Notes

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Studies on Lysergic Acid Diethylamide and Related Compounds. II.[1] Mass Spectra of Lysergic Acid Derivatives[2]

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Recently, Bellman has reported that mass spectrometry can be used to identify hallucinogenic drugs including lysergic acid diethylamide (LSD).[4] Barber, *et al.* have investigated the mass spectrometry of some clavine and ergot-peptide alkaloids.[5] But no mass spectral investigation of N^6-substituted LSD has been described. The authors have been interested in the identification and the structural analysis of lysergic acid derivatives which are anticipated as natural products and transmitter substances in animal tissues and body fluids. In the present investigation the mass spectra of nine derivatives of lysergic acid are examined and the characteristic fragmentation pattens which might be important for structural analysis are discussed. The elemental composition of each fragment is confirmed by high resolution mass spectrometry.

Lysergic acid derivatives possessing various side chain at the 8 position, *d*-lysergic acid (I), *d*-lysergic acid amide (II), *d*-lysergic acid diethylamide (III) and lysergol (IV), have common fragment ions at *m/e* 221, 207,[6] 192, 180, 167 and 154 as shown in Fig. 1.

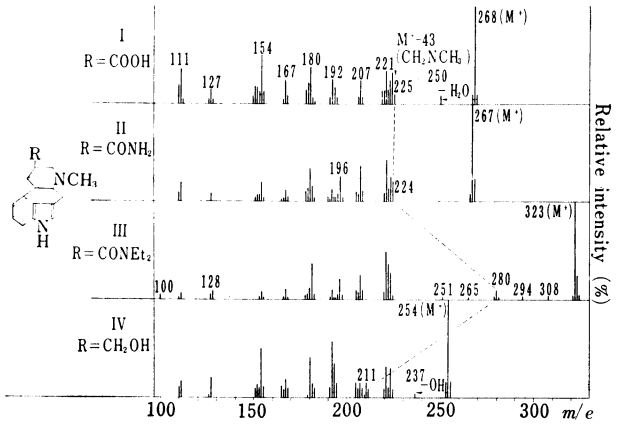


Fig. 1. Mass Spectra of I, II, III and IV

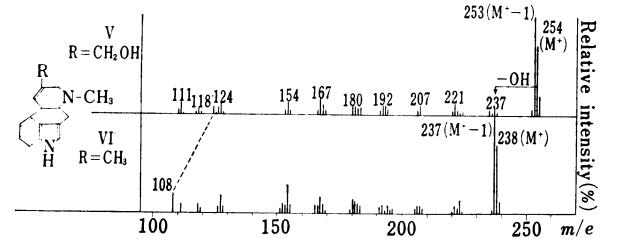
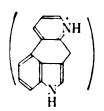
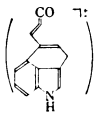


Fig. 2. Mass Spectra of V and VI

1) Part I: Y. Nakahara and T. Niwaguchi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2337 (1971).
2) A part of this work was reported at the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July 1970.
3) Location: *Sanban-cho, Chiyoda-ku, Tokyo.*
4) S.W. Bellman, *J. Ass. Offic. Anal. Chem.*, **51**, 164 (1968).
5) M. Barber, J.A. Weisbach, B. Douglas, and G.O. Dudek, *Chem. Ind.* (London), **1965**, 1072.
6) The peak at *m/e* 207 in the compounds (I), (II), (III), (VIII) and (IX) is observed as doublet, 207.089


and 207.067


Compounds (I—IV) also possess the ions (M^+-43) induced by retro-Diels–Alder reaction as mentioned by Bellman[4] and Barber.[5] In case of compounds (II) and (III), the fragment ions induced by cleavage between the 6 and 7 position and between the 8 and 9 position appear at *m/e* 196.

Elymoclavine (V) and agroclavine (VI) possessing 8—9 double bond are readily distinguished from others, since the ion peaks at M^+-1 are very strong and become the base peaks as shown in Fig. 2. The retro-Diels–Alder reaction is not observed because of migration of the 9—10 double bond to 8—9. The ion at *m/e* 118 may result from indole ring. The ion at *m/e* 124 in the compound (V) is given by the 4—5 and 10—11 cleavages. In case of VI the ion peak produced by the same cleavage shifts to *m/e* 108.

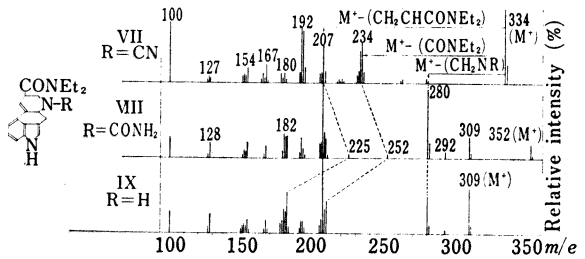


Fig. 3. Mass Spectra of VII, VIII and IX

The fragmentation patterns of *d*-N^6-cyano-N^6-demethyl LSD (VII), *d*-N^6-carbamoyl-N^6-demethyl LSD (VIII) and *d*-N^6-demethyl LSD (IX) are similar to that of the compound (III) as shown in Fig. 3. The fragment ions by elimination of the side chain at the 8 position and by the 6—7 and 8—9 cleavages shift according to the substituent at the N^6 position. Comparison of relative intensities of fragment ion peaks among the compounds (III), (VII), (VIII) and (IX) is shown in Table I.

Table I. Fragment Ion Peaks Produced by Elimination of Side Chain, 6—7 and 8—9 Cleavages, and retro-Diels–Alder Reaction in the Compounds (III), (VII), (VIII) and (IX)

Compound[a]	Elimination of side chain at the 8 position						6—7 and 8—9 cleavages		Retro-Diels–Alder reaction	
	$[M-(CONEt_2)]^+$		$[M-(HCONEt_2)]^+$		$[M-(H_2CONEt_2)]^+$		$[M-(CH_2CHCONEt_2)]^+$		$[M-(CH_2{=}NR^a))]^+$	
	m/e	Relative intensity[b]	*m/e*	Relative intensity[b]	*m/e*	Relative intenstiy[b]	*m/e*	Relative intensity[b]	*m/e*	Relative intensity[b]
III (R=CH_3)	223	9	222	11	221	15	196	61	280	7
VII (R=CN)	234	55	233	44	232	15	207	55	280	3
VIII (R=$CONH_2$)	252	4	251	3	250	1	225	5	280	93
IX (R=H)	209	44	208	43	207	100	182	56	280	50

a) R: N^6-substituent.
b) Relative intensity (%) is normalized with respect to the base peak in spectrum of each compound.

In case of the compound (VIII), the characteristic ion peak produced by elimination of the substituent at the N^6 position occurs distinctly at *m/e* 309 which is equal to the molecular ion of the compound (IX). On the other hand, the ion peak at *m/e* 252 induced by only expulsion of the side chain at the 8 position appears faintly. These facts suggest that the substituent ($CONH_2$) at the N^6 position is easily eliminated. The peak formed by retro-Diels–Alder reaction is very strong. In case of both VIII and IX, the peculiar ion produced by the 5—6 and 6—7 cleavages appears at *m/e* 292.

It is obvious that there are three modes in cleavages of molecular ion of lysergic acid derivatives as shown in Chart 1 : 1. elimination of the side chain at the 8 position, 2. retro-Diels–Alder reaction induced by the 9—10 double bond, 3. the 6—7 and 8—9 cleavages. In the compounds (VII—IX), when the substituent at the N^6 position is CN the peaks derived from the cleavages of the mode 1 and 3 appear strongly, but when it is $CONH_2$ or H the cleavage

of mode 2 appears markedly. Facility for producting the retro-Diels–Alder reaction seems to be due to substituent at the N^6 position, that is $CONH_2 > H \gg CH_3 > CN$ in order. In case of compounds (V) and (VI), the cleavages of the mode 2 and 3 are not observed but the ion peak at M^+-1 appears remarkably. The characteristic peak induced by 4—5 and 10—11 cleavages is observed.

It is elucidated that the fragmentation of lysergic acid derivatives are drastically influenced by the side chain at the 8 position, the double bond between the 9 and 10 position, and the substituent at the N^6 position.

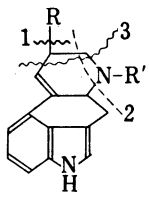


Chart 1

Experimental

Materials——I was obtained from Sigma Chemical Co. II was extracted from seeds of Morning Glory (Ipomoea Nil Roth),[7] purified by column chromatography[8] and identified with the authentic compound. III was prepared from I by Garbrecht's method,[9] IV, V and VI were supplied by Dr. A. Hofmann, Sandoz Laboratory. VII, VIII, and IX were synthesized from III by the method described in the previous paper.[1]

Mass Spectra——The spectra were measured with a JEOL JMS-01SG double focusing mass spectrometer using a direct insertion probe technique: sample temp., 100—180°; ion-chamber temp., 100—250°; ionizing energy, 75 eV; ionizing current, 200 μA.

Acknowledgement The authors are indebted to Dr. A. Hofmann, Sandoz Laboratory for generously supplying the authentic compounds.

7) T. Niwaguchi and T. Inoue, *Eisei Kagaku*, **15**, 290 (1969).
8) T. Niwaguchi and T. Inoue, *J. Chromatog.*, **43**, 510 (1969).
9) W.L. Garbrecht, *J. Org. Chem.*, **24**, 368 (1959).

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Effect of Water on Rate of Charge-Transfer Reaction of Aniline with Chloranil[1]

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Charge-transfer (CT) is known to take part in various complexations and reactions. Because the most phenomena of pharmaceutical interest occur in aqueous media, the effect of water on CT has become an important subject in the pharmaceutical field. The previous study[1b] has demonstrated that water promotes the formation of outer complexes. In the present study, attention has been drawn to the rate of CT reaction. As the example in this work, aniline-chloranil system has been taken on which detailed studies carried out with respect to the outer complex formation[3] and the CT reaction.[4]

1) *a*) This forms Part X of "Spectroscopic Studies on Molecular Interactions"; *b*) Part IX: I. Moriguchi, S. Fushimi, and N. Kaneniwa, *Chem. Pharm. Bull.* (Tokyo), **20**, 258 (1972); *c*) Presented in part before the 90th Annual Meeting of Pharmaceutical Soceity of Japan, Sapporo, July, 1970.
2) Location: *Hatanodai, Shinagawa-ku, Tokyo, 142, Japan.*
3) *a*) P.H. Gore and B.B. Wheals, *Anal. Chim. Acta*, **30**, 34 (1964); D.C. Mukherjee and A.K. Chandra, *J. Phys. Chem.*, **68**, 477 (1964); *b*) I. Moriguchi, S. Fushimi, and N. Kaneniwa *Chem. Pharm Bull.* (Tokyo), **18**, 1553 (1970).
4) T. Nogami, K. Yoshihara, H. Hosoya, and S. Nagakura, *J. Phys. Chem.*, **73**, 2670 (1969).