AMIDES OF D-6-METHYL-8-ERGOLIN-I-YLACETIC ACID*

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Amides of D-6-methyl-8-ergolin-I-ylacetic acid *I*—*XVII* were prepared by the azide method. The isobutylamide in particular shows a distinct antinidation and gonadotropin-stimulating effect in rats.

In an earlier communication[1] we described the preparation and reported informative data on the antifertility and antilactation effect of the amide of D-6-methyl-8-ergolin-I-ylacetic acid (6683-VÚFB, Deprenon^R) and of some other N-substituted amides of the same acid in rats. In view of the significant effect of Deprenon[2-4] we prepared now other simple amides *I*—*VI* and some N′-substituted piperazides *VII*—*XVII* of D-6-methyl-8-ergolin-I-ylacetic acid (Table I) and subjected them to an informative pharmacological evaluation.

Amides *I*—*XVII* were prepared by the azide method, in a reaction of the relatively stable hydrochloride of D-6-methyl-8-ergolin-I-ylacetic acid azide[5] with an excess of the corresponding amine, with the objective of releasing the azide base from its salt and of binding the hydrogen azide formed during the reaction (amides *III*—*V* and *VII*—*XVII*); during the preparation of amide *VI* the excess of (+)-2-aminopropanol was replaced with triethylamine while triethylamine was used as the reaction medium for the preparation of amides *I* and *II*.

During an orientative pharmacological testing of amides *I*—*XVII* carried out here by Drs K. Řežábek, M. Šeda and M. Aušková, amide *III* displayed a distinct antinidation effect (in a dose of 0·5—2·5 mg/kg *p.o.* — for method see[6]) and a gonadotropin-stimulating effect (in a dose of 12·5 mg/kg *p.o.* — for method see[7]) in rats. Detailed data on the pharmacological tests will be published elsewhere.

EXPERIMENTAL

The melting points (or points of decomposition) were determined in Kofler's block and are not corrected. Samples for analysis were dried at 100°C/0·5 Torr (amides *I*, *V*, *VII*—*XVII*) or at 140°C/0·5 Torr (amides *II*—*IV* and *VI*). Specific rotation was determined in a Perkin-Elmer 141 polarimeter. Composition of fractions obtained by column chromatography on Merck silica gel

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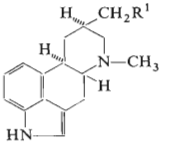
TABLE I

Amides of D-6-Methyl-8-ergolin-I-ylacetic Acid



I–VI, $R^1 = COR^2$

VII–XVII, $R^1 = CON$  $N-R^2$

Compound R^2	Formula (mol. wt.)	M.p., °C (solvent)	$[\alpha]_D^{20}$ [a] (*c*)	Calculated/Found % C	% H	% N
I $NHCH_3$	$C_{18}H_{23}N_3O$ (297·4)	228–229 (methanol)	−75·5 (0·41)	72·70 72·16	7·79 8·08	14·13 13·91
II $N(CH_3)_2$	$C_{19}H_{25}N_3O$ (311·4)	262–264 (methanol)	−82·6 (0·38)	73·28 73·54	8·09 8·37	13·50 13·65
III $NHC(CH_3)_3$	$C_{21}H_{29}N_3O$ (339·5)	218–219 (acetone)	−75·5 (0·38)	74·30 74·11	8·61 8·65	12·37 12·45
IV $NH(CH_2)_2CH(CH_3)_2$	$C_{22}H_{31}N_3O$ (353·5)	198–199 (methanol)	−82·5 (0·42)	74·75 74·60	8·84 9·02	11·89 11·83
V $NHCH_2CH_2OH$	$C_{19}H_{25}N_3O_2$ (327·4)	189–191 (methanol)	−71·3 (0·41)	69·70 69·38	7·69 7·92	12·82 12·99
VI $NHCH(CH_3)CH_2OH$	$C_{20}H_{27}N_3O_2$ (341·4)	220–222 (benzene–methanol)	−80·1 (0·41)	70·36 70·30	7·97 8·24	12·30 12·41
VII CH_3	$C_{22}H_{30}N_4O$ (366·5)	236–237 (ethanol)	−47·2 (0·53)	72·10 71·91	8·25 8·24	15·29 14·98
VIII C_6H_5	$C_{27}H_{32}N_4O$ (428·5)	252–254 (ethanol–chloroform)	−34·3 (0·55)	75·66 75·37	7·53 7·58	13·08 12·96
IX $4\text{-}CH_3C_6H_4$	$C_{28}H_{34}N_4O$ (442·6)	227–228 (acetone)	−46·4 (0·34)	75·98 75·71	7·74 7·76	12·66 12·47
X $3\text{-}CH_3C_6H_4$	$C_{28}H_{34}N_4O$ (442·6)	223–224 (ethanol–chloroform)	−51·4 (0·47)	75·98 75·88	7·74 8·04	12·66 12·79
XI [b] $3\text{-}Cl\text{-}C_6H_4$	$C_{27}H_{31}N_4ClO$ (463·0)	221–222 (ethanol–dichloromethane)	−49·8 (0·48)	70·04 70·06	6·73 6·84	12·10 11·88
XII $4\text{-}CH_3OC_6H_4$	$C_{28}H_{34}N_4O_2$ (458·6)	230–231 (ethanol–chloroform)	−41·3 (0·39)	73·33 73·24	7·47 7·49	12·22 12·45

TABLE I
(*Continued*)

Compound R^2	Formula (mol. wt.)	M.p., °C (solvent)	$[\alpha]_D^{20}$ [a] (*c*)	Calculated/Found % C	% H	% N
XIII CH_2-C_6H_5	$C_{28}H_{34}N_4O$ (442·6)	210–211 (ethanol–chloroform)	−46·5 (0·55)	75·98 / 75·64	7·74 / 7·62	12·66 / 12·38
XIV $COOC_2H_5$	$C_{24}H_{32}N_4O_3$ (424·5)	223–225 (benzene–ethanol–ether)	−62·4 (0·48)	67·89 / 68·14	7·60 / 7·76	13·20 / 13·39
XV $CH_2COOC_2H_5$	$C_{25}H_{34}N_4O_3$ (438·6)	149–150 (ethanol)	−55·3 (0·49)	68·47 / 68·29	7·81 / 7·91	12·78 / 12·84
XVI CH_2CH_2OH	$C_{23}H_{32}N_4O_2$ (396·5)	242–243 (ethanol)	−57·3 (0·40)	69·66 / 69·27	8·14 / 8·20	14·13 / 14·06
XVII $(CH_2)_2N(C_2H_5)_2$	$C_{27}H_{41}N_5O$ (451·6)	210–211 (ethanol)	−47·1 (0·40)	71·80 / 71·62	9·15 / 9·46	15·51 / 15·60

[a] Compounds *I*–*VI*, pyridine, *VII*–*XVII*, dichloromethane–methanol 1 : 1; [b] Cl calculated: 7·66%; found: 7·96%.

and the purity of preparations were examined in thin layers of silica gel G (Merck, according to Stahl) in chloroform–ethanol (9 : 1) (amides *IX, XI, XIII*–*XV*), in ethanol (amides *VII, VIII, X, XII, XVI* and *XVII*) or in methanol (amides *I*–*VI*). Detection was done on the basis of the blue-violet colour appearing after spraying with 10% *p*-toluenesulfonic acid in methanol and heating to 50°C (for analogous detection of ergot alkaloids see[8]).

The aliphatic amines, N-methylpiperazine and N-(2-hydroxyethyl)piperazine were commercial products, the other N-substituted piperazines were prepared by conventional methods. The hydrochloride of D-6-methyl-8-ergolin-I-ylacetic acid azide was prepared from the hydrazide of the same acid[5], was dried in oil-pump vacuum over P_2O_5 at room temperature and kept at 5°C. Solvents used for crystallization of products, some physical properties and analyses of the compounds are shown in Table I.

Amides *I* and *II*

Some 3 ml of dried methylamine or dimethylamine were condensed at −20°C into a suspension of 0·69 g (2 mmol) hydrochloride of D-6-methyl-8-ergolin-I-ylacetic acid azide in 5 ml triethylamine. The mixture was stirred for 4 h at −8 to −10°C (amide *I*) or at 0°C (amide *II*). After 20 h of standing of the mixture at room temperature the mixture was poured into 100 ml water, the precipitate was filtered, washed with water and dried. The crude amides were purified by column chromatography on silica gel (Merck, 30-fold weight excess) in benzene with 5% methanol and finally purified by crystallization. The yield of amide *I* was 57%, of amide *II* 53%.

Amides *III*—*V*

A mixture of 0·69 g (2 mmol) hydrochloride of D-6-methyl-8-ergolin-I-ylacetic acid azide and 40 mmol of the corresponding amine was stirred for 6 h at 20°C and left to stand for 18 h at that temperature. The mixture was stirred with 100 ml water and the solid was filtered, washed with water and dried (fraction A). The filtrate was shaken with 2 × 50 ml of a mixture of chloroform with 10% ethanol, the organic extracts were combined, dried (Na_2SO_4), and the volatile fractions were removed by distillation in water-pump vacuum. The residue was combined with fraction A and chromatographed on silica gel (Merck, 30-fold weight excess) in benzene with 3% methanol (amide *III*), in benzene with 8% methanol (amide *IV*) or in benzene with 5% methanol (amide *V*). The bases thus obtained were purified by crystallization. The yield of amide *III* was 70%, of amide *IV* 75% and of amide *V* 49%.

Amide *VI*

(+)-2-Aminopropanol (0·16 g, 2·16 mmol) was added at 0°C to a suspension of 0·7 g (2·03 mmol) hydrochloride of D-6-methyl-8-ergolin-I-ylacetic acid azide in 1·6 g triethylamine. The mixture was heated under stirring to 20°C and left to stand at that temperature for two days. Then it was poured into 100 ml water, the mixture was stirred, the precipitate was filtered, washed with water and dried at 20°C. Chromatography of the crude product on silica gel (Merck, 30-fold weight excess) in benzene with 6% methanol produced a pure product in a 42% yield; sample for analysis was purified by crystallization.

Amides *VII*—*XVII*

Solution of the appropriate N-substituted piperazine (9 mmol) in 3 ml dichloromethane was added dropwise at 0°C to a mixture of 0·35 g (1·01 mmol) hydrochloride of D-6-methyl-8-ergolin-I-ylacetic acid azide with 3 ml dichloromethane, the mixture was stirred at 20°C for 3 h, diluted with 40 ml chloroform and shaken with 3 × 20 ml 2M sodium carbonate and 20 ml water. After drying the organic phase (Na_2SO_4) and distillation of the solvents *in vacuo* the crude amides were purified by crystallization (amides *VIII*, *X*) or by chromatography on a column of 10 g silica gel (Merck) using chloroform and then methanol (amides *VII*, *IX*, *XVI*) or ethanol (amides *XI*—*XV*, *XVII*) as elution agents and finally purified by crystallization from organic solvents. The yields were as follows: *VII* 52%, *VIII* 70·5%, *IX* 50%, *X* 60%, *XI* 40·5%, *XII* 62%, *XIII* 43%, *XIV* 42%, *XV* 49·5%, *XVI* 31%, *XVII* 37%.

The analyses were done by Mrs M. Komancová and Mr K. Havel at the analytical department (headed by Dr J. Kŏrbl), the polarimetric estimations by Mrs J. Bendová at the physico-chemical department (headed by Dr B. Kakáč) of this institute.

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