SOME UNSATURATED AMIDES OF D-6-METHYL-8-ERGOLIN-I-YLACETIC ACID AND D-DIHYDROLYSERGIC-I ACID*

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Unsaturated amides of D-6-methyl-8-ergolin-I-ylacetic acid *I*—*VII* and of D-dihydrolysergic-I acid *VIII*—*XI*, as well as the 2-butenyl amide of D-1,6-dimethyl-8-ergolin-I-ylacetic acid *XII* were prepared by the azide method. Some amides of D-6-methyl-8-ergolin-I-ylacetic acid displayed *in vitro* a pronounced protracted uterotonic effect; the uterotonic effect of amides of D-dihydrolysergic-I acid followed *in vivo* was comparable with the effect of ergometrine.

The present communication deals with the synthesis of unsaturated amides of D-6-methyl-8-ergolin-I-ylacetic acid *I*—*VII* and of analogous amides of D-dihydrolysergic-I acid *VIII*—*XI* and of the 2-butenyl amide of D-1,6-dimethyl-8-ergolin-I-ylacetic acid *XII* and with the results of an orientative examination of the uterotonic effect of the compounds *in vitro* as well as *in vivo*. The study was stimulated by an earlier finding of an unusually high antinidation and antilactation effect of the unsaturated amide of D-6-methyl-8-ergolin-I-ylacetic acid (Deprenon^R) in rats[1]. Amides of D-dihydrolysergic-I acid were prepared for comparison in the context of studying the structure-activity relationship in this group of D-6-methylergoline-I derivatives. In view of the fact that in many cases the pharmacodynamic effects of ergoline or ergolene derivatives are pronouncedly affected by methylation in position $N_{(1)}$ of their molecule we also prepared the 2-butenyl amide of D-1,6-dimethyl-8-ergolin-I-ylacetic acid (*XII*).

Amides *I*—*XII* (Table I) were prepared by the high-yield azide method, using the relatively stable and readily accessible azide of D-dihydrolysergic-I acid[2] (*XIII*) or of D-6-methyl-8-ergolin-I-ylacetic acid[3] (*XIV*) or of D-1,6-dimethyl-8-ergolin-I-ylacetic acid (*XV*) as starting compounds. Azide *XV* was prepared from D-1,6-dimethyl-8-ergolin-I-ylacetic acid[3] *via* its methyl ester and hydrazide. For the azide reaction we used an excess of the appropriate amine or a molar equivalent of the amine or of its salt with excess triethyl amine. In all cases, the excess organic base served to bind the hydrogen azide which is released during the azide reaction with amines,

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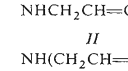
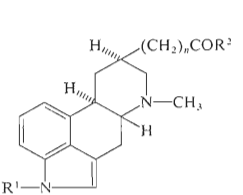
or for releasing the azide base from its hydrochloride. In some cases, the azide reaction was done in dimethylformamide or in dichloromethane (Table I). For biological application, compounds *I–XII* were applied in the form of water-soluble salts, *viz.* normal tartrates.

TABLE I

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

Compound R^2	Formula (mol.wt.)	M.p., °C (solvent)	$[\alpha]_D^{20}$ (*c*, pyridine)	Yield %	Calculated/Found		
					% C	% H	% N
I $NHCH_2CH{=}CH_2$	$C_{20}H_{25}N_3O$ (323·4)	190–192 (methanol)	−80·5° (0·42)	76·5	74·27 74·35	7·79 7·85	12·99 12·92
II $NH(CH_2CH{=}CH_2)_2$	$C_{23}H_{29}N_3O$ (363·5)	202–204 (methanol)	−70·1° (40·0)	85·0	76·00 75·86	8·04 8·25	11·56 11·70
III $NHCH_2CH{=}CHCH_3$	$C_{21}H_{27}N_3O$ (337·5)	207–209 (methanol)	−70·5° (0·38)	86·0	74·74 74·51	8·07 8·31	12·45 12·37
IV CH_3 N $CH_2CH{=}CHCH{=}CH_2$	$C_{23}H_{29}N_3O$ (363·5)	207–208 (benzene–methanol)	−85·4° (0·38)	48·1	76·00 75·80	8·04 7·88	11·56 11·45
V $NHCH_2CH{=}CHC_6H_5$	$C_{26}H_{29}N_3O$ (399·5)	190–192 (acetone)	−68·7° (0·49)	35·9	78·16 78·31	7·32 7·31	10·51 10·84
VI 	$C_{30}H_{33}N_3O$ (451·6)	261–263 (methanol)	−179·4° (0·48	33·1	79·79 79·77	7·36 7·56	9·31 9·44
VII $NHCH_2C{\equiv}CH$	$C_{20}H_{23}N_3O$ (321·4)	223–225 (methanol)	−89·4° (0·47)	44·8	74·74 74·39	7·21 7·50	13·07 12·91
VIII $NHCH_2CH{=}CH_2$	$C_{19}H_{23}N_3O$ (309·4)	236–240 (ethanol)	−132·5° (0·40)	27·6	73·76 73·43	7·49 7·59	13·58 13·25
IX $N(CH_2CH{=}CH_2)_2$	$C_{22}H_{27}N_3O$ (349·5)	138–142 (benzene)	−132·4° (0·47)	48·6	75·61 75·33	7·78 7·71	12·03 12·03
X $NHCH_2CH{=}CHCH_3$	$C_{20}H_{25}N_3O$ (323·4)	246–248 (methanol–benzene)	−128·8 (0·38)	58·7	74·27 74·41	7·79 8·00	12·99 12·79
XI $NHCH_2C{\equiv}CH$	$C_{19}H_{21}N_3O$ (307·4)	253–256 (methanol–benzene)	−127·5° (0·36)	37·0	74·24 74·10	6·88 7·20	13·67 13·51
XII $NHCH_2CH{=}CHCH_3$	$C_{22}H_{29}N_3O$ (351·5)	180–183 (chloroform–hexane)	−82·2° (0·33)	80·1	75·18 75·16	8·32 8·60	11·95 12·04

Amides *I*–*XII* applied to rats showed no antinidation or antilactation activity. On the other hand, some of the compounds were highly uterotonic active. The pertinent tests were carried out in an isolated rat uterus removed from the rat in natural oestrus on the day of experiment. Some of the compounds showed a protracted effect, consisting in bringing about rhythmic contractions rather than a permanent contracture, even at very low concentrations in the nutrient medium. For instance, a high uterotonic activity was found with *IV* at a concentration of 6 ng/ml. It was particularly interesting that the powerful effect persisted, using an initial concentration of 6·25 μg/ml, even after 20 consecutive flushings carried out at 7·5 min intervals. At the same time, the preparation did not affect the reaction of the uterus to subsequently applied oxytocin. An analogous protracted effect was found with *I* and *III* at concentrations of 6·25–3·13 μg/ml nutrient solution. On the other hand, in a series of analogous amides of D-dihydrolysergic-I acid *VIII*–*XI* not even a brief uterotonic effect could be detected at high concentrations (1 mg/ml) *in vitro*. Contrary to expectation, experiments conducted *in vivo* in rats, guinea-pigs and rabbits, exhibited no pronounced uterotonic effect of amides *I*–*VII* as compared with ergometrine while amides of D-dihydrolysergic-I acid *VIII*–*XI* were clearly active *in vivo*. The effective doses and the potency of the effect were comparable to those of ergometrine; compound *XI* was even more effective. 2-Butenyl amide of D-1,6-dimethyl-8-ergolin-I-ylacetic acid (*XII*) showed *in vitro* a lower uterotonic activity than the same derivative of D-6-methyl-8-ergolin-I-ylacetic acid (*III*). More details on biological testing will be published elsewhere.



I–*XI*, $R^1 = H$
XII, $R^1 = CH_3$

I–*VII*, *XII*, $n = 1$
VIII–*XI*, $n = 0$

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. The specific rotation was determined in pyridine and refer to compounds free of crystal solvent. Column chromatography of the reaction mixtures was done on silica gel (Merck) in benzene–methanol. The compounds

were detected by thin-layer chromatography on the basis of their violet colour after spraying with 10% *p*-toluenesulfonic acid in methanol and heating to 50°C.

Amides of D-6-Methyl-8-ergolin-I-ylacetic Acid (*I*— *VIII*)

Amides I—IV: 528·8 mg (1·53 mmol) azide of D-6-methyl-8-ergolin-I-ylacetic acid (*XIV*) was mixed with 1·0 g (17·5 mmol) allylamine (amide *I*) or 1·74 g (18 mmol) diallylamine (amide *II*), or 1·35 g (19·0 mmol) *trans*-2-butenylamine (amide *III*) or 1·0 g (10·4 mmol) *trans*-1,3-pentadienyl-N-methylamine[4] (amide *IV*). The mixture was stirred for 8 h at 20—25°C and left to stand for 16 h at that temperature. After removing most of the excess amine by vacuum distillation, the residue was triturated with 100 ml water, the precipitated compound was filtered, washed with water and purified by chromatography. Combined homogeneous fractions were purified by crystallization (Table I).

Amide V *and* VII: Dimethylformamide (2 ml) and 2 g (20 mmol) triethylamine was added to a mixture of 563 mg (1·63 mmol) azide *XIV* and 304 mg (1·79 mmol) hydrochloride of 1-phenylallylamine (amide *V*) or 165 mg (1·80 mmol) hydrochloride of propargylamine (amide *VII*) and the mixture was stirred for 24 h at room temperature. The volatile fractions were removed by vacuum distillation and the dimethylformamide solution was poured into 100 ml water. The precipitated solid was filtered, purified by chromatography and recrystallized.

Amide VI: Triethylamine (2 g, 20 mmol) was added to a mixture of 653 mg (1·89 mmol) azide *XIV* and 336 mg (2·08 mmol) 2-amino-3-phenylbicyclo[2,2,1]hept-5-ene[5] and the mixture was stirred for 8 h at room temperature. Then it was left to stand for 16 h. The excess triethylamine was removed by distillation and the mixture was poured into 100 ml water. The precipitated product was processed as above.

Amides of D-Dihydrolysergic-I Acid (*VIII*— *XI*)

Amides VIII—X: 730 mg (2·2 mmol) azide of D-dihydrolysergic-I acid (*XIII*) was mixed at 20°C with 1·71 g (30 mmol) allylamine (amide *VIII*) or with 2·49 g (35·0 mmol) 2-butenylamine (amide *IX*) or with 2·52 g (26·0 mmol) dialylamine (amide *X*). The mixture was stirred for 8 h and left to stand for 16 h at room temperature. The excess amine was distilled off and the residue was mixed with 100 ml water, the product was filtered and processed as above.

Amide XI: 616 mg (1·85 mmol) azide *XIII* and 250 mg (2·73 mmol) propargylamine hydrochloride was mixed with 2 ml dimethylformamide, 2 g (20 mmol) triethylamine was added and the mixture was stirred for 8 h at room temperature and left to stand for 16 h. After distillation of triethylamine it was processed as above.

2-Butenylamide of D-1,6-Dimethyl-8-ergolin-I-ylacetic Acid (*XII*)

Solution of 1·0 g (3·35 mmol) D-1,6-dimethyl-8-ergolin-I-ylacetic acid[3] in 200 ml methanol with 2 g hydrogen chloride was refluxed for 2 h. After evaporation, the residue was dissolved in 100 ml water and alkalified with sodium carbonate. The base was extracted with chloroform containing 20% methanol and the organic fraction was evaporated. The crude methyl ester was recrystallized from benzene, m.p. 128—130°C; the yield was 0·67 g (64·0%); $[\alpha]_D^{20}$ −93·3° (*c* 0·37, pyridine). For $C_{19}N_{24}N_2O_2$ (312·4) calculated: 73·05% C, 7·74% H, 8·97% N; found: 72·90% C, 7·93% H, 8·68% N. 1·0 g (3·2 mmol) of the methyl ester was heated with 20 ml 102% hydrazine hydrate in nitrogen to 150—160°C for 2 h. After cooling, the crystalline fraction was filtered and washed with water; the yield was 0·98 g (98·0%); m.p. 221—222°C; $[\alpha]_D^{20}$ −91° (*c* 0·4, pyridine). For

$C_{18}H_{24}N_4O$ (312·4) calculated; 69·20% C, 7·74% H, 17·93% N; found: 69·14% C, 7·42% H, 17·84% N. A 1M solution of sodium nitrite (1·5 ml) was added dropwise under stirring at 0°C to a solution of 400 mg (1·28 mmol) hydrazide of D-1,6-dimethyl-8-ergolin-I-ylacetic acid in 16 ml 0·2M-HCl. The mixture was acidified with 3 ml 0·2M-HCl, cooled to −5°C and the hydrochloride of azide of D-1,6-dimethyl-8-ergolin-I-ylacetic acid (*XV*) was filtered and dried over P_2O_5 at 20°C. 200 mg (0·56 mmol) azide *XV* was mixed with 1·0 g (14·1 mmol) *trans*-2-butenylamine, the mixture was stirred at room temperature for 8 h, left to stand for 16 h and then processed as in the case of amides *I*—*IV*.

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