SOME 2-SUBSTITUTION DERIVATIVES OF D-6-METHYLERGOLINE-I*

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Received February 21st, 1977

Condensation of the methyl ester of D-6-methyl-8-ergolin-I-yl-acetic acid (*IX*) with 2-ethoxy--1,3-dithiolane in chloroform in the presence of titanium tetrachloride gave rise to the methyl ester of D-2-(1,3-dithiolan-2-yl)-6-methyl-8-ergolin-I-ylacetic acid (*II*) which was converted *via* the methyl ester of D-2,6-dimethyl-8-ergolin-I-ylacetic acid (*III*) and its hydrazide to D-2,6-dimethyl-8-ergolin-I-ylacetamide (*VI*). Methyl ester of D-2-chloro or D-2-bromo-6-methyl-8-ergolin--I-ylacetic acid (*X, XI*) was converted to hydrazide *IV* or *V*, corresponding to D-2-chloro or D-2-bromo-6-methyl-8-ergolin-I-ylacetamide (*VII, VIII*). Substitution of the ergoline skeleton in position 2 was reflected in the case of *VI*—*VIII* in an increased hypotensive effect and a decrease of prolactin-inhibiting activity as compared with the unsubstituted *I*.

In an earlier communication we described the synthesis of D-6-methyl-8-ergolin--I-ylacetamide[1] (*I*) (Deprenon) which displayed a pronounced inhibitory effect on the secretion of adenohypophyseal prolactin manifested for instance in an antinidation or antilactation effect[1,2]. At the present time, Deprenon belongs to the most active compounds of this type. It was of interest to examine how the biological properties of *I* will be affected by introducing a substituent into position 2 of the ergoline skeleton. In this context we prepared 2-substitution derivatives of D-6-methylergoline-I *II*—*VIII* (Table I), of which 2-methyl (*VI*), 2-chloro (*VII*) and 2-bromo (*VIII*) derivatives of D-6-methyl-8-ergolin-I-ylacetamide were subjected to an informative pharmacological testing.

To introduce the methyl group into position 2 of *I* we modified the procedure[3] used for introducing the thioacetal function into position 2 of the indole part of the ergoline skeleton. The methyl ester of D-2-(1,3-dithiolan-2-yl)-6-methyl-8 ergolin--I-ylacetic acid (*II*) was prepared from the methyl ester of D-6-methyl-8-ergolin--I-ylacetic acid[4] (*IX*) by condensation with 2-ethoxy-1,3-dithiolane (prepared *in situ* from 1,2-ethanedithiol and ethyl formate), in chloroform under the action of titanium tetrachloride at 20—25°C. Reductive desulfuration of the thioacetal group of *II* with a suspension of Raney nickel in a mixture of dimethylformamide and acetone at laboratory temperature yielded the methyl ester of D-2,6-dimethyl-8-ergolin-I-ylacetic acid (*III*). By boiling *III* with hydrazine hydrate and by a reductive deamination

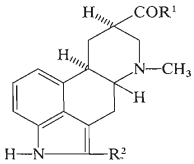
* Part LV in the series Ergot Alkaloids; Part LIV: This Journal *42*, 1886 (1977).

of the hydrazide formed with a suspension of Raney nickel in ethanol we prepared D-2,6-dimethyl-8-ergolin-I-ylacetamide (*VI*).

D-2-Chloro-6-methyl-8-ergolin-I-ylacetamide (*VII*) and D-2-bromo-6-methyl-8-ergolin-I-ylacetamide (*VIII*) were synthesized using the methyl esters of D-2-chloro-

TABLE I

2-Substitution Derivatives of D-6-Methylergoline-I



II, *III*; $R^1 = OCH_3$
IV, *V*; $R^1 = NHNH_2$
VI – *VIII*; $R^1 = NH_2$

Compound R^2	Formula (mol.wt.)	M.p., °C (solvent)	$[\alpha]_D^{20}$ (*c*, pyridine)	Calculated/Found % C	% H	% N	% Cl(Br)
II[a]	$C_{21}H_{26}N_2O_2S_2$ (402·6)	199–200 (chloroform–acetone)	− 83·4 (0·36)	62·65 / 62·35	6·51 / 6·58	6·96 / 6·61	—
III CH_3	$C_{19}H_{24}N_2O_2$ (312·4)	220–223 (chloroform–hexane)	−105·7 (0·35)	73·05 / 72·99	7·74 / 7·95	8·97 / 9·07	—
IV Cl	$C_{17}H_{21}N_4ClO$ (332·8)	263–265 (benzene–methanol)	−110·2 (0·34)	61·35 / 61·38	6·36 / 6·63	16·83 / 16·72	10·65 / 10·66
V Br	$C_{17}H_{21}N_4BrO$ (377·3)	266–267 (benzene–methanol)	−105·5 (0·36)	54·12 / 53·80	5·61 / 5·72	14·85 / 14·54	(21·18) / (21·05)
VI CH_3	$C_{18}H_{23}N_3O$ (297·4)	263–265 (benzene–ethanol)	− 99·6 (0·40)	72·70 / 72·47	7·80 / 7·94	14·13 / 14·31	—
VII Cl	$C_{17}H_{20}N_3ClO$ (317·8)	269–272 (benzene–methanol)	− 95·5 (0·48)	64·25 / 64·51	6·34 / 6·63	13·22 / 13·43	11·16 / 11·33
VIII Br	$C_{17}H_{20}N_3BrO$ (362·3)	267–268 (benzene–ethanol)	− 84·4 (0·38)	56·36 / 56·26	5·56 / 5·72	11·60 / 11·53	(22·06) / (22·09)

[a] Calculated: 15·93% S; found: 16·06% S.

-6-methyl-8-ergolin-I-ylacetic acid[5] (*X*) and of its 2-bromo analogue[5] (*XI*) as starting compounds, proceeding *via* the hydrazides *IV* or *V* as intermediates. In view of the fact that the halogen bound in position 2 of hydrazides *IV* and *V* is rather labile in a reductive milieu[6] they could not be converted to the corresponding amides by reductive deamination with Raney nickel. To prepare the amides from the hydrazides the azide method was hence used. Compounds *VII* or *VIII* could also be prepared by a direct chlorination of *I* with N,2,6-trichloro-4-nitroacetanilide or by bromination with N-bromosuccinimide in dioxane under the conditions shown in ref.[5] but these procedures produce lower yields.

An informative pharmacological testing of *VI*–*VIII* (Drs K. Řežábek, M. Šeda and M. Aušková of this institute for method see ref.[2,7,8]) showed some significant differences in efficiency as compared with the compound unsubstituted in position 2 (ref.[1,2]). 2-Methylation and 2-halogenation of *I* resulted under the same regime and doses in a substantial decrease of the antinidation and antilactation effect and in an increase of the hypotensive effect. The highest hypotensive effect was demonstrated with *VII* which, evaluated in normal-tension rats (Wistar Konárovice) in urethane narcosis, brought about in a dose of 50 μg/kg body weight (applied *i.v.* in the form of an aqueous solution of the base tartrate) a brief depression of the blood pressure by 50% and, at a dose of 0·05 μg/kg body weight, a 10% decrease. The 2-methyl derivative *VI* and the 2-bromo derivative *VIII* were much less hypotensive. The antinidation effect of *VI*–*VIII* was in the same dose comparable with the efficiency of D-6-methyl-8-cyanomethylergoline-I (ref.[4]).

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected. Samples for elementary analysis were dried at 100°C at 0·2 Torr to constant weight. Values of specific rotation were determined in pyridine using a Perkin–Elmer 141 polarimeter and they refer to solvent-free compounds. Purification of the reaction mixtures was done by column chromatography on Merck silica gel in benzene–methanol and by crystallization of homogeneous fractions from suitable solvents (Table I). The compounds were detected by TLC on the basis of a violet colour after spraying with a 10% solution of *p*-toluenesulfonic acid and heating to 50°C.

Methyl Ester of D-2-(1,3-dithiolan-2-yl)-6-methyl-8-ergolin-I-ylacetic Acid (*II*)

1,2-Ethanedithiol (1·13 g, 13 mmol) and a solution of 4·55 g (24 mmol) titanium tetrachloride in 30 ml chloroform were added under stirring to a solution of 1·85 g (6 mmol) methyl ester of D-6-methyl-8-ergolin-I-ylacetic acid (*IX*) in a mixture of 60 ml chloroform and 20 ml ethyl formate. The mixture was left to stand for 96 h at 20–25°C, was then decomposed with 15 ml methanol, diluted with 100 ml water and alkalified with concentrated aqueous ammonia. The product was extracted with chloroform and purified by column chromatography and crystallization (1·41 g; 58%).

Methyl Ester of D-2,6-Dimethyl-8-ergolin-I-ylacetic Acid (*III*)

A suspension of 14 ml Raney nickel in a mixture of dimethylformamide and acetone (1 : 10) was added to a solution of 805 mg (2 mmol) methyl ester *II* in the same mixture and stirred for 3 h at 20—25°C. After filtration of Raney nickel and concentration of the mixture the residue was mixed with water, the precipitate was filtered, dried and crystallized (468 mg; 75%).

D-2,6-Dimethyl-8-ergolin-I-ylacetamide (*VI*)

40 mg (1·28 mmol) methyl ester *III* was refluxed for 2 h in nitrogen atmosphere with 20 ml hydrazine hydrate. The precipitated hydrazide was filtered, dried (320 mg; 80%) and refluxed for 2 h with 3 ml ethanolic suspension of Raney nickel in 150 ml ethanol. After filtration of the catalyst and concentration, the precipitated product was purified by crystallization (203 mg; 66·5%).

2-Halogenated Hydrazides *IV, V*

A mixture of 500 mg (1·5 mmol) methyl ester of D-2-chloro-6-methyl-8-ergolin-I-ylacetic acid (*X*) or 566 mg (1·5 mmol) methyl ester of D-2-bromo-6-methyl-8-ergolin-I-ylacetic acid (*XI*) and 50 ml hydrazine hydrate was refluxed for 10 min in a nitrogen atmosphere. After cooling, the precipitated hydrazide was filtered, dried and recrystallized. A total of 430 mg (86%) hydrazide *IV* or 475 mg (84%) hydrazide *V* was obtained.

2-Halogenated Amides of D-6-Methyl-8-ergolin-I-ylacetic Acid *VII, VIII*

1M sodium nitrite (0·92 ml) was gradually added at 0°C to a solution of 0·25 g (0·75 mmol) hydrazide of D-2-chloro-6-methyl-8-ergolin-I-ylacetic acid (*IV*) or 283 mg (0·75 mmol) hydrazide of D-2-bromo-6-methyl-8-ergolin-I-ylacetic acid (*V*) in 10 ml 0·2M hydrochloric acid. This was followed after 10 min with 3 ml 0·2M hydrochloric acid. The precipitated azide hydrochloride was filtered and mixed while wet with 3 ml concentrated aqueous ammonia. After 1 h of standing of the mixture at 20—25°C the crude amide was filtered and purified by chromatography and crystallization. A total of 188 mg (79%) amide *VII* and 147 mg (54%) amide *VIII* was obtained.

The analyses were done at the analytical department of this institute by Mrs J. Komancová (under the direction of Dr J. Körbl), polarimetric estimations by Mrs I. Bendová at the physico-chemical department (headed by Dr B. Kakáč) of this institute .

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Translated by A. Kotyk.