Tetrahedron. Vol. 33, pp. 1591 to 1593. Pergamon Press 1977. Printed in Great Britain

STUDIES ON LYSERGIC ACID DIETHYLAMIDE AND RELATED COMPOUNDS—VI[1]

STERIC REQUIREMENTS OF VON BRAUN REACTION

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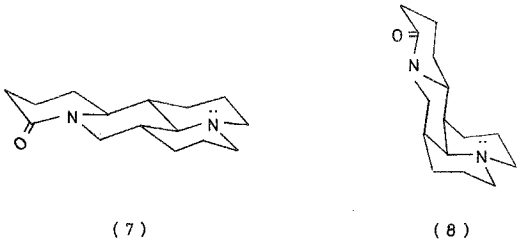
(*Received in Japan* 13 *November* 1976; *Received in UK for publication* 21 *January* 1977)

Abstract—It has been shown that in the ergot alkaloid series the von Braun reaction is hindered if there is a substituent which is 1,3-diaxial with respect to the nitrogen lone pair in the prefered conformation.

In the course of studies on the metabolism of lysergic acid diethylamide (LSD) **1** by animal liver microsomes,[2] we[3] had occasion to examine the von Braun reaction of LSD **1** with cyanogen bromide, and found that N_6-cyanonorlysergic acid diethylamide **2** was produced almost quantitatively. This result seems to be contrary to a widely accepted generalization[4] that cleavage of an *N*-benzyl or an *N*-allyl linkage takes place *prior to* removal of an *N*-methyl group in the von Braun reaction when both groups are located at the same nitrogen. This observation stimulated us to investigate the von Braun reaction of the stereoisomers of LSD **1** and related compounds. In the present paper, we wish to describe our experiments demonstrating that the configuration at C_8 in the substrate is a critical factor.

At the beginning of this research, we examined the von Braun reaction of isolysergic acid diethylamide[5] (isoLSD) **3** which is the C_8 epimer of LSD **1**. Treatment of isoLSD **3** with cyanogen bromide resulted in quantitative recovery of the starting material. This result is quite different from that obtained with LSD,[3] suggesting that the configuration at C_8 position in the starting material plays an important role in this reaction. In order to establish the generality of the effect, we examined the von Braun reaction on two clavine alkaloids, lysergine[1] **4** and isolysergine[1] **5**, which correspond to LSD **1** and isoLSD **3**, respectively, in LSD series, but in which the substituent at C_8 is changed from a diethylamide group to a methyl group. Although lysergine **4** yielded *N*-cyanonorlysergine **6** in good yield on treatment with cyanogen bromide, attack on isolysergine **5** by cyanogen bromide could not be effected, and starting material was recovered almost quantitatively, demonstrating that although the type of substituents at C_8 does not affect the result the configurations are decisive. If it can be assumed that an *N*-methyl group in the prefered conformation of these alkaloids is located at an equatorial position, the preferred conformations of these four alkaloids could be depicted by formula **1**, **3**, **4** and **5**, as in Table 1. These considerations lead us to the conclusion that the von Braun reaction is hindered by the presence of a substituent at a C_8 axial position, in other words, at a position 1,3-diaxial to the lone pair of the tertiary nitrogen atom. This hypothetical steric requirement of von Braun reaction could explain the report that the ring opening reaction takes place smoothly with allomatrine[6] **7** which bears no axial substituents, but not with matrine[6] **8** which has two substituents 1,3-diaxial (its ring C) to the lone pair of the basic nitrogen.



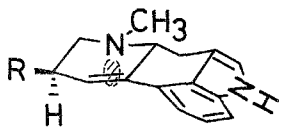
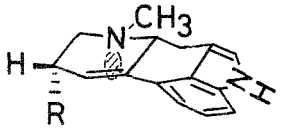
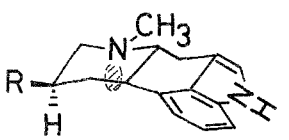
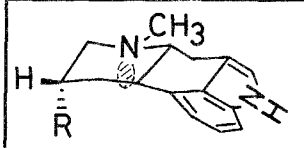
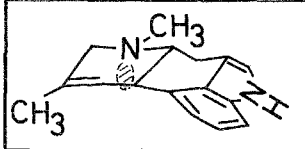
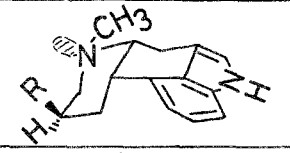
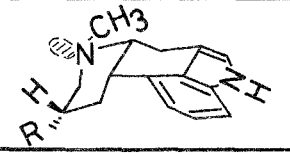
(7) (8)

Chart 1.

In order to confirm the above assumption, the von Braun reaction of dihydrolysergic acid derivatives which have more rigid ring systems was examined. In these experiments, the structures of the demethylated products were established by the following facts: (i) In the mass spectrum of the product the molecular peak was observed at the position corresponding to molecular weight of the *N*-cyano-*N*-demethyl derivate. The elemental composition of the parent peak was determined from high resolution measurements. (ii) In the NMR spectrum, the *N*-methyl signal was absent. (iii) In the IR spectrum, a band due to an N–CN group was observed between 2200–2250 cm^{-1}. (iv) The UV spectrum of the product was essentially the same as that of the starting material.

In a series of the C/D trans alkaloids, dihydrolysergic acid diethylamide (I) **9** and festuclavine **10** which have an 8β substituent (equatorial) were smoothly demethylated by the von Braun reaction to give *N*-6-cyanonordihydrolysergic acid diethylamide (I) **11** and *N*-6-cyanonorfestuclavine **12**, while dihydroisolysergic acid diethylamide (I) **13** and pyroclavine **14** were recovered quantitatively. These results support our interpretation, because the latter two have an 8α substituent in a 1,3-diaxial position with respect to the lone pair of *N*-6 in the prefered conformation showed in Table 1. This

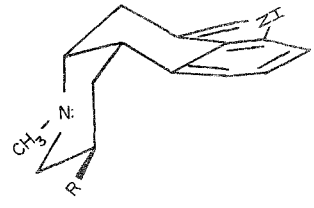
Table 1. The results of von Braun reaction of lysergic acid derivatives

Prefered Conformation	Starting Material	R	Yield
	Lysergic acid diethylamide (1)	$CON^{CH_2CH_3}_{CH_2CH_3}$	92 %
	Lysergine (4)	CH_3	95 %
	Isolysergic acid diethylamide (3)	$CON^{CH_2CH_3}_{CH_2CH_3}$	N R
	Isolysergine (5)	CH_3	N R
	Dihydrolysergic acid diethylamide (I) (9)	$CON^{CH_2CH_3}_{CH_2CH_3}$	85 %
	Festuclavine (10)	CH_3	90 %
	Dihydroisolysergic acid diethylamide(I) (13)	$CON^{CH_2CH_3}_{CH_2CH_3}$	N R
	Pyroclavine (14)	CH_3	N R
	Agroclavine (15)		90 %
	Dihydrolysergic acid diethylamide (II) (17)	$CON^{CH_2CH_3}_{CH_2CH_3}$	N R
	Costaclavine (18)	CH_3	N R
	Dihydroisolysergic acid diethylamide(II) (19)	$CON^{CH_2CH_3}_{CH_2CH_3}$	84 %

N R = no reaction

observation was also supported by the fact that the $\Delta^{8,9}$-alkaloid having a C/D trans ring junction, agroclavine **15**, reacted with cyanogen bromide to give an *N*-6-demethyl product, *N*-6-cyanonoragroclavine **16**.

The situation in a series of the C/D cis alkaloids is more complicated, but provides stronger confirmation of our conclusions. Contrary to the results obtained from the experiments on the C/D trans alkaloids, in the series of the C/D cis alkaloids those having an 8β substituent, [dihydrolysergic acid diethylamide (II) **17** and costaclavine **18**] were recovered from the reaction mixture almost quantitatively, but that having an 8α one [dihydroisolysergic acid diethylamide (II) **19**] on subjection to von Braun reaction gave an *N*-6-cyano-*N*-demethyl product **20**. In the case of the 8β C/D cis alkaloids, two possible conformations must be taken into consideration. In the steroidal geometric forms **17** or **18** about the C/D ring junctions in these 8β C/D trans alkaloids, the 8β substituents [a methyl or a diethylamide group] occupy a 1,3-diaxial position with respect to the lone pair of *N*-6. In the alternative conformation **21**, the C_{10}–C_{11} bond is



(21)

Chart 2.

located at the other 1,3-diaxial position with respect to the same nitrogen.

These experimental facts are enough to show that a substituent at a 1,3-diaxial position with respect to the lone pair of a tertiary nitrogen atom in the preferred conformation hinders attack on the lone pair in the von Braun reaction. The preference of the demethylation to the ring cleavage at an allylic position, the C5–N6 bond in the case of LSD **1** or at the N6–C7 bond in the case of agroclavine **15**, still remains unexplained.

EXPERIMENTAL

M.ps were taken on a hot stage and are uncorrected. IR, NMR with TMS as internal reference, UV, and mass spectra were determined on JASCO DS-701 G, Hitachi-Perkin Elmer R-22 (90 M Hz), EPS-3T, Jeol JMS-01SG spectrometers. The starting materials[1] used in this study were prepared in our laboratory from D-lysergic acid purchased from the Sigma Co. Ltd. The agroclavine was purchased from the Aldrich Chemical Co. Inc.

General procedure for von Braun reaction of lysergic acid derivatives: A solution of freshly sublimed BrCN (1 mmole; 106 mg) in $CHCl_3$ (10 ml) was slowly added to a solution of the starting lysergic acid derivatives (0.1 mmole) in $CHCl_3$ (20 ml) under reflux. After completion of the reaction was confirmed by monitoring on TLC (1–6 h), the solution was cooled, washed with saturated aq. $NaHCO_3$, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was chromatographed on neutral alumina (Brockmann). Elution with benzene-acetone (9:1) to give pure products.

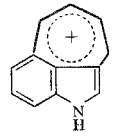
N_6-*Cyanolysergic acid diethylamide* **2**. Treatment of 81 mg of LSD[5] **1** by the general procedure gave 77 mg of N_6-cyanonorlysergic acid diethylamide **2** as colourless needles, m.p. 187–188°, which were recrystallized from ethyl acetate. IR ν_{max}^{KBr} cm^{-1}: 2250 (N–C≡N), 1639 (amide). NMR ($CDCl_3$) δ: 1.18 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 1.29 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 3.0–4.0 (5H, m, aliphatic H), 3.47 (4H, q, J = 7 Hz, $CON(C\underline{H}_2CH_3)_2$), 4.19 (1H, m, C_8–H), 6.30 (1H, s, C_9–H), 6.93 (1H, s, C_2–H), 7.16 (3H, m, aromatic H), 8.30 (1H, br. s, NH). UV λ_{max}^{EtOH} nm (log ϵ): 313 (3.98). High Resolution Mass Spectrum: 334.1779 (M^+, 100%) ($C_{20}H_{22}N_4O$ requires: 334.1793), 234.1018 (M^+-$CONEt_2$, 65%) ($C_{15}H_{12}N_3$ requires: 234.1031), 207.0825 (M^+-CH_2=$CHCONEt_2$, 60%) ($C_{13}H_9N_3$ requires: 207.0800).

N_6-*Cyanonorlysergine* **6**. Treatment of 25 mg of lysergine[1] **8** by the general procedure gave 24.5 mg of N_6-cyanonorlysergine **6** as colourless needles, m.p. 227–229°, which were recrystallized from ethyl acetate. IR ν_{max}^{KBr} cm^{-1}: 2240 (N–C≡N). NMR ($CDCl_3$) δ: 1.19 (3H, d, J = 7 Hz, CH–$C\underline{H}_3$), 2.7–3.6 (6H, m, aliphatic H), 6.31 (1H, br. d, J = 6 Hz, C_9–H), 7.00 (1H, s, C_2–H), 7.22 (3H, m, aromatic H), 8.02 (1H, br. s, NH). UV λ_{max}^{EtOH} nm (log ϵ): 313 (3.96). High Resolution Mass Spectrum: 249.1258 (M^+, 100%) ($C_{16}H_{15}N_3$ requires: 249.1266), 234.1025 (M^+-CH_3, 5%) ($C_{15}H_{12}N_3$ requires: 234.1031).

N_6-*Cyanonordihydrolysergic acid diethylamide* (*I*) **11**. Treatment of 30 mg of dihydrolysergic acid diethylamide (I)[1] **9** by the general procedure gave 26 mg of N_6-cyanonordihydrolysergic acid diethylamide (I) **11** as colourless needles, m.p. 178–179°, which were recrystallized from ethyl acetate. IR ν_{max}^{KBr} cm^{-1}: 2235 (N–C≡N), 1625 (amide). NMR ($CDCl_3$) δ: 1.24 (6H, t, J = 7 Hz, $CON(CH_2C\underline{H}_3)_2$), 1.4–2.1 (5H, m, aliphatic H), 3.0–3.3 (4H, m, aliphatic H), 3.50 (4H, q, $CON(C\underline{H}_2CH_3)_2$), 6.98 (1H, s, C_2–H), 7.30 (3H, m, aromatic H), 8.15 (1H, br. s, NH). UV λ_{max}^{EtOH} nm (log ϵ): 276 (3.79) sh, 282 (3.82), 292.5 (3.73). High Resolution Mass Spectrum: 336.1958 (M^+, 25%) ($C_{20}H_{24}N_4O$ requires: 336.1950), 236.1196 (M^+-$CONEt_2$, 3%) ($C_{15}H_{14}N_3$ requires: 167.0735).

N_6-*Cyanonorfestuclavine* **12**. Treatment of 20 mg of festuclavine[1] **10** by the general procedure gave 18.5 mg of N_6-cyanonorfestuclavine **12** as colourless prisms, m.p. 275–278°, which were recrystallized from ethyl acetate. IR ν_{max}^{KBr} cm^{-1}: 2230 (N–C≡N). NMR ($CDCl_3$) δ: 1.03 (3H, d, J = 8 Hz, >CH–$C\underline{H}_3$), 1.3–1.8 (3H, m, aliphatic H), 2.6–3.6 (6H, m, aliphatic H), 6.93 (1H, s, C_2–H), 6.9–7.2 (3H, m, aromatic H), 8.04 (1H, br. s, NH). UV λ_{max}^{EtOH} nm (log ϵ): 276 (3.80) sh, 282 (3.83), 293 (3.74). High Resolution Mass Spectrum: 251.1433 (M^+, 100%) $C_{16}H_{17}N_3$ requires: 251.1423).

N_6-*Cyanonoragroclavine* **16**. Treatment of 50 mg of agroclavine[1] **15** by the general procedure gave 46.5 mg of N_6-cyanonoragroclavine **16** as colourless prisms, m.p. 207–209°, which were recrystallized from ethyl acetate. IR ν_{max}^{KBr} cm^{-1}: 2231 (N–C≡N). NMR ($CDCl_3$) δ: 1.80 (3H, s, vinyl CH_3), 3.0–3.2 (3H, m, $C_{4\alpha}$–, $C_{4\beta}$– and C_{10}–H), 3.69 (2H, s, $C_{7\alpha}$– and $C_{7\beta}$–H), 3.70 (1H, m, C_5–H), 6.24 (1H, d, J = 2 Hz, C_9–H), 6.96 (1H, d, J = 2Hz, C_2–H), 7.0–7.3 (3H, m, aromatic H), 8.03 (1H, br. s, NH). UV λ_{max}^{EtOH} nm (log ϵ): 277 (3.83) sh, 284 (3.86), 293 (3.80). High Resolution Mass Spectrum: 249.1275 (M^+, 100%) ($C_{16}H_{15}N_3$ requires: 249.1266), 234.1022 (M^+-CH_3, 7%) ($C_{15}H_{12}N_3$ requires: 234.1031).

N_6-*Cyanonordihydroisolysergic acid diethylamide* (*II*) **20**. Treatment of 23 mg of dihydroisolysergic acid diethylamide (II)[1] **19** by the general procedure gave 20 mg of N_6-cyanonordihydroisolysergic acid diethylamide (II) **20** as colourless needles, m.p. 198–201°, which were recrystallized from ethyl acetate. IR ν_{max}^{KBr} cm^{-1}: 2228 (N–C≡N), 1635 (amide). NMR ($CDCl_3$) δ: 1.08 (3H, t, J = 7 Hz, $CONCH_2C\underline{H}_3$), 1.31 (3H, t, J = 7 Hz, $CONCH_2C\underline{H}_3$), 1.8–2.5 (5H, m, aliphatic H), 3.1–3.5 (4H, m, aliphatic H), 3.38 (4H, q, J = 7 Hz, $CON(C\underline{H}_2CH_3)_2$), 6.85 (1H, s, C_2–H), 6.9–7.1 (3H, m, aromatic H), 8.16 (1H, br. s, NH). UV λ_{max}^{EtOH} nm (log ϵ): 277 (3.78) sh, 283 (3.81), 293 (3.74). High Resolution Mass Spectrum: 336.1941 (M^+, 23%) ($C_{20}H_{24}N_4O$ requires: 336.1950), 236.1182 (M^+-$CONEt_2$, 4%) ($C_{15}H_{14}N_3$ require : 236.1188), 167.0750 ( , 100%) ($C_{12}H_9N$ requires: 167.0735).

Results on the recovered materials. Treatment of 39.5 mg of isolysergic acid diethylamide **3**, 5.1 mg of isolysergine **5**, 10.3 mg of dihydroisolysergic acid diethylamide (I) **13**, 4.9 mg of pyroclavine **14**, 15.0 mg of dihydrolysergic acid diethylamide (II) **17**, and 3.4 mg of costaclavine **18** by the general procedure resulted in recovering 37.5 mg **3**, 4.7 mg **5**, 9.7 mg **13**, 4.5 mg **14**, 14.1 mg **17** and 3.1 mg **18** respectively.

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