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REGIOCONTROLLED ELECTROCHEMICAL CYANATION OF ERGOLINES

Karlheinz Seifert, Sigrid Härtling and Siegfried Johne *
Institute of Plant Biochemistry, Academy of Sciences of the GDR,
GDR-4020 Halle/Saale, Weinberg 3

Summary. An electrochemical procedure for the preparation of the 2-cyano ergolines (2) is described.

Some ergot alkaloids are presently used as therapeutic agents. The search continues for more active and especially for more specific acting ergoline compounds [1]. For this reason the substitution in position 2 of the ergoline skeleton is desirable [2,3]. The straightforward synthesis of 2-cyano ergolines should be possible by an anodic cyanation [4].

In a typical experiment, 1a (0.54 mmol) dissolved in a methanolic-aqueous NaCN solution (MeOH 60 ml, H_2O 2 ml, NaCN 400 mg) was electrolyzed at 1.00 V vs standard calomel electrode (SCE) at 22 °C using platinum electrodes in an undivided cell. At the end of the reaction (monitoring by TLC) the crystalline compound 2a was isolated in a yield of 43 %. M.p. 175 °C (acetone); $[\alpha]_D^{24}$ - 146° (c 0.4, pyridine); IR (KBr, cm^{-1}): 2215 (C≡N), 1636 (C=O); MS (m/z): 364 ($M^{+\cdot}$, 100 %); ^1H-NMR (δ ppm, $CDCl_3$, TMS): 7.34 (1H, dd, J 8 Hz, J 6 Hz, arom. H), 7.09 (1H, d, J 8 Hz, arom. H), 6.95 (1H, d, J 6 Hz, arom. H), 3.86 (3H, s, $N-C\underline{H}_3-1$), 3.48 & 3.47 (4H, 2xq, J 7 Hz, $CH_3-C\underline{H}_2-N$), 2.52 (3H, s, $N-C\underline{H}_3-6$), 1.20 & 1.18 (6H, 2xt, J 7 Hz, $C\underline{H}_3-CH_2-N$); ^{13}C-NMR (δ ppm, CD_3OD): 40.5 ($N-\underline{C}H_3-1$),

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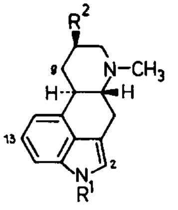
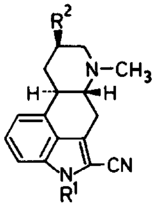


2


a) R^1: CH_3, R^2: $CON(C_2H_5)_2$
b) R^1: CH_3, R^2: $CONH_2$
c) R^1: CH_3, R^2: CH_2CN
d) R^1: CH_3, R^2: CH_2SCH_3
e) R^1: CH_3, R^2: $CH_2SC_6H_5$
f) R^1: $CH_2C_6H_5$, R^2: $CONH_2$

105.7 (C-2), 113.9 (C-3), 27.2 (C-4), 67.6 (C-5), 43.1 (N-$\underline{C}H_3$-6), 60.4 (C-7), 39.7 (C-8), 31.7 (C-9), 41.8 (C-10), 135.3 (C-11), 115.4 (C-12), 128.5 (C-13), 109.0 (C-14), 137.1 (C-15), 125.2 (C-16), 174.5 (C-17), 124.0 (C≡N), 43.5 (N-$\underline{C}H_2$-CH_3), 15.4 (N-CH_2-$\underline{C}H_3$), 13.4 (N-CH_2-$\underline{C}H_3$).
The anodic cyanation of 1b - 1f afforded (2b)[5] and (2c - 2f)[6], respectively, in 41 - 48 % range yield.
The cyanation in position 2 was primarily established by NMR data. In the ^{1}H NMR spectra only the three benzenoid ring protons (H-12, H-13 and H-14) were found. The ^{13}C NMR data of compound 2a are also in agreement with a 2-cyanation. A strong high field shift of C-2 (17.0 ppm) was observed in comparison with 1-methyl-9,10-dihydro-lysergamide[7].

References and Notes

[1] P.A. Stadler, Kem. Ind. 29, 207 (1980).

[2] The electrolysis of ergolines in a 0.5 N methanolic KOH-solution at a potential of 1.30 V yielded the 1-hydroxymethyl derivatives [3] instead of the 2-methoxy ergolines previously postulated by us.

[3] B. Danieli, G. Fiori, G. Lesma and G. Palmisano, Tetrahedron Lett. 24, 819 (1983).

[4] K. Yoshida, J. Am. Chem. Soc. 101, 2116 (1979).

[5] 37 % yield; m.p. 281-83 °C dec (MeOH); $[\alpha]_D^{24}$ - 167° (c 0.5, pyridine); IR (KBr, cm^{-1}): 2218 (C≡N), 1652 (C=O); MS (m/z): 308 M$^{+\cdot}$, 100 %); ^{1}H-NMR ($CDCl_3$/DMSO-d_6 5:1): 7.34 (1H, dd, J 8 Hz, J 6 Hz, arom. H), 7.13 (1H, d, J 8 Hz, arom. H), 6.96 (1H, d, J 6 Hz, arom. H), 3.87 (3H, s, N-$C\underline{H}_3$-1), 2.50 (3H, s, N-$C\underline{H}_3$-6).

[6] The spectroscopic data (IR, MS, ^{1}H NMR) of the 2-cyano ergolines 2c - 2f are in agreement with their structure.
2c: 48 % yield; m.p. 230-32 °C dec (acetone); $[\alpha]_D^{24}$ - 143° (c 0.6, pyridine).
2d: 44 % yield; m.p. 120 °C (MeOH, acetone); $[\alpha]_D^{24}$ - 134° (c 0.8, pyridine).
2e: 41 % yield; m.p. 132 °C (acetone); $[\alpha]_D^{24}$ - 111° (c 0.5, pyridine).
2f: 45 % yield; m.p. 258-60 °C dec (MeOH); $[\alpha]_D^{24}$ - 157° (c 0.2, pyridine).

[7] L. Zetta and G. Gatti, Org. Magn. Res. 9, 218 (1977).

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