D-6-METHYL-8-(β-AMINOETHYL)ERGOLINE-I, ITS $N_{(1)}$-METHYL DERIVATIVE AND SOME OF THEIR N_{β}-ACYL DERIVATIVES*

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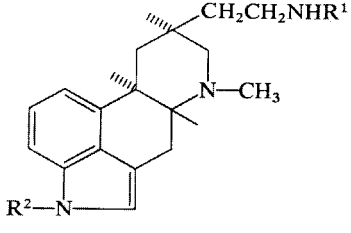
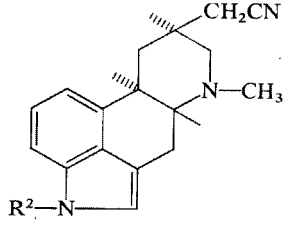
D-6-Methyl-8-cyanomethylergoline-I and its $N_{(1)}$-methyl derivative were reduced to D-6-methyl-8-(β-aminoethyl)ergoline-I and its $N_{(1)}$-methyl derivative which were acylated with carboxylic acyl halides to N_{β}-acylaminoethyl derivatives *III*–*XXV*. Most of the compounds prepared displayed a pronounced antinidation effect in rats and some of them, *e.g.* nicotinoyl- and 3,4,5-trimethoxybenzoylaminoethyl derivatives, were hypotensive for rats.

The present communication deals with the synthesis and with some biological properties of D-6-methyl-8-(β-aminoethyl)ergoline-I (*I*), its D-1,6-dimethyl analogue *II* and their N_{β}-acylated derivatives *III*–*XXV*.



I, $R^1 = H$, $R^2 = H$
II, $R^1 = H$, $R^2 = CH_3$
III–*XXIII*, R^1 = acyl, $R^2 = H$
XXIV, *XXV*, R^1 = acyl, $R^2 = CH_3$



XXVI, $R^2 = H$
XXVII, $R^2 = CH_3$

The compounds were prepared in connection with studying the structure-effect relationships among derivatives of ergolene and ergoline, especially among compounds

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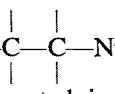
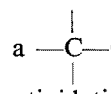
containing a  or a  grouping in position 8. We were particularly interested in the antinidation and hypotensive effects of *I*–*XXV* in connection with the biological properties of the compounds of these two types[1–4].

The 8-β-aminoethyl compound *I* was prepared by catalytic hydrogenation of D-6-methyl-8-cyanomethylergoline-I (*XXVI*) with hydrogen at 60 atm at 50–60°C, in the presence of Raney nickel. Analogously, using D-1,6-dimethyl-8-cyanomethylergoline-I (*XXVII*) as the starting compound, we obtained the corresponding D-1,6-dimethyl-8-(β-aminoethyl)ergoline-I (*II*). The required starting dimethyl compound *XXVII* was prepared by methylation of cyanomethylergoline *XXVI* with methyl iodide in liquid ammonia in the presence of potassium amide (for analogy see ref.[5,6]). The aminoethyl compounds *I* and *II* were converted to the N_β-acylaminoethyl compounds *III*–*XV* and *XVII*–*XXV* by the action of the corresponding acyl halides in the presence of pyridine; compound *XVI* was prepared from 3,4,5-trimethoxyphenylacetic acid and amine *I* by the carbonyldiimidazolyl method.

The yields and some physico-chemical properties of compounds *I*–*XXV* are summarized in Table I. Compounds *I*–*XXV* underwent an orientation study as to their hypotensive and antinidation effect in rats. The results of the tests of selected compounds are summarized in Table II.

Table II shows the pronounced and persistent hypotensive effect of D-6-methyl-8-(β-nicotinoyl)aminoethylergoline-I (*XX*) and D-6-methyl-8-[β-(3,4,5-trimethoxybenzoyl)aminoethyl]ergoline-I (*XII*). The above-mentioned hypotensive effect of *XX* was also confirmed for unanaesthesized rats with DOCA hypertension at a pressure of over 180 Torr and for normal tension unanaesthesized monkeys *Macaca mulatta*. Practically all the compounds tested had an antinidation effect but only at doses substantially greater than cyanomethylergoline *XXVI*. More details on the results of biological evaluation of compounds *I*–*XXV* will be published elsewhere.

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected. Samples for analysis were dried *in vacuo* at about 0·1 Torr at a temperature proportional to their melting point. The values of specific rotation were determined in a Perkin Elmer 141 polarimeter and refer to compounds free of crystal solvent. The homogeneity of the compounds was tested by paper chromatography in 1-butanol–acetic acid–water (4 : 1 : 5) or on a paper impregnated by spraying with 40% formamide and 5% ammonium formate, using chloroform as the mobile phase (the compounds were detected in UV light after previous illumination with sunlight), or on thin layers of silica gel G (Stahl, Merck) in 2-propanol–25% ammonia–water (10 : 1 : 1) or chloroform–ethanol 9 : 1 (the compounds were detected by spraying the chromatogram with 0·5% *p*-dimethylaminobenzaldehyde in cyclohexane and exposing the plate to hydrogen chloride vapour).

TABLE I

8-(β-Aminoethyl)ergolines-I and Their N_β-Acyl Derivatives *III*—*XXV*

Compound	R^1 / R^2	Yield, % / $[\alpha]_D^{20}$ [a]	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found % C	% H	% N	% Cl
I [b]	H	82	175—176	$C_{17}H_{23}N_3$	75·79	8·61	15·60	—
	H	— 71° [c]	(aqueous dioxane)	(269·4)	75·74	8·51	15·66	—
II [d]	H	100	sirup	$C_{18}H_{25}N_3$	—	—	—	—
	CH_3	— 83°		(283·4)				
III	$COCH_3$	68	198—199	$C_{19}H_{25}N_3O$	73·28	8·09	13·49	—
	H	— 98°	(acetone)	(311·4)	73·15	8·37	13·37	
IV	COC_5H_{11}-n	76	117—118	$C_{23}H_{33}N_3O$	75·16	9·05	11·43	—
	H	— 85°	(acetone–hexane)	(367·5)	74·93	9·23	11·16	
V	COC_6H_5	73	206—208	$C_{24}H_{27}N_3O$	77·18	7·28	11·25	—
	H	— 87°	(methanol)	(373·5)	76·94	7·33	11·16	
VI	$COC_6H_4CH_3$-4	76	232—233	$C_{25}H_{29}N_3O$	77·48	7·54	10·84	—
	H	— 86°	(aqueous acetone)	(387·5)	77·77	7·73	10·96	
VII	COC_6H_4Cl-2	75	147—149	$C_{24}H_{26}ClN_3O$	70·67	6·42	10·30	8·69
	H	— 81°	(acetone)	(407·9)	70·41	6·52	10·02	8·78
VIII	COC_6H_4Cl-3	91	135—136	$C_{24}H_{26}ClN_3O$	70·67	6·42	10·30	8·69
	H	— 88°	(acetone)	(407·9)	70·77	6·45	10·21	8·86
IX	COC_6H_4Cl-4	74	206—208	$C_{24}H_{26}ClN_3O$	70·67	6·42	10·30	8·69
	H	— 88°	(acetone)	(407·9)	70·89	6·71	10·42	9·00
X	$COC_6H_3Cl_2$-3,4	90	123—125	$C_{24}H_{25}Cl_2N_3O$	65·16	5·70	9·50	16·03
	H	— 71°	(acetone–hexane)	(442·4)	64·76	5·85	9·59	16·46

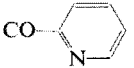
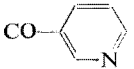
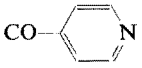
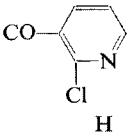
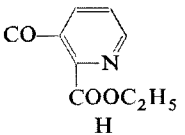
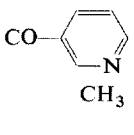
XI	$COC_6H_4OCH_3$-4	91	159—161	$C_{25}H_{29}N_3O_2$	74·41	7·24	10·42	—
	H	— 81°	(aqueous acetone)	(403·5)	74·41	7·46	10·25	
XII	$COC_6H_2(CH_3O)_3$-3,4,5	36	117—119	$C_{27}H_{33}N_3O_4$	69·96	7·17	9·07	—
	H	— 73°	(benzene)	(463·6)	69·55	7·11	8·78	
XIII	$COC_6H_3(CH_2O_2)$-3,4	58	120—121	$C_{25}H_{27}N_3O_3$	71·92	6·52	10·07	—
	H	— 80°	(acetone–benzene)	(417·5)	71·73	6·51	9·78	
XIV	$COC_6H_4NO_2$-4	73	259—260	$C_{24}H_{26}N_4O_3$	68·88	6·26	13·39	—
	H	— 91°	(aqueous dioxane)	(418·5)	68·66	6·31	13·56	
XV	$COCH_2C_6H_5$	59	104—105	$C_{25}H_{29}N_3O$	77·48	7·54	10·84	—
	H	— 82°	(benzene)	(387·5)	77·21	7·79	10·93	
XVI	$COCH_2C_6H_2(CH_3O)_3$-3,4,5	90	102—104	$C_{28}H_{35}N_3O_4$	70·41	7·39	8·80	—
	H	—124°	(acetone–hexane)	(477·6)	70·11	7·48	8·59	
XVII	$COCH_2CH_2C_6H_5$	76	92—94	$C_{26}H_{31}N_3O$	77·77	7·76	10·47	—
	H	— 83°	(acetone–hexane)	(401·5)	77·35	7·78	10·35	
XVIII	$COCH{=}CHC_6H_5$	75	123—124	$C_{26}H_{29}N_3O$	78·16	7·32	10·52	—
	H	— 78°	(acetone–hexane)	(399·5)	77·80	7·27	10·77	
XIX		54	219—221	$C_{23}H_{26}N_4O$	73·76	7·00	14·96	—
	H	— 78°	(aqueous acetone)	(374·5)	73·50	7·09	15·10	
XX		64	196—197	$C_{23}H_{26}N_4O$	73·76	7·00	14·96	—
	H	— 87°	(aqueous acetone)	(374·5)	73·87	7·28	14·85	
XXI		67	228—230	$C_{23}H_{26}N_4O$	73·76	7·00	14·96	—
	H	— 78°	(ethanol)	(374·5)	73·40	7·08	14·99	

TABLE I
(*Continued*)

Compound	R^1 R^2	Yield, % $[\alpha]_D^{20}$ [a]	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found % C	% H	% N	% Cl
XXII	 H	43 — 74°	130—135 (acetone)	$C_{23}H_{25}ClN_4O$ (408·9)	67·56 67·71	6·16 6·39	13·70 13·61	8·67 8·80
XXIII	 H	34 — 73°	271—273 (aqueous acetone)	$C_{26}H_{30}N_4O_3$ (446·5)	69·93 —	6·77 —	12·55 12·62	—
XXIV	COC_6H_4Cl-4 CH_3	55 — 92°	205—208 (acetone)	$C_{25}H_{28}ClN_3O$ (421·9)	71·16 71·02	6·69 6·87	9·96 9·68	8·40 8·45
XXV	 CH_3	61 — 84°	177—178 (acetone)	$C_{24}H_{28}N_4O$ (388·5)	74·20 73·87	7·27 7·05	14·42 14·60	—

[a] *c* 0·5, pyridine. [b] Bis(hydrogen maleate) of the base: m.p. 162—163°C (ethanol); $[\alpha]_D^{20}$ −34° (*c* 0·5, water). For $C_{25}H_{31}N_3O_8$ (501·5) calculated: 59·87% C, 6·23% H, 8·38% N; found: 59·78% C, 6·43% H, 8·25% N. [c] *c* 0·5, ethanol. [d] The base was isolated as bis(hydrogen maleate), m.p. 150—152°C (ethanol); $[\alpha]_D^{20}$ −37° (*c* 0·5, water). For $C_{26}H_{33}N_3O_8$ (515·5) calculated: 60·57% C, 6·45% H, 8·15% N; found: 60·48% C, 6·69% H, 8·23% N.

TABLE II

Hypotensive and Antinidation Effects of 8-β-Aminoethylergolines *I* and *II* and of Some of Their N_β-Acyl Derivatives

Compound	Hypotensive effect at μg/kg[a]			Antinidation effect at the minimum dose, mg/kg[b]
	500	50	5	
I	24 (52)	4 (30)	4 (10)	10 (1)
II	10 (40)	5 (16)	—	(0·5)
III	32 (60)	12 (34)	0 (12)	5
VII	0 (31)	0	—	(0·5) (5)
IX	9 (39)	0 (4)	—	(5)
XI	18 (39)	20 (30)	8 (8)	[c]
XII	24 (45)	19 (25)	0 (24)	5
XX	37 (47)	31 (31)	10 (10)	5
XXI	33 (33)	38 (38)	0 (16)	5 (0·5)
XXIV	29 (48)	17 (30)	6 (16)	(0·5)
XXV	26 (48)	37 (37)	0 (0)	[c]

[a] The hypotensive effect was estimated in male rats weighing about 400 g, in urethane narcosis (1·5 g/kg urethane in 10 ml/kg water, *s.c.*). Solution of 1 mg normal tartrate of the base in 1 ml distilled water was injected into the femoral vein to two animals at a dose of 0·2 ml solution per animal. Analogously, a solution of 10 times lower concentration was used and dilution continued until a practically ineffective concentration was reached. The hypotensive effect is expressed as the percentage drop of blood pressure (arithmetic mean from values determined in the two animals); the value in parentheses was recorded immediately after application, the other value 20 min later. [b] The antinidation effect was determined in a group of 7—8 female rats weighing about 200 g where copulation was checked by the presence of sperm in a vaginal smear. Solutions of normal tartrates of the bases were applied through a gastric probe 5 times, beginning on the 1st, and ending on the 6th day after copulation. At first, 1 mg base tartrate in 1 ml solution was administered per day; analogously, a ten times lower concentration was used. Twenty days after copulation, the animals were killed and their gravidity was tested. A dose preventing gravidity in all cases was taken as effective. A dose (shown in parentheses) which did not prevent gravidity in all cases but which caused its incidence to be significantly lower (P = 95%) than in the control was taken as partly effective. [c] Ineffective at 5 mg/kg.

D-6-Methyl-8-(β-aminoethyl)ergoline-I (*I*) and Its $N_{(1)}$-Methyl Derivative *II*

A mixture of 80% aqueous dioxane (200 ml) saturated at 0—5°C with gaseous ammonia, 8-cyanomethylergoline *XXVI* or *XXVII* (5 g) and 10 g aqueous suspension of Raney nickel was hydrogenated for 3 h at 60—65 atm and 55—60°C. After cooling, the catalyst was filtered, washed with 80% aqueous dioxane and the combined filtrates were freed of the volatile components by distillation at 12 Torr. The residue (5 g) was crystallized from aqueous dioxane, or it was dissolved in five volumes of ethanol and, by adding 2·1 molar equivalents of maleic acid, converted to the poorly soluble bis(hydrogen maleate). The physico-chemical constants of compounds *I* and *II* and of their bis(hydrogen maleates) are shown in Table I.

D-1,6-Dimethyl-8-cyanomethylergoline-I (*XXVII*)

In the atmosphere of nitrogen, liquid ammonia (500 ml) was combined with 0·165 g potassium and with a catalytic amount of ferric nitrate to prepare potassium amide. Cyanomethylergoline *XXVI* (1·0 g) was added to the stirred mixture; this was followed after 15 min of stirring by a solution of methyl iodide (0·70 g) in 5 ml ether. After 1 h of stirring, the ammonia was evaporated and the residue was divided between water and a mixture of chloroform with 20% ethanol. The dried organic fraction (Na_2SO_4) was freed of the solvents at reduced pressure and the crude product (1·0 g) was purified by column chromatography on silica gel, using a mixture of chloroform with increasing amounts of ethanol (1—10%) for elution. The dimethyl derivative *XXVII* forms needles, m.p. 173—175°C (acetone–n-hexane), $[\alpha]_D^{20}$ —105° (*c* 0·5, pyridine).

8-(β-Acylaminoethyl)ergolines-I (*III—XV, XVII—XXV*)

Pyridine (0·14 ml, 1·65 mmol) was added under stirring to a solution of 1·5 mmol derivative *I* or *II* in 16 ml chloroform, then a solution of 1·65 mmol chloride of the corresponding carboxylic acid in 2 ml chloroform was added dropwise at 0—5°C. After 15 min of stirring at 0°C and leaving to stand overnight at 20°C, the mixture was diluted with ethanol (4 ml) and shaken with dilute aqueous ammonia (1 : 10) and water. The dried chloroform solution (Na_2SO_4) was evaporated at reduced pressure and the remainder was chromatographed on a column of silica gel, using a mixture of chloroform with ethanol (9 : 1) for elution. The yields, solvents used for crystallization of the products, the melting points and the optical rotation values of the acylamino compounds *III* to *XV* and *XVII—XXV* are shown in Table I.

D-6-Methyl-8-[β-(3,4,5-trimethoxyphenylacetyl)aminoethyl]ergoline-I (*XVI*)

A solution of N,N′-carbonyldiimidazole (0·35 g, 2·1 mmol) in 10 ml dichloromethane was combined in the absence of air moisture and in the atmosphere of nitrogen with 0·452 g (2 mmol) 3,4,5-trimethoxyphenylacetic acid, the solution was stirred for 1 h at 20°C and a solution of 0·54 g (2 mmol) derivative *I* in 10 ml dichloromethane was added. The mixture was stirred for 2 h and left to stand overnight at 20°C. It was then extracted with water, the dichloromethane solution was dried (Na_2SO_4), the solvent was distilled off at reduced pressure and the residue was chromatographed on a column of silica gel, using a mixture of chloroform with ethanol (9 : 1) for elution. The yield and the physico-chemical properties of *XVI* are shown in Table I.

The analyses were done by Mrs J. Komancová and Mrs V. Šmídová, the compounds were evaluated by paper chromatography by Mrs M. Jelínková of the analytical department of this Institute (under the direction of Dr J. Körbl).

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