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# ON THE ALLEGED ELECTROCHEMICAL METHOXYLATION OF ERGOLINES

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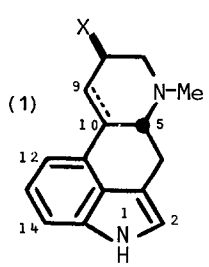
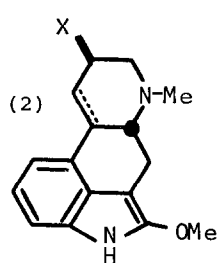
*Summary. The products obtained by controlled potential electrolysis of ergolines (1) in 0.5N KOH-MeOH previously described as 2-methoxy derivatives (2) are actually the 1-hydroxy methyl ergolines (3).*

Although hundreds of ergolines containing substituents in different positions are been synthesized there is a noteworthy lack of 2-alkoxy derivatives in this important class of compounds. The discovery by Yoshida[1] that indoles undergo regiocontrolled anodic cyanation opened the possibility for a straightforward synthesis of the target compounds. A recent German patent[2] claims a general entry to 2-methoxy ergolines (2) by electrochemical methoxylation. In analogy with the results of potentiostatic cyanation[1], a ECE mechanism would be conceivable and the desired compounds were obtained in good yields in spite of the well-known instability of 2-alkoxy indoles[3]. In view of our interest in electrochemical functionalization, the above results caught our attention and, for purpose of comparison, we reexamined the previously reported data. Our observations show not only that different results are obtained but also that the anodic oxidation of (1) in methanol takes a somewhat different course than was originally thought.

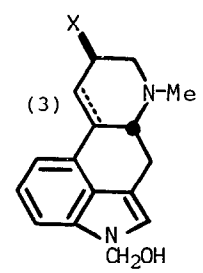
In a typical experiment,(1a)(1.5mmol)in purified MeOH(crudely purged with nitrogen)containing 0.5N KOH was electrolyzed at 1.30V *vs* standard calomel electrode (SCE) at 23°C at graphite electrodes in an undivided cell. The reaction was continued until no more starting material was observable in t.l.c.(4.5F/mol passed) and a nicely crystalline compound was isolated (78%) after work-up. Its m.p. 204°C (dec)|lit.[2] 204-6°C|, $|\alpha|_D^{20}$ -118°(c 0.2,py)|lit.[2]-121.1°|and MS($M^{+\cdot}$ at m/z 299) were identical with those reported[2]. On the basis of spectral data we found that the final product was actually the corresponding 1-hydroxymethyl derivative (3a) instead of 2-methoxy ergoline (2a). The key structural features coming from the PMR analysis were an $A_2X$ spin system (J 6.5Hz) at δ 5.46



(1)



(2)



(3)

a) X:$CONH_2$, 10α-H; b) X:$CONEt_2$, 10α-H; c) X:$CO_2Me$, 10α-H; d) X:$CH_2OH$, $\Delta^9$

and 6.26 (exchangeable with $D_2O$), an upfield aromatic proton (broad singlet, H-2) at δ6.90 and the lack of NH signal which specify the presence and the location of $CH_2OH$ group at N(1). Similar results were obtained in anodic oxidation of (1b), (1c) and (1d) affording (3b)[4], (3c)[5] and (3d)[6], respectively, in 55-80% range yield.

Current-voltage data and products indicated that (1a-d) are electroinactive in the working range of potential available(0-1.5V *vs* SCE)since their addition to solvent-supporting electrolyte system did not cause a cathodic shift in current-voltage behaviour. Therefore the initial step involves not anodic oxidation of (1a-d) but discharge of MeOH to give mainly formaldehyde[7] which in turn undergoes intermolecular capture by N(1). This receives further support from the fact that ergolines (1a-d) readily react with an exhaustively pre-electrolyzed 0.5N KOH solution in MeOH(1.50V *vs* SCE) and with a solution of paraformaldehyde (10 equiv) in 5% KOH-MeOH (r.t., 2 hr) to give the same products (3a-d) in comparable yields. We are forced to conclude that the previous claims for the synthesis of (2) are in error.

In spite of the negative results, successful electrochemical functionalization of ergolines is currently in progress.

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## *References and Notes*

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

[2] Ger.(East)DD 149,667|*Chem.Abstr.*, 96, 104581p(1982)|; K.Seifert and S.Johne, *Die Pharmazie*, 211 (1982). These authors claim that 2-methoxy ergolines act as inhibitors of pituitary prolactin release.

[3] H.Plieninger, H.Bauer, W.Bühler, J.Kurze, and U.Lerch, *Ann.Chem.*, 680, 69 (1964)

[4] 73% yield(1.5V *vs* SCE); m.p. 159°C(dec)(AcOEt-$CH_2Cl_2$); $|\alpha|_D^{20}$ -113°(c 0.2,py)|lit.[2] -90.3°|; *m/z* 355 ($M^{+\cdot}$, 32%), 325($M^{+\cdot}$-$CH_2O$,44), 223(53), 108(100); $\delta_H$($CDCl_3$) 6.86(1H,br s,H-2), 5.56(2H,s,$CH_2OH$), 3.48 & 3.45(4H,2 x q, J 8Hz, $CH_3$-$CH_2$-N), 2.38(3H,s,NMe), 1.30 & 1.18(6H,2 x t,J 8Hz, $CH_3$-$CH_2$-N); $\delta_C$ ($CDCl_3$) 122.8(C-2),111.7(C-3),26.1(C-4),66.0(C-5),59.1(C-7),38.9(C-8),30.4(C-9),39.3(C-10),133.3 (C-11),113.3(C-12),120.6(C-13),107.3(C-14),69.8($CH_2OH$),42.6(NMe),173.2(CO)

[5a] 55% yield(1.2V *vs* SCE); m.p. 191°C(dec)(AcOEt)|lit.[5b] 191-2°C|; $|\alpha|_D^{20}$ -97°(c 0.2,py)|lit.[5b] -100°|; *m/z* 314($M^{+\cdot}$, 100%), 284($M^{+\cdot}$-$CH_2O$, 58); $\delta_H$($CDCl_3$) 6.86(1H,d,J 1.5Hz,H-2), 5.56(2H,s,$CH_2OH$), 3.73 (3H,s,$CO_2$Me), 2.42(3H,s,NMe). [5b] F.Troxler and A.Hofmann, *Helv.Chim.Acta*, 40, 1706 (1957)

[6] 80% yield (1.2V *vs* SCE); m.p. 220°C(dec)(MeOH); $|\alpha|_D^{20}$ +36°(c 0.1,py); *m/z* 284($M^{+\cdot}$,26%), 254($M^{+\cdot}$-$CH_2O$, 100), 223(50), 221(40); $\delta_H$(DMSO-$d_6$) 7.00(1H,br s,H-2), 6.38(1H,br s,H-9), 6.22(1H,t,J 6.5Hz, OH), 5.48(2H,d,J 6.5Hz,N-$CH_2OH$), 2.58(3H,s,NMe)

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