

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

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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<sup>1–7</sup> 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<sup>1</sup> as the starting compound by a conventional method<sup>6</sup>. 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 Koňárovice), esters *I*–*XII* displayed an inhibitory effect on the secretion of adenohipophyseal prolactin, reflected, for instance, in the antinidation effect (for method see<sup>8</sup>). 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<sup>R</sup>)<sup>3,9–11</sup> 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<sup>12</sup>), 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<sup>R</sup>. The value of 217% weight of the remaining ovary, found on application of Deprenon<sup>R</sup> 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<sup>13</sup>, 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<sub>254</sub> (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*

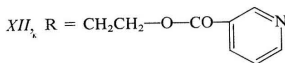
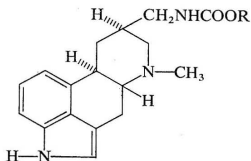
A suspension of 618 mg (2 mmol) azide of D-6-methyl-8-ergolin-I-ylacetic acid<sup>6</sup> in 150 ml benzene was refluxed for 20 min in a nitrogen atmosphere. After cooling to 20–25°C, the mixture was combined with an excess of the appropriate alcohol (15 ml), the mixture was refluxed for 1 h and left 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*)

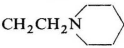
A solution of 343 mg (1 mmol) 2-hydroxyethyl ester of N-(D-6-methyl-8-ergolin-I-ylmethyl)carbamic acid in 10 ml pyridine was combined with 534 mg (3 mmol) hydrochloride of nicotinic acid chloride and the mixture was heated for 1 h to 100°C. After cooling to 20°C, 2 ml water was added, the mixture was stirred for 1 h at 20°C, then it was evaporated, the residue was mixed with 100 ml water, alkalinized 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



Compound R	Formula (mol. wt.)	M.p., °C (solvent)	[α] <sub>D</sub> <sup>20</sup> (c, pyridine), %	Yield %	Calculated/Found		
					% C	% H	% N
<i>I</i> CH <sub>3</sub>	C <sub>18</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub> (313·4)	163—165 (benzene)	—90·0 (0·32)	63·8	68·99 68·76	7·39 7·34	13·41 13·45
<i>II</i> C <sub>2</sub> H <sub>5</sub>	C <sub>19</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub> (327·4)	186—188 (benzene)	—88·0 (0·37)	48·0	69·70 69·94	7·70 7·81	12·83 13·08
<i>III</i> C <sub>3</sub> H <sub>7</sub> -n	C <sub>20</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub> (341·4)	193—195 (methanol)	—83·7 (0·40)	56·0	70·35 70·44	7·97 8·13	12·33 12·32
<i>IV</i> C <sub>4</sub> H <sub>9</sub> -n	C <sub>21</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub> (355·5)	155—157 (ethanol— benzene)	—78·2 (0·40)	84·4	70·96 71·28	8·22 8·32	11·82 12·00
<i>V</i> C <sub>4</sub> H <sub>9</sub> -iso	C <sub>21</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub> (355·5)	140—142 (chloroform— hexane)	—79·2 (0·41)	71·8	70·96 71·12	8·22 8·30	11·82 12·03
<i>VI</i> CH <sub>2</sub> CH=CH <sub>2</sub>	C <sub>20</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub> (339·4)	182—184 (ethanol— hexane)	—81·9 (0·36)	73·9	70·77 70·51	7·42 7·60	12·38 12·18
<i>VII</i> CH <sub>2</sub> C≡CH	C <sub>20</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub> (337·4)	184—186 (methanol— benzene)	—82·5 (0·35)	71·0	71·19 70·95	6·87 6·84	12·45 12·54
<i>VIII</i> C <sub>5</sub> H <sub>9</sub> -cyclo	C <sub>22</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub> (367·5)	146—148 (chloroform— hexane)	—75·8 (0·34)	61·2	71·91 71·66	7·95 7·92	11·43 11·64
<i>IX</i> CH <sub>2</sub> CH <sub>2</sub> OH	C <sub>19</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub> (343·4)	190—192 (benzene— methanol)	84·1 (0·39)	84·0	66·45 66·30	7·34 7·52	12·23 12·52
<i>X</i> CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	C <sub>20</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub> (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 <sub>22</sub> H <sub>30</sub> N <sub>4</sub> O <sub>2</sub> (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 <sub>25</sub> H <sub>28</sub> N <sub>4</sub> O <sub>4</sub> (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. Kőrbl), polarimetric estimations by Mrs I. Bendová in the physico-chemical department (directed by Dr B. Kakáč) of this institute.

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