SOME 6-SUBSTITUTED DERIVATIVES OF D-8-CYANOMETHYLERGOLINE-I AND D-8-METHYLERGOLINE-I*

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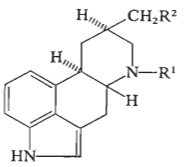
Compounds *III*–*XX* exhibiting antilactation and antinidation effects in tests on rats were prepared on $N_{(6)}$-alkylation of D-8-cyanomethylergoline-I (*I*) or D-8-methylergoline-I (*II*) with corresponding bromo (chloro) derivatives in dimethylformamide. The most distinct prolactin-inhibiting activity was found in compound *III*.

In our previous communication[1] we described the preparation of 6-alkyl derivatives of D-8-cyanomethylergoline-I and D-8-methylergoline-I and also presented the results of the evaluation of their prolactin-inhibiting effect in rats, manifested for example, by antinidation and antilactation activity. We found that on introduction of an ethyl- and n-propyl group into position 6 of D-8-cyanomethylergoline-I (*I*) and D-8-methylergoline-I (*II*) a large increase in antinidation activity is observed in comparison with analogous 6-methyl compounds, by about one order of magnitude. Further alkyl groups (C_4 to C_7) do not have a substantial effect on the mentioned activity, while the isopropyl compounds are practically inactive as prolactin-inhibiting agents. We were then interested to see the effect on biological activity of the introduction of some other substituents into position 6 of compounds *I* and *II*, *i.e.* of substituents that could affect the biological availability of the mentioned substances to a larger extent. Working in this direction we synthetized 6-substituted derivatives *III*–*XX*.



I, $R^1 = H$, $R^2 = CN$
II, $R^1 = R^2 = H$
III–*XX*, see Table I

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Compounds *III*–*VII* were prepared by $N_{(6)}$-alkylation of compound *I* with allyl, propargyl, cyclopentyl and benzyl bromide, or also 2-(diethylamino)ethyl chloride, in dimethylformamide, in the presence of compounds which can bind the liberated hydrogen bromide or hydrogen chloride. In a similar manner, when ethyl chloroformate or the ethyl esters of suitable ω-bromoalkanecarboxylic acids or also corresponding free acids were used as reaction components, we prepared compounds *VIII*–*XIV*. Compounds *XVII*–*XX* were obtained in the analogous reaction of compound *II* with ethyl esters of corresponding ω-bromoalkanecarboxylic acids. Compounds *XV* and *XVI* were prepared on hydrolysis of the ester function of compounds *XI* and *XII* with aqueous-alcoholic sodium hydroxide solution at room temperature. We also obtained compound *IX* by reaction of compound *XIII* with ethanol in dimethylformamide, in the presence of N,N'-dicyclohexylcarbodiimide. The yields and some physico-chemical properties of the prepared compounds are given in Table I; lower yields in compounds *V*, *X* and *XVIII* are due to the competitive dehydrohalogenation of corresponding alkylation reagents.

The antilactation and antinidation effect of compounds *III*–*XX* was evaluated in our Institute by Dr K. Řežábek, Dr M. Aušková and Dr M. Šeda (for the method of evaluation see refs[2-4]). They found that the prepared compounds when administered orally to rats of the Wistar breed (Konárovice) in the form of an aqueous solution of hydrogen tartrate or hydrogen maleate of the base, in one dose the fifth day after copulation of the animals, had antinidation activity. A distinct antinidation effect was found especially in D-6-allyl-8-cyanomethylergoline-I (*III*) which exhibited a 100% inhibitory activity at a dose of 0·3 mg/kg. The antilactation effect of this compound in suckling female rats was still detectable at a 0·4 mg/kg dose, administered *per os*. A slightly weaker effect was also observed in D-6-propargyl-8-cyanomethylergoline-I (*IV*). The activity of compound *III* is approximately 2–3 times higher than the prolactin-inhibiting effect of D-6-methyl-8-cyanomethylergoline-I (ref.[5]). The other tested compounds displayed a similar activity at higher doses only (1 to 5 mg/kg). The observed data are in agreement with our previous finding[1] that the derivatives of ergoline with a three-carbon residue in position 6 of the molecule exhibit the highest prolactin-inhibiting effect.

EXPERIMENTAL

The melting points were determined on a Kofler block if not stated otherwise. They are not corrected. Samples for analysis were dried in a vacuum of 0·2 Torr at a temperature corresponding to their melting point. The specific rotation values were determined in pyridine, unless stated otherwise, using a Perkin–Elmer type 141 polarimeter, and they refer to substances free of solvent of crystallization. The ultraviolet spectra of the prepared substances were measured on an Optica Milano CF 4R spectrophotometer. The purity of the compounds was evaluated by paper chromatography on reflexing silica gel foils with luminiscent indicator (Silufol UV_{254}, Kavalier) in chloroform–ethanol–triethylamine 90 : 10 : 5, using UV light of 254 nm wavelength or a sprav

TABLE I

6-Substituted Derivatives of D-8-Cyanomethylergoline-I and D-8-Methylergoline-I

Compound R^1	Yield %	M.p., °C (solvent)	$[\alpha]_D^{20}$ (c)	Formula (m.w.)	Calculated/Found % C	% H	% N
			R^2 = CN				
III $-CH_2CH{=}CH_2$[a,b,c]	86	234–236 (ethanol)	−116° (0·45)	$C_{19}H_{21}N_3$ (291·4)	78·32 78·08	7·26 7·48	14·42 14·25
IV $-CH_2C{\equiv}CH$[d,e]	98	275–277 (ethanol)	−122° (0·43)	$C_{19}H_{19}N_3$ (289·4)	78·86 78·77	6·62 6·85	14·52 14·78
V C_5H_9-cyclo[f]	16	244–246 (ethanol)	−139° (0·27)	$C_{21}H_{25}N_3$ (319·5)	78·96 78·99	7·89 7·90	13·15 13·44
VI $-CH_2C_6H_5$[g]	91	246–247 ($CHCl_3$–ethanol)	−135° (0·32)	$C_{23}H_{23}N_3$ (341·5)	83·91 83·68	6·79 6·97	12·30 11·99
VII $-CH_2CH_2N(C_2H_5)_2$	80	140–142 (methanol)	− 71° (0·30)	$C_{22}H_{30}N_4$ (350·5)	75·39 75·46	8·63 8·82	15·98 15·87
VIII $-COOC_2H_5$	60	187–188 (ethanol)	−101° (0·5)	$C_{19}H_{21}N_3O_2$ (323·4)	70·56 70·63	6·54 6·46	12·99 13·02
IX $-CH_2COOC_2H_5$[h,i]	98	161–162 (ethanol)	− 52° (0·41)	$C_{20}H_{23}N_3O_2$ (337·4)	71·19 71·41	6·87 7·08	12·46 12·37
X $-(CH_2)_2COOC_2H_5$[j]	15	142–143 (ethanol)	− 43° (0·4)	$C_{21}H_{25}N_3O_2$ (351·5)	71·77 71·54	7·17 7·29	11·96 11·99
XI $-(CH_2)_3COOC_2H_5$[k]	82	135–137 (ethanol)	− 50° (0·4)	$C_{22}H_{27}N_3O_2$ (365·5)	72·30 72·09	7·45 7·65	11·50 11·81
XII $-(CH_2)_4COOC_2H_5$[l]	69	126–127 (ethanol)	− 60° (0·4)	$C_{23}H_{29}N_3O_2$ (379·5)	72·79 72·67	7·70 7·86	11·07 10·84
XIII $-CH_2COOH$[m,n]	86	241–243[o] (water)	− 34° (0·4)	$C_{18}H_{19}N_3O_2$ (309·4)	69·88 69·62	6·19 6·24	13·58 13·78
XIV $-(CH_2)_2COOH$[p]	81	237–240[o] (water)	− 55° (0·3)	$C_{19}H_{21}N_3O_2$ (323·4)	70·56 70·29	6·54 6·56	12·99 12·93
XV $-(CH_2)_3COOH$	81	280–285[o] (water)	− 59°[q] (0·24)	$C_{20}H_{23}N_3O_2$ (337·4)	71·19 71·00	6·87 6·90	12·46 12·40
XVI $-(CH_2)_4COOH$	92	194–196 (water)	− 65° (0·5)	$C_{21}H_{25}N_3O_2$ (351·5)	71·77 71·60	7·17 7·22	11·96 12·34
			R^2 = H				
XVII $-CH_2COOC_2H_5$[r]	73	195–197 (chloroform–hexane)	− 63° (0·3)	$C_{19}H_{24}N_2O_2$ (312·4)	73·05 73·18	7·74 7·71	8·97 8·89

TABLE I
(*Continued*)

Compound R^1	Yield %	M.p., °C (solvent)	$[\alpha]_D^{20}$ (c)	Formula (m.w.)	Calculated/Found % C	% H	% N
XVIII $-(CH_2)_2COOC_2H_5$ [j]	34	120–122 (benzene–hexane)	− 60° (0·3)	$C_{20}H_{26}N_2O_2$ (326·5)	73·59 73·41	8·03 8·16	8·58 8·81
XIX $-(CH_2)_3COOC_2H_5$ [s]	52	112–114 (hexane)	− 55° (0·5)	$C_{21}H_{28}N_2O_2$ (340·5)	74·08 73·84	8·29 8·32	8·23 8·40
XX $-(CH_2)_4COOC_2H_5$ [t]	62	77–79 (benzene–hexane)	− 56° (0·37)	$C_{22}H_{30}N_2O_2$ (354·5)	74·54 74·52	8·53 8·52	7·90 7·78

[a] 0·181 g (1·5 mmol) of allyl bromide, 0·209 g (1·5 mmol) K_2CO_3, 8 h at 20–25°C; [b] UV spectrum (in methanol), λ_{max} (log ε): 291 nm (3·76), 281 (3·84), 270 (3·83), 225 (4·49); [c] hydrogen maleate of the base was prepared by dissolution of 0·291 g (1 mmol) of *III* in a hot solution of 0·127 g (1·1 mmol) of maleic acid in 10 ml of methanol; the precipitated salt was crystallized from methanol, m.p. 103–105°C, $[\alpha]_D^{20} = -57·0°$ (*c* 0·24, methanol); for $C_{23}H_{25}N_3O_4$ (407·5) calculated: 67·80% C, 6·18% H, 10·31% N; found: 67·55% C, 6·28% H, 10·02% N; [d] 0·178 g (1·5 mmol) of propargyl bromide, 0·209 g (1·5 mmol) of K_2CO_3, 7 h at 20–25°C; [e] UV spectrum (in methanol), λ_{max} nm (log ε): 291 (3·76), 281 (3·85), 270 (3·80), 225 (4·51); [f] 0·224 g (1·5 mmol) cyclopentyl bromide, 0·209 g (1·5 mmol) K_2CO_3, 8 h 80°C; [g] 0·256 g (1·5 mmol) benzyl bromide, 0·209 g (1·5 mmol) K_2CO_3, 8 h at 80°C; [h] 0·251 g (1·5 mmol) ethyl bromoacetate, 0·151 g (1·5 mmol) of triethylamine, 24 h at 20–25°C; [i] UV spectrum (in methanol), λ_{max} nm (log ε): 291 (3·76), 281 (3·84), 270 (3·82), 225 (4·53); [j] 0·905 g (5 mmol) of ethyl 3-bromopropionate (in 5 doses after 8 h), 0·505 g (5 mmol) of triethylamine (in 5 parts after 8 h), 40 h at 80–85°C; [k] 0·293 g (1·5 mmol) of ethyl 4-bromobutanoate, 0·209 g (1·5 mmol) of K_2CO_3, 22 h at 80–85°C; [l] 0·314 g (1·5 mmol) of ethyl 5-bromopentanoate, 0·209 g (1·5) mmol) of K_2CO_3, 24 h at 80–85°C; [m] 0·278 g (2 mmol) of bromoacetic acid (in two equal parts after 8 h), 0·303 g (3 mmol) of triethylamine, 24 h at 20–25°C; [n] the sodium salt was prepared by dissolution of 0·309 g (1 mmol) of *XIII* in 1·0 ml (1 mmol) of 1M-NaOH and dilution of the solution with 10 ml of ethanol; the salt containing 11·2% of crystal solvent separated; the substance free of solvent had m.p. 250°C (decomposition), $[\alpha]_D^{20} = -62°$ (*c* 0·39, water); [o] in capillary, under decomposition; [p] 0·46 g (3 mmol) of 3-bromopropionic acid (in three equal parts after 8 h), 0·404 g (4 mmol) of triethylamine, 24 h at 50–60°C; [q] in 0·1M-NaOH; [r] 0·400 g (2·4 mmol) ethyl bromoacetate, 0·209 g (1·5 mmol) of K_2CO_3, 16 h at 80°C; [s] 0·293 g (1·5 mmol) of ethyl 4-bromobutanoate, 0·209 g (1·5 mmol) of K_2CO_3, 16 h at 80°C; [t] 0·314 g (1·5 mmol) of ethyl 5-bromopentanoate, 0·209 g (1·5 mmol) of K_2CO_3, 16 h at 80°C.

consisting of 0·5% of *p*-dimethylaminobenzaldehyde solution in cyclohexane and exposure to hydrogen chloride gas for detection.

6-Substituted D-8-Cyanomethylergoline-I (*III*—*VI*)

Anhydrous potassium carbonate (210 mg; 1·5 mmol) and the alkylation reagent (1·5 to 2 mmol) were added to a solution of 251 mg (1 mmol) of *I* (ref.[1]) in 10 ml of dimethylformamide and the mixture was stirred at 20 to 80°C (for reaction conditions for individual compounds see Table I). After distillation off of half of the dimethylformamide under reduced pressure the mixture was mixed with 30 ml of water, alkalized with aqueous ammonia to pH 7—8, the precipitated product was filtered off and purified by crystallization from a suitable solvent (Table I).

D-6-[2-(Diethylamino)ethyl]-8-cyanomethylergoline-I (*VII*)

2-(Diethylamino)ethyl chloride[6] hydrochloride (6·12 g; 36 mmol) and anhydrous potassium carbonate (12·5 g; 90 mmol) were added to a solution of compound *I* (4·52 g; 18 mmol) in 180 ml of dimethylformamide and the mixture was stirred at 85° to 90°C for 16 h. After working up as above the crude product was purified by column chromatography on silica gel with chloroform containing 8% of ethanol as eluent, and finally by crystallization (Table I).

D-6-Ethoxycarbonyl-8-cyanomethylergoline-I (*VIII*)

Ethyl chloroformate (0·162 g; 1·5 mmol) was added to a solution of I (251 mg; 1 mmol) in pyridine (5 ml) and dimethylformamide (5 ml) under stirring and cooling at 0—5°C and the mixture was allowed to stand at 20—25°C for 12 h. It was poured into 20 ml of water and the precipitated compound dissolved in chloroform. The chloroform solution was washed with a 10% aqueous solution of tartaric acid and then with water, dried over sodium sulfate and the solvent distilled off under reduced pressure. The crude product was purified by crystallization (Table I).

D-6-(ω-Ethoxycarbonylalkyl)-8-cyanomethylergolines-I *IX*—*XII*,
D-6-(ω-Carboxyalkyl)-8-cyanomethylergolines-I *XIII* and *XIV*, and
D-6-(ω-Ethoxycarbonylalkyl)-8-methylergoline-I *XVII*—*XX*

Anhydrous potassium carbonate (0·21 g; 1·5 mmol) or triethylamine (0·151—2·525 g; 1·5—25·0 mmol), and 1·5 to 25 mmol of ethyl ω-bromoalkanoate (for the preparation of compounds *IX*—*XII* and *XVII*—*XX*) or free bromoacid (for compounds *XIII* and *XIV*) were added to a solution of 6-nor-compound (1 mmol; 251 mg of *I* or 226 mg of *II* (ref.[1])) respectively), and the mixture was stirred at 20—85° (for details see Table I). After the evaporation of formamide under reduced pressure the residue was stirred with water in the case of compounds *IX*—*XII* and *XVII*—*XX*, the pH value of the mixture was adjusted to 7·5 with a sodium carbonate solution and the product was extracted with chloroform. After evaporation of the solvent the crude product was purified by column chromatography on silica gel with chloroform–ethanol (9 : 1) (compounds *IX*—*XII*) or benzene with 0·5% of methanol (compounds *XVII*—*XX*) as eluents, and crystallization (Table I). In the case of compounds *XIII* and *XIV* the residue was dissolved in 10 ml of dilute ammonia (1 : 20) and the solution acidified with acetic acid to pH 6. The precipitated crude product was purified by crystallization (Table I).

D-6-Ethoxycarbonylmethyl-8-cyanomethylergoline-I (*IX*) by Esterification of Compound *XIII*

N,N'-Dicyclohexylcarbodiimide (0·124 g; 0·6 mmol) and ethanol (0·1 ml) were added to a solution of compound *XIII* (0·155 g; 0·5 mmol) in 10 ml of dimethylformamide and the mixture was stirred at 20—25°C for 24 h. After evaporation of the solvent under reduced pressure the residue was stirred with 10 ml of a 5% tartaric acid solution, the separated substance was filtered off and the filtrate adjusted to pH 7·5 with sodium hydrogen carbonate. The precipitated crude product was crystallized from ethanol to afford ester *IX*, identical with compound *IX* prepared on alkylation of *I* with ethyl bromoacetate (Table I).

D-6-(3-Carboxypropyl)- and D-6-(4-carboxybutyl)-8-cyanomethylergoline-I (*XV*) and (*XVI*)

Substance *XI* (0·365 g; 1 mmol) or substance *XII* (0·380 g; 1 mmol) was introduced into a stirred mixture of 11 ml (1·1 mmol) of 0·1M sodium hydroxide and 11 ml of ethanol and the mixture was stirred at 20—25°C for 4 h. After standing overnight at the same temperature and distillation off of ethanol the mixture was acidified to pH 6. The separated crude product was purified by crystallization (Table I).

The analyses of the substances were carried out by Mrs J. Komancová of the analytical department of our Institute (head Dr J. Kŏrbl). Polarimetric measurements were carried out by Mrs I. Bendová and the UV *spectra of the substances were measured by Dr J. Vachek of the physico-chemical department of our Institute (head Dr B. Kakáč).*

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