SOME O-ACYL DERIVATIVES OF D-6-METHYL-8-(2-HYDROXYETHYL)ERGOLENE AND D-6-METHYL-8-(2-HYDROXYETHYL)ERGOLINE(I)*,**

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By acylation of D-6-methyl-8-(2-hydroxyethyl)ergolene and the analogous ergoline(I) derivative, obtained on reducing the methyl ester of D-6-methyl-8-ergolin(I)ylacetic acid with lithium aluminium hydride, their derivatives *I*–*V* and *VI*–*XI*, resp. were prepared which are O-acylated by rests of aliphatic, aromatic or heterocyclic acids. Some of the compounds prepared displayed a distinct hypotensive and others a distinct antifertility effect.

In connection with our study of the relationship between structure and biological properties of ergot alkaloid analogues, particularly of derivatives of 6-methylergolene and 6-methylergoline bearing at $C_{(8)}$ of their molecule substituents with the groupings $-CH_2-\underset{|}{\overset{|}{C}}-N-$ and $-CH_2-\underset{|}{\overset{|}{C}}-O-$, resp., we have been engaged both in the synthesis of the O-acyl derivatives of D-6-methyl-8-(2-hydroxyethyl)ergolene *I*–*V* and D-6-methyl-8-(2-hydroxyethyl)ergoline(I) *VI*–*XI* (Table I) and in the informative evaluation of their hypotensive and antifertility effect on rats. Our study of the latter effect was stimulated by the previously observed[1,2] pronounced antifertility activity of D-6-methyl-8-cyanomethylergoline(I) and some amides of D-6-methyl-8-ergolin(I)-ylacetic acid[3] brought about by the inhibiting effect of these compounds on the secretion of the adenohypophysial prolactin.

Compound *I* we have prepared by acetylation of the already earlier by us described D-6-methyl-8-(2-hydroxyethyl)ergolene[4] with acetic anhydride in the presence of pyridine. In preparing compounds *II*–*V* we used for acylation the same starting material, performed always in pyridine, the chlorides of the corresponding carboxylic acids. In the case of compounds *I* and *II* the reaction was carried out at 20°C, in all other cases on a boiling water bath. Compounds *VI* –*XI* have been prepared from

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** The derivatives of ergolene presented in this paper belong to the group of compounds derived from D-lysergic acid, *i.e.* they are $\Delta^{9,10}$-compounds. According to their steric situation, the ergoline(I) derivatives belong to the series of D-dihydrolysergic acid(I).

D-6-methyl-8-(2-hydroxyethyl)ergoline(I) by the same procedure as compounds *I* and *IV*, resp. The required D-6-methyl-8-(2-hydroxyethyl)ergoline(I) was prepared in good yield by reduction the methyl ester of D-6-methyl-8-ergolin(I)ylacetic acid[1] with lithium aluminium hydride in diethyl ether. The yields of the pure substances and some of their physico-chemical properties are listed in Table I. Compounds *I*–*XI* as well as D-6-methyl-8-(2-hydroxyethyl)ergoline(I) give both with van Urk's and Keller's reagents colour reactions typical of natur ergot alkaloids.

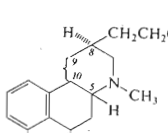
In an informative evaluation of the above substances as to their antifertility effect in rats (K. Ř. and M. Š.) it was found that of the D-6-methyl-8-(2-acyloxyethyl)ergoline(I) derivatives prepared, compounds *VI* and *VIII*–*XI* display an antifertility effect in all the animals of a group of seven impregnated female Whistar rats (in comparison with a group of control animals) after application of an aqueous solution of 5 mg of the normal tartrate/kg, when the drug was administered in five daily doses during the first seven days after copulation. On the other hand, the same O-acyl derivatives of D-6-methyl-8-(2-hydroxyethyl)ergolene, when tested in the same dose and under the same conditions as above, were either ineffective or markedly less effective. The double bond in 9,10 position and its saturation with hydrogen, resp. also exert a distinct influence on the blood pressure in Wistar rats in urethane narcosis. Whilst compounds *I* and *III* have in a single dose of an aqueous solution of 0·6 mg of the tartrate/kg upon intravenous application a protracted hypotensive effect, the corresponding 9,10-dihydrocompounds *VI* and *VIII*, when tested in the same manner (in doses of 0·5 and 1·5 mg of the tartrate/kg), were in this respect practically ineffective or raised the blood pressure of the animals only by a very small degree.

EXPERIMENTAL

The melting or decomposition points of the compounds were determined on a Kofler block and are uncorrected. Samples for analysis were dried at 0·5 Torr, compound *II* at 65°C, compounds *III*–*V* at 80°C, *VI*, *VII*, *X*, *XI*, and D-6-methyl-8-(2-hydroxyethyl)ergoline(I) at 100°C, *VIII* and *IX* at 139°C. The composition of the fraction obtained by column chromatography on alumina and also that of other preparations was investigated on thin layers of silica gel G according to Stahl (Merck) using the solvent system chloroform–ethanol (9 : 1), or by paper chromatography in the solvent system 1-butanol–acetic acid–water 4 : 1 : 5 (with compounds *III*–*XI*), or on paper impregnated with formamide using chloroform as the mobile phase (with compound *I*). In the case of compound *II* the paper was impregnated with both formamide and a small amount of phosphoric acid. The D-6-methylergolene derivatives were detected by their blue ultraviolet fluorescence. In thin-layer chromatography, the D-6-methylergoline(I) derivatives were detected on the basis of the violet-blue colour after spraying the chromatogram with a 10% solution of *p*-toluenesulphonic acid in methanol and heating to about 50°C (for the analogous reaction of ergot alkaloids see ref.[5]), and in paper chromatography they were detected by the fluorescence in ultraviolet light after preceeding irradiation with sunlight.

TABLE I

O-Acyl Derivatives of D-6-Methyl-8-(2-hydroxyethyl)ergolene *I*— *V* and D-6-Methyl-8-(2-hydroxyethyl)ergoline(I) *VI*— *XI*



{ —CH=CH *I*—*V*
{ —CH_2—CH_2 *VI*—*XI* (5,10-*trans*)

Compound R	M.p., °C[a] (yield, %)	$[\alpha]_D^{20}$ (*c*, solvent)[b]	Formula (mol.wt.)	Calculated/Found % C	% H	% N
I	185—186	52·4°	$C_{19}H_{22}N_2O_2$	73·52	7·14	9·03
$COCH_3$	(96)	(0·77)	(310·4)	73·25	7·09	9·27
II[c]	129—130	68·5°	$C_{27}H_{34}N_2O_6$	67·20	7·10	5·81
COC_5H_{11}-n	(73)	(0·25)	(482·5)	66·92	7·32	5·54
III	176—178	23·8°	$C_{24}H_{24}N_2O_2$	77·39	6·50	6·52
COC_6H_5	(80)	(0·52)	(372·5)	77·56	6·62	7·74
IV	166—167	22·0	$C_{27}H_{30}N_2O_5$	70·11	6·54	6·06
$COC_6H_2(CH_3O)_3$-3,4,5	(66)	(0·63)	(462·5)	69·90	6·54	5·96
V	158—160[d]	30·5°	$C_{23}H_{23}N_3O_2$	73·97	6·21	11·25
COC_5H_4N	(79)	(0·56)	(373·4)	73·83	6·33	11·04
VI	189—191	−89·3°	$C_{19}H_{24}N_2O_2$	73·05	7·74	8·97
$COCH_3$	(98)	(0·56)	(312·4)	73·26	7·73	8·98
VII[e]	150—151	−42·0°	$C_{27}H_{36}N_2O_6$	66·93	7·49	5·78
COC_5H_{11}-n	(25)	(0·17)	(484·6)	66·40	7·72	5·49
VIII	211—212[f]	−81·9°	$C_{24}H_{26}N_2O_2$	—	—	7·48
COC_6H_5	(73)	(0·51)	(374·4)			7·42
IX	214—215[f]	−96·1°	$C_{25}H_{28}N_2O_3$	74·23	6·98	6·92
$COC_6H_4OCH_3$-4	(76)	(0·20)	(404·5)	74·51	7·07	6·85
X	146—147[g]	−65·9°	$C_{27}H_{32}N_2O_5$	69·83	6·94	6·03
$COC_6H_2(CH_3O)_3$-3,4,5	(54)	(0·74)	(464·5)	69·66	7·02	6·01
XI	203—204	−82·0°	$C_{23}H_{25}N_3O_2$	73·57	6·71	11·19
COC_5H_4N	(60)	(0·52)	(375·5)	73·28	6·89	11·10

[a] Crystallised from ethanol unless otherwise stated; [b] in pyridine unless otherwise stated; [c] values for the hydrogen maleate, rotation in 50% ethanol; [d] crystallised from benzene–ethanol; [e] values for the hydrogen maleate, rotation in water; [f] crystallized from ethanol–chloroform; [g] crystallized from benzene.

D-6-Methyl-8-(2-acetoxyethyl)ergolene and D-6-Methyl-8-(2-acetoxyethyl)ergoline(I) (*I* and *VI*)

A mixture of D-6-methyl-8-(2-hydroxyethyl)ergolene (0·35 g) or D-6-methyl-8-(2-hydroxyethyl)-ergoline(I), acetic anhydride (7·5 ml), and pyridine (0·1 ml) was allowed to stand at 20°C for 2 h and, after adding ice and 25 ml of water, the solution was adjusted to pH 9 with aqueous ammonia. The separated product was filtered off with suction and washed with water. The crude bases *I* and *VI*, resp. were purified by crystallisation (Table I).

D-6-Methyl-8-(2-acyloxyethyl)ergolenes *II*—*V* and D-6-Methyl-8-(2-acyloxyethyl)ergolines(I) *VII*—*XI*

Except for some deviations stated below, these compounds were prepared by the same procedure and by applying the reactants in the same molar ratio as in the following preparation of compound *IV*: A mixture of D-6-methyl-8-(2-hydroxyethyl)ergolene (0·4 g, 1·49 mmol), pyridine (16 ml), and 3,4,5-trimethoxybenzoyl chloride (1·72 g, 7·45 mmol) was heated with stirring on a boiling water bath for 12 min under exclusion of air moisture and direct light. After addition of 2 ml of water, the mixture was stirred for 2 h at room temperature and then freed from volatiles by distillation in a water-pump vacuum. The solution of the residue in 80 ml of chloroform was shaken with water, dried (Na_2SO_4) and evaporated to dryness. The residue dissolved in chloroform was chromatographed on a column of alumina (Reanal, 27 g, activity III—IV) using the same solvent for elution. The fractions corresponding substance *IV* were combined and further purified by crystallisation (Table I).

In the preparation of compound *II* the reaction time was 1 1/2 h at 20°C. But we did not succeed in obtaining the base in crystalline form. The crystalline hydrogen maleate was prepared by reaction of equimolar amounts of both components in ethanol. In the case of compound *V* the reaction time was 30 min. The separated base hydrochloride was filtered off with suction and combined with a further portion of the same substance obtained by concentrating the mother liquor in water-pump vacuum. The base set free from the salt by alkalization its warm aqueous solution with sodium hydrogen carbonate was taken up in chloroform and the dried solution was chromatographed on a column of alumina under the same conditions as in the preparation of compound *IV*. With compounds *VII* and *X* the reaction time was 30 min, with compound *VIII* 45 min, and with compounds *IX* and *XI* 25 min and 1 hour, resp. Compounds *IX* and *XI* separated from the reaction mixtures in the form of hydrochlorides, which were worked up in the same manner as in the case of compound *V*. Compound *VII* after repeated column chromatography was purified by crystallisation from a mixture of acetone and hexane (1 : 1). Since this purification procedure has only a limited effect, for analysis the base was converted into the hydrogen maleate by reacting equimolar amounts of both components in ethanol.

D-6-Methyl-8-(2-hydroxyethyl)ergoline(I)

A suspension of lithium aluminium hydride (1·0 g) in ether (100 ml) was treated dropwise with a solution of the methyl ester of D-6-methyl-8-ergolin(I)ylacetic acid[1] (1·0 g) in ether (500 ml) and the mixture was refluxed in nitrogen atmosphere for one hour under exclusion of air moisture. After pouring the mixture into ice, the aqueous phase was extracted twice with 150 ml of ether and the combined ethereal extracts were dried (Na_2SO_4) and evaporated to dryness. From the remaining aqueous phase the aluminium hydroxide was filtered off with suction and digested with hot methanol (twice with 200 ml). The product obtained by evaporating the methanolic extract together with that obtained from the ethereal extracts was purified by crystallisation from

ethanol: m.p. 255—257°C, $[\alpha]_D^{20}$ —107° (*c* 0·58, pyridine). For $C_{17}H_{22}N_2O$ (270·4) calculated: 75·52% C, 8·20% H, 10·36% N; found: 75·24% C, 8·43% H, 10·19% N.

The analyses were performed by Mr K. Havel and Mrs Komancová and the paper chromatography by Mrs M. Jelínková in the Analytical Department of our Institute (headed by Dr J. Körbl).

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