ESTERS OF D-6-METHYL-8-ERGOLIN-I-YLACETIC ACID AND THEIR 2-HALOGENO DERIVATIVES

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Esters of D-6-methyl-8-ergolin-I-ylacetic acid *I*—*X* were prepared and some of them were converted to 2-chloro- (*XI*—*XV*) or 2-bromo-derivatives (*XVI*—*XXIV*). Likewise, the methyl ester of D-1,6-dimethyl-8-ergolin-I-ylacetic acid (*XXV*) and its 2-bromo derivative *XXVI* were prepared. Most significant hypotensive activity after *i.v.* application to rats was displayed by ester *XXI*. Methyl esters *XI* and *XVI* were also hypotensive.

To establish the effect of the alcohol residue in the molecule of esters of D-6-methyl--8-ergolin-I-ylacetic acid and their 2-chloro or 2-bromo derivatives on the hypotensive action of the substances we prepared nonhalogenated ester *I*—*X* and esters of the 2-chloro or 2-bromo acids, *XI*—*XV* and *XVI*—*XXIV*, respectively (Table I). In view of the fact that alkylation of ergoline derivatives in position 1 usually affects significantly biological activity we prepared for comparison the methyl ester of D-1,6--dimethyl-8-ergolin-L-ylacetic acid (*XXV*) and its 2-bromo derivative *XXVI* (Table I).

Of the esters of D-6-methyl-8-ergolin-I-ylacetic acid only the methyl ester has been prepared so far, in a reaction of the acid with diazomethane, or by hydrolysis of the hydrochloride of the methyl ester of carboximidic acid obtained in a reaction of D-6--methyl-8-cyanomethylergoline-I with a methanolic solution of hydrogen chloride[1]. Esters *I*—*X* and *XXV* as well as the methyl ester were now prepared by esterification of the acid using excess alcohol and hydrogen chloride, or sulfuric acid or *p*-toluene--sulfonic acid as catalyst. In contrast with D-lysergic acid, the D-6-methyl-8-ergolin--I-ylacetic acid does not isomerize at $C_{(8)}$ under acid conditions because of stabilization of the D ring of the ergoline skeleton. Esters *XI*—*XV* chlorinated in position 2 were obtained by a reaction of the corresponding nonhalogenated esters with N,2,6--trichloro-4-nitroacetanilide in dioxane at 20°C. Bromination of esters resulting in 2-bromo compounds *XVI*—*XXIV* and *XXVI* was carried out using N-bromosuccinimide in dioxane at 60—65°C (ref.[2]).

During an orientative pharmacological testing the aqueous solution of the tartrate of methyl ester of 2-bromo acid *XVI*, applied *i.v.* to rats with normal blood pressure

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in urethane narcosis, brought about a drop of blood pressure by more than 20% (lasting for 20 min) beginning with a dose of 150 μg/kg. With the methyl ester of 2-chloro acid *XI* a similar effect was observed beginning with a dose of 50 μg/kg. The most striking hypotensive effect was found with the 2-hydroxyethyl ester of 2-bromo acid *XXI*: it depressed the blood pressure by more than 20% of the original value in a dose of 5 μg/kg. Extension of the ester group chain (*XII* and *XX*) or introduction of an aromatic ring into the ester group (*XXIV*) results in lower hypotensive activity of the halogenated esters. Nonhalogenated esters *I*—*X* and *XXV* are less hypotensive or completely inactive; like the halogenated esters *XI*—*XXIV* and *XXVI*, they had no particular antinidation, antiserotonine, uterotonic or gonadotropin-stimulating effect (up to 1 mg/200 g).

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected. Samples for analysis were dried at 0·5 Torr, compounds *XX* and *XV* at room temperature, compounds *III*, *IV*, *XIV*, *XVIII*, *XIX*, *XXV*, *XXVI* at 65°C, compounds *V* and *XIII* at 78°C, others at 100°C. None of the compounds contained crystal solvent. The specific rotation of the compounds was determined using a Perkin-Elmer type 141 polarimeter. The composition of fractions obtained by column chromatography on silica gel (Kieselgel Merck) was followed by thin-layer chromatography on silica gel (Merck, according to Stahl) using methanol (compounds *I*—*X* and *XXV*) or in chloroform–acetone 3 : 2 (compounds *XI*—*XXIV*). Detection of esters *I*—*X* and *XXV* was done[3] on the basis of their blue-violet colour after spraying with 10% solution of *p*-toluene-sulfonic acid in methanol and heating to 50°C. A similar colour in position 2 of halogenated derivatives *XI*—*XXIV* and *XXVI* is less intense, with 2-chloro derivatives it is blue.

Esters *I*—*X*, *XXV*

Esterifications were done with the potassium salt of D-6-methyl-8-ergolin-I-ylacetic acid[1]; only with the methyl ester of *XXV*, the free acid was used. Crude ester bases were purified by column chromatography on silica gel (Kieselgel, Merck) in benzene using ethanol for elution. The properties of the esters and the solvents used for their crystallization are shown in Table I.

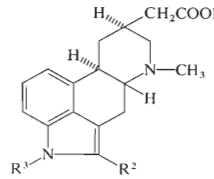
Esters *I*—*III*, *VI*—*X* and *XXV* were characterized as bases, esters *IV* and *V* as hydrogen maleates, *IV* also as methanesulfonate because of their poor crystallization.

Method A: A mixture of 0·5 g potassium salt of D-6-methyl-8-ergolin-I-ylacetic acid, 20 ml alcohol and 0·3 g dry hydrogen chloride was refluxed for 2 h in nitrogen, the solution was evaporated under water-pump vacuum and the residue was dissolved in 70 ml water. The ester base released by alkalification with a sodium carbonate solution was filtered, washed with water and dried at room temperature. Analogous procedure was applied to the preparation of the methyl ester of D-6-methyl-8-ergolin-I-ylacetic acid (92% yield) corresponding by its properties to the ester obtained in the reaction of acid with diazomethane[1], of esters *I* (46%), *IV* (53%) and *XXV* (64%).

Method B: A mixture of 0·5 g potassium salt D-6-methyl-8-ergolin-I-ylacetic acid, 0·5 ml concentrated sulfuric acid and 10 ml alcohol was cooled to 20°C, stirred at room temperature for 48 h and poured into 50 ml water. The solution was alkalified with concentrated ammonia

TABLE I

Derivatives of D-6-Methyl-8-ergolin-I-ylacetic Acid



R^2, R^3 = H	*I–X*
R^2 = H, R^3 = CH_3	*XXV*
R^2 = Cl, R^3 = H	*XI–XV*
R^2 = Br, R^3 = H	*XVI–XXIV*
R^2 = Br, R^3 = CH_3	*XXVI*

Compound	Formula	M.p., °C	$[\alpha]_D^{20}$	Calculated/Found, %				
R^1	(mol. wt.)	(solvent)	(*c*, pyridine)	C	H	N	Cl	Br
I	$C_{19}H_{24}N_2O_2$	176–177	−98·0°	73·05	7·74	8·97	—	—
CH_3CH_2	(312·4)	(benzene)	(0·46)	73·42	7·71	8·79	—	—
II	$C_{21}H_{28}N_2O_2$	152–153	−93·9°	74·08	8·29	8·23	—	—
$CH_3(CH_2)_3$	(340·5)	(benzene)	(0·56)	74·18	8·11	8·10	—	—
III	$C_{24}H_{34}N_2O_2$	130–132	−80·9°	75·35	8·96	7·32	—	—
$CH_3(CH_2)_6$	(382·6)	(methanol)	(0·46)	75·55	8·82	7·34	—	—
IV[a,b]	$C_{29}H_{40}N_2O_6$	128–130	−34·0°[c]	67·95	7·86	5·46	—	—
$CH_3(CH_2)_7$	(512·7)	(methanol)	(0·40)	68·17	7·80	5·31	—	—
V[a]	$C_{31}H_{44}N_2O_6$	138–139	−31·8°	68·86	8·20	5·18	—	—
$CH_3(CH_2)_9$	(540·7)	(methanol)	(0·46)	68·58	8·39	5·39	—	—
VI	$C_{19}H_{24}N_2O_3$	182–183	−96·7°	69·49	7·36	8·53	—	—
$HOCH_2CH_2$	(328·4)	(ethanol–n-hexane)	(0·52)	69·78	7·70	8·38	—	—
VII	$C_{20}H_{26}N_2O_3$	179–181	−83·7	70·15	7·65	8·18	—	—
$HOCH_2(CH_2)_2$	(342·4)	(acetone)	(0·41)	70·07	7·78	8·16	—	—
VIII	$C_{20}H_{26}N_2O_4$	170–172	−81·8°	67·02	7·31	7·81	—	—
$HOCH_2(HO)CHCH_2$	(358·4)	(ethanol–n-hexane)	(0·42)	67·03	7·30	7·56	—	—
IX	$C_{24}H_{26}N_2O_2$	188–189	−92·0°	76·97	7·00	7·48	—	—
$C_6H_5CH_2$	(374·5)	(ethanol)	(0·35)	76·93	6·95	7·43	—	—
X	$C_{23}H_{30}N_2O_2$	212–214	−100·6°	75·37	8·25	7·64	—	—
cyclo-C_6H_{11}	(366·5)	(methanol–acetone)	(0·44)	75·49	8·22	7·42	—	—
XI	$C_{18}H_{21}ClN_2O_2$	210–212	−109·6°	64·96	6·36	8·42	10·65	—
CH_3	(332·9)	(chloroform–n-hexane)	(0·42)	64·81	6·42	8·27	10·91	—
XII	$C_{19}H_{23}ClN_2O_2$	149–151	−105·7°	65·79	6·68	8·08	10·22	—
CH_3CH_2	(346·9)	(chloroform–n-hexane)	(0·37)	65·82	6·78	8·19	10·25	—

TABLE I
(*Continued*)

Compound R[1]	Formula (molwt.)	M.p., °C (solvent)	$[\alpha]_D^{20}$ (*c*, pyridine)	Calculated/Found, % C	H	N	Cl	Br
XIII $CH_3(CH_2)_3$	$C_{21}H_{27}ClN_2O_2$ (374·9)	135—136 (chloroform–n-hexane)	−95·7° (0·32)	67·27 67·04	7·26 7·52	7·47 7·52	9·46 9·33	— —
XIV $CH_3(CH_2)_6$	$C_{24}H_{33}ClN_2O_2$ (417·0)	123 (methanol)	−86·8° (0·34)	69·13 69·05	7·98 8·10	6·72 6·64	8·50 8·66	— —
XV $CH_3(CH_2)_9$	$C_{27}H_{39}ClN_2O_2$ (459·1)	91—93 (methanol)	−89·0° (0·30)	70·64 70·37	8·56 8·56	6·10 5·93	7·73 7·78	— —
XVI CH_3	$C_{18}H_{21}BrN_2O_2$ (377·3)	212—213 (chloroform–n-hexane)	−98·4° (0·49)	57·30 57·35	5·61 5·66	7·43 7·22	— —	21·18 21·44
XVII CH_3CH_2	$C_{19}H_{23}BrN_2O_2$ (391·3)	143—145 (benzene)	−102·5° (0·45)	58·32 58·52	5·92 6·15	7·16 7·21	— —	20·42 20·54
XVIII $CH_3(CH_2)_3$	$C_{21}H_{27}BrN_2O_2$ (419·4)	114—116 (benzene)	−94·0° (0·54)	60·15 60·15	6·49 6·50	6·68 6·58	— —	19·05 19·23
XIX $CH_3(CH_2)_6$	$C_{24}H_{33}BrN_2O_2$ (461·5)	121—122 (methanol)	−86·0° (0·48)	62·47 62·78	7·21 7·56	6·07 6·07	— —	17·32 17·48
XX $CH_3(CH_2)_9$	$C_{27}H_{39}BrN_2O_2$ (503·5)	76—78 (methanol)	−113·5° (0·22)	64·41 64·64	7·81 7·86	5·56 5·44	— —	15·87 16·08
XXI $HOCH_2CH_2$	$C_{19}H_{23}BrN_2O_3$ (407·3)	190—191 (acetone)	−97·4° (0·39)	56·03 55·93	5·69 5·73	6·88 6·70	— —	19·62 19·74
XXII $HOCH_2(CH_2)_2$	$C_{20}H_{25}BrN_2O_3$ (421·3)	167—168 (benzene)	−99·4° (0·33)	57·01 57·25	5·98 6·08	6·65 6·46	— —	18·97 18·96
XXIII $HOCH_2(HO)CHCH_2$	$C_{20}H_{25}BrN_2O_4$ (437·3)	167—168 (acetone)	−90·0° (0·39)	54·93 55·15	5·76 5·83	6·41 6·38	— —	18·27 18·12
XXIV $C_6H_5CH_2$	$C_{24}N_{25}BrN_2O_2$ (453·4)	183—185 (acetone)	−95·7° (0·40)	63·58 63·27	5·56 5·53	6·17 5·90	— —	17·63 17·74
XXV CH_3	$C_{19}H_{24}N_2O_2$ (312·4)	128—130 (methanol)	−93·3° (0·37)	73·05 72·90	7·74 7·93	8·97 8·68	— —	— —
XXVI CH_3	$C_{19}H_{23}BrN_2O_2$ (391·3)	114—115 (benzene–n-hexane)	−103·2° (0·44)	58·32 58·50	5·92 5·94	7·16 6·86	— —	20·42 20·71

[a] Hydrogen maleate. [b] Methanesulfonate of ester *IV*; m.p. 159—160°C (ethanol–ether), $[\alpha]_D^{20}$ −36·3° (*c* 0·41, methanol). For $C_{26}H_{40}O_5S$ calculated: 63·39% C, 8·18% H, 5·68% N; found: 63·57% C, 8·12% H, 5·83% N. [c] Specific rotation measured in methanol.

to pH 8, the ester base was extracted with chloroform and the chloroform extract was dried with Na_2SO_4 and evaporated under water-pump vacuum. In the case of benzyl ester *IX* the remaining chloroform-extracted benzyl alcohol was evaporated *in vacuo* in a 120—125°C bath. The yield of *VII* was 42%, of *VIII* 16% and of *IX* 35%.

Method C: A mixture of 0·5 g potassium salt of D-6-methyl-8-ergolin-I-ylacetic acid, 1 g *p*-toluenesulfonic acid and 50 ml alcohol was refluxed under stirring for 6·5 h on a 50°C water bath and then left to stand at room temperature for 20 h. After evaporation under oil-pump vacuum (bath temperature 120—125°C) the residue was extracted with a mixture of aqueous sodium carbonate and chloroform with 5% ethanol; the organic phase was dried with Na_2SO_4 and evaporated; the residues represented the ester. Yields: *II* 68%, *III* 78%, *V* 70%, *VI* 71% and *X* 15%.

Methyl Ester of D-2-Chloro-6-methyl-8-ergolin-I-ylacetic Acid (*XI*)

N,2,6-Trichloro-4-nitroacetanilide (0·736 g, 2,6 mmol) was introduced into a solution of 0·597 g (2 mmol) methyl ester of D-6-methyl-8-ergolin-I-ylacetic acid in 100 ml, dioxane and the solution was stirred in the absence of moisture and light for 24 h at room temperature. Dioxane was then distilled *in vacuo*, the residue was dissolved in 150 ml chloroform and the solution was extracted with 1% sodium hydroxide and water. The residue of the crude product was purified by chromatography on a column of silica gel in a mixture of benzene with 1% ethanol and finally purified by crystallization from a mixture of chloroform and n-hexane. The yield was 0·25 g (38%); analogously *XII* (33%), *XIII* (52%), *XIV* (28%), *XV* (34%).

Methyl Ester of D-2-Bromo-6-methyl-8-ergolin-I-ylacetic Acid (*XVI*)

A solution of 0·5 g (1·7 mmol) methyl ester of D-6-methyl-8-ergolin-I-ylacetic acid in 50 ml dioxane with 0·360 g N-bromosuccinimide (2 mmol) was stirred in the absence of moisture and light for 30 min in a 60—65°C bath. Dioxane was distilled *in vacuo*, the residue was dissolved in 75 ml chloroform and the solution was extracted with a 10% aqueous solution of sodium carbonate and water. The crude product residue was purified by chromatography on a column of silica gel in a mixture of benzene with 1% ethanol and by crystallization from a mixture of chloroform and n-hexane. The yield was 0·25 g (40%); analogously *XVII* (35%), *XVIII* (30%), *XIX* (36%), *XX* (39·5%), *XXI* (15%), *XXII* (27·5%), *XXIII* (21%) *XXIV* (28%) and *XXVI* (26%).

The analyses were done at the analytical department of this institute by Mrs J. Komancová and Mr K. Havel (under the direction of Dr J. Körbl).

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