SOME CONDENSATION PRODUCTS OF ERGOLINE - I DERIVATIVES WITH KETONES*

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Monotopic bis-ergolin-2-yl derivatives of alkanes and cycloalkanes (*I*—*VIII*) were prepared on reaction of derivatives of ergoline-I (*XI*—*XV*) with ketones in the presence of sulfuric acid or *p*-toluenesulfonic acid. Esterification of compound *XV* with cyclohexanol under catalysis with-*p*-toluenesulfonic acid gave condensation product *IX* after previous separation of cyclohexyl ester *XVI*. The condensation products did not exhibit prolactin inhibiting effect.

In previous communications we have described the synthesis of derivatives of ergoline-I* substituted in position 2 with a chlorine or bromine atom or with 1,3-dithiolan-2-yl or methyl group, as well as the results of a preliminary pharmacological evaluation of these compounds[1-3]. Generally, the substitution in the position 2 led to an increase in the hypotensive effect and to a decrease of the prolactin inhibiting effect, manifested by the antinidation and antilactation effect, in comparison with substances unsubstituted in position 2.

In this communication we concentrated on the reaction of ergoline derivatives with ketones, taking place under the effect of acid catalysts (sulfuric acid, *p*-toluenesulfonic acid), and on the elucidation of the structures of the products formed. We condensed selected derivatives of ergoline-I with acetone, 2-butanone, cyclopentanone or cyclohexanone and prepared the series of condensates *I*—*X* (Table I) which we submitted to an informative pharmacological testing.

The structures of the condensation products were determined on the basis of ^{1}H-NMR and mass spectral analysis of selected compounds. The absence of the signal of the corresponding hydrogen atom in position 2 showed that the reaction of the ketone with the ergoline derivative takes place in this position. From the results of elemental analysis and from the determination of the molecular ion and mass spectral fragmentation we deduced that the reaction of ketone with ergoline-I derivative leads to the formation of monotopically disubstituted alkane, or cycloalkane, the substituents being ergoline-I derivative residues, bound in position 2 of the ergoline skeleton.

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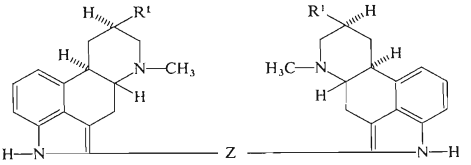
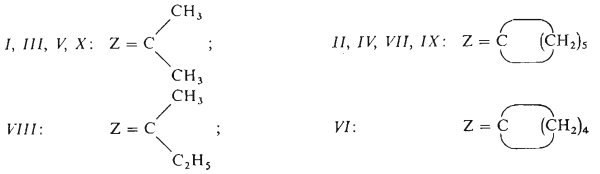
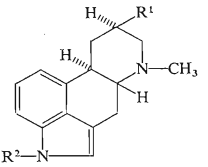




Compounds *I* and *II* were prepared on condensation of D-6-methyl-8-cyanomethyl-ergoline-I (ref.[4]) (*XI*) with acetone or cyclohexanone in a mixture of chloroform and methanol, under catalysis with *p*-toluenesulfonic acid at room temperature. Condensation of D-dihydrolysergic-I acid[5] (*XII*) with acetone in boiling methanol in the presence of sulfuric acid or *p*-toluenesulfonic acid gave compound *IH* under simultaneous esterification of the carboxylic function in position 8. Analogous condensation of the potassium salt of D-6-methyl-8-ergolin-I-ylacetic acid[4] (*XIII*) with acetone, cyclohexanone or 2-butanone in methanol and in the presence of *p*-toluenesulfonic acid gave compounds *V*, *VII* or *VIII*, respectively. On reaction of methyl ester of D-dihydrolysergic-I acid[5] (*XIV*) with cyclohexanone in chloroform and methanol, under catalysis with *p*-toluenesulfonic acid, we obtained compound *IV*, and by analogous condensation of methyl ester of D-6-methyl-8-ergolin-I-ylacetic acid[4] (*XV*) with cyclopentanone, compound *VI*.



XI: $R^1 = CH_2CN$; $R^2 = H$
XII: $R^1 = COOH$; $R^2 = H$
XIII: $R^1 = CH_2COOK$; $R^2 = H$
XIV: $R^1 = COOCH_3$; $R^2 = H$
XV: $R^1 = CH_2COOCH_3$; $R^2 = H$
XVI: $R^1 = CH_2COOC_6H_{11}$-cyclo; $R^2 = H$
XVII: $R^1 = CH_2COOH$; $R^2 = CH_3$
XVIII: $R^1 = CH_2COOCH_3$; $R^2 = CH_3$

Compound *IX* was prepared on esterification of compound *XIII* with cyclohexanol in the presence of *p*-toluenesulfonic acid, as the main product, after previous separation of the cyclohexyl ester of D-6-methyl-8-ergolin-I-ylacetic acid[2] (*XVI*) by column chromatography. In the reaction mixture oxidation of cyclohexanol to cyclohexanone took place under the effect of *p*-toluenesulfonic acid. A similar reaction course was also observed in the esterification of compound *XIII* with 2-propanol, but we were unable to separate the condensation product from the isopropyl ester, formed as the main product.

Compound *X* was synthetized from the condensation product *III* the ester group of which was reduced to a primary alcoholic function using the procedure described

TABLE I
Condensation Products of Ergoline-I Derivatives with Ketones

Compound R[1]	Formula (mol.w.)	M.p., °C (solvent)	$[\alpha]_D^{20}$	Yield %	Calculated/Found %C	%H	%N
I	$C_{37}H_{42}N_6$	266—269	—73·9°	50·5	77·86	7·42	14·72
CH_2CN	(570·7)	(chloroform)	(0·37)		77·58	7·58	14·54
II	$C_{40}H_{46}6_6$	203—204	—116°	65·2	79·83	7·17	12·99
CH_2CN	(646·8)	(methanol)	(0·26)		80·02	7·36	13·25
III	$C_{38}H_{46}N_4O_4$	204—206	—101°	67·0	73·28	7·44	8·99
$COOCH_3$	(622·8)	(chloroform–methanol)	(0·33)		73·06	7·54	9·01
IV	$C_{41}H_{50}N_4O_4$	170—173	—94·2°	78·5	74·29	7·60	8·45
$COOCH_3$	(662·8)	(chloroform–methanol)	(0·33)		73·98	7·48	8·45
V	$C_{39}H_{48}N_4O_4$	250—252	—55·2°	89·5	73·56	7·60	8·80
CH_2COOCH_3	(636·8)	(chloroform–methanol)	(0·38)		73·28	7·53	8·87
VI	$C_{41}H_{50}N_4O_4$	165—167	—68·4°	40·5	74·29	7·60	8·45
CH_2COOCH_3	(662·8)	(chloroform–methanol)	(0·37)		74·33	7·67	8·26
VII	$C_{42}H_{52}N_4O_4$	148—150	—61·3°	59·5	74·52	7·74	8·28
CH_2COOCH_3	(676·9)	(chloroform–methanol)	(0·40)		74·66	7·60	8·36
VIII	$C_{40}H_{50}N_4O_4$	218—220	—62·8°	30·8	73·82	7·74	8·61
CH_2COOCH_3	(650·9)	(chloroform–methanol)	(0·35)		73·52	7·64	8·72
IX	$C_{52}H_{68}N_4O_4$	142—146	—54·2°	27·1	76·81	8·43	6·89
$CH_2COOC_6H_{11}$	(813·2)	(chloroform–methanol)	(0·40)		76·69	8·48	6·99
X	$C_{47}H_{50}N_6O_4$	162—165	—53·3°	39·3	73·99	6·61	11·01
CH_2OOC— 	(762·9)	(methanol)	(0·26)		73·60	6·71	10·67

in ref.[4], *i.e.* with sodium boro-hydride in methanol, and the product formed was submitted to acylation with nicotinoyl chloride hydrochloride in pyridine without further purification.

The condensation reaction of ketone with two molecules of ergoline-I derivative, leading to condensation products *I*—*IX*, takes place in the presence of alcohol. This fact led us to the assumption that the reactive form of the ketone could be a ketal formed on reaction of the ketone with the alcohol, catalysed with sulfuric acid or *p*-toluenesulfonic acid, which condenses in acid medium with two molecules of ergoline-I. This assumption was confirmed by carrying out the reaction of compound *XIII* with 2,2-dimethoxypropane instead of acetone, in which we isolated compound *V* from the reaction mixture. Probably this reaction is similar to that described by Stütz and Stadler[6] for the introduction of the thioacetal function into position 2 of the ergoline skeleton. Attempts at the condensation of D-1,6-dimethyl--8-ergolin-I-ylacetic acid[4] (*XVII*) with acetone under simultaneous esterification with methanol in the presence of sulfuric acid were unsuccessful. Methyl ester of D-1,6-dimethyl-8-ergolin-I-ylacetic acid[2] (*XVIII*) only was always isolated. It seems that the presence of a proton on the nitrogen atom in position 1 of the ergoline skeleton is indispensable for the course of the condensation reaction.

During the informative pharmacological evaluation compounds *I*—*X* did not display any prolactin inhibiting effect.

EXPERIMENTAL

The melting points of the compounds were determined on a Kofler block and they are not corrected. Samples for elemental analysis were dried *in vacuo* at 70 Pa and 100°C. Specific rotations were measured on a Perkin–Elmer 141 polarimeter in pyridine, and they correspond to substances free of solvent of crystallization. The compounds were purified by column chromatography on silica gel (Merck) and crystallization of homogeneous fractions from suitable solvents (Table I). Chromatographic purity of the compounds was checked by thin-layer chromatography on silica gel containing a luminescent indicator (Silufol UV_{245}, Kavalier) in chloroform–ethanol–triethylamine (90 : 10 : 5). Detection was carried out under UV light of 254 nm wave-length or by spraying the reflexing foil with a 0·5% solution of *p*-dimethylaminobenzaldehyde in cyclohexane and exposure to HCl vapours. The ^{1}H-NMR spectra were recorded with a Tesla BS487C spectrometer in deuteriochloroform (10% solutions) using tetramethylsilane as internal reference. The mass spectra were measured with a spectometer MS-902 AET.

Condensation of Ergoline-I Derivatives (*XI*, *XIV* and *XV*) with Ketones (compounds *I*, *II*, *IV* and *VI*)

p-Toluenesulfonic acid (1·38 g, 8 mmol) was added to a suspension of 2 mmol of derivative *XI* or *XIV* or *XV* in a mixture of chloroform, methanol and the ketone and the mixture was stirred at 20—25°C for 2 to 3 days. After evaporation of volatile components in a vacuum the residue was triturated with water, alkalized with aqueous ammonia to pH 8 and the separated substance was filtered off under suction and dried. The crude product was purified by column chromatography, using benzene with 2% of ethanol for elution, and crystallization (Table I).

2,2-*Bis*(D-6-*methyl*-8-*cyanomethylergolin*-I-2-*yl*)*propane* (I): Compound *XI* (531 mg) in a mixture of chloroform (30 ml), methanol (5 ml) was reacted with acetone (10 ml) for 48 h.

1,1-*Bis*(D-6-*methyl*-8-*cyanomethylergolin*-I-2-*yl*)*cyclohexane* (II): Compound *XI* (531 mg) in a mixture of 30 ml of chloroform and 2 ml of methanol was reacted with 10 ml of cyclohexanone for 72 h.

1,1-*Bis*(D-6-*methyl*-8-*methoxycarbonylergolin*-I-2-*yl*)*cyclohexane* (IV): Methyl ester of D-dihydrolysergic-I acid (*XIV*) (570 mg) in a mixture of chloroform (20 ml) and methanol (1 ml) was reacted with cyclohexanone (5 ml) for 72 h.

1,1-*Bis*(D-6-*methyl*-8-*methoxycarbonylmethylergolin*-I-2-*yl*)*cyclopentane* (VI): Methyl ester of D-6-methyl-8-ergolin-I-ylacetic acid (*XV*) (596 mg) in a mixture of 20 ml of chloroform and 1 ml of methanol was reacted with 5 ml of cyclopentanone for 72 h.

2,2-Bis(D-6-methyl-8-methoxycarbonylergolin-I-2-yl)propane (*III*)

Sulfuric acid (11·6 g; 120 mmol) was added to a suspension of 8·1 g (30 mmol) of D-dihydrolysergic-I acid (*XII*) in 150 ml of methanol and 100 ml of acetone and the mixture was refluxed for 16 h. After evaporation of the volatile components the residue was mixed with 300 ml of water and alkalized with aqueous ammonia to pH 8. The precipitated product was filtered off under suction, dried and crystallized (Table I).

Condensation of the Potassium Salt of D-6-Methyl-8-ergolin-I-yl-acetic Acid (*XIII*) with Ketones or with 2,2-Dimethoxypropane (compounds *V*, *VII* and *VIII*)

p-Toluenesulfonic acid (4 mole-equivalents) was added to a suspension of compound *XIII* in a mixture of methanol and the corresponding ketone, or 2,2-dimethoxypropane, and the mixture was refluxed for 16 h. It was then worked up as in the case of compound *III*.

2,2-*Bis*(D-6-*methyl*-8-*methoxycarbonylmethylergolin*-I-2-*yl*) *propane* (V): *a*) Compound *XIII* (9·66 g; 30 mmol) in 300 ml of methanol was refluxed with 75 ml of acetone and 20·6 g (120 mmol) of *p*-toluenesulfonic acid for 12 h. ^{1}H-NMR spectrum: δ 10·45 (bs, 2 H, NH), 6·50—7·10 (m, 6 H, ArH), 3·54 (s, 6 H, OCH_3), 2·40 (bs, 6 H, NCH_3), 1·75 (bs, 6 H, CCH_3). *b*) Compound *XIII* (0·96 g; 3 mmol) in 15 ml of methanol was refluxed with 2 ml of 2,2-dimethoxypropane and 2·06 g (12 mmol) of *p*-toluenesulfonic acid for 6 h.

1,1-*Bis*(D-6-*methyl*-8-*methoxycarbonylmethylergolin*-I-2-*yl*)*cyclohexane* (VII): Compound *XIII* (1·95 g; 6 mmol) in 70 ml of methanol was reacted with 2 ml of cyclohexanone and 4·1 g (24 mmol) of *p*-toluenesulfonic acid. ^{1}H-NMR spectrum: δ 8·00 (bs, 2 H, NH), 6·80—7·20 (m, 6 H, ArH), 3·70 (s, 6 H, OCH_3), 2·18 (s, 6 H, NCH_3).

2,2-*Bis*(D-6-*methyl*-8-*methoxycarbonylmethylergolin*-I-2-*yl*)*butane* (*VIII*): Compound *XIII* (1·95 g; 6 mmol) in 60 ml of methanol was reacted with 15 ml of 2-butanone and 4·1 g (24 mmol) of *p*-toluenesulfonic acid.

1,1-Bis(D-6-methyl-8-cyclohexyloxycarbonylmethylergolin-I-2-yl)cyclohexane (*IX*)

A suspension of compound *XV* (645 mg; 2 mmol) and *p*-toluenesulfonic acid (1·72 g; 10 mmol) in cyclohexanol (10 ml) was stirred at 50—55°C for 48 h, then decomposed with water and alkalized with aqueous ammonia to pH 8. The cyclohexanol layer was separated and evaporated in a vacuum. The crude product was purified by column chromatography with benzene containing 2% of ethanol. In the first fractions 220 mg of compound *IX* were eluted. From subsequent fractions,

using benzene with 5% of ethanol for elution, compound *XVI* (ref.[2]) was obtained. ^{1}H-NMR spectrum: δ 7·92 (bs, 2 H, NH), 6·70—7·20 (m, 6 H, ArH), 4·80 (bm, 2 H, OCH), 2·18 (s, 6 H, NCH_3).

2,2-Bis(D-6-methyl-8-nicotinoyloxymethylergolin-I-2-yl)propane (*X*)

Sodium borohydride (1·5 g; 40 mmol) was added in parts to a suspension of 623 mg (1 mmol) of compound *III* in 40 ml of methanol, and the mixture was refluxed for 2 h. After decomposition with 100 ml of water the precipitated product was suction-dried and boiled with 40 ml of a 0·5% solution of sodium hydroxide (10 min). After filtration under suction, washing with water and drying to constant weight (510 mg; m.p. 268—270°C) the substance was suspended together with 710 mg (4 mmol) of nicotinoyl hydrochloride in 20 ml of pyridine and heated at 80°C for 8 h. After decomposition with 3 ml of water and evaporation of the volatile components in a vacuum and trituration of the residue with water and alkalization with aqueous ammonia to pH 8 the precipitated product was filtered off under suction and purified by column chromatography with chloroform–ethanol mixture (19 : 1). The combined pure fractions (300 mg) were purified by crystallization (Table I). ^{1}H-NMR spectrum: δ 9·21 (mcs, J = 1·8 Hz, 2 H, 1-C_{py}), 8·72 (mcd, J = 5·0 Hz; 1·8 Hz; 2 H, 5-C_{py}), 8·28 (dt, J = 8·0 Hz, 1·8 Hz, 2 H, 3-C_{py}), 8·09 (bs, 2 H, NH), 7·21 (dd, J = 8·0 Hz, 5·0 Hz, 2 H, 4-C_{py}), 6·70—7·20 (m, 6 H, ArH), 4·30 (bm, 4 H, OCH_2), 2·25 (bs, 6 H, NCH_3), 1·92 (bs, 6 H, CCH_3). Mass spectrum: m/e 762 ($C_{47}H_{50}N_6O_4$).

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