24. Electrochemical Oxidation of Ergolines

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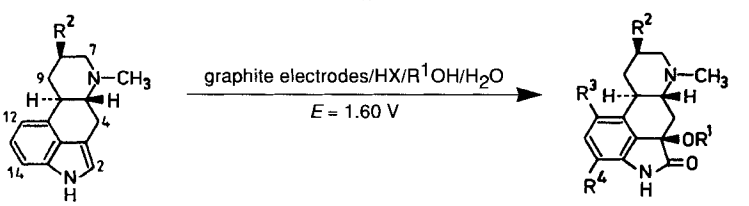
An electrochemical procedure for the preparation of D-3-alkoxy-halogen-2,3-dihydro-6-methyl-2-oxoergolines-I is described.

Introduction. – Ergot is a drug known to mankind for centuries, and some ergot derivatives such as ergotamine, 9,10-dihydroergotamine, and 2-bromo-α-ergocryptine are presently used as therapeutic agents. The search continues for more active and especially more specifically acting ergot compounds [1]. For this reason, the oxidative electrochemical functionalization of the ergoline skeleton attracts interest [2] [3].

Results. – In the cyclic voltammetry of 9,10-dihydrolysergic acid methyl ester (**1**; *Scheme 1*), two irreversible peaks of oxidation at 1.01 V and 1.35 V are observed

Scheme 1



	R^2
1	CO_2CH_3
2	CH_2OH

	R^1	R^2	R^3	R^4
3a	C_2H_5	CO_2CH_3	Cl	Cl
b	C_2H_5	CO_2CH_3	Cl	H
c	CH_3	CH_2OH	Cl	Cl
d	CH_3	CH_2OH	Cl	H
e	C_2H_5	CH_2OH	Cl	Cl
f	C_2H_5	CH_2OH	Cl	H
g	CH_3	CH_2OH	Br	Br

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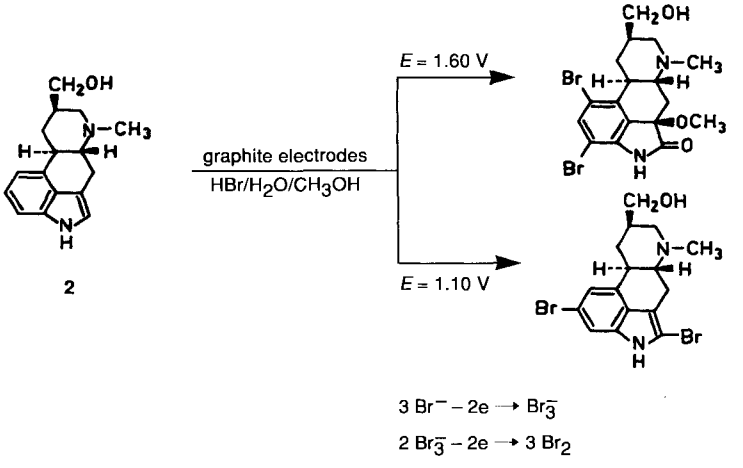
(electrolyte, DMF/0.1*m* $NaClO_4$, sweep rate 10 V/min). The amount of electricity consumed in each step of oxidation is *ca.* 1.9 F/mol. Preparative electrolysis of **1** and 9,10-dihydrolysergol (**2**) in the electrolytes $EtOH/HCl/H_2O$, $MeOH/HCl/H_2O$, and $MeOH/HBr/H_2O$ at a potential of 1.60 V yields the (+)-3-alkoxy-halogeno-2,3-dihydro-6-methylergolin-2-ones (**3a–g**). The theoretical amount of electricity for **3a**, **3c**, **3e**, **3g** is 8 F/mol and for **3b**, **3d**, **3f** 6 F/mol. The coulometry of the preparative electrolysis gives 7.2–9.4 F/mol.

The question is whether the reaction is a direct (formation of an ergoline radical cation as the first step) or an indirect (formation of Cl_2 or Br_2 as the first step) electrosynthesis. The electrolysis of **2** in the electrolyte $MeOH/HBr/H_2O$ (the same electrolyte is used for the synthesis of **3g**) at a potential of 1.10 V leads to 2,13-dibromo-9,10-dihydrolysergol. The brominating agent Br_2 can be produced at the anode at a potential of 1.10 V [4] ($3\ Br^- - 2e \rightarrow Br_3^-$, $2\ Br_3^- - 2e \rightarrow 3\ Br_2$), but the deeper oxidation of the ergoline skeleton only at the higher potential of 1.60 V takes place where (+)-12,14-dibromo-2,3-dihydro-8β-(hydroxymethyl)-3β-methoxy-6-methylergolin-2-one (**3g**) is formed (*Scheme 2*). This result indicates a direct electrosynthesis.

Scheme 2



The structures of the compounds were established by their spectral data and X-ray analysis of **3g** (*Fig.*, *Table*). The two Br-atoms of **3g** are at C(12) and C(14). The bond distances and angles do not show any abnormal values, but there is probably a weak intramolecular H-bond between H–N(1) and Br–C(14). The geometry is as follows: N···Br 3.330 Å, NH···Br 2.980 Å, NH···Br 103°. Based on the known configurations at C(5) and C(8) of ergotamine (5*R*,8*R*), and C(5), C(8), and C(10) of 9,10-dihydroergotamine (5*R*,8*R*,10*R*) [5] (X-ray analysis), the absolute configuration at C(3) of **3g** is derived as *R*.

The CD spectrum of **3g** is characterized by three main CD bands (314 nm (−3.90), 278 nm (−10.71), 259 nm (+10.78)). The CD spectra of compounds **3a–f** are very similar to that of **3g**. Accordingly, the absolute configuration at C(3) of the ergolines **3a–f** is also *R*.

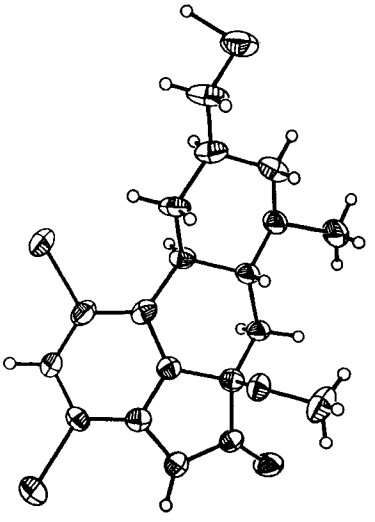


Figure. *ORTEP Drawing of* **3g** *with thermal ellipsoids at the 50% probability level.* For systematic numbering, see *Scheme 1.*

Table. *Atomic Coordinates and Temperature Factors* [Å^2]

Atom	x	y	z	U_{eq}[a])
N(1)	0.0774(6)	0.2148(9)	0.0375(5)	0.037(2)
C(2)	−0.0322(7)	0.2072(8)	0.0980(5)	0.032(2)
O(2)	−0.0989(6)	0.1015(7)	0.1085(5)	0.045(2)
C(3)	−0.0500(7)	0.3632(8)	0.1414(5)	0.031(2)
O(3)	−0.1502(4)	0.4324(6)	0.0698(4)	0.033(1)
C(4)	−0.0778(7)	0.3793(8)	0.2580(5)	0.031(2)
C(5)	−0.0759(7)	0.5463(8)	0.2793(5)	0.030(2)
N(6)	−0.1171(6)	0.5890(8)	0.3845(5)	0.036(2)
C(7)	−0.1398(8)	0.7500(11)	0.3859(6)	0.045(3)
C(8)	−0.0161(8)	0.8361(9)	0.3653(6)	0.039(2)
C(9)	0.0411(9)	0.7855(10)	0.2627(6)	0.040(2)
C(10)	0.0628(8)	0.6181(8)	0.2694(5)	0.030(2)
C(11)	0.1352(7)	0.5517(8)	0.1815(5)	0.031(2)
C(12)	0.2671(7)	0.5832(10)	0.1615(6)	0.037(2)
Br(12)	0.3720(1)	0.7232(2)	0.2428(1)	0.063(1)
C(13)	0.3324(7)	0.5077(10)	0.0874(6)	0.036(2)
C(14)	0.2750(7)	0.3875(9)	0.0356(5)	0.034(2)
Br(14)	0.3673(1)	0.2798(2)	−0.0622(1)	0.055(1)
C(15)	0.1483(7)	0.3438(9)	0.0601(5)	0.031(2)
C(16)	0.0806(7)	0.4323(9)	0.1255(5)	0.028(2)
C(17)	−0.2803(8)	0.3742(11)	0.0664(8)	0.053(3)
C(18)	−0.2430(10)	0.5165(12)	0.4082(8)	0.059(3)
C(19)	−0.0417(12)	1.0019(10)	0.3622(7)	0.051(3)
O(19)	−0.0916(7)	1.0540(9)	0.4563(5)	0.059(2)
Ca	0.3343(20)	0.2385(36)	0.3063(15)	0.134(6)[b])
Cb	0.3841(16)	0.3097(25)	0.3976(12)	0.106(5)[b])
Cc	0.5021(18)	0.2664(26)	0.4501(13)	0.118(5)[b])
Cd	0.5797(21)	0.1466(30)	0.4028(16)	0.131(6)[b])
Ce	0.5372(30)	0.0837(41)	0.3012(24)	0.184(11)[b])
Cf	0.4055(23)	0.1330(39)	0.2612(18)	0.155(8)[b])

[a]) Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.
[b]) Isotropic temperature factor.

The IR spectra of **3a–g** show a C=O band at 1715–1755 cm^{-1} for the C(2)=O group [6]. The C(2)=O and the MeO_2C moiety of **3a** and **3b** have the same absorption at 1730 cm^{-1}. In the UV, two typical maxima at 261–266 and 307–314 nm are observed [7]. The mass spectra show the molecular ions.

In the ^{1}H-NMR spectra of the monochloro compounds **3b**, **3d**, and **3f**, 2*d* (J = 8 Hz) in the range of 7.18–7.29 and 6.65–6.75 ppm, respectively, are observed. The ^{1}H-NMR chemical shifts (in $CDCl_3$) of H–C(6) and H–C(7) of 5-chloro-2,3-dihydro-3-methyl-3-(methylthio)indol-2-one [8] are known (7.20 ppm (*dd*, J = 8, 2, H–C(6)); 6.87 ppm (*dd*, J = 8, 1, H–C(7))) and in good agreement with those of **3b**, **3d**, and **3f** (C(12), C(13), and C(14) of the ergoline correspond to C(5), C(6), and C(7) of the indole). The ^{1}H-NMR spectra of the dichloro compounds **3a**, **3c**, and **3e** show a *s* at 7.28–7.32 ppm, which is in the range of the chemical shift of H–C(13) (7.18–7.29) of the monochloro compounds **3b**, **3d**, and **3f**. So, the substances **3a**, **3c**, and **3e** should be 12,14-dichloro-substituted (the influence of a Cl-atom on the chemical shift of a proton in *ortho*-position is very small [9]).

On the basis of the ^{13}C-NMR data of 2,3-dihydroindol-2-one, 5-chloro-2,3-dihydroindol-2-one [10], 9,10-dihydrolysergic acid methyl ester, festuclavine [11], and 10α-methoxy-9,10-dihydrolysergic acid methyl ester [12], the ^{13}C-NMR signals of **3e**, **3f**, and **3g** are assigned and are in accordance with the structures.

We wish to thank Prof. Dr. *G. Snatzke* and Dr. *Guo Jia*, Ruhr University Bochum (FRG), for measuring and interpretation of the CD spectra.

Experimental Part

General. TLC: silica gel HF_{254} (*Merck*). Column chromatography (CC): glass powder *CPG-10* (120–200 mesh, *Electro-Nucleonics Inc.*). M.p.: *Kofler* hot stage. $[\alpha]_D$: in MeOH. UV: λ_{max} in nm (lg ε). CD: in MeCN, λ_{max} in nm ($\Delta\varepsilon_{max}$). IR: in KBr, $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR: at 100 MHz (*Varian XL 100*) and 200 MHz (*Bruker WP 200*), δ in ppm, J in Hz. ^{13}C-NMR: at 50 MHz (*Bruker WP 200*). MS: mass spectrometer of the Research Institute '*Manfred von Ardenne*', Dresden, data in m/z (rel. %).

Controlled-Potential Electrolysis. The nondivided cell consists of a 800-ml vessel, equipped with two cylindrical carbon electrodes (surface 6 cm^2) and a magnetic stirrer. The reference electrode is a sat. calomel electrode (SCE). *9,10-Dihydrolysergic acid methyl ester* (**1**) and *9,10-dihydrolysergol* (**2**) (0.4–1.2 mmol) are dissolved in 240–720 ml of $EtOH/H_2O/HCl$ (*Method A*), $MeOH/H_2O/HCl$ (*Method B*) (0.21–0.63 mol of HCl, 0.70–2.11 mol of H_2O in EtOH and MeOH, resp.) and $MeOH/H_2O/HBr$ (*Method C*; 0.091–0.27 mol of HBr, 0.70–2.11 mol of H_2O) and electrolyzed at r.t. The anodic oxidation is performed at a constant potential of 1.60 V. At the end of the electrolysis, half of the electrolyte is evaporated, $NaHCO_3$ is added followed by extraction with $CHCl_3$ (4 ×). The combined org. phases are evaporated, and the residue is purified by CC on glass powder.

(+)-Methyl 12,14-Dichloro-3β-ethoxy-2,3-dihydro-6-methyl-2-oxoergoline-8β-carboxylate (**3a**; *Method A*). Yield 24%. Crystals (benzene). M.p. 116–118°. $[\alpha]_D^{23}$ = +56 (c = 0.31). CD: 314 (–3.70), 276 (–9.22), 256 (+10.93), 227 (+9.33). IR: 1730, 1620, 1455, 1270, 1075. UV (dioxan): 224 (4.34), 263 (3.76), 313 (3.28). ^{1}H-NMR ($CDCl_3$): 7.28 (*s*, H–C(13)); 2.44 (*s*, CH_3–N(6)); 1.16 (*t*, J = 7, CH_3CH_2). MS: 412[2]) (17, M^+), 397[2]) (5), 383[2]) (35), 368[3]) (98), 366[2]) (100), 351[2]) (21), 338[2]) (28), 307[2]) (27), 279[2]) (29), 254[3]) (38), 252[2]) (26).

(+)-Methyl 12-Chloro-3β-ethoxy-2,3-dihydro-6-methyl-2-oxoergolin-8β-carboxylate (**3b**; *Method A*). Yield 10%. Crystals (benzene/acetone). M.p. 114°. $[\alpha]_D^{23}$ = +36 (c = 0.24). CD: 308 (–6.42), 274 (–10.22), 255 (+13.34), 233 (–1.56). IR: 1730, 1610, 1450, 1260, 1230, 1070. UV (dioxan): 219 (4.24), 261 (3.75), 307 (3.16). ^{1}H-NMR

[2]) ^{35}Cl.

[3]) ^{35}Cl superimposed with ^{37}Cl of the fragment ion which is 2 mass units smaller.

($CDCl_3$): 7.18 (*d*, *J* = 8, H–C(13)); 6.65 (*d*, *J* = 8, H–C(14)); 2.37 (*s*, CH_3–N(6)); 1.11 (*t*, *J* = 7, CH_3CH_2). MS: 378^2) (8, M^+), 349^2) (27), 334^3) (82), 332^2) (100), 317^2) (20), 304^2) (42), 273^2) (33), 245^2) (38), 220^3) (44), 218^2) (41).

(+)-12,14-Dichloro-2,3-dihydro-8β-(hydroxymethyl)-3β-methoxy-6-methylergolin-2-one (**3c**; *Method B*). Yield 30%. Crystals (benzene/MeOH). M.p. 130–132°. $[\alpha]_D^{23}$ = +62 (*c* = 0.34). CD: 313 (–5.26), 276 (–13.07), 257 (+14.78), 236 (–2.47), 226 (+9.44), 210 (–4.09). IR: 1740, 1610, 1450, 1220, 1050. UV (MeOH): 224 (4.34), 264 (3.75), 314 (3.30). ^{1}H-NMR ($CDCl_3$/CD_3OD 1:1): 7.29 (*s*, H–C(13)); 3.29 (*s*, CH_3O); 2.43 (*s*, CH_3–N(6)). MS: 370^2) (100, M^+), 355^2) (56), 340^3) (78), 338^2) (67), 327^2) (17), 310^2) (34), 307^2) (69), 279^2) (10), 254^3) (27), 252^2) (27).

(+)-12-Chloro-2,3-dihydro-8β-(hydroxymethyl)-3β-methoxy-6-methylergolin-2-one (**3d**; *Method B*). Yield 12%. Crystals (benzene/MeOH). M.p. 260–262°. $[\alpha]_D^{23}$ = +42 (*c* = 0.36). CD: 308 (–5.52), 274 (–11.20), 253 (+11.26), 232 (–1.12), 221 (+10.69), 202 (–4.02). IR: 1725, 1610, 1450, 1230, 1050. UV (MeOH): 219 (4.30), 263 (3.80), 309 (3.07). ^{1}H-NMR (CD_3OD): 7.29 (*d*, *J* = 8, H–C(13)); 6.75 (*d*, *J* = 8, H–C(14)); 3.22 (*s*, CH_3O); 2.40 (*s*, CH_3–N(6)). MS: 336^2) (100, M^+), 321^2) (60), 306^3) (81), 304^2) (81), 293^2) (35), 276^2) (38), 273^2) (73), 245^2) (19), 220^3) (22), 218^2) (30).

(+)-12,14-Dichloro-3β-ethoxy-2,3-dihydro-8β-(hydroxymethyl)-6-methylergolin-2-one (**3e**; *Method A*). Yield 23%. Crystals (acetone). M.p. 198°. $[\alpha]_D^{23}$ = +60 (*c* = 0.33). CD: 312 (–3.46), 276 (–8.41), 254 (+8.78), 277 (+8.16). IR: 1745, 1715, 1615, 1450, 1360, 1220, 1070. UV (MeOH): 224 (4.26), 263 (3.72), 314 (3.28). ^{1}H-NMR (CD_3OD): 7.32 (*s*, H–C(13)); 2.42 (*s*, CH_3–N(6)); 1.14 (*t*, *J* = 7, CH_3CH_2). ^{13}C-NMR (CD_3OD): 178.4 (*s*, C(2)); 77.8 (*s*, C(3)); 33.4 (*t*, C(4)); 65.6 (*d*, C(5)); 43.1 (*q*, CH_3–N(6)); 60.0 (*t*, C(7)); 39.7 (*d*, C(8)); 30.5 (*t*, C(9)); 42.0 (*d*, C(10)); 136.5 (*s*, C(11)); 130.2 (*s*, C(12)); 133.0 (*d*, C(13)); 115.1 (*s*, C(14)); 140.3 (*s*, C(15)); 129.1 (*s*, C(16)); 66.0 (*t*, CH_2OH); 62.7 (*t*, CH_3CH_2); 15.8 (*q*, CH_3CH_2). MS: 384^2) (97, M^+), 369^2) (14), 355^2) (83), 340^3) (100), 338^2) (81), 327^2) (29), 310^2) (60), 307^2) (73), 279^2) (29), 254^3) (48), 252^2) (38).

(+)-12-Chloro-3β-ethoxy-2,3-dihydro-8β-(hydroxymethyl)-6-methylergolin-2-one (**3f**; *Method A*). Yield 12%. Crystals (EtOH). M.p. 272–274°. $[\alpha]_D^{23}$ = +49 (*c* = 0.42). CD: 307 (–6.66), 274 (–12.32), 253 (+12.35), 233 (–1.42), 219 (+13.41). IR: 1740, 1725, 1610, 1450, 1380, 1240, 1070. UV (MeOH): 218 (4.35), 263 (3.83), 308 (3.23). ^{1}H-NMR (CD_3OD): 7.27 (*d*, *J* = 8, H–C(13)); 6.72 (*d*, *J* = 8, H–C(14)); 2.40 (*s*, CH_3–N(6)); 1.11 (*t*, *J* = 7, CH_3CH_2). ^{13}C-NMR (CD_3OD): 179.1 (*s*, C(2)); 77.3 (*s*, C(3)); 33.4 (*t*, C(4)); 65.9 (*d*, C(5)); 43.4 (*q*, CH_3–N(6)); 60.4 (*t*, C(7)); 39.7 (*d*, C(8)); 30.8 (*t*, C(9)); 42.1 (*d*, C(10)); 137.9 (*s*, C(11)); 129.0 (*s*, C(12)); 133.7 (*d*, C(13)); 110.7 (*d*, C(14)); 142.5 (*s*, C(15)); 128.6 (*s*, C(16)); 66.1 (*t*, CH_2OH); 62.9 (*t*, CH_3CH_2); 15.8 (*q*, CH_3CH_2). MS: 350^2) (65, M^+), 335^2) (5), 321^2) (65), 306^3) (100), 304^2) (80), 293^2) (27), 276^2) (63), 273^2) (63), 245^2) (27), 220^3) (58), 218^2) (58).

(+)-12,14-Dibromo-2,3-dihydro-8β-(hydroxymethyl)-3β-methoxy-6-methylergolin-2-one (**3g**; *Method C*). Yield 30%. Crystals (benzene/acetone). M.p. 144–146°. $[\alpha]_D^{23}$ = +58 (*c* = 0.53). CD: 314 (–3.90), 278 (–10.58), 258 (+10.72), 239 (–1.83), 220 (+6.16). IR: 1755, 1610, 1440, 1220, 1060, 680. UV (dioxan): 227 (4.19), 266 (3.83), 314 (3.38). ^{1}H-NMR (CD_3OD): 7.68 (*s*, H–C(13)); 3.24 (*s*, CH_3O); 2.40 (*s*, CH_3–N(6)). ^{13}C-NMR (CD_3OD): 177.1 (*s*, C(2)); 78.4 (*s*, C(3)); 33.5 (*t*, C(4)); 65.6 (*d*, C(5)); 44.5 (*q*, CH_3–N(6)); 62.7 (*t*, C(7)); 39.7 (*d*, C(8)); 30.1 (*t*, C(9)); 41.9 (*d*, C(10)); 138.7 (*s*, C(11)); 117.3 (*s*, C(12)); 138.9 (*d*, C(13)); 102.4 (*s*, C(14)); 138.7 (*s*, C(15)); 129.7 (*s*, C(16)); 66.0 (*t*, CH_2OH); 51.8 (*q*, CH_3O). MS: 460^4) (100, M^+), 445^4) (72), 428^4) (91), 397^4) (85).

X-Ray Analysis. Diffraction data are collected at r.t. on a *Nicolet-R3* diffractometer (Mo*K*α radiation) using the ω-scan technique. Unit cell dimensions are determined by least-squares refinement of the setting angles of 25 accurately centered, independent strong reflections with $20° < 2\Theta < 30°$. Three standard reflections are monitored every 300 reflections, and show no significant variation in intensity. Raw data are corrected for *Lorentz* and polarization effects and for absorption (analytical correction, transmission factors in the range 0.73–0.85). The two Br positions are determined from the *Patterson*. The structure is expanded using *Fourier* techniques (SHELXTL, version 5.1) [13]. The absolute configuration is established based on the known configurations at C(5), C(8), and C(10). There is one molecule of benzene solvent per molecule of the main compound. All H-atoms are located in a difference *Fourier* synthesis (with the exception of those of the solvent) and are refined using a riding model. A correction for extinction is applied ($F^* = F_c/(1+0.0000058^* F_c^2/\sin 2\Theta)^{0.25}$). (The * indicates multiplication.) Crystal data: $C_{17}H_{20}N_2O_3Br_2 \cdot C_6H_6$, Formula wt. 538.28, monoclinic, space group $P2_1$, a = 10.0587 (9) Å, b = 9.111 (1), Å c = 12.689 (1) Å, β = 95.055 (8)°, V = 1158.4 (3) Å^3, Z = 2, D_x = 1.543 g/cm^3, μ = 3.489 mm^{-1}, R = 0.058, R_w = 0.061, weighting function $w = (\sigma^2(F)+0.00676^* F^2)^{-1}$.

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4) $^{79}Br^{81}Br$.

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