Chem. Pharm. Bull. 19(11)2337—2341(1971)

UDC 547.751.04 : 547.831.04

Studies on Lysergic Acid Diethylamide and Related Compounds. I. Synthesis of *d*-N^6-Demethyl-lysergic Acid Diethylamide[1]

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(Received May 4, 1971)

d-N^6-Demethyl lysergic acid diethlyamide (V) was synthesized by the following procedures. von Braun reaction of *d*-lysergic acid diethylamide (LSD) (I) gave *d*-N^6-cyano-N^6-demethyl LSD (II), followed by alkaline hydrolysis in dioxane to give mainly urea type compound (IV) together with a trace of V. The conversion of IV to V was achieved by treatment with sodiun nitrite and tartaric acid. On the other hand, alkaline hydrolysis of II in MeOH gave isourea type compound (VI) and a small amount of V.

Since *d*-lysergic acid diethylamide (LSD) (I) was prepared by Stoll and Hofmann in 1943,[3] various related compounds of I, such as carbonamide-derivatives at the 8 position,[4] halogeno-derivatives at the 2 position,[5] alkyl derivatives at the 1 position[6] and dihydro-derivatives at the 9—10 position,[7] have been synthesized and their psychotomimetic effects have been examined.[8,9] LSD is the strongest hallucinogens among these compounds and produces the

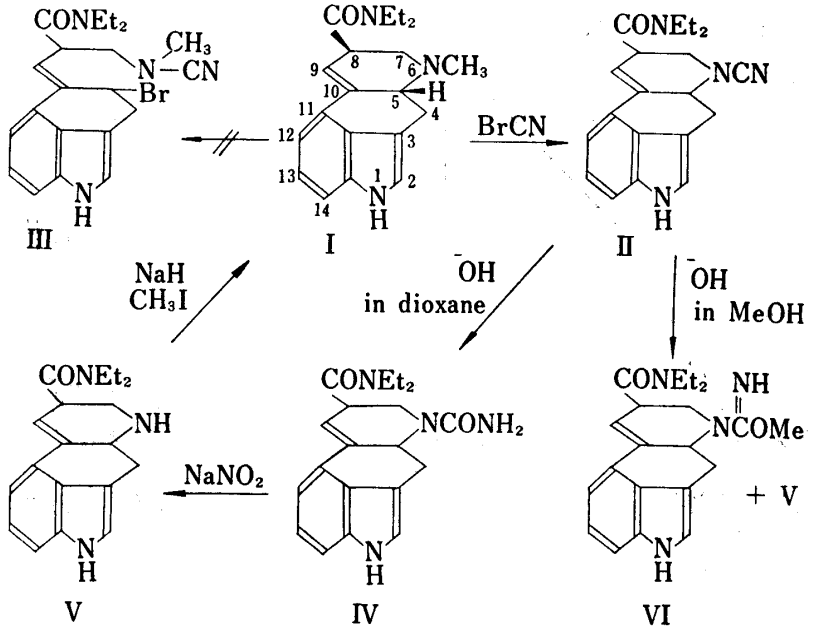

Chart 1

1) A part of this work was reported at the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July 1970.
2) Location: *Sanban-cho, Chiyoda-ku, Tokyo.*
3) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 944 (1943).
4) A. Stoll, J. Rutschmann and A. Hofmann, *Helv. Chim. Acta*, **37**, 820 (1954).
5) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **40**, 2160 (1957).
6) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **40**, 1706 (1957).
7) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **38**, 421 (1955).
8) E. Rothlin, *J. Pharm. Pharmacol.*, **9**, 569 (1957).
9) E. Rothlin, *Ann. N.Y. Acad. Sci.*, **66**, 668 (1957).

action in man by only 1 μg/kg. It has been considered that N-methyl group at the 6 position plays an important role in causing psychotomimetic action, because some phenethylamines and 3-ethylaminoindole have been implicated as psychotomimetics. Furthermore, it has been anticipated that *d*-N^6-demethyl LSD (V) is formed by enzymatic demethylation of I in animal tissues. The present paper deals with a successful conversion to V *via* II and IV from I. von Braun reaction of I in carbon tetrachloride gave *d*-N^6-cyano-N^6-demethyl LSD (II) in 92% yield. The infrared (IR) spectrum showed a CN band at 2250 cm^{-1}, the ultraviolet (UV) spectrum was similar to that of I, the mass spectrum showed molecular ion (M$^+$) at *m/e* 334.177 ($C_{20}H_{22}ON_4$) and in the nuclear magnetic resonance (NMR) spectrum N-methyl siganl disappeared. From these data it was concluded that structure of th product was II. Although it has been known that relative easiness of cleavages of amines by von Braun reaction is ordinarily allyl>benzyl>methyl,[10] in the present reaction the demethylation was easier than ring cleavage. It was supposed that steric hindrance around the 5 position interrupted attack of a bromide ion at the allyl position.

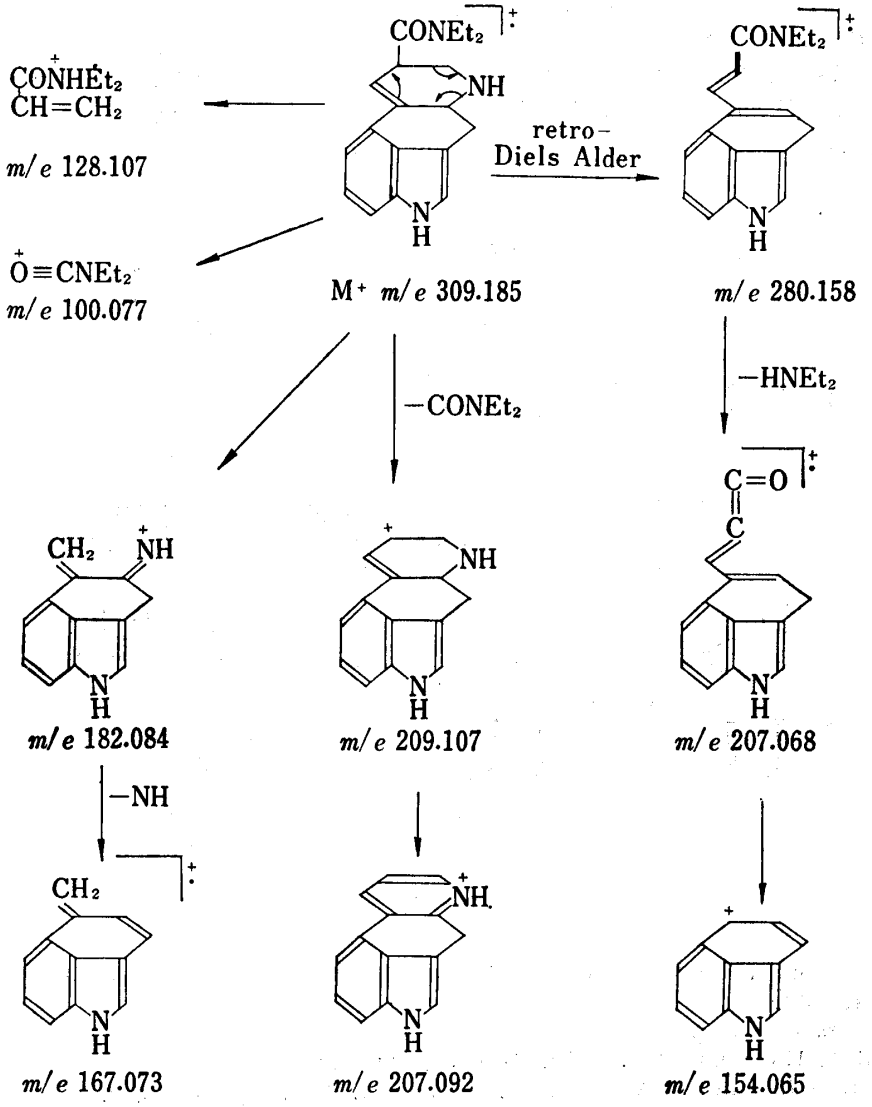

Chart 2

10) H.A. Hageman, "Organic Reactions," Vol. 7, ed. by R. Adams, John Wiley and Sons, Inc., New York, N.Y., 1953, p. 231.

Alkaline hydrolysis of II in dioxane gave an urea-type compound (IV) in 75% yield with a trace of V. The IR spectrum of IV showed disappearance of CN band and appearance of a band at 1663 cm^{-1} to be ascribed to $CONH_2$, and the UV spectrum was similar to that of I. The NMR spctrum showed singlet signal at 5.46 τ due to $CONH_2$, which was decreased by addition of deutrium oxide. In its mass spectrum M^+ occurred at *m/e* 352.191 ($C_{20}H_{24}O_2N_4$). These results supported the structure of IV. The conversion of IV to V was achieved by treatment with sodium nitrite and tartaric acid in 91% yield, whereas the yellow product which was presumed to be N^1-nitroso-compound[11] of V was obtained by using acetic acid instead of tartaric acid. The UV spectrum of V was similar to that of I. The broad singlet signal at 5.38 τ observed in the NMR spectrum of V shown in Fig. 1 was decreased when deuterium oxide added. Consequently, it could be concluded that the signal was assigned to N^6-proton. The mass spectrum showed M^+ at *m/e* 309.186 ($C_{19}H_{23}ON_3$) and the fragmentation pattern elucidated by investigation of metastable ion was shown in Chart 2. A chracteristic ion peak revealed at *m/e* 280, which was induced by retro-Diels-Alder reaction from the parent ion.

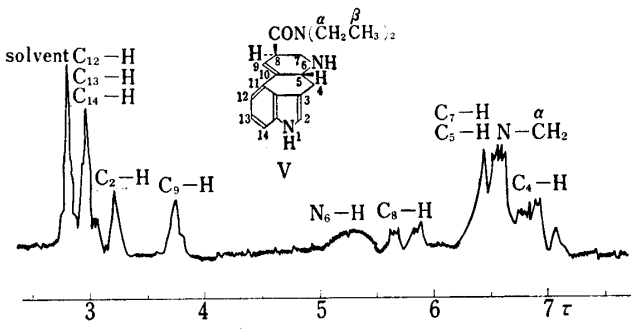

Fig. 1. NMR Spectrum of N^6-Demethyl LSD (V) in $CDCl_3$ (60 Mc)

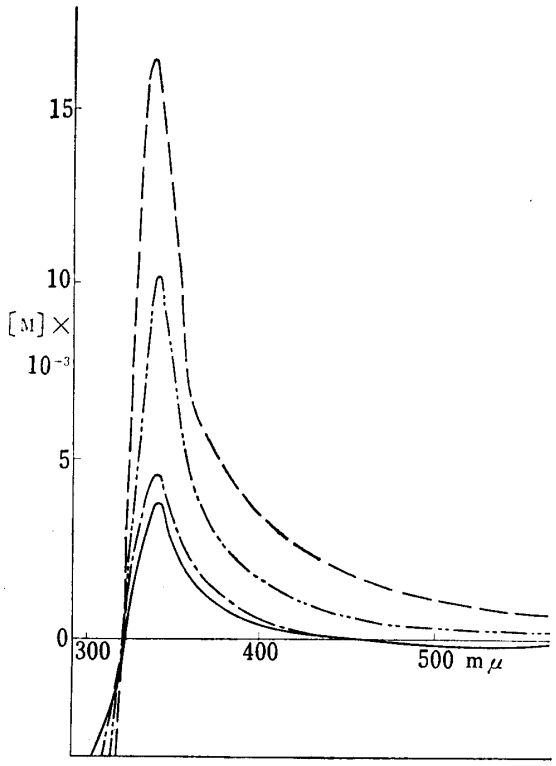

Fig. 2. ORD Curves in MeOH

– – – –: iso LSD —·—·—: I
————: IV ————: V

Acetylation of V in pyridine gave N^6-acetyl-N^6-demethyl LSD, whose mass spectrum showed M^+ at *m/e* 351. Methylation of V using sodium hydride and methyl iodide in dioxane gave mainly I and N^1-methyl-N^6-demethyl LSD as a by-product. These facts elucidated that the compound (V) was a demethyl derivative at the 6 position of I and that our synthetic process was performed with retention of β-configuration of diethylamide group at the 8 position. Thus, V was eventually obtained from I in about 70% yield. On the other hand, alkaline hydrolysis of II in methanol gave V in 20% yield and isourea-type compound (VI) in 46%. The NMR spectrum of VI showed an O-methyl signal at 6.22 τ and the molecular ion in the mass spectrum was observed M^+ at *m/e* 366.203 ($C_{21}H_{26}O_2N_4$). The main product obtained by alkaline hydrolysis of II in methanol was different from that in dioxane. This result agreed with that of syntheses of O-methyl-isoureas having morphinan dihydronormethine skeleton as reported by Seki.[12] The products synthesized were listed in Table I.

11) A. Stoll, F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **35**, 1259 (1952).
12) I. Seki and H. Takagi, *Chem. Pharm. Bull.* (Tokyo), **18**, 1104 (1970).

Table I. N^6-Substituted Lysergic Acid Diethylamide Derivatives

Compound No.	mp (°C)	UV λ_{max}^{EtOH} mμ	$[\alpha]_D$ (°)	Mass measurement for M^+		
				Formula	Calcd.	Found
I	82	312	+30	$C_{20}H_{25}ON_3$	323.200	323.201
II	181	313		$C_{20}H_{22}ON_4$	334.179	334.177
IV	195—196	310	+12	$C_{20}H_{24}ON_4$	352.190	352.191
V	185—186	311	+21	$C_{19}H_{23}ON_3$	309.184	309.185
VI	215—218	311		$C_{21}H_{26}O_2N_4$	366.205	366.203

The optical rotatory dispersion curves of IV and V were shown in Fig. 2 comparing with those of I and iso LSD.

Experimental

All melting points were measured on a hot stage apparatus and were uncorrected. UV spectra were recorded in EtOH on a Hitachi Model EPS-3T spectrophotometer, IR spectra in KBr disk on a JASCO Model DS-201 infrared spectrophotometer and NMR spectra in $CDCl_3$ containing TMS as an internal reference on a JNM-C-60HL spectrometer. Optical rotations were taken in pyridine on JASCO Model DIP 180 polarimeter, optical rotatory dispersion (ORD) curves in MeOH on a JASCO/UV-5. Mass spectra were determined on a JEOL JMS-01SG double focusing mass spectrometer.

***d*-N^6-Cyano-N^6-demethyl LSD (II)**——A solution of 81 mg of LSD (I)[13] in 20 ml of CCl_4 was added to a solution of 110 mg of BrCN in 5 ml of CCl_4 under reflux for 1 hr and continued to reflux for additional 6 hr. The reaction mixture was extracted with 1% tartaric acid solution to exclude the starting material. The CCl_4 solution was evaporated to dryness and the residue was chromatographed on Al_2O_3.[14] The first fraction eluted with 2 liters of benzene–acetone (9:1) was evaporated *in vacuo* and gave colorless needles, mp 181°. UV λ_{max}^{EtOH} mμ: 313. IR ν_{max}^{KBr} cm^{-1}: 3410 (NH), 2250 (CN), 1639 ($CONEt_2$). NMR ($CDCl_3$) τ: 8.75 (6H, triplet, (CH_2-$\underline{CH_3}$)$_2$), 6.53 (4H, quartet, N-($\underline{CH_2}$-CH_3)$_2$), 6.14 (1H, triplet, C_5-H), 5.80 (1H, broad quartet, C_8-H), 3.70 (1H, singlet, C_9-H), 3.07 (1H, singlet, C_2-H), 2.80 (3H, multiplet, arom.-H), 1.70 (1H, broad singlet, N^1-H). Principal peaks in mass spectrum were shown in Table II.

Table II. The Principal Peaks in Mass Spectrum of the Compound (II)

m/e	Observed	Calculated	Assignment	
334	.177	.179	$C_{20}H_{22}ON_4$	M^+
234	.101	.103	$C_{15}H_{12}N_3$	$(M\text{-}CONEt_2)^+$
207	.083	.080	$C_{13}H_9N_3$	$(M\text{-}^{CONEt_2}_{CH=CH_2})^+$
192	.081	.081	$C_{14}H_{10}N$	$[M\text{-}(HCONEt_2+HNCN)]^+$

***d*-N^6-Carbamoyl-N^6-demethyl LSD (IV)**——A solution of 55 mg of II in 5 ml of dioxane was added to 2 ml of 1% NaOH solution and the reaction mixture was left to stand for 2 days at room temperature. Water was added to the mixture, followed by extraction with five 10 ml portions of $CHCl_3$, the organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give reddish oil, which was chromatographed on Al_2O_3.[14] The first fraction eluted with $CHCl_3$ gave a few mg of II, the second fraction with AcOEt was excluded and the third fraction with AcOEt–MeOH (20:1) gave 43 mg (75%) of IV. Recrystallization from AcOEt gave colorless needles, mp 195—196°. $[\alpha]_D^{25}$ +12° (c=0.585, pyridine). UV λ_{max}^{EtOH} mμ: 310, 238 (shoulder). IR ν_{max}^{KBr} cm^{-1}: 3390 (NH), 3340 ($CONH_2$), 1663 ($CONH_2$), 1643 ($CONEt_2$). NMR ($CDCl_3$) τ: 8.88 and 8.75 (6H, triplet, (CH_2-$\underline{CH_3}$)$_2$), 6.58 (4H, quartet, N-($\underline{CH_2}$-CH_3)$_2$), 6.38 (1H, triplet, C_5-H), 5.75 (1H, broad singlet, C_8-H), 5.46 (2H, broad singlet, $CONH_2$), 3.77 (1H, singlet, C_9-H), 3.27 (1H, singlet, C_2-H), 2.8—2.3 (3H, multiplet, arom.-H), 1.70 (1H, singlet, N^1-H). ORD (c=0.0279, MeOH) $[M]^{29}$ (mμ): 0° (589), 0° (400), +4600° (340) (peak), −23700° (255) (trough), +40400° (236) (peak), +13800° (220) (trough), +16400° (215) (peak). Principal peaks in mass spectrum were shown in Table III.

13) W.L. Garbrecht, *J. Org. Chem.*, **24**, 368 (1959).
14) Column chromatography was carried out on aluminum oxide, Merck, Grade II—III.

Table III. The Principal Peask in Mass Spectrum of the Compound (IV)

m/e	Observed	Calculated	Assignment	
352	.191	.190	$C_{20}H_{24}O_2N_4$	M^+
309	.186	.184	$C_{19}H_{23}ON_3$	$(M\text{-}CONH)^+$
280	.158	.158	$C_{18}H_{20}ON_2$	$(M\text{-}CH_2{=}NCONH_2)^+$
207	.090	.092	$C_{14}H_{11}N_2$	$[m/e\ 309\text{-}(HCONEt_2{+}H)]^+$

***d*-N⁶-Demethyl LSD (V)**——To a solution of 35 mg of IV in 3 ml of MeOH, 2 ml of 1% $NaNO_2$ solution and a drop of 1% tartaric acid solution were added and the reaction mixture was left to stand for 10 hr at room temperature. Residue obtained by evaporation of the solvent of the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhydrous sodium sulfate and evaporated to give slightly brownish crystals. Recrystallization from AcOEt gave 28 mg (91%) of colorless needles, mp 185—186°. $[\alpha]_D^{25}$ +21° (c=0.34, pyridine). UV λ_{max}^{EtOH} mμ: 311. IR ν_{max}^{KBr} cm⁻¹: 3360 (indole-NH), 3300 (NH), 1642 ($CONEt_2$), 1090 (NH). NMR ($CDCl_3$) τ: 8.83 and 8.70 (6H, triplet, $(CH_2\text{-}\underline{CH_3})_2$), 6.54 (4H, quartet, N-$(\underline{CH_2}\text{-}CH_3)_2$), 5.75 (1H, double doublet, J_1=7 cps, J_2=1.8 cps, C_8-H), 5.38 (1H, broad singlet, N⁶-H), 3.77 (1H, singlet, C_9-H), 3.26 (1H, singlet, C_2-H), 2.7—3.1 (3H, multiplet, arom.-H), 1.68 (1H, singlet, N¹-H). ORD (c=0.0307, MeOH) $[M]^{29}$ (mμ): −100° (589), −140° (550) (trough), +3700° (340) (peak), −6800° (280) (shoulder), −15000° (256) (trough), +58500° (236) (peak). CD (c=0.0307, MeOH) $[\theta]^{29}$ (mμ): +72000 (317) (positive maximum), −24800 (248) (negative maximum), +39000 (223) (positive maximum).

Acetylation of V——One ml of acetic anhydride was added to a solution of 15 mg of V in 1 ml of pyridine, left to stand at room temperature over-night, and evaporated to dryness *in vacuo*. Mass spectrum of the product which showed practically one spot on thin-layer chromatography (TLC)[15] showed M^+ at *m/e* 351. Additional principal peaks revealed at *m/e* 309, 280, 251, 224, 207, 192, 182, 181, 180, 167, 154, 128, 100 and 72. These peaks suggest that the acetyl-compound is *d*-N⁶-acetyl-N⁶-demethy LSD.

Methylation of V——Excess CH_3I was added to a solution of V (1 mg) and NaH (2 eq.) in 1 ml of dioxane, and stood for 2 days at room temperature. The solvent was evaporated to dryness. The residue gave a main spot at *Rf* 0.50 and another trace spot at *Rf* 0.75 on TLC (MeOH–$CHCl_3$–*n*-hexane, 1:4:2). Mass spectrum of the main spot showed M^+ at *m/e* 323, and principal peaks revealed at *m/e* 280,, 223 and 221. *Rf* values of this product on TLC[15] of three solvent systems were identical with those of the authentic LSD. Mass spectrum of minor spot (*Rf* 0.75) showed M^+ at *m/e* 323 and fragment ion produced by retro-Diels–Alder reaction at *m/e* 294. UV spectrum was identical with N¹-methyl LSD.[16] Therefore, this by-product is presumed to be N¹-methyl-N⁶-demethyl LSD.

Hydrolysis of II in MeOH——To a solution of 54 mg of II in 20 ml MeOH, 12 ml of 2% NaOH solution was added, the reaction mixture was stirred for 7.5 hr at room temperature, followed by evaporation to half volume and extracted with five 15 ml portions of $CHCl_3$. The $CHCl_3$ layer was evaporated to dryness and the residue was chromatographed on Al_2O_3.[14] After elution with benzene the fraction eluted with $CHCl_3$–benzene (2:1) gave 26 mg (46%) of N⁶-isourea type compound (VI) and the fraction eluted with AcOEt gave 11 mg (20%) of (V). Recrystallization of VI from AcOEt gave colorless needles, mp 215—218°. UV λ_{max}^{EtOH} mμ: 311. IR ν_{max}^{KBr} cm⁻¹: 3380 (indole-NH), 3300 (NH), 1643 ($CONEt_2$). NMR ($CDCl_3$) τ: 6.22 (3H, singlet, OCH_3). Principal peaks in mass spectrum were shown in Table IV.

Table IV. The Principal Peaks in Mass Spectrum of the Compound (VI)

m/e	Observed	Calculated	Assignment	
366	.203	.205	$C_{21}H_{26}O_2N_4$	M^+
334	.180	.179	$C_{20}H_{22}ON_4$	$(M\text{-}CH_3OH)^+$
323	.203	.200	$C_{20}H_{25}ON_3$	$(M\text{-}CONH)^+$
309	.187	.184	$C_{19}H_{23}ON_3$	$(M\text{-}CH_3OCN)^+$
266	.131	.130	$C_{16}H_{16}ON_3$	$(M\text{-}CONEt_2)^+$
280	.158	.158	$C_{18}H_{20}ON_2$	$(M\text{-}CH_2{=}NC\langle^{NH}_{OCH_3})^+$
207	.070	.068	$C_{14}H_9ON$	$(m/e\ 280\text{-}HNEt_2)$

Acknowledgement The authors are indebted to Mr. K. Kanota, National Institute of Hygienic Science, for NMR spectral measurements, and to JAPAN Spectroscopic Co. Ltd. for ORD and CD measurements.

15) Thin-layer chromatography was carried out on Silica gel G with the following solvent system: MeOH–$CHCl_3$ (1:4), MeOH–$CHCl_3$–*n*-hexane (1:4:2), and acetone–$CHCl_3$ (4:1).
16) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **40**, 1721 (1957).