SOME 8-(β-ALKYLAMINOETHYL) AND 8-(β-DIALKYLAMINOETHYL) DERIVATIVES OF D-6-METHYL- AND D-1,6-DIMETHYLERGOLINE-I *

A.ČERNÝ, M.KRAJCROVÁ, M.ŠEDA, M.AUŠKOVÁ, K.ŘEŽÁBEK and M.SEMONSKÝ

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

Received November 19th, 1975

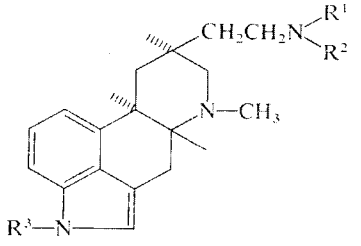
Reductive alkylation of D-6-methyl-8-(β-aminoethyl)ergoline-I (*I*) and its $N_{(1)}$-methyl derivative *II* with aliphatic and aromatic aldehydes, aliphatic ketones and acetophenone, or reduction of D-6-methyl-8-(β-acetylaminoethyl)ergoline-I and dimethylamide of D-6-methyl-8-ergolin-I--ylacetic acid with lithium aluminium hydride yielded 8-(β-alkylaminoethyl)ergolines *III*—*XV* and 8-(β-dimethylaminoethyl)ergoline *XVI*. Compounds *III*—*XI*, mainly D-6-methyl-8-(β-isopropylaminoethyl)ergoline-I (*V*), inhibit the adenohypophyseal secretion of prolactin in rats and significantly stimulate the secretion of gonadotropins by hypophysis. Some of the compounds are also hypotensive.

In a previous communication of this series[1], we described the preparation and, orientatively, the biological properties of D-6-methyl-8-(β-aminoethyl)ergoline-I (*I*), its $N_{(1)}$-methyl derivative *II* and some of its N_{β}-acyl derivatives. It was of interest to establish the effect on biological efficiency of *I* and *II* brought about by alkylation at the aminoethyl nitrogen. To this end we prepared D-6-methyl-8-(β-alkylaminoethyl)ergolines-I *III*—*XIV*, D-1,6-dimethyl-8-(β-isopropylaminoethyl)ergoline-I (*XV*) and D-6-methyl-8-(β-dimethylaminoethyl)ergoline-I (*XVI*).

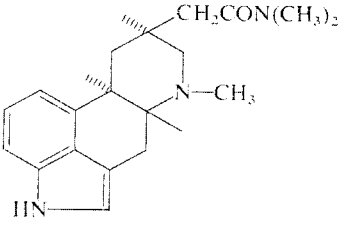
Most of the 8-(β-alkylaminoethyl) derivatives of ergoline shown in Table I were prepared by reductive alkylation of the β-aminoethyl compound *I* or *II* with the corresponding aldehyde or ketone and with hydrogen in the presence of platinum catalyst or Raney nickel. Using aliphatic and aromatic aldehydes and aliphatic ketones, the reaction proceeded at normal pressure and a slightly increased temperature relatively rapidly and yielded the desired compounds *III*—*VIII*, *X*—*XIII* and *XV* in fine yields. On the other hand, acetophenone reacted under the above reaction conditions very slowly and even when using higher hydrogen pressures (70 atm) and higher temperatures (115—120°C) compound *XIV* was not obtained in a sufficient yield.

* Part XLVII in the series Ergot Alkaloids; Part XLVI: This Journal *41*, 2761 (1976).

Besides the above described way, the ethyl derivative *III* was obtained in a sufficient yield by reduction of D-6-methyl-8-(β-acetylaminoethyl)ergoline-I (*XVII*)[1] with lithium aluminium hydride in boiling tetrahydrofuran. The n-pentyl derivative *IX* was obtained by direct alkylation of compound *I* with pentyl bromide in ethanol at 100°C. The reaction proceeded relatively slowly and resulted in a mixture of substances in which, besides *I* and *IX*, other, probably more highly alkylated, products were present. D-6-Methyl-8-(β-dimethylaminoethyl)ergoline-I (*XVI*) was formed as the main product during hydrogenation of a mixture of *I* with 2 molar equivalents of formaldehyde by hydrogen at 60 atm and 40–50°C in the presence of Raney nickel. Likewise, reduction of dimethylamide of D-6-methyl-8-ergolin-I-ylacetic acid[2] (*XVIII*) with lithium aluminium hydride in boiling tetrahydrofuran produced a fine yield of *XVI*.



I–*XVII*



XVIII

I, $R^1 = R^2 = R^3 = H$
II, $R^1 = R^2 = H$, $R^3 = CH_3$
III–*XIV*, R^1 = alkyl, aralkyl (see Table I)
$R^2 = R^3 = H$
XV, $R^1 = (CH_3)_2CH$, $R^2 = H$, $R^3 = CH_3$
XVI, $R^1 = R^2 = CH_3$, $R^3 = H$
XVII, $R^1 = CH_3CO$, $R^2 = R^3 = H$

8-(β-Alkylaminoethyl)ergolines *III*–*XV* were isolated in the form of bis-hydrogen maleates; it was in this form (which is readily water-soluble) that the compounds were tested biologically. The yields and some physico-chemical properties of bis-hydrogen maleates of bases *III*–*XV* are shown in Table I.

8-(β-Alkylaminoethyl)ergolines *III*–*XI* which carry lower alkyl groups with a straight or a branched chain at the aminoethyl nitrogen, significantly inhibit the adenohypophyseal secretion of prolactin and strikingly stimulate the secretion of gonadotropins by the same gland in rats. The final effect of prolactin inhibition is in antinidation and antilactation activity while the gonadotropin-stimulating effect brings about oestrus. The final effects associated with inhibition of prolaction secretion can be relieved by exogenous prolatin. The antinidation effect in rats was

determined as described before[1]. For example, compound *III* applied *per os* as an aqueous solution of bis-hydrogen maleate prevented the pregnancy of all the experimental animals after individual daily doses of 0·1 mg base per animal (appro-

TABLE I

Bis-hydrogen Maleates of 8-(β-Alkylaminoethyl)ergolines-I

Compound R[1]	M.p., °C (yield, %)	$[\alpha]_D^{20}$ [a]	Formula (mol. wt.)	Calculated/Found		
				% C	% H	% N
III	183—185	−38·5°	$C_{27}H_{35}N_3O_8$	61·23	6·67	7·93
C_2H_5	(98)		(529·6)	61·40	6·65	7·91
IV	104—106	−36·4°	$C_{28}H_{37}N_3O_8$	61·87	6·86	7·73
n-C_3H_7	(81)		(543·6)	61·67	6·78	7·55
V[b]	169—172	−39·0°	$C_{28}H_{37}N_3O_8$	61·87	6·86	7·73
$(CH_3)_2CH$	(96)		(543·6)	61·58	6·98	7·94
VI	117—118	−37·0°	$C_{29}H_{39}N_3O_8$	62·47	7·05	7·54
n-C_4H_9	(84)		(557·6)	62·24	7·02	7·46
VII	155—156	−39·0°	$C_{29}H_{39}N_3O_8$	62·47	7·05	7·54
$(CH_3)_2CHCH_2$	(79)		(557·6)	62·50	7·22	7·45
VIII	147—148	−35·0°	$C_{29}H_{39}N_3O_8$	62·47	7·05	7·54
$C_2H_5(CH_3)CH$	(75)		(557·6)	62·13	7·29	7·76
IX	171—173	−40·0°	$C_{30}H_{41}N_3O_8$	63·03	7·23	7·35
n-C_5H_{11}	(40)		(571·7)	62·62	7·13	7·08
X	140—141	−34·0°	$C_{30}H_{41}N_3O_8$	63·03	7·23	7·35
$C_3H_7(CH_3)CH$	(75)		(571·7)	63·46	7·43	7·39
XI	183—184	−37·0°	$C_{30}H_{41}N_3O_8$	63·03	7·23	7·35
$(C_2H_5)_2CH$	(43)		(571·7)	62·62	7·13	7·09
XII	179—181	−35·0°	$C_{32}H_{37}N_3O_8$	64·95	6·47	7·10
$C_6H_5CH_2$	(45)		(591·7)	64·91	6·45	6·97
XIII	148—149	−42·0°	$C_{33}H_{39}N_3O_9$	63·75	6·32	6·77
4-$(CH_3O)C_6H_4CH_2$	(96)		(621·7)	63·52	6·58	6·57
XIV	126—128	−35·0°	$C_{33}H_{39}N_3O_8$	65·45	6·49	6·95
$C_6H_5(CH_3)CH$	(15)		(605·7)	65·79	6·80	7·26
XV	193—195	−41·0°	$C_{29}H_{39}N_3O_8$	62·47	7·05	7·54
$(CH_3)_2CH$	(86)		(557·6)	61·94	6·81	7·62

[a] Water, c 0·5. [b] Base liberated from bis-hydrogen maleate: m.p. 105—107°C (acetone–hexane), $[\alpha]_D^{20}$ −95° (*c* 0·5, pyridine). For $C_{20}H_{29}N_3$ (311·4) calculated: 77·14% C, 9·39% H, 13·49% N; found: 76·71% C, 9·52% H, 13·33% N.

ximately 0·5 mg/kg). Compound *V* prevented the pregnancy of all female rats when applied on the 1st to the 5th day after copulation even at a daily dose of 0·015 mg base per animal. The same effect was achieved with rats after a single *p.o.* application of the compound in an amount of 0·06 mg base per animal administered 5 days after mating. The antinidation effect of the last-named compound is somewhat greater than the same effect of the reference compound, the amide of D-6-methyl--8-ergolin-I-ylacetic acid[2]. The effect of the compounds on lactation was examined in lactating Wistar rats[3]. After application of a solution of bis-hydrogen maleate of *V* at a daily dose of 0·05 mg base/kg and higher, an inhibition or complete blockade of lactation ensued. After doses of 0·5 – 1 mg per kg all the off-spring died due to insufficient nutrition. The mean effective dose of the base (ED_{50}) was found to be 0·12 mg/kg when determined on the basis of weight increments compared with a control, and 0·06 mg/kg when determined from an estimation of "milk spots" of the young animals. Stimulation of gonadotropin secretion was assessed from the degree of hypertrophy of the ovary remaining after unilateral castration[4]. If the efficiency of the reference compound, the amide of D-6-methyl-8-ergolin-I-ylacetic acid, is set equal to 1 (at doses of 0·02 and 0·1 mg base per animal), the effect of the isopropyl derivative *V* is equal to 0·7, that of D-6-methyl-8-cyanomethylergoline-I (ref.[5]) to about 0·15. The effect of *III – XVI* on blood pressure was assessed by a previously described method[1]. Compound *V* brings about a relatively protracted drop of blood pressure starting with a dose of 0·0015 mg base per kg; this effect does not rise as the dose is increased. Compound *VIII* has a similarly hypotensive effect starting with a dose of 0·15 mg base per kg. A deeper drop of blood pressure was found directly after application. More details about the biological evaluation of the compounds *III – XVI* will be published elsewhere.

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected. Samples for analysis were dried at 0·1 Torr at a temperature proportional to their melting point. Specific rotation was measured in a Perkin-Elmer type 141 polarimeter and refer to compounds free of the crystal solvent. The homogeneity of the compounds was evaluated by paper chromatography in 1-butanol–acetic acid–water (4 : 1 : 5) after detection in UV light following illumination of the chromatogram with sunlight, or on reflective silica gel plates with a luminescence indicator (Silufol UV 254 Kavalier) in chloroform–ethanol–triethylamine 90 : 10 : 5 (detection with UV light at 254 nm or with a 0·5% solution of *p*-dimethylaminobenzaldehyde in cyclohexane followed by hydrogen chloride vapour).

8-(β-Alkylaminoethyl)ergolines *III – VIII, X – XIII* and *XV*

A solution of 0·27 g (1 mmol) *I* or 0·28 g (1 mmol) *II*, in 15 ml ethanol was combined with 1·1 mmol of the appropriate aldehyde or ketone and with 15 mg Adams catalyst. The mixture was hydrogenated under shaking at 30 – 40°C at an excess pressure of about 20 Torr until the theoretical consumption of hydrogen was reached (about 25 ml, 5 – 10 h). After separation of the cata-

lyst, the filtrate was freed of the volatile fractions by distillation at about 12 Torr. The residue was dissolved in methanol (2 ml), combined with 0·25 g maleic acid in 1 ml methanol and the bis--hydrogen maleate prepared was purified by crystallization from ethanol. The yields, melting points and values of optical rotation of the salts are shown in Table I.

D-6-Methyl-8-[β-(α-phenylethylamino)ethyl]ergoline-I (*XIV*)

A solution of 0·27 g (1 mmol) *I* in 10 ml ethanol was combined with 0·13 g (1·1 mmol) acetophenone and 15 mg Adams catalyst and the mixture was hydrogenated in an autoclave for 15 h at 115—120°C and 70 atm of hydrogen. After filtration of the catalyst and distillation of the volatile components, the residue was purified by column chromatography on silica gel, using a mixture of chloroform and ethanol in a ratio of 9 : 1 for elution. Crude base *XIV* was converted in a reaction with 2·2 molar equivalents of maleic acid in methanol to bis-hydrogen maleate. The yield, melting point and optical rotation are shown in Table I.

D-6-Methyl-8-(β-pentylaminoethyl)ergoline-I (*IX*)

A solution of 0·27 g (1 mmol) *I* in 5 ml ethanol was combined with 0·158 g (1·05 mmol) n-pentyl bromide and the mixture was heated in a sealed tube under exclusion of direct light and in the atmosphere of nitrogen, for 24 h on a boiling-water bath. The residue after evaporation of the mixture was divided between dilute ammonia (5 ml, 1 : 10) and a mixture of chloroform and ethanol (25 ml, 9 : 1), the chloroform fraction was dried (Na_2SO_4), the solvents were distilled off at reduced pressure and the residue which contained amine *I*, the pentyl derivative *IX* and the assumed D-6-methyl-8-(β-dipentylaminoethyl)ergoline-I at a ratio of about 2 : 2 : 1, was purified by column chromatography on silica gel, using a mixture of chloroform with ethanol (9 : 1) for elution. The base obtained was converted in the above way to bis-hydrogen maleate which was recrystallized from ethanol; the yields, melting point and optical rotation of the salt are shown in Table I.

D-6-Methyl-8-(β-dimethylaminoethyl)ergoline-I (*XVI*)

A. *Reductive methylation of* I: A solution of 0·27 g (1 mmol) *I* in 15 ml methanol was combined with 0·22 ml (3 mmol) aqueous 44% formaldehyde and with some 0·3 ml aqueous suspension of Raney nickel and the mixture was hydrogenated in an autoclave for 2 h at 40—50°C and 60 atm hydrogen. After separation of the catalyst the filtrate was freed of the volatile components by distillation at reduced pressure and the residue (0·27 g, 91%) was recrystallized from acetone. Compound *XVI* forms plates melting at 200—202°C (with decomposition); $[\alpha]_D^{20}$ −97·5° (*c* 0·5, pyridine). For $C_{19}H_{27}N_3$ (297·5) calculated: 76·72% C, 9·15% H, 14·13% N; found: 76·94% C, 9·17% H, 13·89% N.

B. *Reduction of dimethylamide of* D-6-*methyl*-8-*ergolin*-I-*ylacetic acid* (XVIII): A suspension of 0·2 g (about 5 mmol) lithium aluminium hydride in 25 ml tetrahydrofuran was combined under stirring at room temperature and under nitrogen with a solution of 0·31 g (1 mmol) dimethylamide *XVIII* in 30 ml tetrahydrofuran which was added dropwise. The reaction mixture was boiled for 2 h and then decomposed by adding 10 ml 95% aqueous ethanol. The inorganic fraction was filtered, washed with a mixture of chloroform and ethanol (4 : 1) and the solvents were distilled off from the pooled filtrates at reduced pressure. The crude product (0·29 g) was recrystallized from acetone to yield a pure compound (0·22 g, 74%) which was identical with the compound prepared under *A*.

D-6-Methyl-8-(β-ethylaminoethyl)ergoline-I (*III*) by Reduction of D-6-Methyl-8-(β-acetylaminoethyl)ergoline-I (*XVII*)

Reduction of *XVII* (0·31 g, 1 mmol) with lithium aluminium hydride (0·2 g, 5 mmol) in tetrahydrofuran (55 ml) was carried out in the same way as the redution of dimethylamide *XVIII*. The crude base (0·3 g) was converted to the bis-hydrogen maleate which was recrystallized from ethanol to a compound identical with the salt of base *III* prepared by reductive ethylation of *I*.

The analyses were done by Mrs J. Komancová, evaluation by paper chromatography was done by Mrs M. Jelínková from the analytical department of this Institute (directed by Dr J. Körbl).

REFERENCES

1. Černý A., Řežábek K., Šeda M., Trčka V., Semonský M.: This Journal *41*, 1042 (1976).
2. Semonský M., Kucharczyk N., Beran M., Řežábek K., Šeda M.: This Journal *36*, 2200 (1971).
3. Aušková M., Řežábek K., Zikán V., Semonský M.: Endocrinol. Exp. *8*, 51 (1974).
4. Benson B., Sorrentino S., Evans J. S.: Endocrinology *84*, 369 (1969).
5. Semonský M., Kucharczyk N.: This Journal *33*, 577 (1968).

Translated by A. Kotyk.