and $H_{4\beta}$ respectively, allowing the assignment of H_5 at 3.40 p.p.m. In addition, $H_{5\beta}$ is uniquely situated at a bridgehead position which is attached to nitrogen which permits an assessment of its environment with respect to the nitrogen lone pair of electrons (14); methine hydrogens in structurally related fragments which are *gauche* to the nitrogen lone pair are deshielded by about 0.6–0.8 p.p.m. relative to those oriented *trans*-axially which are found at ~3.2 p.p.m. The observed chemical shift of $H_{5\beta}$ at 3.20 p.p.m. suggests it to be the latter with the N-lone pair directed in a *trans*-axial relationship with H_5. Such an arrangement can only be realized if ring D exists in that half-chair conformation in which C-5, -10, -9, and -8 are more or less in the same plane. Carbon-7 is above this plane on the same side as H_5; the heterocyclic nitrogen and its lone pair are directed below.

The remaining 3.8 Hz splitting associated with $H_{5\beta}$ can be related to the broad unresolved multiplet at 3.98 p.p.m. This resonance is transformed on double irradiation at 6.36 p.p.m. (H_9) into a symmetrical first-order eight-line multiplet of splittings $J = 3.5$, 10.5, and 5.0 Hz.

The larger couplings are also found in the mutually coupled ($J_{gem} = -11.2$ Hz) signals at 2.89 and 3.08 p.p.m. respectively. The analysis of the $H_{8\alpha}$, $H_{7\alpha}$, $H_{7\beta}$ subsystem indicates that $J_{7\beta,8\alpha}(\text{a–a}) = 10.5$, $J_{7\alpha,8\alpha}(\text{e–a}) = 5.2$, and $J_{7\alpha,7\beta}$ (*gem*) = (−)11.3 Hz. The common 3.8 Hz coupling between H_5 and H_8 is a homoallylic long-range interaction (13) which clearly portrays their relative orientations with each other and the olefinic double bond. For appreciable coupling, both dihedral angles involved for maximum σ–π overlap (15) must approach 90°. The dihedral angles $\theta_{5,9}$ and $\theta_{8,9}$ measured from models in the conformation depicted in Fig. 1 are 90 and 75° respectively. The latter is of such magnitude as to expect a small vicinal coupling between the sp^2–sp^3 bonded hydrogens on C-9 and -8. Its presence is responsible for the unresolved appearance of the unperturbed $H_{8\alpha}$ resonance at 3.98 p.p.m.

The only remaining unaccounted coupling is evident in $H_{7\alpha}$ at 3.08 p.p.m. This multiplet also loses a coupling of about 1 Hz on irradiating H_9 and is compatible with a long-range W coupling between H_9 and H_7. These are more or less in one plane because of the half-chair conformation imposed on ring D. A self-consistent analysis could not be obtained if the other ψ-chair form (compare conformation **II**) were present to any great extent.

The spectrum of **3** measured in C_6D_6 gave chemically shifted resonances (16) as summarized in Table 2, where $\Delta = \delta(CDCl_3) - \delta(C_6D_6)$. Consideration of the data for H_5, H_7, H_8, and 6-NCH_3 suggests that the rotameric conformation of the amide function is possibly as shown in conformation **I**.

These results support conformation **I** proposed by Chothia and Pauling (17) for LSD, and for lysergic acid by Stoll *et al.* (8) at least in the solvents considered here.

iso-Lysergic Acid Dimethylamide (4)

The pertinent 220 MHz n.m.r. spectra are reproduced in Figs. 3 and 4. In $CDCl_3$, the dimethylamide singlets overlap with those of H_4 and H_7 but are preferentially shifted upfield in C_6D_6 thereby allowing the complete coupling data for the ring hydrogens to be extracted. The assignments were confirmed by double resonance experiments in $CDCl_3$ solution.

The assignments of $H_{4\alpha}$, $H_{5\beta}$, and $H_{8\beta}$ follow arguments similar to those presented for **3**; however, the identification of $H_{7\alpha}$ and $H_{7\beta}$ in the *iso*-compound is less clear. Conformations **II** and **III** represent **4** with ring D in a ψ-chair form

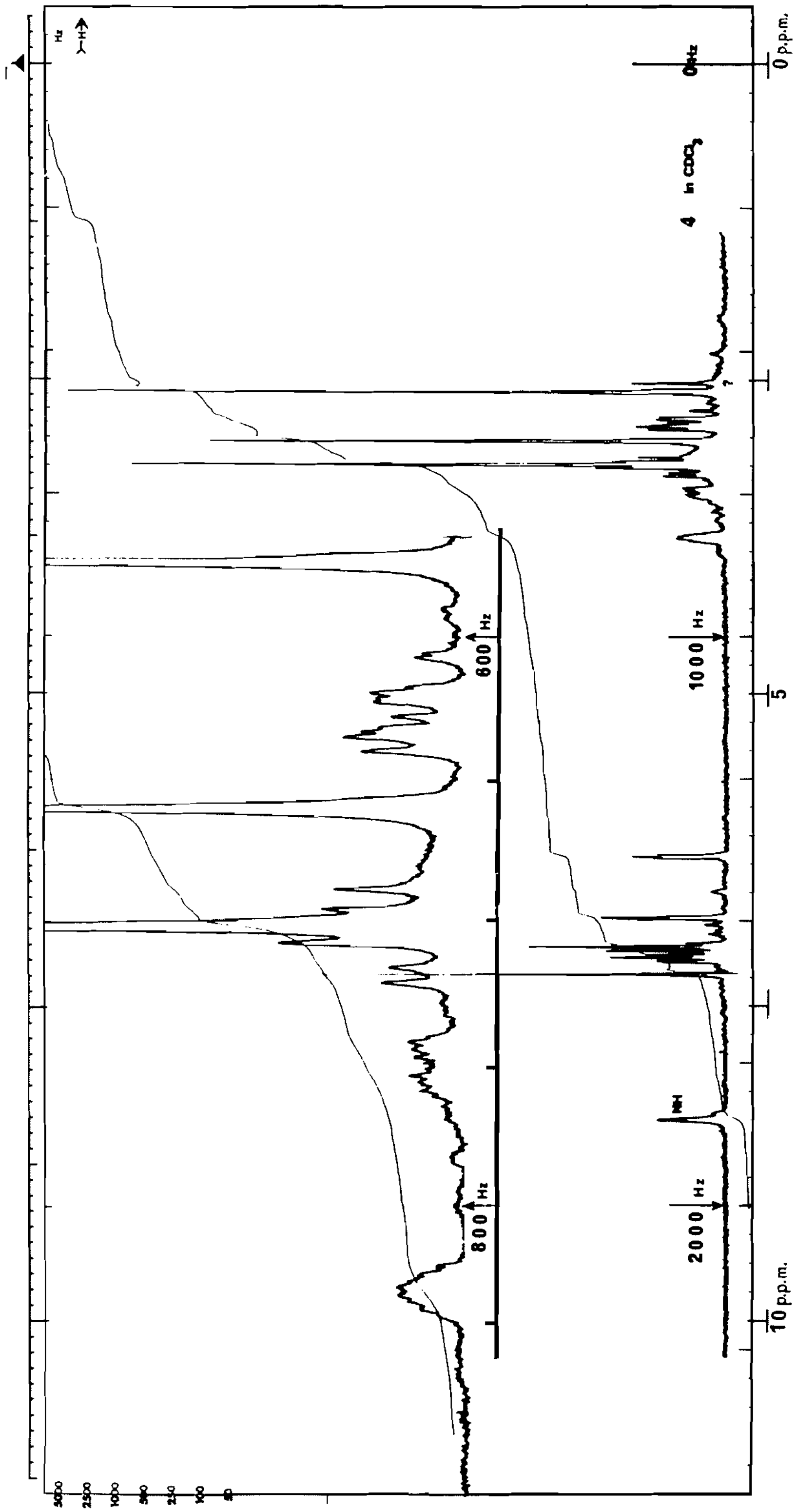


FIG. 3. 220 MHz spectrum of **4** in CDCl$_3$ solution. Lower trace: sweep width 2500 Hz. Insert: 5 × expansion of signals from δ 2.59–3.78 p.p.m.

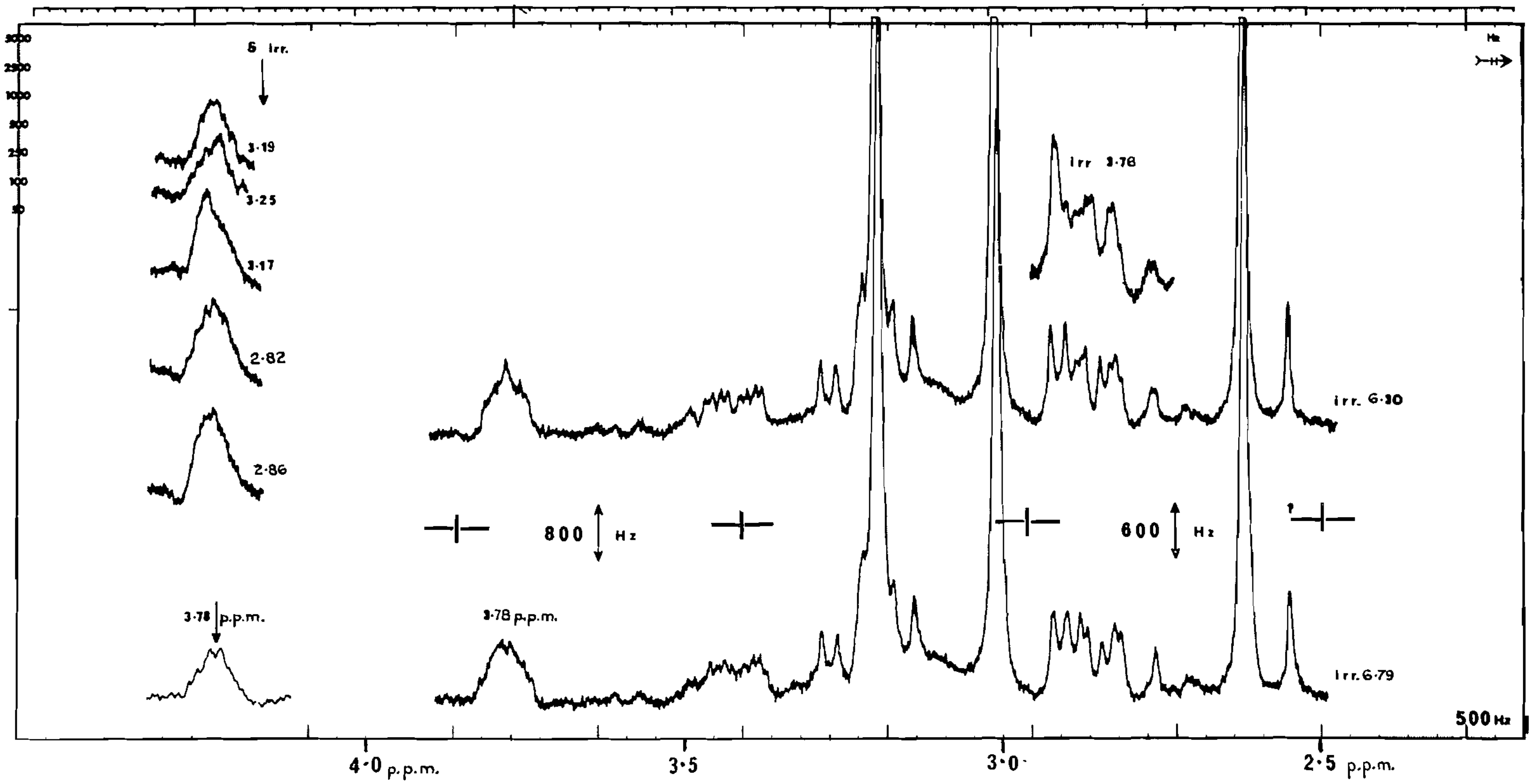


FIG. 4. 220 MHz spectrum of 4 in $CDCl_3$ solution, sweep width 500 Hz, signals from δ 2.59–3.78 p.p.m. Upper main trace with irradiation at δ 6.30 p.p.m.; lower trace with irradiation at δ 6.79 p.p.m. Inserts as in Fig. 2.

in which $H_{8\beta}$ is axial and equatorial, respectively. The 6-NCH$_3$ is considered equatorially displaced for minimum steric interaction in both conformers, only the 7 and 8 hydrogens interchange their axial or equatorial positions.

Consideration of the ψ-chair form illustrated in conformation **II** shows that only one realistic assignment can be made. The resonance at 2.86 p.p.m. is attributed to $H_{7\beta}$ (equatorial) with $J_{7\beta,8\beta}$(e–a) = 5.2 Hz while that at 3.18 p.p.m. to $H_{7\alpha}$ (axial) with $J_{7\alpha,8\beta}$(a–a) = 7.5 Hz.[1] The geminal coupling $J_{7\alpha,7\beta} = (-)12.1$ Hz is common to both resonances. The observed slight sharpening of the proposed $H_{7\beta}$ resonance at 2.86 p.p.m. on double irradiation of the olefinic H_9 at 6.36 p.p.m. may be ascribed to a long-range W coupling as was observed in **3**. Since the 6, 7, 8, 9 system possesses almost the same relative geometry to that of **3** in conformation **I**, similar vicinal couplings constants are expected in this 7, 8 subsystem. The smaller 7.5 Hz *trans*-axial vicinal coupling constant appears to be anomalous compared to that in **3**; however, it is not unlike that obtained from a similar arrangement found in shikimic acid (19) and other systems (20) which display J_{aa} = 6.2–8.4 Hz in half-chair conformations.

The alternative conformer, **III**, can be assigned as follows: $H_{7\alpha}$ (equatorial) at 2.86 p.p.m. and $H_{7\beta}$ (axial) at 3.18 p.p.m. with $J_{7\alpha,8\beta}$(e–e) = 5.2, $J_{7\beta,8\beta}$(a–e) = 7.5 Hz. Molecular models suggest that $\theta_{7\alpha,8\beta} = 80$ and $\theta_{7\beta,8\beta} = 40°$. An interchange of assignments for the 7-hydrogens forces an unrealistic set of J_{vic} which does not conform with the general view of the Karplus relationship. As before, this assignment also accounts for the decoupling of the equatorial $H_{7\alpha}$ while irradiating H_9. The fact that only one of these H_7 protons shows an observable long-range coupling does not negate the possibility of a dynamic equilibrium between conformations **II** and **III**, since the averaging process is expected to reduce $J_{7,9}$ perhaps making it too small to detect in the signal at 3.18 p.p.m. Rough calculations from coupling constants expected in frozen conformations ($J_{ae} = 5.3$, $J_{aa} = 10.4$ Hz in **II** (see **3**); J_{ae} = 3–4, J_{ee} = 1.5–3.0 Hz in **III**) for the observed $J_{7,9}$ couplings indicate that **II**:**III** $\simeq$ 2:1 if $H_{7\beta}$ is at 2.86 and $H_{7\alpha}$ is at 3.18, but self-consistent results cannot be obtained with the reverse assignment. Although the case here is less clear than for the lysergamides, the analysis thus supports conformation **II** for the *iso*-lysergamides in the solutions examined here.

The solvent-shift Δ values suggest that the amide–carbonyl bond is directed as shown in **II** (pointing towards the $H_{4\alpha}$ bond projection). Comparing the chemical shifts of **3** and **4**, H_9, 6-NCH$_3$, and Δ6-NCH$_3$ are very similar and indicate that the anisotropic amide group disposition with respect to H_9 and 6-NCH$_3$ is much the same on epimerization at C-8 (the conformations **I**, **II**, and **III** all satisfy this condition.)

Spectra of **3** and **4** in CDCl$_3$ with an added excess of trifluoracetic acid were not very useful because of the complexities of protonation at different sites, peak broadening, and poor resolution. However, the amide **3** clearly displayed two protonated forms (21) at 23 °C for each of its methyl groups and the complex aromatic region; each amide methyl group displayed a doublet (δ = 3.0 and 3.2 p.p.m., J = 10 Hz) and the two $CH_3\overset{+}{N}H$ doublets at 3.05 and 3.10 p.p.m. ($J_{CH_3\overset{+}{N}H}$=4.8 Hz) collapsed to singlets on irradiation of the broad $\overset{+}{N}H$ peaks at 9.91 and 10.05 p.p.m. The amide **4** displayed only one doublet for each of its CH$_3$ groups, the doublet $CH_3\overset{+}{N}H$ (J = 5 Hz) collapsing on irradiation of the $\overset{+}{N}H$ at 9.21 p.p.m.

Conclusion

The D ring of the *N*,*N*-dimethylamide of D-lysergic acid and its 8-epimer exist in different conformations in CDCl$_3$. The gross stereochemical features of these amides are essentially the same in that the N_6-methyls as well as the *N*,*N*-dimethylamide groups are in pseudo-equatorial positions. The different biological activities of the two series of amides may be in part

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[1] This analysis stems from a generalization of the Karplus equation (18) that when both vicinal coupling constants are greater than about 5 Hz in a —CH$_2$—CH$_x$— system where the geminal "dihedral" angle is 120°, then H_x must lie outside the *gem* protons. The only conformation consistent with this is that shown in conformation **II** and possibly the less favored boat form in which both 6-NCH$_3$ and the amide group assume pseudo-equatorial positions. However, J_0 values required to calculate J's from estimated dihedral angles are unrealistic, see ref. 19.

due to the relative orientation of the 6-nitrogen lone pair of electrons. In LSD, the latter is *trans*-axial to $H_{5\beta}$ and on the concave α-face while for the *iso*-compounds, it is essentially *gauche* and on the β-face of the molecule.

Spectra at 60 MHz were determined by Mr. H. W. Avdovich using a Varian A 60-A, Department of National Health and Welfare, Health Protection Branch, Research Laboratories, Ottawa; at 100 MHz on a Varian XL-100 through the courtesy of Dr. G. Buchanan, Department of Chemistry, Carleton University, Ottawa; and at 220 MHz with a Varian HR-220 at the Canadian 220 MHz n.m.r. Centre. Mlle. D. Verner and Monsieur D. Legault of the Department of National Health and Welfare are thanked for assistance in the preparation and purification of the amides examined.

1. A. Bebbington and R. W. Brimblecombe. Br. Med. Bull. **25**, 293 (1969).
2. Drugs and the brain (Part 1). P. Black, Editor. The Johns Hopkins Press, Baltimore. 1969.
3. A. Balestrieri and D. Fontanari. Arch. Gen. Psychiatr. **1**, 279 (1959); A. Balestrieri. *In* Psychotropic drugs. S. Garattini and V. Ghetti, Editors. Elsevier Publishing Co., Amsterdam. 1957.
4. H. Isbell, A. B. Wolbach, A. Wikler, and E. J. Miner. Psychopharmacol. **2**, 147 (1961); A. B. Wolbach, H. Isbell, and E. J. Miner. Psychopharmacol. **3**, 1 (1962).
5. S. Garattini and L. Valzelli. Serotonin. Elsevier Publishing Co., New York. 1965.
6. H. G. Leemann and S. Fabbri. Helv. Chim. Acta, **42**, 1696 (1959).
7. F. A. Bovey. Nuclear magnetic resonance spectroscopy. Academic Press, New York, N.Y. 1969.
8. A. Stoll, T. Petrzilka, J. Rutschmann, A. Hofmann, and H. H. Gunthard. Helv. Chim. Acta, **37**, 2039 (1954).
9. R. P. Pioch. U.S. Pat. 2 736 728. Chem. Abstr. **50**, 10 803 (1956).
10. A. Stoll and A. Hofmann. Helv. Chim. Acta, **38**, 421 (1955).
11. L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop. J. Am. Chem. Soc. **82**, 2184 (1960).
12. L. M. Jackman and S. Sternhell. Applications of nuclear magnetic resonance spectroscopy in organic chemistry. Pergamon Press, Oxford. 1969.
13. S. Sternhell. Quart. Rev. **23**, 236 (1969).
14. T. A. Crabb, R. F. Newton, and D. Jackson. Chem. Rev. **71**, 109 (1971).
15. M. Karplus. J. Chem. Phys. **33**, 1842 (1960); J. Am. Chem. Soc. **82**, 4431 (1960).
16. N. S. Bhacca and Dudley H. Williams. Applications of NMR spectroscopy in organic chemistry. Holden Day Inc., San Francisco. 1966. Chapt. 7.
17. C. Chothia and P. Pauling. Proc. Natl. Acad. Sci. **63**, 1063 (1969).
18. R. J. Abraham and J. S. E. Holken. J. Chem. Soc. 806 (1963).
19. L. D. Hall. J. Org. Chem. **29**, 297 (1964).
20. B. Coxon, H. J. Jennings, and K. A. McLauchlan. Tetrahedron, **23**, 2395 (1967).
21. J. C. N. Ma and E. W. Warnhoff. Can. J. Chem. **43**, 1849 (1965).