(5*R*, 8*S*, 10*R*)-6-ALKYL-8-ERGOLINECARBOXYLIC ACIDS AND SOME OF THEIR DERIVATIVES*

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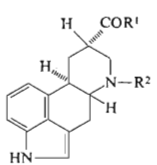
(5*R*,8*S*,10*R*)-6-Methyl-8-methoxycarbonylergoline (*VIIb*) was converted *via Ib* and *IIb* into its 6-analogues *IIIb*—*VIb*, which, in turn, were converted into acids *IIIa*—*VIa* and hydrazides *IIIc*—*VIc*. Some of the esters prepared, mainly *IVb*, had inhibitory effects on the secretion of prolactin in rats.

(5*R*,8*S*,10*R*)-6-Alkyl-8-ergolinecarboxylic acids (*IIIa*–*VIa*) and some of their derivatives, mainly the methyl esters *IIIb*–*VIb* and hydrazides *IIIc*–*VIc*, were synthetized as starting compounds for the intended study of relations between structure and biological properties in a series of 8α-substituted ergolines.



Ia, *Ib*, $R^2 = CN$
IIb, $R^2 = H$
IIIa—*IIIc*, $R^2 = C_2H_5$
IVa—*IVc*, $R^2 = n\text{-}C_3H_7$
Va—*Vc*, $R^2 = n\text{-}C_4H_9$
VIa—*VIc*, $R^2 = -CH_2CH{=}CH_2$
VIIb, $R^2 = CH_3$

Ia, *IIIa*—*VIa*, $R^1 = OH$
Ib—*VIIb*, $R^1 = OCH_3$
IIIc—*VIc*, $R^1 = NHNH_2$

To prepare the desired esters *IIIb*–*VIb* we used the route described by Fehr and coworkers[1] for the preparation of (5*R*,8*R*,10*R*)-6-alkyl-8-ergolinecarboxylic acids from (5*R*,8*R*,10*R*)-8-methoxycarbonyl-6-methylergoline (methyl ester of D-9,10-

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TABLE I

6-Substituted (5*R*,8*S*,10*R*)-8-ergolinecarboxylic acids, their methyl esters and hydrazines

Compound	R^2	Yield, % (method)	M.p., °C (solvent)*	$[\alpha]_D^{20}$	Formula (mol.mass)	Calculated/Found		
R^1						% C	% H	% N
Ia[a]	CN	96[b]	230–235[c]	+ 55·8	$C_{16}H_{15}N_3O_2$	68·31	5·37	14·94
OH		(*B*)	(water)		(281·3)	68·35	5·26	15·10
Ib[d]	CN	86	157–158	+ 96·3	$C_{17}H_{17}N_3O_2$	69·13	5·80	14·23
OCH_3			(Ac)		(295·3)	69·30	5·83	14·32
IIb[e]	H	70	88–90	− 47·4	$C_{16}H_{18}N_2O_2$	71·09	6·71	10·36
OCH_3			(Ac–He)		(270·3)	71·27	7·02	10·16
IIIa[f]	C_2H_5	75[g]	250–255	−106·7	$C_{17}H_{20}N_2O_2$	71·81	7·09	9·85
OH		(*B*)	(water)		(284·4)	71·49	7·03	10·00
IIIb[h]	C_2H_5	88[i]	184–186	− 84·5	$C_{18}H_{22}N_2O_2$	72·45	7·43	9·39
OCH_3		(*A*)	(Ac)		(298·4)	72·63	7·74	9·44
IIIc[j]	C_2H_5	92	188–190	− 23·4	$C_{17}H_{22}N_4O$	68·43	7·43	18·78
$NHNH_2$		(*C*)	(CH_3OH–H_2O)		(298·4)	68·93	7·58	19·21
IVa[k]	C_3H_7-n	71[l]	210–215[c]	− 85·0	$C_{18}H_{22}N_2O_2$	72·45	7·43	9·39
OH		(*B*)	(water)		(298·4)	72·22	7·57	9·44
IVb[m]	C_3H_7-n	76[n]	168–170	− 62·7	$C_{19}H_{24}N_2O_2$	73·05	7·74	8·97
OCH_3		(*A*)	(Ac)		(312·4)	72·94	7·87	8·95
IVc[o]	C_3H_7-n	92	151–153	− 15·0	$C_{18}H_{24}N_4O$	69·19	7·74	17·93
$NHNH_2$		(*C*)	(CH_3OH)		(312·4)	68·90	7·40	18·24
Va[p]	C_4H_9-n	30[q]	193–203[c]	− 47·7	$C_{19}H_{25}ClN_2O_2$	65·41	7·22	8·03
OH		(*B*)	(water)		(348·9)	65·38	7·24	7·90
Vb[r]	C_4H_9-n	98[s]	118–119	− 50·1	$C_{20}H_{26}N_2O_2$	73·59	8·03	8·58
OCH_3		(*A*)	(Ac)		(326·4)	73·41	8·24	8·49
Vc[t]	C_4H_9-n	82	192–195	− 4·8	$C_{19}H_{26}N_4O$	69·91	8·03	17·16
$NHNH_2$		(*C*)	(CH_3OH)		(326·5)	70·33	8·30	17·03
VIa[u]	$CH_2CH{=}CH_2$	91[v]	218–222[c]	− 94·5	$C_{18}H_{20}N_2O_2$	72·95	6·80	9·45
OH		(*B*)	(water)		(296·4)	72·99	6·78	9·38
VIb[w]	$CH_2CH{=}CH_2$	91[x]	160–162	− 83·5	$C_{19}H_{22}N_2O_2$	73·53	7·14	9·03
OCH_3		(*A*)	(Ac)		(310·4)	73·41	7·21	9·12
VIc[y]	$CH_2CH{=}CH_2$	97	132–134	− 22·7	$C_{18}H_{22}N_4O$	69·65	7·15	18·05
$NHNH_2$		(*C*)	(CH_3OH)		(310·4)	69·47	7·36	18·45

* Ac = ethyl acetate, He = hexane; [a] UV spectrum: λ_{max} (log ε): 291 (3·76), 281 (3·84), 275 infl. (3·81), 223 (4·57) nm; IR spectrum: 1 730, 2 980 wide band (COOH), 2 230 (CN), 3 420 (NH), 1 605, 1 620, 1 565 (aromatic bands) cm^{-1}; [b] reaction time 2 h, the acid was recrystallized by dissolving in hot dilute ammonia (diluted 1 : 100), followed by the addition of dilute (1 : 1) hydrochloric acid to bring pH to 3·5; [c] m.p., in a capillary, with decomposition (Kofl.), [d] UV spectrum: λ_{max} (log ε) 291 (3·76), 281 (3·82), 275 infl. (3·80), 224 (4·53) nm; IR spectrum: 1 715 (ester), 2 180 (CN), 3 300 (NH), 1 500, 1 560, 1 590, 1 615 (aromatic bands) cm^{-1}; ^1H NMR spectrum:

TABLE I
(*Continued*)

δ 8·25 (bs, 1 H, NH); 6·70 → 7·20 (m, 4 H, ArH); 3·78 (s, 3 H, OCH_3); 1·55 (dt, J = 13·3 Hz, 4,8 Hz, 1 H, $C_{(9)}$—H_{ax}); [e] UV spectrum: λ_{max} (log ε) 292 (3·75), 282 (3·82) 276 infl. (3·80), 223 (4·55) nm; IR spectrum: 1 735 (ester), 3 420 (NH), 1 555, 1 606, 1 621 (aromatic bands) cm^{-1}; ^{1}H NMR spectrum: δ 8·22 (bs, 1 H, NH); 6·85 → 7·20 (m, 3 H, ArH); 6·79 (bd, 1 H, $C_{(2)}$—H); 3·70 (s, 3 H, OCH_3); 1·85 (s, 1 H, disappears after D_2O, NH); 1·72 (dt, J = 13·3 Hz, 4·8 Hz, 1 H, $C_{(9)}$—H_{ax}); [f] UV spectrum: λ_{max} (log ε) 291 (3·76), 281 (3·85), 275 infl. (3·82), 223 (4·55) nm; IR spectrum: 1 600 (COO^-), 3 380 (NH), 3 240 (quaternary ammonium salt) cm^{-1}; [g] reaction time 12 h; [h] UV spectrum: λ_{max} (log ε) 290 (3·78), 279 (3·86), 274 infl. (3·84), 223 (4·55) nm; IR spectrum 1 715 (ester), 3 340 (NH), 1 555, 1 610, 1 620 (aromatic bands), 2 780, 2 835, (NC_2H_5) cm^{-1}; ^{1}H NMR spectrum: δ 8·15 (bs, 1 H, NH); 6·85 → 7·20 (m, 3 H, ArH); 6·80 (bs, 1 H, $C_{(2)}$—H); 3·70 (s, 3 H, OCH_3); 2·90 (q, J = 7·0 Hz, 2 H, N—CH_2); 1·00 (t, J = 7·0 Hz, 3 H, N—CH_2CH_3); 1·55 (dt, J = 13·3 Hz, 4·8 Hz, 1 H, $C_{(9)}$—H_{ax}); [i] 0·74 g (6·75 mmol) of ethyl bromide, 0·93 g (6·75 mmol) of K_2CO_3, 21 h at 25—30°C; [j] UV spectrum: λ_{max} (log ε) 293 (3·72), 282·5(3·80), 278 infl. (3·77), 225 (4·50) nm; IR spectrum: 1 640, 1 615, 1 530 ($CONHNH_2$), 3 320, 3 200 (NH, NH_2), 2 800 (NC_2H_5) cm^{-1}; [k] UV spectrum: λ_{max} (log ε) 292·5 (3·78), 282 (3·86), 276 infl. (3·83), 224 (4·57) nm; IR spectrum: 1 580, 1 380, 1 340 (COO^-, inner salt), 3 380 (NH), 1 640 (aromatic band) cm^{-1}; [l] reaction time 15 h; [m] UV spectrum: λ_{max} (log ε) 293 (3·74), 282 (3·83), 277 infl. (3·80), 224 (4·57) nm; IR spectrum: 1 735 (ester), 1 610, 1 600, 1 510 (aromatic bands), 3 150 (NH) cm^{-1}; ^{1}H NMR spectrum: δ 8·04 (bs, 1 H, NH); 6·80 → → 7·20 (m, 3 H, ArH); 6·75 (bs, 1 H, $C_{(2)}$—H); 3·65 (s, 3 H, OCH_3); 1·57 (dt, J = 13·3 Hz, 4·8 Hz, 1 H, $C_{(9)}$—H_{ax}); 1·30 (m, 2 H, $NCH_2CH_2CH_3$); 0·85 (t, J = 7·0 Hz, 3 H, CH_2CH_3); [n] 0·55 g (4·5 mmol) of n-propyl bromide, 0·62 g (4·5 mmol) of K_2CO_3, 21 h at 50°C; [o] UV spectrum: λ_{max} (log ε) 293 (3·76), 282·5 (3·84), 277 infl. (3·82), 225 (4·55) nm; IR spectrum: 3 180 (NH, NH_2), 1 630, 1 490, 1 600 (aromatic bands), 1 660 (amide I), 1 500 (amide II) cm^{-1}; [p] UV spectrum: λ_{max} (log ε) 292 (3·66), 282 (3·74), 277 infl. (3·71) nm; IR spectrum: 1 720 (COO^-, inner salt), 1 620, 1 580, 1 550 (aromatic bands), 3 350 (NH) cm^{-1}; [q] reaction time 10 h; the crude acid was purified by preparative TLC in the system S 3; the zone containing the acid was eluted with aqueous methanolic ammonia (10 : 90 : 0·5), the dry residue (50 mg) was dissolved in 0·1M-HCl, the solution was taken to dryness and the hydrochloride *Va* was recrystallized from water; [r] UV spectrum: λ_{max} (log ε) 294 (3·77), 283 (3·85), 275 infl. (3·81), 225 (4·56) nm; IR spectrum: 1 730 (ester), 3 155 (NH), 1 600, 1 610 (aromatic bands) cm^{-1}; ^{1}H NMR spectrum: δ 8·00 (bs, 1 H, NH); 6·70 → 7·20 (m, 4 H, ArH and $C_{(2)}$—H); 3·68 (s, 3 H, OCH_3); 1·55 (dt, J = 13·3 Hz, 4·8 Hz, 1 H, $C_{(9)}$—H_{ax}); 1·40 (m, 4 H, $(CH_2)_2$); 0·90 (t, 3 H, CH_2CH_3); [s] 1·31 g (7·12 mmol) of n-butyl iodide, 0·50 g (3·6 mmol) of K_2CO_3, 4 h at 50°C and 24 h at 60°C; [t] UV spectrum: λ_{max} (log ε) 292 (3·75), 281 (3·85), 275 infl. (3·81), 224 (4·31) nm; IR spectrum: 1 650($CONHNH_2$), 3 410, 3 380 (NH_2), 3 170 (NH), 1 520, 1 610 (aromatic bands) cm^{-1}; [u] UV spectrum: λ_{max} (log ε) 293 (3·75), 281 (3·81), 275 infl. (3·79), 224 (4·54) nm; IR spectrum: 1 600 (COO^-, inner salt), 3 360 (NH), 3 240 (=NH^+), 1 550, 1 580, 1 640 (aromatic bands) cm^{-1}; [v] reaction time 22 h; [w] UV spectrum: λ_{max} (log ε) 297 (3·70), 281 (3·79), 275 infl. (3·76), 222 infl. (4·46), 208 (4·72) nm; IR spectrum: 1 750 (ester), 3 050 (=CH_2), 3 470 (sec-amine) cm^{-1}; ^{1}H NMR spectrum: δ 8·00 (bs, 1 H, NH), 6·80 → 7·20 (m, 3 H, ArH), 6·70 (bs, 1 H, $C_{(2)}$—H), *c.* 5·85 (m, 1 H, CH=CH_2), 5·18 (bd, J = 16·0 Hz, 1 H, *trans* CH=CH_2), 5·10 (bd, J = 10·0 Hz, 1 H, *cis* CH=CH_2), 3·61 (s, 3 H, OCH_3), 3·31 (bd, 2 H, NCH_2), 1·50 (dt, J = 13·3 Hz, 4·8 Hz, 1 H, $C_{(9)}$—H_{ax}); [x] 0·544 g (4·5 mmol) of allyl bromide, 0·62 g (4·5 mmol) of K_2CO_3, 8 h at room temperature; [y] UV spectrum: λ_{max} (log ε) 291 (3·75), 280 (3·83), 275 infl. (3·81), 223 (4·57) nm; IR spectrum: 1 660, 1 520 ($CONHNH_2$), 3 100 (C=C), 3380, 3 280 (NH, NH_2) cm^{-1}.

-dihydrolysergic acid I**). Von Braun's demethylation of the known (5*R*,8*S*,10*R*)-8-methoxycarbonyl-6-methylergoline, *VIIb* (methyl ester of D-9,10-dihydroisolysergic-I acid*)[3], with cyanogen bromide in dichloromethane gave a good yield of the 6-cyano derivative *Ib*, which was hydrogenated in dimethylformamide, with Raney nickel as catalyst, to the 6-nor derivative *IIb*. Alkylation of the ester *IIb* with alkyl halides in dimethylformamide in the presence of potash afforded good yields of esters of 6-alkyl-8-ergolinecarboxylic acids, *IIIb* – *VIb*. The acids *Ia* and *IIIa* – *VIa* were obtained by hydrolysis of the corresponding esters in aqueous alcoholic sodium hydroxide at an elevated temperature; compared to alkali hydrolysis of analogous esters of 8β-ergolinecarboxylic acids[1], the hydrolysis of the esters *IIIb* – *VIb* proceeded at a much slower rate. Finally, the hydrazides *IIIc* – *VIc* were prepared by hydrazinolysis of the esters *IIIb* – *VIb* at approx. 100°C.

The yields, physico-chemical and spectral properties of the compounds prepared are listed in Table I. Their ^{1}H NMR spectra allowed us to determine the position of the substituent on $C_{(8)}$ in methyl esters of 8α- and 8β-ergolinecarboxylic acids. The axial hydrogen of the methylene group on $C_{(9)}$ is strongly shielded by the induced diamagnetic ring field of the aromatic nucleus. As a result, its signal is shifted to higher values of the magnetic field compared to the signals of the other hydrogens of the CH_2 groups in the ring. This makes it possible to determine the constants of its interaction with the vicinal hydrogens (^3J). The geminal interaction constant of the hydrogens on $C_{(9)}$ (^2J = 13·3 Hz) has the same values as the vicinal interaction constant of the axial hydrogen on $C_{(9)}$ with the axial hydrogen on $C_{(10)}$ (^{3}J). The signal multiplicity of the axial hydrogen on $C_{(9)}$ is governed by the position of the substituent on $C_{(8)}$. With the α position of this substituent (esters *Ib* – *VIIb*) the hydrogen on $C_{(8)}$ is equatorial. The interaction constant of $H_{(9ax)}$ with $H_{(8eq)}$ ($^3J_{axial\text{-}equat}$) is substantially lower than the geminal constant (^2J) and $^3J_{axial\text{-}axial}$ with $H_{(10)}$ ($J_{H(8eq),H(9ax)}$ = 4·8 Hz). The signal of the axial hydrogen on $C_{(9)}$ has the pattern of a doubled triplet, with interaction constants 13·3 Hz and 4·8 Hz. With the β position of the substituent on $C_{(8)}$ the hydrogen on this carbon is axial and the interaction constant is identical with the geminal and the vicinal constants of $H_{(9ax)}$. The signal has the pattern of a quartette with an interaction constant of 13·3 Hz. The influence of interaction over more bonds broadens the signal in either case.

The compounds prepared were tested pharmacologically for their inhibitory effects on the secretion of adenohypophyseal prolactin in rats; these effects were classified as antilactation and antinidation effect. In the *p.o.* administration of aqueous solutions of the compounds in the form of hydrogen tartrates to suckling rats Wistar significant antilactation effects were observed with esters *IIIb* (ED_{50} 0·45 and 0·52 mg/kg, respectively), *IVb* (ED_{50} 0·023 and 0·053 mg/kg, respectively) and *VIb* (ED_{50}

* Nomenclature according to Stoll and coworkers[2].

0·28 and 0·49 mg/kg, respectively). The mean effective doses (ED_{50}) were determined on the basis of weight increases of the suckled young rats (compared with weight increases of the controls) and by filling the stomachs of the young rats with milk (assessment of the so-called "milk spots", expressed by the second values); the methods were described previously[4,5].

EXPERIMENTAL

The melting points were determined on the Kofler stage (unless otherwise stated) and were not corrected. The analytical samples were dried at about 30 Pa and 80–100°C. The specific rotations were determined in pyridine at $c = 0{\cdot}2$, using a polarimeter Perkin–Elmer 141, and correspond to compounds free of the crystallization solvent. The UV spectra were measured with a spectrophotometer Unicam SP 8000 at a concentration of about 0·001% in methanol. The IR spectra in KBr pellets were recorded with an apparatus Perkin–Elmer 577. The ^1H NMR spectra were measured, employed a spectrophotometer Tesla BSC 487 (80 MHz), at a concentration of about 10% in deuteriochloroform, with tetramethylsilane as internal standard; the values of δ are given in ppm. The purity of the compounds was checked by TLC on reflex foils of silica gel with a luminiscent indicator (Silufol UV 254 Kavalier) in systems chloroform–ethanol–triethylamine 90 : 10 : 5 (S1) or benzene–dioxan–ethanol–triethylamine 50 : 40 : 10 : 5 (S2) (the systems S1 and S2 were used for esters *Ib*–*VIIb* and hydrazides *IIIc*–*VIc*), or in system water –0·5% of concentrated ammonia (S3) (for acids *Ia*, *IIIa*–*VIa*); the spots were detected under UV light of 254 nm or by spraying the plate with a 0·5% solution of *p*-dimethylaminobenzaldehyde in cyclohexane, followed by its exposure to vapour of hydrogen chloride. In column chromatography we used silica gel Merck Kieselgel 60 or Silpearl Kavalier, preparative TLC was conducted on silica gel plates Merck PSC Fertigplatte Kieselgel 60 KF 254.

(5*R*,8*S*,10*R*)-6-Cyano-8-methoxycarbonylergoline (*Ib*)

To a solution of the methyl ester *VIIb* (2·84 g, 0·01 mol) in dichloromethane (30 ml) was added cyanogen bromide (4·23 g, 0·02 mol), the mixture was stirred 5 h at about 20°C, then left standing overnight at room temperature. The volatile portions were distilled off *in vacuo*, the residue was dissolved in dichloromethane (150 ml) and the solution was washed with a 10% aqueous solution of tartaric acid and with water. The organic layer was dried with Na_2SO_4 and filtered through a short column of silica gel (3 g), the solvent was removed and the residue (2·54 g) was recrystallized (Table I).

(5*R*,8*S*,10*R*)-8-Methoxycarbonylergoline (*IIb*)

To a solution of the methyl ester *Ib* (2·70 g, 0·01 mol) in dimethylformamide (55 ml) was added Raney nickel (*c.* 1·5 g suspended in dimethylformamide) and the mixture was hydrogenated 130 h at room temperature and about 4 kPa. The catalyst was filtered off, the solvent removed *in vacuo* and the residue was shaken between a chloroform–ethanol mixture (95 : 5) and a 5% solution of tartaric acid. The aqueous portion was alkalinized with ammonia, the base was taken into the chloroform–ethanol (95 : 5) mixture, the organic portion was dried (Na_2SO_4), the solvents were distilled off *in vacuo* and the residue was recrystallized (Table I).

(5*R*,8*S*,10*R*)-6-Alkyl-8-methoxycarbonylergolines *IIIb*—*VIb* (Method *A*)

To a solution of the methyl ester *IIb* (0·81 g, 3 mmol) in dimethylformamide (20 ml) was added anhydrous potassium carbonate (0·50—0·933 g, 3·6—6·75 mmol) and an alkyl halide (4·5—7·12 mmol) and the mixture was stirred, in some cases with warming, until *IIb* had disappeared (for the reaction conditions see Table I). The solvent was distilled off *in vacuo*, the residue was stirred up with 20 ml of water that had been acidified with acetic acid (0·3 ml), pH was brought to 7·2 to 7·5, and the separated solid was collected on a filter. The crude product was purified by column chromatography on silica gel, with chloroform as eluant. The qualitatively identical fractions were combined and taken to dryness; the residues were recrystallized (Table I).

(5*R*,8*S*,10*R*)-6-Alkyl-8-ergolinecarboxylic Acids *Ia* and *IIIa*—*VIa* (Method *B*)

A suspension of the ester *Ib* or *IIIb*—*VIb* (1 mmol) in a mixture of 0·2M-NaOH (10·5 ml, 2·1 mmol) and methanol (10·5 ml) was heated to 60—65°C until the hydrolysis of the ester was complete (the reaction times are given in Table I). The mixture was acidified with 2M-HCl, pH was brought to 5·0—5·5 (~1·05 ml). The solution was densified to the volume 3 ml and the separated acid was filtered and recrystallized (Table I). In the case of the acid *Va* the crude product was purified by preparation TLC and the acid was isolated in the form of its hydrochloride (Table I).

Hydrazides of (5*R*,8*S*,10*R*)-6-alkyl-8-ergolinecarboxylic Acids *IIIc*—*VIc* (Method *C*)

A suspension of the ester *IIIb*—*VIb* (2 mmol) in 100% hydrazine hydrate (12 ml) was heated under stirring for 3 h to 95—100°C. The hot solution was then diluted with water (1 ml). The separated hydrazide was collected on a filter and recrystallized (Table I).

The elemental analyses were performed by Mrs J. Komancová (Analytical Department, head Dr J. Körbl), the UV *and* IR *spectra were measured by Dr J. Vachek, the polarimetric measurements were carried out by Mrs Hanusová (both of the Physico-Chemical Department, head Dr B. Kakáč).*

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