DERIVATIVES OF 3-(D-6-METHYL-8β-ERGOLIN-I-YL)PROPANOIC ACID*

Miloš BERAN, Jan BENEŠ and Jiří KŘEPELKA

Research Institute for Pharmacy and Biochemistry, 130 00 Prague 3

Received October 26th, 1981

Amide *I* was prepared both by hydration of nitrile *III* under the conditions of ion pair extraction, and from nitrile *III*, *via* methyl ester *IX*, hydrazide *X* and azide *XI*. Ethyl ester *XII* and 2-hydroxyethyl ester *XIII* of acid *VIII* were also prepared. Amide *I* and nitrile *III* in rats have a lower antinidation and antilactation activity than corresponding lower homologues, *i.e.* amide *II* and nitrile *XIV*.

In the present paper the synthesis and some biological properties of 3-(D-6-methyl-8β-ergolin-I-yl)propanoic acid amide (*I*) are described. This compound was prepared because its corresponding lower homologue, D-6-methyl-8β-ergolin-I-yl-acetic acid amide (Deprenon R; *II*), displayed distinct antilactation and antinidation activity[1-3].

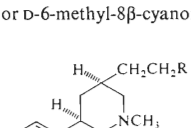
We prepared the starting D-6-methyl-8β-(2-cyanoethyl)ergoline-*I* (*III*) from D-6-methyl-8β-(2-hydroxyethyl)ergoline-I (*IV*) (ref.[4]), which we converted to corresponding 8β-(2-methanesulfonyloxyethyl)- (*V*) or 8β-[2-(*p*-toluenesulfonyloxy)ethyl]-compound (*VI*), respectively. These were reacted with sodium cyanide in dimethyl sulfoxide to give nitrile *III*. The preparation of this compound has been described earlier[5] by reaction of D-6-methyl-8β-bromomethylergoline-I (*VII*) with acetonitrile in the presence of n-butyllithium in tetrahydrofuran at −60°C[5]. When reproducing this procedure we found that it gives the required nitrile in a very low yield only.

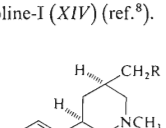
Amide *I* was prepared in two ways. In the first case (procedure *A*) we converted nitrile *III* directly to amide *I* by hydration of the nitrile group in a two-phase system composed of aqueous pyridine and an aqueous phase saturated with tetraalkylamonnium base, under refluxing and stirring and under nitrogen, *i.e.* using a method which we used for the preparation of similar amides[6]. In the second case (procedure *B*) we started with 3-(D-6-methyl-8β-ergolin-I-yl)propanoic acid (*VIII*) or its potassium salt which we prepared on alkaline hydrolysis of nitrile *III* with methanolic potassium hydroxide. Amide *I* was then obtained via the methyl ester *IX*, hydrazide *X* and azide *XI*, which was not characterized in detail, by its reaction with a concentrated aqueous ammonia solution.

* Part LXVI in the series Ergot Alkaloids; Part LXV: This Journal *47*, 1757 (1982).

In addition to the above mentioned substance we also prepared ethyl ester *XII* and 2-hydroxyethyl ester *XIII* from the same acid. The properties of compounds *I*, *III*, *V*, *VI*, *IX*, *X*, *XII* and *XIII* are given in Table I.

The evaluation of antinidation and antilactation effects, manifested by the inhibition of the secretion of adenohypophyseal prolactin, was carried out on Wistar rats (Konárovice) with amide *I* and nitrile *III*, using the described methods[2,7]. Amide *I* displayed a 100% antinidation effect in a 5 mg/kg *p.o.* dose, nitrile *III* in the same dose in 60% of animals only. Both substances show only a negligible antilactation activity with a 1 mg/kg dose administered *p.o.* Hence, the activities of the substances tested are substantially lower than the activities of corresponding lower homologues, *i.e.* amide[1-3] (*II*) or D-6-methyl-8β-cyanomethylergoline-I (*XIV*) (ref.[8]).





I, R = $CONH_2$
III, R = CN
IV, R = OH
V, R = OSO_2CH_3
VI, R = $OSO_2C_6H_4$-*p*-CH_3
VIII, R = COOH
IX, R = $COOCH_3$
X, R = $CONHNH_2$
XI, R = CON_3
XII, R = $CO_2C_2H_5$
XIII, R = $CO_2CH_2CH_2OH$
II, R = $CONH_2$
VII, R = Br
XIV, R = CN

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Samples for analysis were dried over P_2O_5 at 27 Pa and a temperature close to their melting point. The infrared spectra (ν, cm^{-1}) were recorded in KBr pellets (compounds *I*, *V*, *VI* and *X*) or in $CHCl_3$ (compounds *III*, *IX*, *XII* and *XIII*) on a Perkin–Elmer 577 instrument, the ^1H NMR spectra in C^2HCl_3 on a Tesla BSC 487 (80 MHz) spectrometer; the values δ are given in ppm. The specific rotations values were determined on a Perkin–Elmer 141 polarimeter and they correspond to substances free of solvents. The purity of the compounds was checked by thin-layer chromatography on silicagel (Silufol UV_{254}, Kavalier) in benzene–dioxane–ethanol–ammonia (5 : 4 : 1 : 0·5). The substances were detected by spraying the chromatogram with a 0·5% 4-dimethylaminobenzaldehyde solution in cyclohexane and exposure to hydrogen chloride vapours. The melting points and further data on the properties of the substances are given in Table I.

D-6-Methyl-8β-(2-methanesulfonyloxyethyl)ergoline-I (*V*)

A mixture of 2·02 ml (0·026 mol) of methanesulfonyl chloride and 60 ml of pyridine was added dropwise and under nitrogen, at 20°C, to a suspension of 2·7 g (0·01 mol) of compound[4] *IV*

in 70 ml of pyridine. After 1 h standing the mixture was poured into 500 ml of a saturated sodium hydrogen carbonate solution, then diluted with 2 000 ml of water and allowed to stand at +5°C overnight. The separated product was crystallized from ethanol.

TABLE I

Derivatives of 3-(D-6-methyl-8β-ergolin-I-yl)propanoic acid

Compound R	M.p., °C (yield, %)	$[\alpha]_D^{20}$ (*c*, pyridine)	Formula (mol.weight)	Calculated/Found		
				% C	% H	% N
I[a]	222–223	−92·7	$C_{18}H_{23}N_3O$	72·70	7·79	14·13
$CONH_2$	(47)[b]	(0·2)	(297·4)	71·92	7·99	13·93
III[c]	221–223	−97·3	$C_{18}H_{21}N_3$	77·38	7·58	15·04
CN	(98)	(0·5)	(279·4)	77·16	7·81	14·94
V[d]	144–146	−89·9	$C_{18}H_{24}N_2SO_3$	—	—	8·04
OSO_2CH_3	(83)	(0·5)	(348·5)			7·82
VI[e]	129–130	−48·4	$C_{24}H_{28}N_2SO_3$	67·90	6·65	6·60
$OSO_2C_6H_4$-*p*-CH_3	(23)	(0·2)	(424·6)	67·69	6·65	6·71
IX[f]	191–192	−98·3	$C_{19}H_{24}N_2O_2$	73·05	7·74	8·97
CO_2CH_3	(81)	(0·2)	(312·4)	72·93	7·89	8·87
X[g]	176–177	−95·0	$C_{18}H_{24}N_4O$	69·20	7·74	17·93
$CONHNH_2$	(59)	(0·2)	(312·4)	69·48	7·77	17·45
XII[h]	156–158	−95·5	$C_{20}H_{26}N_2O_2$	73·59	8·03	8·58
$COOC_2H_5$	(62)	(0·2)	(326·4)	73·60	8·05	8·69
XIII[i]	170–171	−83·5	$C_{20}H_{26}N_2O_3$	70·15	7·65	8·18
$COOCH_2CH_2OH$	(63)	(0·2)	(342·4)	70·12	7·62	8·07

[a] IR spectrum: 3 380 (NH, NH_2), 1 660 (CO, amide); ^{1}H NMR spectrum: δ 10·40 (bs, 1 H, $N_{(1)}$—H), 6·70–7·20 (m, 4 H, ArH), 6·50 (bs, 2 H, —$CONH_2$), 2·30 (s, 3 H, N—CH_3); [b] yield by procedure *A*; yield by procedure *B* from nitrile *III*: 27%; [c] IR spectrum: 3 470 (NH), 2 240 (CN); ^{1}H NMR spectrum: δ 10·60 (bs, 1 H, $N_{(1)}$—H), 6·70–7·20 (m, 4 H, ArH), 2·60 (t, *J* = 7·5 Hz, 2 H, —CH_2CN), 2·30 (s, 3 H, N—CH_3); [d] IR spectrum: 3 420 (NH), 1 340 (SO_2); ^{1}H NMR spectrum: δ 10·45 (bs, 1 H, $N_{(1)}$—H), 6·70–7·20 (m, 4 H, ArH), 4·30 (t, *J* = 7·0, Hz, 2 H, —CH_2—O—); calculated: 9·20% S, found: 9·25% S; [e] IR spectrum: 3 420 (NH), 1 350 (SO_2); calculated: 7·55% S, found: 7·51% S; [f] IR spectrum: 3 470 (NH), 1 723 (CO, ester); ^{1}H NMR spectrum: δ 8·22 (bs, 1 H, $N_{(1)}$—H), 6·70–7·20 (m, 4 H, ArH), 3·68 (s, 3 H, —CO_2CH_3), 2·48 (s, 3 H, N—CH_3); [g] IR spectrum: 3 480, 3 400 (NH, NH_2), 1 650 (CO, amide); ^{1}H NMR spectrum: δ 10·40 (bs, 1 H, $N_{(1)}$—H), 8·85 (bs, 1 H, —CONH—), 6·70–7·20 (m, 4 H, ArH), 3·75 (bs, 2 H, —$NHNH_2$), 2·30 (s, 3 H, N—CH_3); [h] IR spectrum: 3 470 (NH), 1 720 (CO, ester); ^{1}H NMR spectrum: δ 8·30 (bs, 1 H, $N_{(1)}$—H), 6·70–7·20 (m, 4 H, ArH), 4·14 (q, *J* = 7·0 Hz, 2 H, —CO_2CH_2—), 2·42 (s, 3 H, N—CH_3), 1·25 (t, *J* = 7, Hz, 3 H, —$CO_2CH_2CH_3$); [i] IR spectrum: 3 470 (NH), 1 720 (CO, ester).

D-6-Methyl-8β-[2-(*p*-toluenesulfonyloxy)ethyl]ergoline-I (*VI*)

A mixture of 2·7 g (0·01 mol) of compound *IV* (ref.[4]), 135 ml of pyridine and 9 g (0·47 mol) of *p*-toluenesulfonyl chloride was stirred at 20°C under nitrogen for 4 h. After 24 h standing at room temperature the mixture was poured into 45 ml of water, alkalized with a saturated sodium hydrogen carbonate solution, diluted with 1 800 ml of water and allowed to stand at 5°C overnight. The separated product was crystallized from methanol.

D-6-Methyl-8β-(2-cyanoethyl)ergoline-I (*III*)

A mixture of 3·48 g (0·01 mol) of compound *V* and 3 g (0·16 mol) of sodium cyanide in 50 ml of dimethyl sulfoxide was heated at 130°C under stirring for 2·5 h (under nitrogen). After cooling it was poured into 140 ml of water and then allowed to stand at 5°C overnight. Crystallization was carried out from ethanol. Nitrile *III* was prepared in a similar manner from compound *VI*.

Methyl 3-(D-6-methyl-8β-ergolin-I-yl)propanoate (*IX*)

A mixture of 2·79 g (0·01 mol) of nitrile *III*, 10 g (0·18 mol) of potassium hydroxide, 44 ml of ethanol and 11 ml of water was refluxed under nitrogen for 22 h. After 20 h standing at 5°C the separated potassium salt of acid *VIII* was filtered, washed with ethanol and suction-dried. It was suspended in 50 ml of methanol containing 2 g of hydrogen chloride. The mixture was refluxed under nitrogen for 2 h, then evaporated in a vacuum and the residue dissolved in 300 ml of water. After alkalization of the solution with a saturated sodium carbonate solution the separated product was filtered off under suction, washed with water, dried at 50°C, purified by chromatography on a silica gel column (Merck) in benzene with 10% of methanol, and crystallized from acetone.

Hydrazide of 3-(D-6-methyl-8β-ergolin-I-yl)propanoic Acid (*X*)

A mixture of 3·12 g (0·01 mol) of ester *IX* and 44 ml of 100% hydrazine hydrate was refluxed under nitrogen for 3 h. After 20 h standing at room temperature the separated hydrazide was filtered off under suction, washed with water, dried and crystallized from a mixture of pyridine, ethanol and water.

Amide of 3-(D-6-methyl-8β-ergolin-I-yl)propanoic Acid (*I*)

A) Tetraethylammonium bromide 11·6 g (55 mmol) and a solution of 3·08 g (55 mmol) of potassium hydroxide in 26 ml of water were added to a solution of 1·12 g (4 mmol) of nitrile *III* in 52 ml of pyridine and the mixture was refluxed under nitrogen for 7 h. After cooling and dilution with 40 ml of water the mixture was extracted with 100 ml of chloroform, the extract was evaporated and the residue disolved in a mixture of benzene and 20% ethanol. This solution was then chromatographed on a silica gel column (Merck) using the same solvent mixture. Final purification of the substance obtained was done by crystallization from a mixture of ethanol, pyridine and water.

B) A 5·1 ml of 1M-$NaNO_2$ solution was added dropwise and under stirring and cooling (0°C) to a solution of 1·6 g (5·1 mmol) of hydrazide *X* in a mixture of 15 ml of dimethylformamide and 15 ml of acetic acid. After 15 min standing at 0°C the mixture was poured into 500 ml of water and alkalized with solid sodium carbonate. The separated azide *XI* was filtered off under suction and dried and then mixed with an excess of concentrated aqueous ammonia. After 20 h standing

at room temperature the separated amide was washed with water, dried and submitted to chromatography on a silica gel column (Merck) using benzene + 20% ethanol for elution. The product obtained was crystallized from a mixture of pyridine, ethanol and water. The product obtained was identical with that prepared under *A*).

Ethyl- (*XII*) and 2-Hydroxyethyl-3-(D-6-methyl-8β-ergolin-I-yl) propanoate (*XIII*)

A mixture of 2·79 g (0·01 mol) of nitrile *III*, 10 g (0·18 mol) of potassium hydroxide, 44 ml of ethanol and 11 ml of water was refluxed under nitrogen for 22 h. After dilution with 135 ml of water and acidification with glacial acetic acid to pH 5 and standing overnight in a refrigerator the product (acid *VIII*, m.p. 296 to 298°C) was filtered and suction-dried (3·01 g). It was used for the preparation of ester *XII* or *XIII*, respectively, without further purification. A mixture of 0·5 g (1·68 mmol) of acid *VIII*, 1 g of *p*-toluenesulfonic acid and 50 ml of ethanol (for the preparation of ester *XII*) or 50 ml of ethylene glycol (for the preparation of ester *XIII*) was heated on a water-bath at 50°C under stirring. After standing overnight at room temperature the mixture was poured into 200 ml of water, alkalized with 5 ml of concentrated aqueous ammonia and extracted with chloroform. The extract was washed with water and dried over sodium sulfate. The residue was purified by chromatography on a silica gel column (Merck) in benzene + 10% of ethanol, and then crystallized from acetone.

The pharmacological evaluation of compounds I *and* III *was carried out by Drs K. Řežábek, M. Šeda and M. Aušková. The analyses were carried out by Mrs M. Komancová and Mr K. Havel of the analytical department (head Dr J. Körbl), the polarimetric measurements by Miss H. Bezděková, the determination and the interpretation of the* IR *spectra by Dr J. Vachek, and of the* ^{1}H NMR *spectra by Dr J. Holubek of the physico-chemical department (head Dr B. Kakáč) of our Institute.*

REFERENCES

1. Semonský M., Kucharczyk N., Beran M., Řežábek K., Šeda M.: This Journal *36*, 2200 (1971).
2. Aušková M., Řežábek K., Semonský M.: Arzneim.-Forsch. *23*, 617 (1973).
3. Krejčí P., Aušková M., Řežábek K., Bílek J., Semonský M.: Experientia *29*, 1262 (1973).
4. Beran M., Řežábek K., Šeda M., Semonský M.: This Journal *39*, 1768 (1974).
5. U.S. 3, 985, 752.
6. Beran M., Křepelka J., Semonský M.: This Journal *44*, 3385 (1979).
7. Benson B., Sorrentino S., Evans J. S.: Endocrinology *84*, 369 (1969).
8. Řežábek K., Semonský M., Kucharczyk N.: Nature (London) *221*, 667 (1969).

Translated by Ž. Procházka.