SYNTHESIS OF NITRILE AND AMIDE OF D-6-METHYL-8-ISOERGOLIN-I-YLACETIC ACID AND OF NITRILE OF D-ISOERGOLIN-II-YLACETIC ACID

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Using D-6-methyl-8-hydroxymethylisoergoline-I and -II, the nitrile and the amide of D-6-methyl--8-isoergolin-I-ylacetic acid (*I* and *III*) and the nitrile of isomeric isoergolin-II-ylacetic acid (*II*) were synthesized as potential inhibitors of secretion of hypophyseal prolactin in rats. Compound *I* had a pronounced antilactation and antinidation activity while *III* possessed an antiserotonine activity in rats.

N-(D-6-Methyl-8-isoergolin-I-yl)-N'-substituted ureas were found[1] to possess a pronounced antilactation and antinidation effect on rats due to inhibited secretion of hypophyseal prolactin. The biological efficiency of the compounds is stereospecific, the isomeric isoergolin-II-yl and ergolin-I-yl compounds being either much less effective or completely ineffective[1]. On the other hand, other ergolin-I-yl compounds, D-6-methyl-8-cyanomethylergoline-I (ref.[2]) and particularly the amide of D-6-methyl-8-ergolin-I-ylacetic acid[3] are clearly effective. It was of interest to establish to what extent an effect will be displayed by the isomeric D-6-methyl-8-cyanomethylisoergoline-I and -II (*I* and *II*) and by the amide of D-6-methyl-8-isoergolin-I-ylacetic acid (*III*).

The starting compound for the synthesis of nitrile *I* and amide *III* was D-6-methyl--8-hydroxymethylisoergoline-I (ref.[4]) which was boiled with phosphorus oxychloride and converted to the analogous 8-chloromethyl compound *IV* which reacted with sodium cyanide in dimethyl sulfoxide to nitrile *I*. Nitrile *I* was saponified by boiling with aqueous-ethanolic potassium hydroxide to acid *V*, or to its potassium salt which was boiled with methanolic hydrogen chloride and converted to the methyl ester of *VI*. This was boiled with hydrazine hydrate to hydrazide *VII*. From the hydrazide, amide *III* was obtained by splitting off ammonia, using Raney nickel in boiling 95% ethanol. D-6-Methyl-8-cyanomethylisoergoline-II (*II*) was obtained in analogy to nitrile *I* from D-6-methyl-8-hydroxymethylisoergoline-II (ref.[4]) *via* 8-chloromethyl compound *VIII*.

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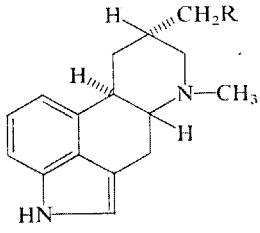

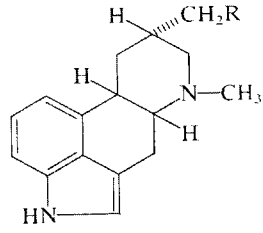

I, R = CN
III, R = $CONH_2$
IV, R = Cl

V, R = COOH
VI, R = $COOCH_3$
VII, R = $CONHNH_2$

II, R = CN
VIII, R = Cl

The following conclusion could be drawn from an informative pharmacological study of *I*—*III*. Compound *I* and the isomeric D-6-methyl-8-cyanomethylergoline-I applied in a dose of 1 mg per day per kg body weight show approximately the same antilactation activity in rats (method in ref.[5]), decreasing the value of lactation to about one-half. At a daily dose of 0·5 mg/kg, compound *II* has practically no effect while the above two compounds still possess a substantial activity. In comparison with the amide of D-6-methyl-8-ergolin-I-ylacetic acid, compound *III* shows only an insignificant activity: at a daily dose of 1 mg/kg, *III* is ineffective toward lactation while a daily dose of 0·2 mg/kg of the isomeric ergolin-I-yl compound decreases lactation to one-half. In the antinidation effect on rats, a daily dose of 5 mg/kg of *I* and of the isomeric D-6-methyl-8-cyanomethylergoline-I brought about a 100% and compound *II* a 50% decrease. Compound *III* applied at a dose of 0·5 mg/kg when the amide of D-6-methyl-8-ergolin-I-ylacetic acid is 100% effective, was completely ineffective (for method see ref.[6]). At a dose of 0·5 mg/kg compound *III* showed a 60% and the amide of D-6-methyl-8-ergolin-I-ylacetic acid a 39% inhibition of serotonine edema of rat paw (method in ref.[7]).

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected. Samples for analysis were dried *in vacuo* (0·1 Torr) at a temperature proportional to their melting point. The values of specific rotation refer to compounds free of the crystal solvent. The purity of the compounds was checked by paper chromatography; for compounds *I*, *II*, *IV* and *VII* we used formamide–ammonium formate as the stationary phase and a mixture of benzene–chloroform (1 : 1) as the mobile phase, for compound *V* we used 1-butanol–acetic acid–water (4 : 1 : 5). The compounds were detected on the basis of their fluorescence in UV light after previous illumination with sunlight. Compounds *III* and *VI* were evaluated in a thin layer of silica gel (Silufol, Kavalier) and detected as above. Compound *VI* was chromatographed in chloroform–benzene–ethanol (3 : 2 : 1), compound *III* in ethyl acetate–2-propanol–ammonia–water (60 : 20 : 17·5 : 15), after previous illumination with sunlight, detecting with UV light at 254 and 366 nm. The homogeneity of *VII* was checked on a thin layer of silica gel with gypsum according to Stahl in chloroform–benzene–ethanol (3 : 2 : 1). Detection was done by spraying with 5% methanolic solution of *p*-toluenesulfonic acid and heating under an IR lamp.

D-6-Methyl-8-chloromethylisoergoline-I (*IV*)

A mixture of 6·1 g (23·8 mmol) D-6-methyl-8-hydroxymethylisoergoline-I (ref.[4]) and 410 ml phosphorus oxychloride was refluxed for 1 h in the absence of air moisture. After distillation of phosphorus oxychloride in water-pump vacuum residue was dried at 60°C (10 Torr), covered with 290 ml 5% $NaHCO_3$, the mixture was heated for 30 min to 90°C and left to stand for 20 h at 20°C. The filtered substance was dissolved in 500 ml hot chloroform and the filtrate was evaporated in water–pump vacuum; a total of 6·0 g (92%) product was obtained which melted at 149—150°C. For analysis it was recrystallized from cyclohexane, m.p. 154—155°C. $[\alpha]_D^{20}$ —76·4° (*c* 0·5, pyridine). For $C_{16}H_{19}ClN_2$ (274·8) calculated: 69·93% C, 6·97% H, 12·90% Cl, 10·20% N; found: 69·97% C, 7·13% H, 13·02% Cl, 10·49% N.

D-6-Methyl-8-cyanomethylisoergoline-I (*I*)

A mixture of 5·25 g (113 mmol) sodium cyanide, 5·56 g (20 mmol) *IV* and 140 ml dimethyl sulfoxide was stirred at 120°C for 3 h. After pouring into 500 ml water the precipitated compound was filtered and stirred for 30 min with 100 ml water at 60°C. The crude product was dried over P_2O_5 (4·38 g, 82%) and purified by chromatography on a column of silica gel (50 g, grain size 0·05—0·2 mm) using chloroform as elution agent. The appropriate homogeneous fractions were combined (3 g) and crystallized from ethanol; m.p. 163—164°C, $[\alpha]_D^{20}$ —73·4° (*c* 0·23, pyridine). For $C_{17}H_{19}N_3$ (265·4) calculated: 76·94% C, 7·22% H, 15·84% N; found: 76·50% C, 7·67% H, 16·07% N.

D-6-Methyl-8-isoergolin-I-ylacetic Acid (*V*)

A mixture of 2·05 g (7·72 mmol) nitrile *I*, 60 ml ethanol, and a solution of 10 g potassium hydroxide in 20 ml water was refluxed for 15 h using a KOH stopper. After dilution with 60 ml ethanol, the mixture was left to stand for 48 h at 3°C. The acid was liberated from the salt (2·29 g, 52%) with carbon dioxide introduced into a hot solution of the salt. For analysis, acid *V* was recrystallized from water and dried at 78°C and 0·1 Torr. On heating above 210°C the acid is decomposed without melting. $[\alpha]_D^{20}$ —54·2° (*c* 0·43, dimethylformamide). For $C_{17}H_{20}N_2O_2$ (284·4) calculated: 9·85% N; found: 9·64% N.

Methyl Ester of D-6-Methyl-8-isoergolin-I-ylacetic Acid (*VI*)

A mixture of 1·1 g (3·4 mmol) potassium salt of acid *V*, 60 ml methanol and 6 ml 50% methanolic hydrochloric acid was refluxed for 2 h under exclusion of air moisture. After distillation of the volatile fractions in water-pump vacuum, the residue was refluxed for 45 min with 50 ml 90% aqueous methanol, the hot solution was filtered, the filtrate was diluted with 70 ml water and 30 ml 1M-$NaHCO_3$ and left to stand for 1 h at 3°C. Filtration yielded 0·66 g (65%) methyl ester which was recrystallized from benzene, m.p. 139—141°C. $[\alpha]_D^{20}$ — 59·6° (*c* 0·3, pyridine). For $C_{18}H_{22}N_2O_2$ (298·4) calculated: 72·44% C, 7·43% H, 9·40% N; found: 72·88% C, 7·48% H, 9·55% N.

Hydrazide of D-6-Methyl-8-isoergolin-I-ylacetic Acid (*VII*)

0·35 g (1·17 mmol) methyl ester *VI* was refluxed with gentle boiling in the presence of 5 ml 100% hydrazine hydrate in an atmosphere of nitrogen for 3 h and left to stand for 48 h at 0°C. The gel product was filtered, washed with water and dried at 35°C and 3 Torr (0·29 g, 83%).

For analysis it was purified by precipitation from aqueous methanol, m.p. 112–114°C. $[\alpha]_D^{20}$ −45·3° (*c* 0·35, pyridine). For $C_{17}H_{22}N_4O$ (298·4) calculated: 68·42% C, 7·43% H, 18·78% N; found: 68·04% C, 7·63% H, 18·90% N.

Amide of D-6-Methyl-8-isoergolin-I-ylacetic Acid (*III*)

A mixture of 200 mg (0·67 mmol) hydrazide *VII*, 3 g Raney nickel and 100 ml 95% ethanol was refluxed for 1 h. Raney nickel was filtered, washed with 30 ml 95% ethanol and the filtrate was evaporated in water-pump vacuum. The product (180 mg, 95%) was recrystallized for analysis from a mixture of chloroform and methanol; m.p. under decomposition about 245°C. $[\alpha]_D^{20}$ −44·4°C (*c* 0·31, pyridine). For $C_{17}H_{21}N_3O$ (283·4) calculated: 14·82% N; found: 14·52% N. Hydrogen tartrate was obtained in a reaction of the two components in methanol; on heating, it melts diffusely under decomposition at about 247°C. $[\alpha]_D^{20}$ −11·1° (*c* 0·135, water). For $C_{21} . H_{27}N_3O_7$ (433·5) calculated: 9·69% N; found: 9·46% N.

D-6-Methyl-8-chloromethylisoergoline-II (*VIII*)

A mixture of 0·64 g (2·49 mmol) D-6-methyl-8-hydroxymethylisoergoline-II and 43 ml phophorus oxychloride was refluxed for 1 h. The phosphorus oxychloride was distilled off in water-pump vacuum and the residue was heated for 15 min with 30 ml 5% $NaHCO_3$. After 24 h of standing at 20°C, the precipitated substance was filtered, dissolved in 25 ml chloroform and purified by chromatography on a column of silica gel (35 g) using chloroform for elution. The appropriate fractions were pooled (0·438 g, 64%) and crystallized from aqueous ethanol; m.p. 187–189°C, $[\alpha]_D^{20}$ +5·0° (*c* 0·4, pyridine). For $C_{16}H_{19}ClN_2$ (274·8) calculated: 69·93% C, 6·97% H, 12·90% Cl, 10·20% N; found: 69·68% C, 7·07% H, 12·88% Cl, 10·10% N.

D-6-Methyl-8-cyanomethylisoergoline-II (*II*)

A mixture of 0·45 g (1·63 mmol) *VIII*, 0·45 g (9 mmol) sodium cyanide and 15 ml dimethylsulfoxide was heated under stirring for 3 h to 120°C and then poured into 50 ml water. After 24 h of standing at 5°C, the precipitate was filtered, washed with water and heated for 15 min with 40 ml water at 65°C. The filtered product (0·29 g, 67%) was crystallized from ethanol, m.p. 180–181°C, $[\alpha]_D^{20}$ −19·5° (*c* 0·4, pyridine). For $C_{17}H_{19}N_3$ (265·4) calculated: 76·94% C, 7·22% H, 15·84% N; found: 76·57% C, 7·41% H, 15·94% N.

The analyses reported here were done by Mrs M. Komancová and Mrs V. Šmídová from the analytical department of this institute under the direction of Dr J. Körbl. The paper chromatography checks were carried out by Mrs M. Jelínková of the same department.

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