SOME ESTERS OF N-(D-6-METHYL-8-ERGOLIN-I-YLMETHYL)-CARBAMIC ACID*

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Received September 17th, 1976

Condensation of N-(D-6-methyl-8-ergolin-I-ylmethyl) isocyanate with alcohols led to esters of N-(D-6-methyl-8-ergolin-I-ylmethyl) carbamic acid *I*—*XI*; the 2-hydroxyethyl ester *IX* was converted to the 2-nicotinoyloxyethyl ester *XII*. Ester *II* displayed a pronounced antinidation activity and a stimulating effect on the secretion of hypophyseal gonadotropins in rats.

In earlier communications we described the synthesis of a number of ergolin derivatives[1-7] which possess prolactin inhibiting, antinidation and antilactation effects in experimental animals. In the present paper we describe the preparation of esters of N-(D-6-methyl-8-ergolin-I-ylmethyl)carbamic acid *I*—*XII* (Table I) which were subjected to a similarly oriented pharmacological testing.

Esters *I*—*XI* were prepared by condensation with N-(D-6-methyl-8-ergolin-I-ylmethyl) isocyanate with the corresponding alcohols in benzene. The solution of isocyanates in benzene was prepared using the azide of D-6-methyl-8-ergolin-I-ylacetic acid[1] as the starting compound by a conventional method[6]. The 2-nicotinoyloxyethyl ester of N-(D-6-methyl-8-ergolin-I-ylmethyl)carbamic acid (*XII*) was prepared by condensation of the 2-hydroxyethyl ester *IX* with the hydrochloride of nicotinic acid chloride in pyridine at 100°C.

For biological testing the compounds were applied in the form of aqueous solutions of their hydrogen tartrates. In the tests on rats (Wistar Konárovice), esters *I*—*XII* displayed an inhibitory effect on the secretion of adenohypophyseal prolactin, reflected, for instance, in the antinidation effect (for method see[8]). The antinidation effect which was apparent in all the experimental animals, was displayed by *II* at 0·5 mg base/kg, if applied in a single dose *p.o.* on the 5th day after mating. At a dose of 0·3 mg base/kg, *II* may be compared in its effect with the amide of D-6-methyl-8-ergolin-I-ylacetic acid (Deprenon^{R})[3,9-11] and it is the most potent compound in this series. A clear antinidation activity was exhibited by *I* and *V* (0·5 mg base/kg), compound *I* approaching practically *II* in its potency. The other esters displayed a similar effect only at doses of 5 mg base/kg. Ester *II* was also evaluated as to the

* Part LIV in the series Ergot Alkaloids; Part LIII: This Journal *42*, 1417 (1977).

stimulation of secretion of hypophyseal gonadotropins (for method see[12]), using a 10-day continuous application of the daily dose of 0·5 and 0·1 mg base/kg, respectively, in hemicastrated female rats, and compared with Deprenon^R. The value of 217% weight of the remaining ovary, found on application of Deprenon^R in a dose of 0·5 mg base/kg does not differ statistically from the value of 210% found after application of *II*. Analogous values were found after application of 0·1 mg base/kg standard (185%) and of *II* (183%). Using the method of Doepfner and Cerletti[13], we could demonstrate a slight antiserotonin effect after a single dose of *I*–*XII* (0·5 mg base/kg).

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected. For elementary analysis, the compounds were dried to constant weight at a temperature proportional to their m.p. and at 0·5 Torr. The values of specific rotation were determined in a Perkin-Elmer type 141 polarimeter and refer to compounds free of solvent. The composition of fractions from column chromatography (Kieselgel Merck) was followed on luminescent plates Silufol UV_{254} (Kavalier) in chloroform–ethanol–triethylamine (9 : 1 : 0·5); detection was done under UV light at 254 nm or with a 0·5% solution of *p*-dimethylaminobenzaldehyde in cyclohexane and with hydrogen chloride vapour.

Esters of N-(D-6-Methyl-8-ergolin-I-ylmethyl)carbamic Acid *I*–*XI*

A suspension of 618 mg (2 mmol) azide of D-6-methyl-8-ergolin-I-ylacetic acid[6] in 150 ml benzene was refluxed for 20 min in a nitrogen atmosphere. After cooling to 20–25°C, the mixture was combined with an excess of the appropriate alcohol (15 ml), the mixture was refluxed for 1 h and left to stand for 2 h (*I*–*VIII* and *X*–*XI*) or for 20 h (*IX*) at 20–25°C. After distillation of the volatile fractions in water-pump vacuum the residue was purified by column chromatography in benzene with 3% methanol. The pooled homogeneous fractions were further purified by crystallization from suitable solvents (Table I).

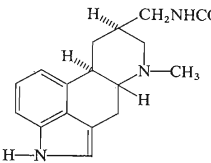
Ester IX: After distillation of benzene, the ethylene glycol layer was mixed with 150 ml water, the mixture left to stand for 1 h at 5°C, the precipitate was filtered and washed with 100 ml water, purified by column chromatography in benzene with 10% methanol and the pooled fractions were recrystallized (Table I).

2-Nicotinoyloxyethyl Ester of N-(D-6-Methyl-8-ergolin-I-ylmethyl)carbamic Acid (*XII*)

A solution of 343 mg (1 mmol) 2-hydroxyethyl ester of N-(D-6-methyl-8-ergolin-I-ylmethyl)carbamic acid in 10 ml pyridine was combined with 534 mg (3 mmol) hydrochloride of nicotinic acid chloride and the mixture was heated for 1 h to 100°C. After cooling to 20°C, 2 ml water was added, the mixture was stirred for 1 h at 20°C, then it was evaporated, the residue was mixed with 100 ml water, alkalified with concentrated ammonia to pH 9 and the precipitated base was extracted with 3× 50 ml of a mixture of chloroform with 10% ethanol. After evaporation of the combined chloroform fractions the residue was purified by chromatography on a column of silica gel in benzene with 2% methanol; homogeneous fractions were pooled (350 mg, 79·2%) and recrystallized (Table I).

TABLE I

Some Esters of N-(D-6-Methyl-8-ergolin-I-ylmethyl)carbamic Acid



XII$_x$ R = CH_2CH_2—O—CO— 

Compound R	Formula (mol.wt.)	M.p., °C (solvent)	$[\alpha]_D^{20}$ (*c*, pyridine), %	Yield %	Calculated/Found % C	% H	% N
I CH_3	$C_{18}H_{23}N_3O_2$ (313·4)	163—165 (benzene)	−90·0 (0·32)	63·8	68·99 68·76	7·39 7·34	13·41 13·45
II C_2H_5	$C_{19}H_{25}N_3O_2$ (327·4)	186—188 (benzene)	−88·0 (0·37)	48·0	69·70 69·94	7·70 7·81	12·83 13·08
III C_3H_7-n	$C_{20}H_{27}N_3O_2$ (341·4)	193—195 (methanol)	−83·7 (0·40)	56·0	70·35 70·44	7·97 8·13	12·33 12·32
IV C_4H_9-n	$C_{21}H_{29}N_3O_2$ (355·5)	155—157 (ethanol–benzene)	−78·2 (0·40)	84·4	70·96 71·28	8·22 8·32	11·82 12·00
V C_4H_9-iso	$C_{21}H_{29}N_3O_2$ (355·5)	140—142 (chloroform–hexane)	−79·2 (0·41)	71·8	70·96 71·12	8·22 8·30	11·82 12·03
VI $CH_2CH{=}CH_2$	$C_{20}H_{25}N_3O_2$ (339·4)	182—184 (ethanol–hexane)	−81·9 (0·36)	73·9	70·77 70·51	7·42 7·60	12·38 12·18
VII $CH_2C{\equiv}CH$	$C_{20}H_{23}N_3O_2$ (337·4)	184—186 (methanol–benzene)	−82·5 (0·35)	71·0	71·19 70·95	6·87 6·84	12·45 12·54
VIII C_5H_9-cyclo	$C_{22}H_{29}N_3O_2$ (367·5)	146—148 (chloroform–hexane)	−75·8 (0·34)	61·2	71·91 71·66	7·95 7·92	11·43 11·64
IX CH_2CH_2OH	$C_{19}H_{25}N_3O_3$ (343·4)	190—192 (benzene–methanol	84·1 (0·39)	84·0	66·45 66·30	7·34 7·52	12·23 12·52
X $CH_2CH_2OCH_5$	$C_{20}H_{27}N_3O_3$ (357·5)	157—159 (acetone–hexane)	−76·5 (0·35)	56·2	67·20 67·15	7·61 7·49	11·76 11·57

TABELLE I
(*Continued*)

Compound R	Formula (mol.wt.)	M.p., °C (solvent)	$[\alpha]_D^{20}$ (*c*, pyridine), %	Yield %	Calculated/Found % C	% H	% N
XI	$C_{22}H_{30}N_4O_2$ (382·5)	154—156 (chloroform–hexane)	−71·4 (0·33)	32·6	69·08 68·89	7·91 8·04	14·65 14·50
XII	$C_{25}H_{28}N_4O_4$ (448·5)	98—100 (benzene–hexane)	−63·2 (0·28)	79·2	66·95 66·88	6·29 6·52	12·49 12·45

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

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Translated by A. Kotyk.