SOME 6-ALKYL DERIVATIVES OF D-8-ERGOLIN-I-YLACETAMIDE*

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D-6-Alkyl-8-cyanomethylergolines-I were converted either by known procedures *via* the corresponding methyl esters *I—III* and hydrazides *IV—VI* to amides *VII—IX*, or by hydration of the nitrile group under the conditions of ionic pair extraction to amides *VIII* and *X—XIII*. In the same system D-6-methyl-8-ergolin-I-ylacetamide (Deprenon^R) was prepared from D-6-methyl-8--cyanomethylergoline-I. Amides *VII*, *VIII* and *XI* had a considerably higher prolactin inhibiting activity than Deprenon.

In one of our preceding studies[1] we found that the introduction of alkyl groups different from the methyl group into position 6 of D-8-cyanomethylergoline-I and D-8--methylergoline-I affected their antilactation and antinidation effect considerably, while the introduction of the ethyl or the n-propyl group led to an increase in both activities mentioned. Therefore we were interested to see to what extent the antilactation and the antinidation effect of D-6-methyl-8-ergolin-I-ylacetamide (6683-VÚFB; Deprenon^R) would be affected if other alkyl groups are introduced into position 6.

The starting D-6-alkyl-8-cyanomethylergolines-I were prepared by a method described by us earlier for the alkylation of D-8-cyanomethylergoline-I (ref.[1,3]). 6-Ethyl-, 6-n-propyl- and 6-n-butyl-8-cyanoergoline-I were then hydrolysed with aqueous–ethanolic potassium hydroxide[4] to corresponding carboxylic acids, and their potassium salts were converted without further purification to methyl esters *I—III* on boiling with methanolic hydrogen chloride solution[5]. Compounds *I—III* were converted to hydrazides *IV—VI* using a known method[4]. Reductive cleavage of ammonia from the hydrazides *IV* and *V* with Raney nickel in ethanol[2] gave amides *VII* and *VIII*. Amide *IX* was prepared from hydrazide *VI via* azide[4].

In view of the relatively low yields we attempted the preparation of the amides from nitriles using the method described by Li and coworkers[6], who converted D-6-methyl-8-cyanomethyl-$\Delta^{8,9}$-ergolene to D-6-methyl-8- ergol-$\Delta^{8,9}$-enylacetamide on reaction with 30% hydrogen peroxide and sodium hydroxide in ethanol (modification of the method of Radziszewski[7]). When we applied this method we were unable to isolate the required amides from the mixture in any case. Therefore we studied the

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reaction conditions and looked for a suitable medium for the hydration of the nitrile group in D-6-alkyl-8-cyanomethylergolines-I, including the more easily accessible 6-methyl compound[4]. We found that in a two-phase system, composed of aqueous pyridine and an aqueous phase saturated with a tetraalkylammonium base, under refluxing and stirring under nitrogen, amides are formed, while their hydrolysis to carboxylic acid is considerably suppressed. For the reaction we used tetraethylammonium hydroxide set free *in situ* from tetraethylammonium bromide with an equivalent amount of aqueous potassium hydroxide solution. Further ammonium bases were used with the same result, for example the base liberated in the same manner from triethylbenzylammonium chloride. D-6-Methyl-8-ergolin-I-ylacetamide (Deprenon^R), D-6-isopropyl- (*X*), D-6-allyl- (*XI*), D-6-propargyl- (*XII*) and D-6-benzyl-8-ergolin--I-ylacetamide (*XIII*), as well as amides *VII*–*IX* were prepared in good yields using this method. This is a case of the "extraction of ion pairs", as described for example by Brändström and coworkers[8], in which the hydroxide ion is extracted into the aqueous–pyridine phase in the form of an ammonium hydroxide ion pair. From the experiments carried out in the two-phase system composed of pyridine and water saturated with potassium hydroxide, or with equivalent amounts of potassium hydroxide and tetraalkylammonium salt, we found that the hydration of the nitrile takes place under the last mentioned conditions considerably faster, while the amount of the acid formed, which did not exceed 10%, does not increase with a prolongation of the reaction time. In contrast to this, the degree of the hydrolysis of the amide is substantially higher when potassium hydroxide alone is used. The low solubility of our nitriles in chloroform and dichloromethane, *i.e.* in solvents which are most commonly used for the extraction of ion pairs, did not permit their use. From a study of the available literature it appears that this procedure has not yet been used for the preparation of amides from nitriles. The new procedure enabled us to obtain the required amounts of substances for pharmacological testing.

The evaluation of antinidation and antilactation effects (Dr K. Řežábek, Dr M. Šeda and Dr M. Aušková of our Institute), that are a manifestation of the inhibition of the secretion of adenopituitary prolactin, was carried out on rats Wistar (from Konárovice), using known methods[9,10]. An especially important antinidation effect is observed when single doses of 0·03 mg/kg of amide *VII*, 0·005 mg/kg of amide *VIII*, or 0·05 mg/kg of amide *XI* are administered orally in the form of aqueous solutions of tartrates of bases, the fifth day after copulation. A prevention of pregnancy took place in all experimental animals. The minimum 100% antinidation active dose of amide *XII* was higher than 2·5 mg/kg, of amide *IX* and *X* higher than 5 mg/kg while amide *XIII* is inactive at a 5 mg/kg dose. Hence amides *VII* and *XI*, and especially amide *VIII*, considerably exceed the antinidation effect of Deprenon for which the single dose eliciting a 100% antinidation effect is 0·3—0·2 mg/kg. Similarly, the antilactation effect of amides *VII* and *VIII*, determined from the weight increase of the litter of suckling female rats and expressed as the mean active antilactation dose ED_{50} = 11 μg or 6 μg/kg/day, respectively, administered *p.o.* to suckling females, is about 20 times higher than in Deprenon. The minimum 100% antilactation dose of amides *VII*, *VIII* and *XI* is 0·05 mg/kg. Amide *XIII* is ineffective at a 1 mg/kg dose. When unilateral ovariectomy was used in rats (for method see[11]) it was found that amides *VII* and *VIII* also

distinctly increase the secretion of pituitary gonadotropins. The toxicity of amides *VII*, *VIII* and *XI* is very low in comparison with their active doses. Amide *VII* displayed acute LD_{50} on application equal to 38·5 mg/kg, amide *VIII* 9·1 mg/kg and amide *XI* 60 mg/kg. The substances were applied in the form of a solution of the tartrate of the base in 0·9% aqueous sodium chloride solution.

From the above mentioned results it follows that the substitution of the methyl group in the position 6 of 8-ergolin-I-ylacetamide by an ethyl, n-propyl and allyl group led to an increase in the antinidation and antilactation effect, while the introduction of the propargyl group or larger groups, such as isopropyl, n-butyl and benzyl groups, led to a decrease or complete loss of activity, within the range of the doses studied.

EXPERIMENTAL

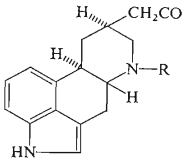
The melting points were determined on a Kofler block and they are not corrected. Samples for analysis were dried in a vacuum at 67 Pa and 100°C. Specific rotations were determined in pyridine on a Perkin–Elmer 141 polarimeter, and they correspond to substances free of solvent of crystallization. The compounds are purified by column chromatography on silica gel Merck and crystallization of homogeneous fractions from suitable solvents (Table I). The yields and melting points are also given in Table I. The homogeneity of the compounds was controlled by thin-layer chromatography on silica gel plates with a luminescent indicator (Silufol UV_{254}) in the system chloroform–ethanol–triethylamine (90 : 10 : 5). The detection was carried out under UV light at 254 nm wave-length or with a 0·5% solution of *p*-dimethylaminobenzaldehyde in cyclohexane and hydrogen chloride gas.

Methyl Esters of 6-Alkyl-8-ergolin-I-ylacetic Acids (*I*—*III*)

Methyl ester I: A mixture of 0·6 g (2·15 mmol) of D-6-ethyl-8-cyanomethylergoline-I[1], 2·15 g of potassium hydroxide, 9·5 ml of ethanol and 2·5 ml of water was refluxed under nitrogen for 24 h. After 20 h standing at 5°C the precipitated potassium salt of D-6-ethyl-8-ergolin-I-ylacetic acid was filtered off under suction, washed with ethanol and dried. It was then suspended in 26·5 ml of methanol containing 0·6 g of hydrogen chloride and refluxed for 2 h. After evaporation under reduced pressure the residue was triturated with 100 ml of water. After alkalization with aqueous sodium carbonate the precipitated product was filtered off under suction, washed with water and dried at 50°C and purified by column chromatography in chloroform + 1% of ethanol, and finally by crystallization.

Methyl esters II and III: Hydrolysis of the starting D-6-n-propyl-[1] (0·63 g; 2·15 mmol) and D-6--n-butyl-8-cyanomethylergoline-I[1] (0·66 g; 2·15 mmol) was carried out in the same manner as the hydrolysis of the D-6-ethyl compound. The mixture after hydrolysis was extracted with 95 ml of benzene and then 60 ml of a mixture of benzene with 20% of ethanol. The combined extracts were evaporated *in vacuo*, the residue dissolved in 45 ml of water and the filtrate acidified with acetic acid to pH 5·5. A mixture of the product obtained in this manner with 105 ml of methanol containing 0·6 g of hydrogen chloride was refluxed for 2 h, then evaporated and the residue dissolved in 150 ml of water. The ester (base) was set free by alkalization with solid sodium carbonate at pH 7·5 and extracted with chloroform. The residue of the base was purified by crystallization.

TABLE I



I—III $R^1 = OCH_3$
IV—VI $R^1 = NHNH_2$
VII—XIII $R^1 = NH_2$

Compound/R	Yield, %[a] m.p. °C	Solvent	$[\alpha]_D^{20}$[b] (c)	Formula (mol. w.)	Calculated/Found % C	% H	% N
I	82·8	chloroform–	—91·8	$C_{19}H_{24}N_2O_2$	73·05	7·74	8·97
CH_2CH_3	178—179	n-hexane	(0·34)	(312·4)	72·76	7·81	8·90
II	51·8	methanol	—64·1	$C_{20}H_{26}N_2O_2$	73·59	8·03	8·58
$CH_2CH_2CH_3$	191—193		(0·42)	(326·4)	73·20	7·92	8·28
III	37·1	benzene–	—63·6	$C_{21}H_{28}N_2O_2$	74·08	8·29	8·23
$CH_2CH_2CH_2CH_3$	184—185	n-hexane	(0·38)	(340·5)	74·22	8·62	8·32
IV	97·0	benzene–	—91·1	$C_{18}H_{24}N_4O$	69·20	7·76	17·93
CH_2CH_3	238—241	methanol	(0·34)	(312·4)	69·53	7·66	18·02
V	98·4	benzene–	—61·7	$C_{19}H_{26}N_4O$	70·76	7·90	17·01
$CH_2CH_2CH_3$	244—245	methanol	(0·35)	(326·4)	70·03	8·09	17·29
VI	92·4	benzene–	—68·0	$C_{20}H_{28}N_4O$	70·56	8·29	16·45
$CH_2CH_2CH_2CH_3$	226—228	methanol–n-hexane	(0·25)	(340·5)	70·61	8·04	16·99
VII[c]	57·8	benzene–	—86·2	$C_{18}H_{23}N_3O$	72·68	7·79	14·13
CH_2CH_3	263—265	methanol	(0·23)	(297·3)	72·76	7·93	14·03
VIII[d]	63·0	chloroform	—66·7	$C_{19}H_{25}N_3O$	73·28	8·09	13·49
$CH_2CH_2CH_3$	260—261		(0·09)	(311·4)	73·18	8·41	13·71
IX	37·3	ethanol	—66·4	$C_{20}H_{27}N_3O$	73·81	8·36	12·91
$CH_2CH_2CH_2CH_3$	218—220		(0·10)	(325·5)	73·73	8·57	13·26
X	59·4	pyridine–	—82·3	$C_{19}H_{25}N_3O$	73·28	8·09	13·49
$CH_2(CH_3)_2$	279—281	ethanol–water	(0·17)	(311·4)	73·52	8·09	13·36
XI	64·2	pyridine–	—90·5	$C_{19}H_{23}N_3O$	73·76	7·49	13·58
$CH_2—CH=CH_2$	284—286	ethanol–water	(0·20)	(309·4)	73·48	7·82	13·26
XII	48·2	pyridine–	—93·1	$C_{19}H_{21}N_3O$	74·24	6·89	13·67
$CH_2—C\equiv CH$	293—294	ethanol	(0·22)	(307·4)	74·54	6·90	13·99
XIII	64·6	benzene–	—85·8	$C_{23}H_{25}N_3O$	76·85	7·01	11·69
$CH_2C_6H_5$	215—217	ethanol	(0·33)	(359·5)	76·86	7·30	11·40

Hydrazides *IV—VI*

A mixture of 2 mmol of methyl ester (625 mg of *I*, 653 mg of *II*, 681 mg of *III*) and 16 ml of hydrazine hydrate (102%) was refluxed under nitrogen for 2 h. After 20 h standing at 5°C the separated hydrazide was filtered off under suction and washed with water.

Amides *VII—XIII*

A (amides *VII* and *VIII*): A mixture of 2 mmol of hydrazide (625 mg of *IV*, 653 mg of *V*) and 6·5 ml of a Raney-nickel suspension in 300 ml of ethanol was refluxed under stirring, then the catalyst was eliminated and the filtrate evaporated in a vacuum. The residue was purified by column chromatography in a mixture of benzene and 40% of methanol.

B (amide *IX*): Sodium nitrite solution (1·99 ml of 1M concentration) was added dropwise and under cooling at 0°C to a solution of hydrazide *VI* (681 mg; 2 mmol) in 2·2 ml of 0·2M hydrochloric acid. After 10 min stirring at 0°C the mixture was diluted with 6·4 ml of 0·2M hydrochloric acid, the separated hydrochloride of the azide was filtered off under suction, washed with 0·2M hydrochloric acid, dried, and stirred with an excess of concentrated aqueous ammonia. After 20 h standing at room temperature the amide was filtered off under suction, dried and then purified by column chromatography with a mixture of chloroform and 10% of methanol.

C (amides *VIII, X—XIII*): A solution of 5·8 g of tetraethylammonium bromide (27·5 mmol) and 1·54 g of potassium hydroxide (27·5 mmol) in 13 ml of water was added to a solution of 2 mmol of D-6-n-propyl-8-cyanomethylergoline-I[1] (587 mg), or of the corresponding D-6-isopropyl-[1] (587 mg), D-6-allyl-[3] (583 mg), D-6-propargyl-[3] (579 mg) and D-6-benzyl compound[3] (683 mg) in 26 ml of pyridine and the mixture refluxed under stirring and under nitrogen for 7·5 h. After cooling it was diluted with 20 ml of water and extracted with 50 ml of chloroform. During the preparation of amides *VIII*, *XII* and *XIII* the chloroform extract was chromatographed with chloroform containing 20% of ethanol. Amides *X* and *XI* crystallized out from the chloroform extract after 20 h standing at 5°C and they were recrystallized. Using the method *C* D-6-methyl-8-ergolin-I-ylacetamide (Deprenon^R)[2] was prepared from D-6-methyl-8-cyanomethylergoline-I[4]. In this case the chloroform extract was evaporated and the residue purified by column chromatography in benzene, using methanol as eluent. Yield, 58%. The properties of the substance prepared in this manner are identical with those of an authentic sample[5]. The salts of amides *VII* and *VIII* were prepared with the use of equimolar amounts of acids in methanol.

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[a] In the case of compounds *I—XI* the yields are always referred to the preceding synthetic step, and in the case of compounds *X—XIII* to the corresponding D-6-alkyl-8-cyanomethylergoline-I; [b] in pyridine; [c] hydrogen maleate: m.p. 112—115°C (methanol); $[\alpha]_D^{20}$ — 41·5° (*c* 0·24, methanol); for $C_{22}H_{27}N_3O_5.CH_3OH$ (445·5) calculated: 62·01% C, 7·01% H, 9·43% N; found 62·09% C, 6·70% H, 9·53% N. Hydrogen tartrate: m.p. 232—235°C (ethanol); $[\alpha]_D^{20}$ — 35·2° (*c* 0·19, methanol); for $C_{22}H_{29}N_3O_7$ (447·4) calculated: 59·06% C, 6·53% H, 9·39% N; found: 58·77% C, 6·52% H, 9·88% N. Tartrate: m.p. 244—250°C (ethanol); $[\alpha]^{20}$ — 37·6° (*c* 0·26, methanol); for $C_{40}H_{52}N_6O_8$ (744·9) calculated: 64·50% C, 7·04% H, 11·28% N; found: 63·99% C, 6·90% H, 11·15% N. β-Naphthalenesulfonate: m.p. 234—238°C (ethanol); $[\alpha]_D^{20}$ — 34·7° (*c* 0·10, methanol); for $C_{28}H_{31}N_3O_4S$ (505·6) calculated: 66·51% C, 6·18% H, 8·31% N, 6·35% S; found: 66·51% C, 6·57% H, 8·46% N, 6·49% S; [d] Tartrate: m.p. 228—230°C (ethanol); $[\alpha]_D^{20}$ — 30·6° (*c* 0·19, methanol); for $C_{42}H_{56}N_6O_8$ (772·9) calculated: 65·27% C, 7·30% H, 10·87% N; found: 64·78% C, 7·56% H, 11·28% N.

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