# 2-FORMYL DERIVATIVES OF 6-METHYLERGOLINE-I*

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Reaction of ergoline derivatives *I*, *III*—*VI* with 2-alkoxy-1,3-dithiolan, generated *in situ*, gave the 2-(1,3-dithiolan-2-yl) derivatives *VII*, *XI*—*XIV*. Hydrolysis of the thioacetal group in these compounds produced 2-formylergoline derivatives, *XV*—*XIX*, which proved to have only a weak inhibitory effect on the secretion of prolactin.

The introduction of a substituent to position 2 of the ergoline skeleton is known to be associated with a marked pharmacological effect. The recently prepared[1] 2-halogen and 2-methyl derivatives of D-6-methyl-8-ergoline-I-ylacetamide (Deprenon$^R$), compared to the non-substituted compound, had much higher hypotensive effects and lower inhibitory effects on the secretion of prolactin. The possibility of further chemical modifications at position 2 of the ergoline skeleton has been limited by paucity of suitable methods for introducing more reactive groups. Good starting compounds for such modifications are 2-formyl derivatives of ergoline, whose preparation is described in the present paper.

Direct formylation into position 2 had not yet been accomplished. The literature[1,2] describes a Friedel–Crafts reaction, by which the derivatives *I* and *II* were converted into thioacetal *VII* and its homologue *VIII*. The compound *VII* was reduced with lithium aluminium hydride in tetrahydrofuran to the alcohol *IX*, which was converted *in situ* to the *p*-toluenesulphonate *X*. Its reaction with sodium cyanide in dimethyl sulphoxide gave a low yield of the nitrile *XI*, which we were unable to hydrolyse to the amide *XII*. We tried another route and have found that the modified Friedel–Crafts thioacetalization[2] of the ergoline derivatives *III*—*VI*, using 2-alkoxy-1,3-dithiolan prepared *in situ* from 1,2-ethanedithiol and an ester of formic acid, with titanium(IV) chloride as catalyst, is compatible with the presence of not only the ester group, but also other common functional groups, including the amide one, and affords high yields of the thioacetals *XI*—*XIV* (Table I).

Following conversion of the thioacetals *VII*, *XI*—*XIV* into the corresponding aldehydes *XV*—*XIX*, we tried hydrolysis in the presence of mercuric salts[2]; the reaction products contained mercury and were difficult to purify. Of the numerous

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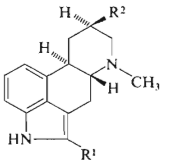
methods described[3], the best one proved to be the modification[4] using a heterogeneous reaction system, *viz.* moist silica gel – sulphuryl chloride in chloroform. The desired aldehydes *XV–XIX* were obtained in high yields and purity (Table II).



*I–VI*, $R^1 = H$

*I*, $R^2 = COOCH_3$
*II*, $R^2 = CH_2COOCH_3$
*III*, $R^2 = CH_2CN$
*IV*, $R^2 = CH_2CONH_2$
*V*, $R^2 = CH_3$
*VI*, $R^2 = CH_2Cl$

*VII–XIV*, $R^1 = CH$

*VII*, $R^2 = COOCH_3$
*VIII*, $R^2 = CH_2COOCH_3$
*IX*, $R^2 = CH_2OH$

*X*, $R^2 = CH_2OSO_2$ 

*XI*, $R^2 = CH_2CN$
*XII*, $R^2 = CH_2CONH_2$
*XIII*, $R^2 = CH_3$
*XIV*, $R^2 = CH_2Cl$

*XV–XIX*, $R^1 = CHO$

*XV*, $R^2 = CO_2CH_3$
*XVI*, $R^2 = CH_2CN$
*XVII*, $R^2 = CH_2CONH_2$
*XVIII*, $R^2 = CH_3$
*XIX*, $R^2 = CH_2Cl$

The compounds *XV–XIX* were informatively tested for the antinidation and antilactation effects, which indicate inhibition of secretion of the adenohypophyseal prolactin. The assays were carried out with rats Wistar (Konárovice), the usual methods being used[5]. In doses 0·1 mg/kg the prolactin-inhibitory effects were not significant.

## EXPERIMENTAL

The melting points, determined on the Koffler block, are not corrected. Samples for analysis were dried at a pressure of about 60 Pa over phosphorus pentoxide at temperatures adequate to the melting points. UV/VIS spectra were recorded with an apparatus Unicam SP 8000, IR spectra with a spectrophotometer Unicam SP 200G, $^1$H-NMR spectra ($\delta$ values) with an apparatus Tesla BS487C (80 MHz) with tetramethylsilane as internal standard (unless otherwise specified), the optical rotations with a polarimeter Perkin–Elmer 141 and mass spectra with a spectrometer Varian MAT 44S. Homogeneity of the compounds prepared was checked by thin-layer chromatography on Silufol UV 254 in systems chloroform–ethanol–triethylamine (92 : 6 : 2) and benzene–dioxan–ethanol–ammonium hydroxide (48 : 38 : 10 : 5). The starting compounds, *I*, *III–VI*, were obtained by reported procedures[6–9].

2-(1,3-Dithiolan-2-yl)-6-methyl-8-*p*-toluenesulphonyloxymethylergoline-I (*X*)

A solution of the ester *VII* (0·776 g, 2 mmol) in tetrahydrofuran (10 ml) was added dropwise to a suspension of lithium aluminium hydride (0·152 g, 4 mmol) in tetrahydrofuran (10 ml). The mixture was stirred 1 h at room temperature and decomposed with water. The precipitate was collected on a filter and extracted with tetrahydrofuran (50 ml). The filtrate and the extract were combined and distilled *in vacuo*; the residue was dissolved in pyridine (50 ml). To the cooled solution (0°C) was added *p*-toluenesulphonyl chloride (0·42 g, 2·2 mmol) and after 48 h the mixture was poured into an excess of water. The precipitate was collected on a filter, chromatographed (silica gel, 2% methanol–chloroform) and crystallized.

TABLE I

8-Substituted derivatives of 2-(1,3-dithiolan-2-yl)-6-methylergolin-I

| Compound | Yield, % m.p., °C | Solvent | $[\alpha]_D^{20}$ [a] | Formula (mol.mass.) | Calculated/Found % C | % H | % N |
|---|---|---|---|---|---|---|---|
| *X* [b] | 63<br>167—171 | ethanol | −67·7 | $C_{26}H_{30}N_2O_3S_3$<br>(514·7) | 60·67<br>60·31 | 5·87<br>5·74 | 5·44<br>5·40 |
| *XI* [c] | 87<br>241—244 | chloroform–ethanol | −99·7 | $C_{20}H_{23}N_3S_2$<br>(369·5) | 65·00<br>64·90 | 6·27<br>6·19 | 11·37<br>11·57 |
| *XII* [d] | 58<br>262—267 | methanol | −78·8 | $C_{20}H_{25}N_3OS_2$<br>(387·67) | 61·98<br>61·78 | 6·50<br>6·49 | 10·84<br>10·46 |
| *XIII* [e] | 96<br>213—216 | chloroform–ethanol | −96·0 | $C_{19}H_{24}N_2S_2$<br>(344·5) | 66·24<br>66·49 | 7·02<br>6·87 | 8·13<br>8·29 |
| *XIV* [f] | 96<br>336—339 | chloroform ethanol | −88·7 | $C_{19}H_{23}ClN_2S_2$<br>(379·0) | 60·21<br>60·29 | 6·12<br>6·12 | 7·39<br>7·37 |

[a] Concentration 0·5; pyridine; [b] UV spectrum (methanol): $\lambda_{max}(\log \varepsilon) = 286$ (4·15), 225 (4·60) nm; IR spectrum (KBr): 3 340 (NH), 1 355, 1 170 ($OSO_2$), 840 (*p*-disubstituted Ar) $cm^{-1}$; $^1$H-NMR spectrum ($CD_3SOCD_3$): $\delta = 10·60$ (s, 1 H, NH); 7·80 (d, $J = 8·5$ Hz, 2 H, ArH); 7·40 (d, $J = 8·5$ Hz, 2 H, ArH); 6·50—7·10 (m, 3 H, ArH); 6·00 (s, 1 H, SCHArS); 3·98 (d, $J = 5·5$ Hz, 2 H, $CH_2O$); 2·40 (s, 3 H, $NCH_3$); 2·28 (s, 3 H, $ArCH_3$). [c] UV spectrum (methanol): $\lambda_{max}(\log \varepsilon) = 287$ (4·09), 231 (4·36) nm; IR spectrum (KBr): 3 360 (NH), 2 225 (CN) $cm^{-1}$; mass spectrum: $m/e = 369$ ($M^+$); $^1$H-NMR spectrum (pentadeuteropyridine, hexamethyldisiloxane): $\delta = 11·60$ (s, 1 H, NH); 6·60—7·20 (m, 3 H, ArH); 6·20 (s, 1 H, SCHArS); 2·12 (s, 3H, $NHC_3$); [d] UV spectrum (methanol): $\lambda_{max}(\log \varepsilon) = 286$ (4·13), 230 (4·36) nm; IR spectrum (KBr): 3 330 (NH), 1 610 (CO) $cm^{-1}$; mass spectrum: $m/e = 387$ ($M^+$); [e] UV spectrum (methanol): $\lambda_{max}(\log \varepsilon) = 282$ (4·05), 227 (4·38) nm; IR spectrum (KBr): 3 340 (NH) $cm^{-1}$; $^1$H-NMR spectrum ($CDCl_3$): $\delta = 8·20$ (s, 1 H, NH); 7·00 (m, 3 H, ArH); 5·92 (s, 1 H, SCHArS); 3·40 (m, 4 H, $SCH_2CH_2S$); 2·41 (s, 3 H, $NCH_3$); 0·97 (d, 3 H, $CH_3$); [f] UV spectrum (methanol): $\lambda_{max}(\log \varepsilon) = 287$ (4·09), 231 (4·33) nm; IR spectrum (KBr): 3 360 (NH) $cm^{-1}$; mass spectrum: $m/e = 379$ ($M^+$); $^1$H-NMR spectrum (pentadeuteropyridine, hexamethyldisiloxane): $\delta = 11·60$ (s, 1 H, NH); 6·60—7·20 (m, 3 H, ArH); 6·20 (s, 1 H, SCHArS); 2·15 (s, 3 H, $NCH_3$).

2-(1,3-Dithiolan-2-yl)-8-cyanomethyl-6-methylergoline-I (*XI*)

To a solution of the *p*-tolylsulphonate *X* (0·438 g, 1 mmol) in dimethyl sulphoxide (60 ml) was added a solution of NaCN (0·735 g, 15 mmol) in water (10 ml). The mixture was stirred for 5 h at 90°C under argon, poured into a large excess of water, and the precipitate was collected on a filter. The product (0·133 g, 36%) was chromatographed (silica gel, 3% methanol–chloroform) and crystallized.

Thioacetals *XI*—*XIV*

A modified method[2] was used; ethyl formate instead of the low-boiling methyl ester was used, the yields being comparable. The reaction time was reduced to 24 h and the mixture was decomposed with methanol at −20°C. Use of freshly distilled 1,2-ethanedithiol and work under the inert gas kept the yields constant.

TABLE II

8-Substituted derivatives of 2-formyl-6-methylergoline-I

| Compound | Yield, % m.p. °C | Solvent | $[\alpha]_D^{20}$ [a] | Formula (mol.mass) | Calculated/Found | | |
|---|---|---|---|---|---|---|---|
| | | | | | % C | % H | % N |
| *XV* [b] | 78<br>203—204 | ethanol | −152·2 | $C_{18}H_{20}N_2O_3$<br>(312·7) | 69·20<br>— | 6·51<br>— | 9·02<br>— |
| *XVI* [c] | 86<br>275—280 | chloroform–ethanol | −119·4 | $C_{18}H_{19}N_3O$<br>(293·4) | 73·69<br>73·51 | 6·53<br>6·54 | 13·32<br>14·11 |
| *XVII* [d] | 61<br>[e] | ethanol | − 81·8 | $C_{18}H_{21}N_3O_2$<br>(311·4) | 69·43<br>68·99 | 6·80<br>7·08 | 13·49<br>13·25 |
| *XVIII* [f] | 91<br>283—287 | chloroform–ethanol | −145·3 | $C_{17}H_{20}N_2O$<br>(268·4) | 76·09<br>75·75 | 7·51<br>7·80 | 10·44<br>10·24 |
| *XIX* [g] | 93<br>264—267 | chloroform–ethanol | −100·0 | $C_{17}H_{19}ClN_2O$<br>(302·8) | 67·43<br>67·38 | 6·32<br>6·41 | 9·25<br>9·05 |

[a] Concentration 0·5; pyridine; [b] reported[2] m.p. 198—202°C; $(\alpha)_D^{20} = -150·6$ ($c = 1$, pyridine); [c] UV spectrum (methanol): $\lambda_{max}(\log \varepsilon) = 315$ (4·44), 242 (4·22), 205 (4·36) nm; IR spectrum (KBr): 2 220 (CN), 1 650 (CO) $cm^{-1}$; mass spectrum: $m/e = 293$ ($M^+$); [c] UV spectrum (methanol): $\lambda_{max}(\log \varepsilon) = 312$ (4·35), 240 (4·14), 226 (4·23), 208 (4·17) nm; IR spectrum (KBr): 3 380, 3 185, 1 650, 1 640 ($CONH_3$), 3 290 (NH), 1 660 (CO) $cm^{-1}$; mass spectrum: $m/e = 311$ ($M^+$); $^1$H-NMR spectrum ($CD_3SOCD_3$): $\delta = 11·45$ (bs, 1 H, NH); 9·90 (s, 1 H, CHO); 6·60—7·40 (m, 3 H, ArH); 3·78; 2·60 (dd, 2 H, $CH_2CON$); 2·35 (s, 3 H, $NHC_3$); 2·10 (m, 1 H, $CHCH_2CON$); [e] not melting up to 350°C; [f] UV spectrum (methanol): $\lambda_{max}(\log \varepsilon) = 315$ (4·41), 242 (4·22), 205 (4·35) nm; IR spectrum (KBr): 3 060 (NH), 1 645 (CO) $cm^{-1}$; mass spectrum: $m/e = 268$ ($M^+$); [g] UV spectrum (methanol): $\lambda_{max}(\log \varepsilon) = 315$ (4·38), 242 (4·20), 205 (4·35) nm; IR spectrum (KBr): 3 060 (NH), 1 650 (CO) $cm^{-1}$; mass spectrum: $m/e = 303$ ($M^+$).

Aldehydes *XV–XIX*

To a stirred solution of the thioacetal (10 mmol) in a minimum amount of chloroform silica gel (7·5 g, particle size 0·063–0·2 mm) was added, then water (7·5 ml) was added dropwise. Under constant stirring of the suspension, kept below 20°C, a solution of sulphuryl chloride (3·24 g,, 24 mmol) in chloroform (50 ml) was added dropwise in the course of 15 min. After 2 more hours of stirring at room temperature potassium carbonate (12 g, 87 mmol) was added and the stirring was continued for 20 min. The mixture was filtered, the filter cake was washed with chloroform, moistened with ethanol, taken into a saturated solution of NaCl (200 ml) and repeatedly shaken with chloroform. The chloroform portions and the filtrate were combined, dried ($MgSO_4$) and distilled *in vacuo*. The products were purified by chromatography and crystallization from suitable solvents.

*Pharmacological tests of the compounds were carried out by Dr K. Řežábek and coworkers, elemental analyses by Mrs J. Komancová at the Analytical Department (head Dr J. Kőrbl), polarimetric measurements by Mrs I. Bendová.* UV, $^1$H NMR *and mass spectra were measured and interpreted by Dr J. Vachek, Dr J. Holubek and Dr J. Schlanger of the Physico-chemical Department (head Dr B. Kakáč).*

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