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Studies on Lysergic Acid Diethylamide and Related Compounds. V.[1] Syntheses of Dihydrolysergic Acid Diethylamides and Related Compounds

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Epimeric pairs of dihydrolysergic acid diethylamide and dihydroisolysergic acid diethylamide were synthesized by hydrogenation of lysergic acid diethylamide (LSD) and iso LSD.

Lysergol was obtained by LAH reduction of methyl lysergate which was prepared by treatment of a solution of lysergic acid in HMPA with diazomethane. From lysergol, lysergine and isolysergine were prepared. Festuclavine, pyroclavine, and costaclavine were synthesized by reduction of agroclavine with metal sodium in butanol and their structures were chemically confirmed.

ORD curves of these alkaloids were determined and discussed.

Keywords——syntheses; epimeric pairs; dihydrolysergic acid diethylamide; dihydroisolysergic acid diethylamide; festuclavine; pyroclavine; costaclavine; ORD curves

In the course of our studies[3,4] on the metabolic pathway of lysergic acid diethylamide (LSD) (**1**), a powerful hallucinogen, we[4] occasionally found that treatment of LSD (**1**) with cyanogen bromide gave N_6-cyanonorlysergic acid diethylamide (**2**) almost quantitatively, demonstrating that LSD (**1**) reacted contrary to the widely accepted generalization[5] that in the von Braun reaction a benzylic or an allylic linkage to a nitrogen is more susceptible to cleavage than removal of a methyl group at the same nitrogen. This observation prompted us to investigate von Braun reaction of compounds related to LSD (**1**). In this paper, we present syntheses and structural establishments of the compounds used in this examination.

We first aimed at synthesizing various stereoisomers of dihydrolysergic acid diethylamide about the two chiral centers, C_8 and C_{10}. These had already been described[6] but all of the reported preparative sequences involved the step of diethylamidation of an acid azide. These methods seemed to be unsuitable, since lysergic acid derivatives are apt to epimerize at C_8 under these reaction conditions to give a mixture of diastereoisomers. Therefore, we examined the catalytic hydrogenation of LSD (**1**) and isolysergic acid diethylamide (isoLSD) (**3**). LSD (**1**) was hydrogenated over 5% palladised charcoal in methanol at room temperature and atmospheric pressure for 70 min to give dihydrolysergic acid diethylamide (I)[7-9] [2H–LSD (I)] (**4**)

1) Part IV: T. Niwaguchi, Y. Nakahara, and H. Ishii, *Yakugaku Zasshi*, **96**, 673 (1976).
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3) T. Niwaguchi, T. Inoue, and Y. Nakahara, *Biochem. Pharmacol.*, **23**, 1073 (1971).
4) Y. Nakahara and T. Niwaguchi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2337 (1971).
5) H. Hageman, "Organic Reactions," Vol. 7, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1953, p. 231.
6) A. Stoll and A. Hofmann, "The Alkaloids," Vol. 8, ed. by R.H.F. Manske, Academic Press, New York, 1965, Chapter 21; P.A. Stadler and P. Stütz, "The Alkaloids," Vol. 15, ed. by R.H.F. Manske, Academic Press, New York, 1965, Chapter 21; P.A. Stadler and P. Stütz, "The Alkaloids," Vol. 15, ed. by R.H.F. Manske, Academic Press, New York, 1975, Chapter 1.
7) *a*) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **38**, 421 (1955); *b*) A. Stoll, Th. Petrzilka, J. Rutschmann, A. Hofmann, and Hs. H. Günthard, *Helv. Chim. Acta*, **37**, 2039 (1954).
8) A. Stoll and J. Rutschmann, *Helv. Chim. Acta*, **36**, 1512 (1953).
9) L. Bernardi, G. Bosisio, and B. Camerino, *Gazz. Chim. Ital.*, **94**, 961 (1964) [*Chem. Abstr.*, **62**, 4070*d* (1965)]; L. Bernardi, B. Camerino, B. Patelli, and S. Radaelli, *ibid.*, **94**, 936 (1964) [*Chem. Abstr.*, **62**, 4069*b* (1965)].

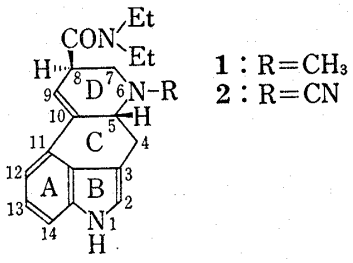

Chart 1

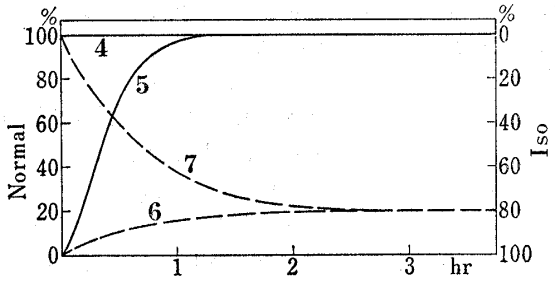

Fig. 1. Equilibration of Dihydrolysergic Acid Diethylamides by Treatment with KOH in Butanol at 100°

4, 2H-LSD(I). **5**, 2H-isoLSD(I).
6, 2H-isoLSD(II). **7**, 2H-LSD(II).

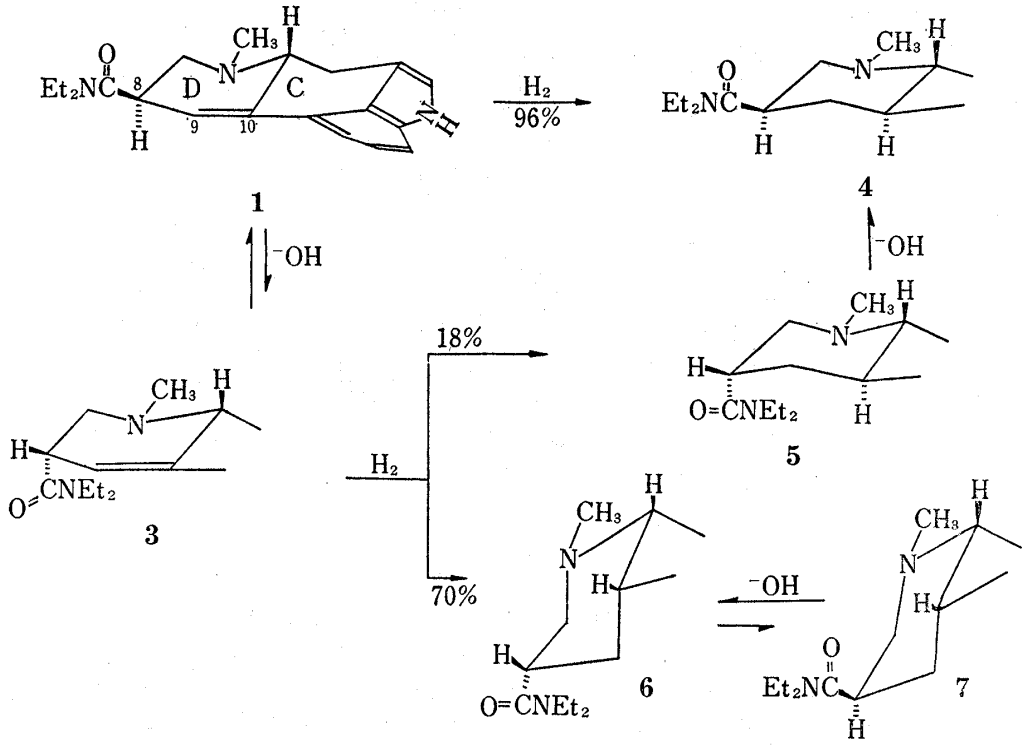

Chart 2

in 96% yield as a sole product, while hydrogenation of isoLSD (**3**) took 480 min for completion of the reaction under the same conditions and gave a mixture of dihydroisolysergic acid diethylamide (I)[7,8] [2H–isoLSD (I)] (**5**) (18%) and dihydroisolysergic acid diethylamide (II)[10] [2H-isoLSD (II)] (**6**) (70%). These experimental results could be rationalized by the following considerations. LSD (**1**) was hydrogenated exclusively from the unhindered α side of the molecule to give 2H-LSD (I) (**4**) bearing a C/D trans ring juncture. But, in the case of hydrogenation of isoLSD (**3**), the presence of an axial diethylamide group at the C_8 position caused attack of hydrogen atoms from the α side to be fairly hindered, therefore requiring a longer time for completion of the reaction. Moreover, as this situation allows attack by hydrogen atoms from both sides of the molecule, hydrogenation of isoLSD (**3**) afforded a

10) L. Bernardi and W. Barbieri, *Gazz. Chim. Ital.*, **95**, 375 (1965) [*Chem. Abstr.*, **63**, 11641*a* (1965)]. They reported preparation of 2H-isoLSD (II) in the body of this paper, but we could not find description of experimental part and any physical constant of it in this paper.

mixture of a C/D *trans* product, 2H-isoLSD (I) (**5**) and a C/D *cis* product, 2H-isoLSD (II) (**6**), which were formed by attack from the α side and the β side, respectively.

Discrimination of the structures of these products was easily performed by equilibrium experiments of them. Treatment of 2H-isoLSD (I) (**5**) with base provided 2H-LSD (I) (**4**) irreversibly, indicating that both compounds have a C/D *trans* ring juncture and moreover that the former has a diethylamide group at the C_8 axial position, but the latter at the equatorial, in other words, both are present as chair forms.

On the other hand, the same treatment of 2H-isoLSD (II) (**6**) gave an equilibrium mixture which was composed of 2H-isoLSD (II) (**6**) and the fourth isomer, dihydrolysergic acid diethylamide (II)[11] [2H-LSD (II)] (**7**), at a ratio of 4: 1. Furthermore, this pure fourth isomer (**7**) was converted to the same equilibrium mixture on treatment with base.

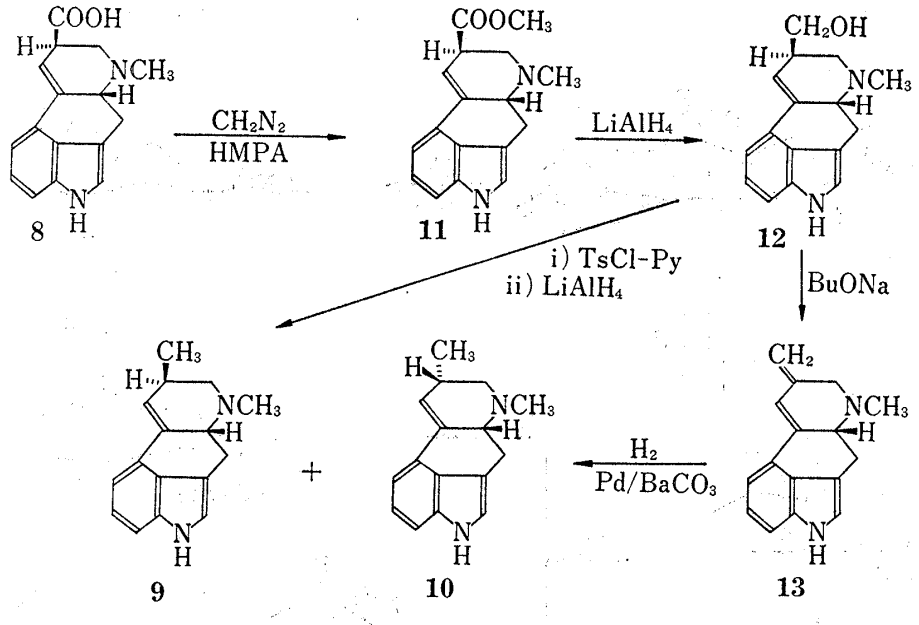

Chart 3

It was of importance to compare the behaviour of a derivative of LSD on von Braun reaction with that of the corresponding compound which has a methyl group at C_8 instead of a diethylamide. A number of such products occur in nature and are classified as clavine alkaloids.[6] But, since almost all of these alkaloids were unavailable in this country, commercially available lysergic acid (**8**) was converted to the desired compounds. For the purpose of the preparation of lysergine[12] (**9**) and isolysergine[13] (**10**) corresponding to LSD (**1**) and isoLSD (**3**) respectively in the LSD series, improvement of the method of esterification of lysergic acid (**8**) was studied. Treatment of lysergic acid (**8**) with diazomethane[14] using hexamethylphosphorylamide (HMPA) as a solvent gave methyl lysergate[15] (**11**) as a sole product in 86% yield. Reduction of methyl lysergate (**11**) with lithium aluminium hydride gave lysergol[16] (**12**) in 78% yield. Following the reported method,[17] lysergol (**12**) was treated

11) L. Bernardi, O. Goffredo, and B. Patelli, *Gazz. Chim. Ital.*, **94**, 955 (1964) [*Chem. Abstr.*, **62**, 4070*b* (1965)].
12) S. Yamatodani and M. Abe, *Bull. Agr. Chem. Soc. Japan*, **20**, 95 (1956).
13) E. Schreier, *Helv. Chim. Acta*, **41**, 1984 (1958).
14) This is a very convenient method for methylation of water-soluble compounds, for example amino acids, quaternary bases, *etc.* Universal application of this procedure to many other compounds will be reported in near future (H.I.).
15) W.A. Jacobs and L.C. Craig, *J. Biol. Chem.*, **104**, 547 (1934).
16) *a*) S. Yamatodani and M. Abe, *Bull. Agr. Chem. Soc. Japan*, **21**, 200 (1957); *b*) A. Hofmann, *Planta Med.*, **9**, 354 (1961).
17) S. Yamatodani and M. Abe, *Bull. Agr. Chem. Soc. Japan*, **20**, 95 (1956).

with sodium butoxide to give lysergene[17] (**13**) in 51% yield. Catalytic hydrogenation of lysergene (**13**) over palladium on barium carbonate followed by column-chromatography gave lysergine (**9**) and isolysergine (**10**) in 57% and 30% yields, respectively. Structural assignment of these products was based on the fact that the specimen of lysergine (**9**) mentioned above was identified with a sample which was prepared by tosylation of lysergol (**12**) followed by reduction with lithium aluminium hydride.

In order to prepare the clavine alkaloids having an ergoline skeleton in their molecules, we intended to repeat the reported reduction[17] of commercially available agroclavine (**14**) with metal sodium in alcohol. A solution of agroclavine (**14**) in butanol was treated with metal

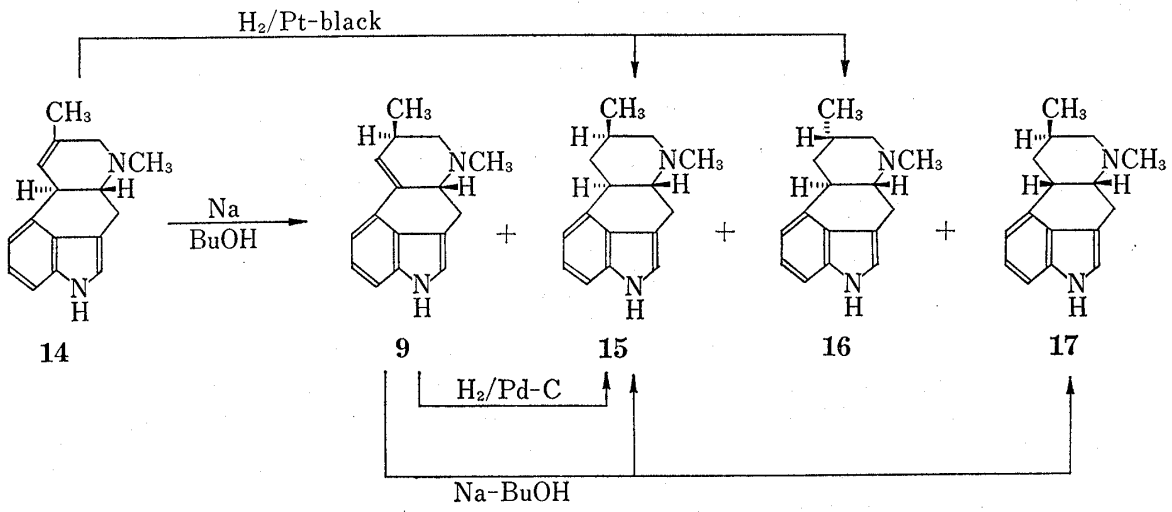

Chart 4

sodium to give four products, (**9**), (**15**), (**16**), and (**17**) in 67%, 10%, 8%, and 2% yields, respectively. The first was found to be lysergine (**9**) which was formed by rearrangement of a double bond from C_8–C_9 to C_9–C_{10}. Three others should be stereoisomeric dihydro-derivatives of agroclavine (**14**), because the results of high resolution mass spectrometry of them suggested the same molecular formula, $C_{16}H_{20}N_2$. Configurations of them were disclosed by the following experiments. Catalytic hydrogenation of agroclavine (**14**) on platinum black gave a mixture of the second (**15**) and the third (**16**) products, indicating that both products maintain a C/D *trans* juncture of the starting material (**14**). On the other hand, similar reaction of lysergine (**9**) afforded only the second product (**15**), determining that the methyl group of it occupies C_8-β position. These evidences allowed us to assign the second to festuclavine[18] (**15**) and the third to pyroclavine[19] (**16**).

These considerations leave only the possibility of a C/D *cis* juncture for the configuration

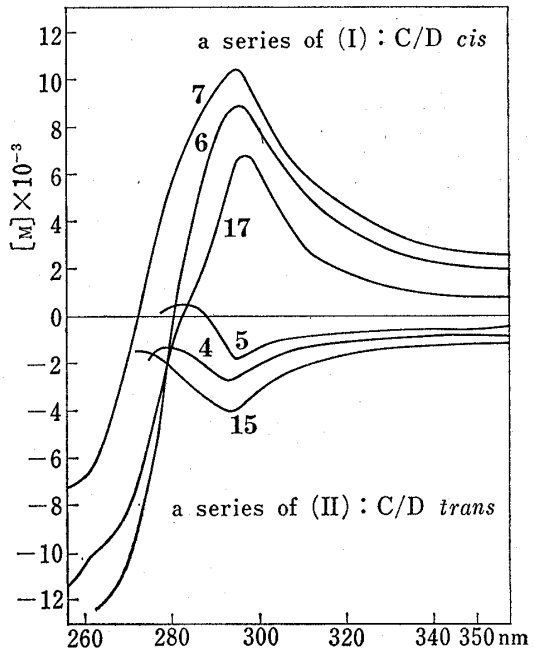

Fig. 2. ORD Curves of Dihydrolysergic Acid Derivatives in MeOH

4, 2H-LSD(I). **5**, 2H-isoLSD(I). **6**, 2H-isoLSD(II). **7**, 2H-LSD(II). **15**, Festuclavine. **17**, Costaclavine.

18) J.F. Spilsbury and D. Wilkinson, *J. Chem. Soc.*, **1957**, 2085.
19) M. Abe, S. Yamatodani, T. Yamano, and M. Kusumoto, *Bull. Agr. Chem. Soc. Japan*, **20**, 59 (1956).

of the fourth product (**17**). This configuration was also supported by the fact that reduction of lysergine (**9**) with metal sodium under the same conditions gave a mixture of festuclavine (**15**) (50%) and the fourth product (**17**) (16%). Furthermore, since Yamatodani, *et al.*[19] described formation of costaclavine (**17**) having a C/D *cis* ring juncture in this reaction and the observed melting point of our fourth product, mp 183—184°, was in accordance with the reported figure, mp 182°, for costaclavine[19] (**17**), we may safely assign the fourth product to costaclavine (**17**).

We would like to mention here the optical rotatory dispersion curves of derivatives of dihydrolysergic acid (see Fig. 2). The alkaloids having a C/D *trans* ring system, 2H-LSD (I) (**4**), 2H-isoLSD (I) (**5**), and festuclavine (**15**), show a fairly weak negative Cotton effect at 295—300 nm, while those having a C/D *cis* ring system, 2H-LSD (II) (**7**), 2H-isoLSD (II) (**6**), and costaclavine (**17**) exhibit a strong positive Cotton effect, caused by an indolic chromophor at the same region. These phenomena could be understood by the following considerations. The compounds in the former series have two substituents at C_5 and C_{10} as equatorial bonds about their C ring and form relatively flat structures. On the other hand, in the latter series, the substituent at C_{10} occupies an axial position about the C ring and contributes strongly to the indolic chromophor.

Experimental

All melting points were observed on a microscopic hot stage and are uncorrected. ORD, NMR (tetramethylsilane as internal reference), UV, and mass spectra were obtained with JASCO ORD/UV-5, Hitachi Perkin-Elmer R-22 (90 MHz), EPS-3T, and JEOL JMS-01SG spectrometers, respectively. Confirmation of purity by thin-layer chromatography on silica gel G (Merck) was performed on each product with three solvent systems: (A) $CHCl_3$–MeOH [4: 1 (v/v)], (B) $CHCl_3$-acetone [1: 4 (v/v)], (C) MeOH–$CHCl_3$–hexane [1: 4: 2 (v/v/v)]. Detection on TLC was effected with UV-light (365 nm) and/or Ehrlich reagent (*p*-dimethylaminobenzaldehyde in alcoholic HCl). Column chromatography was performed using Al_2O_3 (Brockmann, neutral, grade II—III). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; sh, shoulder. D-Lysergic acid (**8**) was purchased from the Sigma Co. Ltd. and agroclavine (**14**) from the Aldrich Chemical Co. Inc. For preparation of LSD (**1**) and isoLSD (**3**) our procedure[20] was applied.

Hydrogenation of LSD (1). Dihydrolysergic Acid Diethylamide (I) (4)——A solution of 90 mg of LSD (**1**) in 50 ml of MeOH was hydrogenated over 80 mg of 5% Pd–C at atmospheric pressure at room temperature for 70 min and the catalyst was filtered off. The filtrate was evaporated to dryness *in vacuo*. The oily residue was purified by column chromatography on Al_2O_3. Elution with benzene–acetone (9: 1) gave 87 mg of colourless rods, mp 128—129° (lit.[7a] mp 130—135°), which were recrystallized from ethyl acetate. $[\alpha]_D^{20}$ −102° (c=0.491, pyridine) [lit.[7a] $[\alpha]_D^{20}$ −114° (c=0.5, pyridine)]. ORD (c=0.0747, MeOH) $[M]^{22}$ (nm): −280° (589), −390° (500), −670° (400), −1180° (330), −3960° (293) (trough), −1920° (272) (peak), −4660° (260), −10250° (240). MS *m/e*: 325 (M^+, 100%), 225 (M^+−$CONEt_2$, 60%). High Resolution MS: M^+, *m/e*: 325.216. Calcd. for $C_{20}H_{27}N_3O$: M, 325.215. IR ν_{max}^{KBr} cm^{-1}: 3250 (NH), 1625 (amide). UV λ_{max}^{EtOH} nm (log ε): 276 (3.79) sh, 282 (3.81), 292 (3.73). NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7 Hz, $CONCH_2\underline{CH_3}$), 1.25 (3H, t, J=7 Hz, $CONCH_2\underline{CH_3}$), 1.86 (2H, m, C_9–H×2), 2.52 (3H, s, NCH_3), 2.3—3.2 (7H, m, aliphatic H), 3.47 (4H, q, J=7 Hz, CON ($\underline{CH_2}CH_3$)$_2$), 6.86 (1H, s, C_2–H), 6.9—7.2 (3H, m, aromatic H), 8.24 (1H, s, NH).

Hydrogenation of isoLSD (3)——A sclution of 71 mg of isoLSD (**3**) in 40 ml of MeOH was hydrogenated over 65 mg of Pd–C at atmospheric pressure at room temperature for 480 min. The filtrate was evaporated to dryness *in vacuo*. The oily mixture of products was dissolved in benzene–acetone (9: 1) and chromatographed on Al_2O_3.

i) Dihydroisolysergic Acid Diethylamide (I) (**5**): Elution with benzene–acetone (9: 1) gave 13 mg of colourless prisms, mp 236—240° (lit.[7a] mp 240—243°), which were recrystallized from EtOH. $[\alpha]_D^{20}$ −65° (c=0.23, pyridine) [lit.[7a] $[\alpha]_D^{20}$ −68° (c=0.3, pyridine)]. ORD (c=0.0560, MeOH) $[M]^{22}$ (nm): −230° (589), −310° (500), −580° (400), −840° (330), −1850° (296) (trough), −1020° (276) (peak), −2300° (270). MS *m/e*: 325 (M^+, 100%), 225 (M^+−$CONEt_2$, 53%). High Resolution MS: M^+, *m/e*: 325.215. Calcd. for $C_{20}H_{27}N_3O$: M, 325.215. IR ν_{max}^{KBr} cm^{-1}: 3330 (NH), 1635 (amide). UV λ_{max}^{EtOH} nm (log ε): 275 (3.77) sh, 283 (3.80), 293 (3.74). NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7 Hz, $CONCH_2\underline{CH_3}$), 1.23 (3H, t, J=7 Hz, $CONCH_2\underline{CH_3}$), 1.83 (2H, m, C_9–H×2), 2.55 (3H, s, NCH_3), 2.4—3.8 (7H, m, aliphatic H), 3.41 (4H, q, J=7 Hz, CON ($\underline{CH_2}CH_3$)$_2$), 6.88 (1H, s, C_2–H), 7.0—7.2 (3H, m, aromatic H), 8.30 (1H, br. s, NH).

20) Y. Nakahara and T. Niwaguchi, *Yakugaku Zasshi*, **94**, 407 (1974).

ii) Dihydroisolysergic Acid Diethylamide (II) (**6**): Successive elution with benzene–acetone (8: 1) on the above column chromatography gave 50 mg of colourless prisms, mp 179—181°, which were recrystallized from ethyl acetate. $[\alpha]_D^{20}$ +34° (c=0.495, pyridine). ORD (c=0.0565, MeOH) $[M]^{22}$ (nm): +270° (589), +460° (500), +1140° (400), +2300° (350), +9040° (295) (peak), 0° (280), −15700° (240) (trough), −10800° (230). MS: *m/e* 325 (M^+, 100%), 225 ($M^+-CONEt_2$, 65%). High Resolution MS: M^+, *m/e*: 325.213. Calcd. for $C_{20}H_{27}N_3O$: M, 325.215. IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1633 sh, 1608 (amide). UV λ_{max}^{EtOH} nm (log ε): 276 (3.78) sh, 283 (3.80), 293 (3.73). NMR ($CDCl_3$) δ: 1.08 (3H, t, J=7 Hz, $CONCH_2C\underline{H}_3$), 1.28 (3H, t, J=7 Hz, $CONCH_2C\underline{H}_3$), 1.82 (2H, m, C_9–H×2), 2.60 (3H, s, NCH_3), 2.7—3.6 (7H, m, aliphatic H), 3.38 (4H, q, J=7 Hz, $CON(C\underline{H}_2CH_3)_2$), 6.80 (1H, s, C_2–H), 6.9—7.2 (3H, m, aromatic H), 8.22 (1H, s, NH).

Equilibration of the Derivatives of Dihydrolysergic Acid Diethylamide——To each solution of 5 mg of 2H-LSD (I) (**4**), 2H-LSD (II) (**7**), 2H-isoLSD (I) (**5**), and 2H-isoLSD (II) (**6**) in 3 ml of BuOH was added 3 ml of 1 N KOH aq. Each solution was heated for 4 hr at 100°. Every 15 min, samples were removed from the reaction vessels and developed on TLC using a mixed solution of MeOH–CH_3CCl_3 (1: 6) as a solvent. The product ratio in each sample was followed by measuring[21] the densities of the TLC spots at 550 nm with Hitachi MPF-2 densitometer after colour development by Ehrlich reagent. The results are shown in Fig. 1.

Dihydrolysergic Acid Diethylamide (II) (**7**)——To a solution of 70 mg of dihydroisolysergic acid diethylamide (II) (**6**) was added 10 ml of 1 N KOH aq. The mixed solution was refluxed for 3 hr and cooled. The reaction mixture was diluted with a large quantity of water and extracted with benzene. The organic layer was again extracted with 1% tartaric acid *aq*. The acid solution was basified with 1 N NaOH aq. and extracted with $CHCl_3$. The chloroform solution was dried over anhydr. Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was dissolved in benzene–acetone (9: 1) and chromatographed on Al_2O_3.

Elution with benzene–acetone (9: 1) gave 48 mg of the starting material (**6**).

Further elution with benzene–acetone (5: 1) afforded crude dihydrolysergic acid diethylamide (II) (**7**) containing a minute amount of the starting material (**6**). Purification of the crude product due to preparative TLC on SiO_2 using MeOH–CH_3CCl_3 (1: 6) as a developing solvent (*Rf*: 0.13) gave 12 mg of colourless prisms, mp 190—191° (lit.[11] mp 190—191°), which were recrystallized from ethyl acetate. $[\alpha]_D^{20}$ +30° (c=0.367, pyridine) [lit.[11] $[\alpha]_D^{25}$ +26° (c=0.6, pyridine)]. ORD (c=0.0302, MeOH) $[M]^{22}$ (nm): +330° (589), +510° (500), +1030° (400), +3400° (330), +10670° (295) (peak), 0° (272), −10200° (250) (trough), −8950° (240). MS *m/e*: 325 (M^+, 100%), 225 ($M^+-CONEt_2$, 60%). High Resolution MS: M^+, *m/e*: 325.216. Calcd. for $C_{20}H_{27}N_3O$: M, 325.215. IR ν_{max}^{KBr} cm^{-1}: 1640 (amide). UV λ_{max}^{EtOH} nm (log ε): 276 (3.76) sh, 282 (3.79), 292 (3.72). NMR ($CDCl_3$) δ: 1.08 (3H, t, J=7 Hz, $CONCH_2C\underline{H}_3$), 1.28 (3H, t, J=7 Hz, $CONCH_2C\underline{H}_3$), 1.87 (2H, m, C_9–H×2), 2.58 (3H, s, NCH_3), 2.4—3.5 (7H, m, aliphatic H), 3.33 (4H, q, J=7Hz, $CON(C\underline{H}_2CH_3)_2$), 6.92 (1H, s, C_2–H), 7.0—7.2 (3H, m, aromatic H), 8.39 (1H, s, NH).

Methyl Lysergate (11)——To a solution of 55 mg of lysergic acid (**10**) in 2 ml of HMPA was added a freshly prepared solution of diazomethane in ether. The mixed solution was allowed to stand in a refrigerator overnight and evaporated to dryness *in vacuo*. After purification by column chromatography on Al_2O_3, the residue was recrystallized from benzene to give 49 mg of colourless prisms, mp 166—168° [lit.[15] mp 168°]. IR ν_{max}^{KBr} cm^{-1}: 1730 ($COOCH_3$). ORD (c=0.0423, MeOH) $[M]^{21}$ (nm): +330° (589), +2000° (400), +10400° (340) (peak), 0° (319), −9660° (300) (trough), −5660° (266) (peak), −18300° (253) (trough), 0° (245). MS *m/e*: 282 (M^+, 100%), 221 ($M^+-HCOOCH_3$–H, 55%). High Resolution MS: M^+, *m/e*: 282.136. Calcd. for $C_{17}H_{18}N_2O_2$: M, 282.137.

Lysergol (12)——A solution of 70 mg of methyl lysergate (**11**) and 40 mg of $LiAlH_4$ in 20 ml of dry THF was refluxed for 1 hr and cooled. After filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$ and chromatographed on Al_2O_3. Elution with $CHCl_3$ gave 7 mg of the starting material (**11**).

Subsequent elution with AcOEt–MeOH (5: 1) gave 49 mg of colourless prisms, mp 255—256° (lit.[16a] mp 253—255°), which were recrystallized from EtOH. MS *m/e*: 254 (M^+, 100%). IR ν_{max}^{KBr} cm^{-1}: 3370 (OH). UV λ_{max}^{EtOH} nm (log ε): 242 (4.25), 313 (3.92).

Lysergene (13)——A solution of 82 mg of lysergol (**12**) in 15 ml of BuOH containing 57 mg of metal sodium was refluxed for 8 hr. The reaction mixture was diluted with a large quantity of water and extracted with benzene. The organic layer was extracted with 1% tartaric acid. The acid solution was made alkaline with 1 N NaOH aq. and extracted with $CHCl_3$. The chloroform solution was dried over anhydr. Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on Al_2O_3 using $CHCl_3$ as a solvent and was recrystallized from ethyl acetate to give 40 mg of colourless needles, mp 243—245° (lit.[17] mp 244—245°). MS *m/e*: 236 (M^+, 100%). UV λ_{max}^{EtOH} nm (log ε): 243 (4.30), 264 (4.15) sh, 337 (4.07). NMR ($CDCl_3$) δ: 2.10 (3H, s, NCH_3), 3.5—4.0 (5H, m, aliphatic H), 4.10 (1H, s, olefinic H), 4.17 (1H, s, olefinic H), 6.33 (1H, s, C_9–H), 7.1—7.3 (3H, m, aromatic H), 8.18 (1H, br. s, NH).

Catalytic Hydrogenation of Lysergene (13)——A solution of 30 mg of lysergene (**13**) in 10 ml of MeOH was hydrogenated over 10 mg of 5% Pd–$BaCO_3$ at atmospheric pressure at room temperature and the catalyst was filtered off. The filtrate was evaporated to dryness *in vacuo*. Preparative TLC of the residue on SiO_2 using the solvent system C (*vide ante*) gave two fractions corresponding to *Rf* 0.45 and *Rf* 0.30 respectively.

21) K. Genest, *J. Chromatogr.*, **19**, 531 (1965).

Lysergine (9)——The fraction showing *Rf* 0.45 was recrystallized from ethyl acetate to give 17 mg of colourless needles, mp 267—268° (lit.[12] mp 265—267°). MS *m/e*: 238 (M^+, 100%), 237 (M^+-1, 80%), 223 (M^+-CH_3, 10%), 195 ($M^+-CH_2=NCH_3$ (retro Diels Alder), 18%). High Resolution MS: M^+, *m/e*: 238.146. Calcd. for $C_{16}H_{18}N_2$: M, 238.147. UV λ_{max}^{EtOH} nm (log ε): 239 (4.20), 311 (3.51). NMR ($CDCl_3$) δ: 1.14 (3H, d, $J=7$ Hz, CH–C<u>H</u>$_3$), 2.55 (3H, s, NCH_3), 3.0—4.0 (6H, m, aliphatic H), 6.32 (1H, diffused d, $J=6$ Hz, C_9–H), 6.99 (1H, s, C_2–H), 7.2—7.3 (3H, m, aromatic H), 8.04 (1H, br. s, NH).

Isolysergine (10)——The fraction showing *Rf* 0.30 was recrystallized from acetone–hexane to give 9 mg of colourless prisms, mp 139—140° (lit.[13] mp 136—137°). MS *m/e*: 238 (M^+, 100%), 237 (M^+-1, 75%), 223 (M^+-CH_3, 8%), 195 ($M^+-CH_2=NCH_3$ (retro Diels Alder), 20%). High Resolution MS: M^+, *m/e*: 238.147. Calcd. for $C_{16}H_{18}N_2$: M, 238.147. UV λ_{max}^{EtOH} nm (log ε): 240 (4.22), 312 (3.55). NMR ($CDCl_3$) δ: 1.20 (3H, d, $J=7$ Hz, CH–C<u>H</u>$_3$), 2.52 (3H, s, NCH_3), 2.8—4.0 (6H, m, aliphatic H), 6.34 (1H, d, $J=5$Hz, C_9–H), 6.97 (1H, s, C_2–H), 7.2—7.4 (3H, m, aromatic H), 8.07 (1H, br. s, NH).

Direct Formation of Lysergine (9) from Lysergol (12)——A solution of 50 mg of lysergol (12) and 123 mg of TsCl in 5 ml of pyridine was allowed to stand at room temperature overnight. A large quantity of benzene and 1% tartaric acid aq. was added to the reaction mixture and the acid solution was separated from the organic phase. The separated aqueous solution was made alkaline with 1 N NaOH aq. and extracted with $CHCl_3$. The chloroform solution was dried over anhydr. Na_2SO_4 and the solvent and pyridine were evaporated under reduced pressure. The residue was chromatographed on Al_2O_3. Elution with benzene–acetone (9: 1) gave 73 mg of a pale yellow oil (lysergol tosylate) which shows a single spot on TLC [*Rf*: 0.75 (the solvent system A)].

A solution of 41 mg of the above pale yellow oil (lysergol tosylate) and 50 mg of $LiAlH_4$ in dry THF was refluxed for 5 hr. After filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on Al_2O_3.

Elution with benzene–acetone (9: 1) afforded colourless prisms, mp 267—269°, which were recrystallized from ethyl acetate. This material was identified by its IR spectrum with a sample of lysergine (9) prepared by hydrogenation of lysergene (13).

Elution with ethyl acetate afforded 8 mg of lysergol (12).

Reduction of Agroclavine (14) with Metal Sodium in Butanol——To a solution of 60 mg of agroclavine (14) in 30 ml of BuOH under reflux was added 100 mg of metal sodium in limited amounts during 3 hr. The reaction mixture was diluted with a large quantity of water and extracted with ethyl acetate. The organic layer was extracted with 1% tartaric acid aq. The acid solution was basified with 1 N NaOH aq. and extracted with ethyl acetate again. The organic layer was dried over anhydr. Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was separated by column chromatography on Al_2O_3 into two fractions, elution with benzene–acetone (9: 1) (fraction A) and elution with ethyl acetate (fraction B). Fraction B which is positive for Ehrlich reagent but shows no fluorescence with UV-light was further fractionated by preparative TLC on SiO_2 using solvent system A to give fraction B_1 (*Rf*: 0.43), fraction B_2 (*Rf*: 0.37), and fraction B_3 (*Rf*: 0.18).

i) Lysergine (9): Recrystallization of fraction A from ethyl acetate gave 40 mg of colourless prisms, mp 266—268°, which were identified by comparison of IR and MS and *Rf* value of TLC with those of an authentic sample of lysergine (9).

ii) Festuclavine (15): Recrystallization of fraction B_1 from MeOH gave 6 mg of colourless prisms, mp 239—241° (lit.[18] mp 238—239°). ORD ($c=0.0675$, MeOH) $[M]^{19°}$ (nm): −340° (589), −470° (500), −890° (400), −1670° (330), −5300° (295) (trough), −2200° (280). MS *m/e*: 240 (M^+, 100%), 225 (M^+-CH_3, 8%). High Resolution MS: M^+, *m/e*: 240.163. Calcd. for $C_{16}H_{20}N_2$: M, 240.163. UV λ_{max}^{EtOH} nm (log ε): 275 (3.82) sh, 282 (3.85), 292 (3.80). NMR ($CDCl_3$) δ: 0.99 (3H, d, $J=6$ Hz, CH–C<u>H</u>$_3$), 1.2—2.6 (3H, m, aliphatic H), 2.0—3.4 (6H, m, aliphatic H), 2.49 (3H, s, NCH_3), 6.90 (1H, s, C_2–H), 7.06 (3H, m, aromatic H), 8.04 (1H, br. s, NH).

iii) Pyroclavine (16): Recrystallization of fraction B_2 from ethyl acetate gave 5 mg of colourless prisms, mp 202—205° (lit.[19] mp 204°). ORD ($c=0.0320$, MeOH) $[M]^{19°}$ (nm): −630° (400), −1180° (330), −2400° (296) (trough), −850° (280). MS *m/e*: 240 (M^+, 100%), 225 (M^+-CH_3, 10%). High Resolution MS: M^+, *m/e*: 240.164. Calcd. for $C_{16}H_{20}N_2$: M, 240.163. UV λ_{max}^{EtOH} nm (log ε): 275 (3.81) sh, 281 (3.84), 292 (3.79).

iv) Costaclavine (17): Recrystallization of fraction B_3 from ethyl acetate gave 1 mg of colourless prisms, mp 180—183° (lit.[19] mp 182°), which was identical with the sample prepared by reduction of lysergine (9) with metal sodium in BuOH.

Catalytic Hydrogenation of Agroclavine (14)——A solution of 5 mg of agroclavine (14) in 10 ml of MeOH was hydrogenated over 5 mg of Pt-black at atmospheric pressure at room temperature for 30 min and the catalyst was filtered off. The filtrate was evaporated to dryness *in vacuo*. Preparative TLC of an oily residue on SiO_2 gave two components (*Rf*: 0.43 and 0.37).

i) Festuclavine (15): Recrystallization of the main component (*Rf*: 0.43) from MeOH gave 4.0 mg of colourless prisms, mp 239—241°, which were identical with the sample of festuclavine (15) obtained by reduction of agroclavine (14) with metal sodium in BuOH.

ii) Pyroclavine (16): Recrystallization of the minor component (*Rf*: 0.37) from ethyl acetate gave 0.4 mg of colourless prisms, mp 203—205°, which were identical with the sample of pyroclavine (16) prepared

by reduction of agroclavine (**14**) with metal sodium in BuOH.

Catalytic Hydrogenation of Lysergine (9) [Festuclavine (15)]——A solution of 12 mg of lysergine (**9**) in 8 ml of MeOH was hydrogenated over 10 mg of 5% Pd–C at atmospheric pressure at room temperature for 3 hr and the catalyst was filtered off. The filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from MeOH gave 10.5 mg of colourless prisms, mp 238—240°, which were identical with the sample of festuclavine (**15**) prepared by reduction of agroclavine (**14**) with metal sodium in BuOH.

Reduction of Lysergine (9) with Metal Sodium in Butanol——To a solution of 20 mg of lysergine (**9**) in 10 ml of BuOH under reflux was added 40 mg of metal sodium during 5 hr. The reaction mixture was diluted with a large quantity of ethyl acetate and water. The organic layer was separated and extracted with 1% tartaric acid aq. The acid solution was basified with 1 N NaOH aq. and extracted with ethyl acetate again. The ethyl acetate solution was dried over anhydr. Na_2SO_4 and evaporated to dryness *in vacuo*. Preparative TLC of the residue on SiO_2 using the solvent system A gave two fractions (*Rf*: 0.43 and 0.18).

i) Festuclavine (**15**): The residue which was obtained from the fraction corresponding to an *Rf* value 0.43 was recrystallized from MeOH to give 10 mg of colourless prisms, mp 238—240°, which were identical with the sample of festuclavine (**15**) prepared by reduction of agroclavine (**14**) with metal sodium in BuOH.

ii) Costaclavine (**17**): The residue which was obtained from the fraction corresponding to an *Rf* value 0.18 was recrystallized from ethyl acetate to give 3 mg of colourless prisms, mp 183—184° [lit.[19] mp 182°]. ORD (c=0.0461, MeOH) $[M]^{19°}$ (nm): +150° (589), +790° (400), +6770° (299) (peak), 0° (282), −10800° (260). MS *m/e*: 240 (M^+, 100%), 225 (M^+-CH_3, 7%). High Resolution MS: M^+, *m/e*: 240.163. Calcd. for $C_{16}H_{20}N_2$: M, 240.163. UV λ_{max}^{EtOH} nm (log ε): 275 (3.83) sh, 282 (3.86), 292 (3.81).

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