D-1-CARBOXYMETHYL-8β-CARBOXY-6-METHYLERGOLINE AND SOME 1,8-DISUBSTITUTED ERGOLINES DERIVED FROM IT*

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Reaction of D-8β-carboxy-6-methylergoline (*I*) with ethyl bromo acetate gave D-1-carboxy-8β--carboxy-6-methylergoline (*II*), whose dimethyl ester *III* was reduced with sodium borohydride, either selectively to D-1-(2-hydroxyethyl)-8β-methoxycarbonyl-6-methylergoline (*IV*) or completely to D-1-(-2-hydroxyethyl)-8β-hydroxymethyl-6-methylergoline (*V*). Derivatives *VI*—*XV* of compounds *IV* and *V* have also been prepared.

In the preceding communication[1] we described alkylation of 8β-ergoline derivatives at position $N_{(1)}$. The present paper deals with the synthesis of $N_{(1)}$-substituted 8β-ergolines having two functional groups.

Reaction of D-8β-carboxy-6-methylergoline, *I* (D-9,10-dihydrolysergic–I acid), with ethyl bromoacetate under the conditions described[1] gave D-(1-carboxymethyl)--8β-carboxy-6-methylergoline (*II*); its dimethyl ester *III* was reduced with sodium borohydride in two degrees. Selective reduction of the ester group at position 1 produced D-1-(2-hydroxyethyl)-8β-methoxycarboxyl-6-methylergoline (*IV*). The structure of the ester *IV* was confirmed by its ^{1}H-NMR spectrum. The multiplets 4·10 and 3·90 (δ, ppm) prove safely the presence of the group $N_{(1)}$—CH_2—CH_2—OH. A large excess of sodium borohydride reduced both ester groups, with the formation for D-1-(2-hydroxyethyl)-8β-hydroxymethyl-6-methylergoline (*V*).

The diol *V* was converted by reaction with methanesulphonyl chloride into the dimesyl derivative *VI*, which, in turn, by the action of potassium cyanide in dimethylformamide at 100°C, gave the dinitrile *VII*. At higher temperatures (170°C) the reaction product was D-8β-cyanomethyl-6-methylergoline (*VIII*), as a result of the β-elimination reaction at $N_{(1)}$. Hydrogenation of the dinitrile *VII* afforded the diamine *IX*, which was characterized as the diacetyl derivative *X*. The diol *V* was converted by phosphorus oxychloride into the dichloro derivative *XI*, or by acetic anhydride into the diacetate *XII*. Reaction of the diester *III* with hydrazine hydrate gave the dihydrazide *XIII*. Analogously, the hydroxy ester *V* yielded, *via* the mesylate *XIV*, the cyanoester *XV*.

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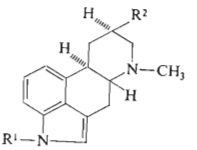

	R^1	R^2
I	H	COOH
II	CH_2COOH	COOH
III	CH_2COOCH_3	$COOCH_3$
IV	CH_2CH_2OH	$COOCH_3$
V	CH_2CH_2OH	CH_2OH
VI	$CH_2CH_2OSO_2CH_3$	$CH_2OSO_2CH_3$
VII	CH_2CH_2CN	CH_2CN
VIII	H	CH_2CN
IX	$CH_2CH_2CH_2NH_2$	$CH_2CH_2NH_2$
X	$CH_2CH_2CH_2NHCOCH_3$	$CH_2CH_2NHCOCH_3$
XI	CH_2CH_2Cl	CH_2Cl
XII	$CH_2CH_2OCOCH_3$	CH_2OCOCH_3
XIII	$CH_2CONHNH_2$	$CONHNH_2$
XIV	$CH_2CH_2OSO_2CH_3$	$COOCH_3$
XV	CH_2CH_2CN	$COOCH_3$

For biological application these compounds were brought to the form of hydrogen tartrates, which were applied as aqueous solutions. Secretion of prolactin was inhibited, but less than by compounds prepared earlier[2]. These tests were performed by a team of workers, under the supervision of Dr Řeřábek, in the Research Institute of Pharmacy and Biochemistry.

EXPERIMENTAL

The melting points, determined on the Boetius block, are not corrected. Samples for analysis were dried at a pressure of 30 Pa and room temperature or at 77°C. Specific rotations were determined in a polarimeter Perkin–Elmer 141 and refer to compounds free of the crystallization solvent. The ^{1}H-NMR spectrum was measured in a spectrometer Tesla BS 487C at 80 MHz (δ in ppm). Purity of the compounds was checked by thin-layer chromatography on silica gel; the spots were detected with UV light of wave lengths 254 and 366 nm.

D-1-Carboxymethyl-8β-carboxy-6-methylergoline (*II*)

To a suspension of pulverized potassium hydroxide (3·4 g, 60 mmol) in dimethyl sulphoxide (30 ml) was added D-9,10-dihydrolysergic acid (*I*, 2·7 g, 10 mmol). After 30 min stirring the mixture was cooled down to 17°C and at this temperature ethyl bromo acetate (1·92 g, 12·5 mmol)

was added dropwise in the course of 5 min. The stirring was continued for another 5 min. The solution was poured into water (300 ml) and brought to pH 6 with acetic acid. The precipitate was collected on a filter and dissolved in 1% ammonia (100 ml). The solution was filtered and brought to pH 6 with acetic acid. The product (acid *II*) was dried at 100°C/30 Pa; m.p. above 360°C, $(\alpha)_D^{20}$ −68° (*c* 0·5, 0·1M-NaOH). For $C_{18}H_{20}N_2O_4$ (328·4) calculated: 65·84% C, 6·14% H, 8·53% N; found: 65·95% C, 6·28% H, 8·31% N.

D-1-Methoxycarbonylmethyl-8β-methoxycarbonyl-6-methylergoline (*III*)

A solution of the acid *II* (11·5 g, 35 mmol) in methanol (115 ml) was saturated with anhydrous hydrogen chloride for 6 h and the solvent was evaporated. The dry residue was stirred up in a saturated solution of hydrogen carbonate (100 ml), the separated base was taken into chloroform, the extract was dried ($MgSO_4$) and the solvent was distilled off. Recrystallization from aqueous methanol gave 10·3 g (82·5%) of the diester *III*, m.p. 103—104°C; $(\alpha)_D^{20}$ −95° (*c* 0·5, pyridine). For $C_{20}H_{24}N_2O_4$, (356·4) calculated: 67·39% C, 6·79% H, 7·86% N; found: 67·53% C, 6·85% H, 7·93% N.

D-1-Hydroxyethyl-8β-methoxycarbonyl-6-methylergoline (*IV*)

To a stirred solution of the diester *III* (3·6 g, 10 mmol) in methanol (100 ml) was added $NaBH_4$ (3·8 g, 0·1 mol) in portions in the course of 1 h. The mixture was refluxed for 1 h, cooled and poured into water (400 ml). The precipitate was dried and recrystallized from methanol 0·92 g, 28%, m.p. 174—176°C; $(\alpha)_D^{20}$ −100·6° (*c* 0·5, pyridine). For $C_{19}H_{24}N_2O_3$ (328·4) calculated: 69·49% C, 7·37% H, 8·53% N; found: 69·54% C, 7·51% H, 8·69% N. ^{1}H-NMR spectrum ($CDCl_3$): 4·10 (m, 2 H, $N_{(1)}$ CH_2CH_2OH), 3·90 (m, 2 H, $N_{(1)}$ CH_2CH_2OH), 3·69 (s, 3 H, $COOCH_3$), 2·30 (s, 3 H, $N_{(6)}$ CH_3).

D-1-(2-Hydroxyethyl)-8β-hydroxymethyl-6-methyl-ergoline (*V*)

To a stirred solution of the diester *III* (10 g, 28 mmol) in methanol (350 ml) was gradually added $NaBH_4$ (53·2 g, 1·40 mol). The mixture was refluxed for 1 h, cooled and poured into water (350 ml). The precipitate was dried and recrystallized from methanol; needles (5·8 g, 69%) melting at 203—204°C; $(\alpha)_D^{20}$ −86° (*c* 0·5, pyridine). For $C_{18}H_{24}N_2O_2$ (300·4) calculated: 71·97% C, 8·05% H, 9·33% N; found: 71·57% C, 8·24% H, 9·22% N.

D-1-(2-Cyanomethyl)-8β-cyanomethyl-6-methylergoline (*VII*)

To a stirred solution of compound *V* (6·0 g, 20 mmol) in acetonitrile (100 ml) and pyridine (60 ml) at 5°C was slowly added dropwise a solution of methanesulphonyl chloride (8 ml) in acetonitrile (20 ml). The mixture was stirred 1 h, poured into water (1 000 ml), alkalinized with a solution of sodium hydroxide and extracted into chloroform. The solvent was distilled of and the dimesyl derivative *VI* was obtained as an oil. To a stirred solution of the derivative *VI* in dimethylformamide (200 ml) was added dropwise a solution of potassium cyanide (13 g) in water (20 ml). The mixture was kept at 100°C for 4 h, cooled and poured into water (1 500 ml). The precipitate was collected on a filter and recrystallized from ethanol; yield 5·1 g (80·1%), m.p. 206—208°C; $(\alpha)_D^{20}$ −92° (*c* 0·4, pyridine). For $C_{20}H_{22}N_4$ (318·4) calculated: 75·44% C, 6·97% H, 17·60% N; found: 75·62% C, 6·97% H, 17·28% N.

D-8β-(2-Acetylaminoethyl)-1-(3-acetylaminopropyl)-6-methylergoline (*X*)

A mixture of the dinitrile *VII* (1·24 g, 4 mmol), ethanol (100 ml) and Raney nickel (6 g) was hydrogenated at 40°C and an atmospheric pressure for 5 h. The catalyst was filtered off and the ethanol removed by evaporation. The diamine *IX* was left as an oil. To a solution of the diamine *IX* in a mixture of chloroform (25 ml) and triethylamine (1 ml) acetyl chloride (0·8 ml) was added dropwise at 0°C. The mixture was stirred for 3 h, poured into water and alkalinized with aqueous $NaHCO_3$. The product was taken into chloroform, the solvent was distilled off and the residue was recrystallized from methanol; yield 0·65 g (39·6%) of the diacetyl derivative *X*, m.p. 198—200°C; $(\alpha)_D^{20}$ −68° (*c* 0·4, pyridine). For $C_{24}H_{34}N_4O_2$ (410·5) calculated: 70·21% C, 8·35% H, 13·65% N; found: 69·92% C, 8·12% H, 13·39% N.

D-1-(2-Chloroethyl)-8β-chloromethyl-6-methylergoline (*XI*)

A mixture of the diol *V* (6·0 g, 20 mmol) in phosphorus oxychloride (100 ml) was refluxed for 0·5 h. The volatile components were distilled off *in vacuo*, the residue was poured into water and alkalinized with aqueous $NaHCO_3$. The product was taken into chloroform, the solvent was distilled off and the residue was recrystallized from ethanol; yield 2·3 g (34·1%) of the dichloro derivative *XI*, m.p. 165—168°C; $(\alpha)_D^{20}$ −84° (*c* 0·4, pyridine). For $C_{18}H_{22}Cl_2N_2$ (337·3) calculated: 64·09% C, 6·58% H, 21·02% Cl, 8·31% N; found: 64·01% C, 6·82% H, 21·62% Cl, 8·07% N.

D-1-(2-Acetyloxyethyl)-8β-acetyloxymethyl-6-methylergoline (*XII*)

A mixture of the diol *V* (6·0 g, 20 mmol) and acetic anhydride (60 ml) was heated to 100°C for 1 h. The acetic anhydride was removed *in vacuo*, the residue was poured into water, alkalinized with aqueous $NaHCO_3$ and the product was extracted into chloroform. After distilling off the solvent the diacetyl derivative *XII* was recrystallized from ethanol; yield 5·2 g (67·7%), m.p. 99—100°C, $(\alpha)_D^{20}$ −78° (*c* 0·4, pyridine). For $C_{21}H_{26}N_2O_4$ (384·5) calculated: 68·72% C, 7·34% H, 7·28% N; found: 68·61% C, 7·38% H, 7·05% N.

Dihydrazide of D-1-Carboxymethyl-8β-carboxy-6-methylergoline (*XIII*)

A mixture of the diester *III* (2·14 g, 6 mmol) and 100% hydrazine hydrate (12 ml) was refluxed for 4 h. After cooling water was added (12 ml), the precipitate was collected on a filter and recrystallized from ethanol; yield 1·8 g (84·2%), m.p. 252—255°C. For $C_{18}H_{24}N_6O_2$ (356·4) calculated: 60·65% C, 6·78% H, 23·58% N; found: 60·51% C, 6·99% H, 23·89% N.

D-1-(2-Cyanomethyl)-8β-methoxycarbonyl-6-methylergoline (*XV*)

To a stirred solution of the hydroxy ester *IV* (1·31 g, 4 mmol) in acetonitrile (20 ml) and pyridine (12 ml) at 5°C was added dropwise a solution of methanesulphonyl chloride (0·63 ml) in acetonitrile (4 ml). After stirring for 1 h the mixture was poured into water (200 ml), alkalinized with aqueous NaOH and the product was taken into chloroform. The solvent was distilled off, leaving the oily mesyl derivative *XIV*. This was dissolved in dimethylformamide (100 ml), potassium cyanide (2·6 g) was added and the mixture was heated to 100°C for 4 h. It was then cooled, poured into water (1 500 ml) and the product was extracted into chloroform. The solvent was distilled off and the cyanoester *XV* was recrystallized from methanol; yield 0·82 g (60·8%), m.p. 134 to 135°C, $(\alpha)_D^{20}$ −94° (*c* 0·5, pyridine). For $C_{20}H_{23}N_3O_2$ (337·4) calculated: 71·20% C, 6·87% H, 12·45% N; found: 71·35% C, 6·92% H, 12·21% N.

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