SOME N-(D-6-METHYL-8-ERGOLIN-I-YLMETHYL)-N′-SUBSTITUTED UREAS AND N-(D-6-METHYL-2-CHLORO-8-ISOERGOLIN-I-YL)--N′,N′-DIETHYL UREA*

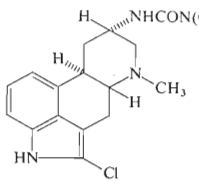
M.BERAN, J.KŘEPELKA, V.ZIKÁN, K.ŘEŽÁBEK, M.ŠEDA and M.SEMONSKÝ

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

Received July 23rd, 1976

Condensation of N-(D-6-methyl-8-ergolin-I-ylmethyl) isocyanate with amines led to N-(D--6-methyl-8-ergolin-I-ylmethyl) ureas *I*—*IX* and chlorination of N-(D-6-methyl-8-isoergolin-I-yl)--N′,N′-diethylurea, using N,2,6-trichloro-4-nitroacetanilide, led to its 2-chloro derivative *X*. Ureas *I* and *II* displayed a significant antinidation effect in rats; compound *X* was ineffective against nidation.

The synthesis and the information study of N-(D-6-methyl-8-ergolin-I-ylmethyl)--N′-substituted ureas *I*—*IX* (Table I) was stimulated by the significant antinidation and antilactation effect of N-(D-6-methyl-8-isoergolin-I-yl)-N′-substituted ureas, especially N′,N′-diethylurea[1], caused by a depression of secretion of hypophyseal prolactin. In view of the fact that in many cases the pharmacodynamic effects of ergoline derivatives are affected by substitution of the ergoline skeleton in position 2 with halogen[2] we prepared the 2-chloro derivative *X* of N-(D-6-methyl-8-isoergolin--I-yl)-N′,N′-diethylurea.



X

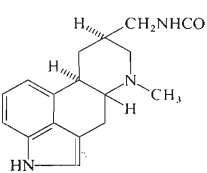
Substituted ureas *I*—*IX* were prepared by condensation of N-(D-6-methyl-8-ergolin--I-ylmethyl) isocyanate (*XI*) with appropriate amines in an inert medium. Isocyanate *XI* was obtained by thermal degradation from the azide of D-6-methyl-8-ergolin-I-

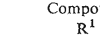
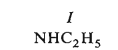
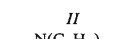
* Part LIII in the series Ergot Alkaloids; Part LII: This Journal *42*, 1412 (1977).

-ylacetic acid (*XII*), released from the hydrochloride of azide *XII* (ref.[3]) using of water solution of natrium bicarbonate, by thermal degradation in boiling benzene. The benzene solution of isocyanate *XI* was used without isolation of the compound for a reaction with amines.

TABLE I

N-(D-6-Methyl-8-ergolin-I-ylmethyl)-N′-substituted Ureas



Compound R^1	Formula (mol.wt.)	M.p., °C (solvent)	$[\alpha]_D^{20}$ (*c*, pyridine)	Yield %	Calculated/Found % C	% H	% N
I NHC_2H_5	$C_{19}H_{26}N_4O$ (326·5)	238—240 (benzene–methanol)	−105·2° (0·38)	89·0	69·91 69·96	8·02 7·92	17·10 17·33
II $N(C_2H_5)_2$	$C_{21}H_{30}N_4O$ (354·5)	165—167 (methanol)	−81·7° (0·36)	86·4	71·15 70·88	8·53 8·42	15·81 16·03
III 	$C_{22}H_{30}N_4O$ (366·5)	128—130 (acetone–benzene)	−86·4° (0·34)	68·1	72·10 71·99	8·25 8·43	15·28 15·08
IV 	$C_{22}H_{30}N_4O$ (366·5)	142—144 (methanol)	−81·7° (0·25)	91·8	72·09 71·83	8·25 8·44	15·28 14·98
V 	$C_{23}H_{32}N_4O$ (380·5)	161—163 (methanol)	−84·5° (0·27)	85·7	72·59 72·30	8·47 8·55	14·72 14·57
VI $NH(CH_2)_2CH_3$	$C_{20}H_{28}N_4O$ (340·5)	224—225 (benzene–methanol)	−76·5° (0·51)	92·0	70·55 70·54	8·29 8·23	16·46 16·55
VII $NH(CH_2)_3CH_3$	$C_{21}H_{30}N_4O$ (354·5)	188—191 (benzene–methanol)	−89·9° (0·42)	74·4	71·15 70·84	8·53 8·44	15·81 15·76
VIII 	$C_{21}H_{28}N_4O$ (352·5)	248—250 (benzene–methanol)	−96·9° (0·42)	72·2	71·56 71·36	8·01 8·10	15·90 16·24
IX 	$C_{21}H_{28}N_4O_2$ (368·5)	234—236 (benzene–methanol)	−85·8° (0·42)	52·7	68·45 68·26	7·66 7·82	15·22 15·44

N-(D-6-Methyl-2-chloro-8-isoergolin-I-yl)-N',N'-diethylurea (*X*) was prepared by chlorination of N-(D-6-methyl-8-isoergolin-I-yl)-N',N'-diethylurea (*XIII*), using N,2,6-trichloro-4-nitroacetanilide in dioxane.

For biological testing, *I*—*X* were applied as aqueous solutions of hydrogen tartrates. Substituted ureas *I*—*IX* displayed in rats an inhibitory effect on the secretion of adenohypophyseal prolactin, manifested in an antinidation effect. The antinidation activity was especially pronounced with *I* and *II*, at a dose of 2·5 mg base/kg (Wistar rats from Konárovice) applied in one *p.o.* administration on the 5th day after mating (for method see[4]). Compound *II* stimulated the secretion of hypophyseal gonadotropins, as shown on a 10-day continuous application of daily doses of 0·5 mg base/kg (for method see[5]). Compound *X* is practically ineffective against lactation and nidation in rats at doses when the starting nonhalogenated urea *XII* is active[1]. Chlorination of *XIII* in position 2 led simultaneously to the appearance of a slight hypotensive effect of *X* in rats with normal blood pressure in urethane narcosis (for method see[4]) which is in agreement with an earlier finding that the 2-halogenation of ergoline derivatives generally results in a decrease of antinidation and antilactation activity while the hypotensive activity is increased[2]. Using the method of Doepfner and Cerletti[6], a single application of *X* in a dose of 0·5 mg base/kg decreased serotonine edema by some 60%.

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 the melting point at 0·5 Torr. The specific rotation was determined in a Perkin-Elmer type 141 polarimeter and refer to compounds free of crystal solvent. The composition of fractions obtained by column chromatography on silica gel (Kieselgel, Merck for *I*—*IX*) or on alumina (Reanal, activity IV — for *X*) was investigated by thinlayer chromatography on silica gel (Merck, according to Stahl) using methanol as solvent. The compounds were detected by the blue-violet colour after spraying with 10% *p*-toluenesulfonic acid in methanol and heating to 50°C (compounds *I*—*IX*) or by paper chromatography in formide–ammonium formate as anchored phase and benzene–chloroform (3 : 7) as the mobile phase, detecting the compounds with UV light (compound *X*).

Hydrochloride of azide *XII* was prepared from the hydrazide of the same acid[3] and was converted to the base by the action of an aqueous solutions of sodium hydrogen carbonate. The precipitated base was filtered and dried at 0·5 Torr over P_2O_5 at 20—25°C and kept at 5°C.

N-(D-6-Methyl-8-ergolin-I-ylmethyl)-N'-substituted Ureas *I*—*IX*

Suspension of 618 mg (2 mmol) azide of *XII* in 150 ml benzene was refluxed for 20 min in nitrogen. After cooling to 20—25°C, 2 ml of the appropriate amine in 20 ml benzene was added, the mixture was refluxed for 1 h and left to stand for 3 h (compounds *I*—*III* and *VI*—*IX*) or for 24 h (compounds *IV* and *V*) at 20—25°C. After distillation of the volatile components the residue was purified by column chromatography on silica gel in benzene with 8% methanol. The pooled homogeneous fractions were purified by crystallization from suitable solvents (Table I).

M-(D-6-Methyl-2-chloro-8-isoergolin-I-yl)-N',N'-diethylurea (*X*)

A solution of 0·54 g (1·9 mmol) N,2,6-trichloro-4-nitroacetanilide in 15 ml dioxane was poured into a solution of 0·5 g (1·47 mmol) N-(D-6-methyl-8-isoergolin-I-yl)N',N'-diethylurea in 25 ml dioxane and the mixture was left to stand for 20 h at room temperature. Dioxane was distilled off and the residue was dissolved in 25 ml chloroform and extracted with 1% tartaric acid in water. The aqueous extracts were alkalified with solid sodium carbonate, the precipitated base was extracted with chloroform and the solution was evaporated to dryness. The crude product was purified by chromatography on a column of alumina using chloroform for elution. The homogeneous fractions were combined (0·27 g, 50·8%) and recrystallized from acetone; m.p. 161 to 162°C, $[\alpha]_D^{20}$ +29·3° (*c* 0·3, pyridine). For $C_{20}H_{27}ClN_4O$ (374·9) calculated: 64·07% C, 7·26% H, 14·94% N, 9·45% Cl; found: 63·72% C, 7·41% H, 14·75% N, 9·19% Cl. The IR spectrum measured in a KBr pellet is identical with the spectrum of the starting compound but absorption bands corresponding to =CHR bonds are missing in the region of 790—870 or 2800 and 1400 to 1420 cm^{-1}. The ^{1}H-NMR spectrum measured in hexadeuteriodimethyl sulfoxide, using tetramethyl silane as internal standard, does not contain the signal of 1 proton at 6·75—7·20 ppm in the region of olefinic protons of ergoline type.

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

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Translated by A. Kotyk.