SOME 6-SUBSTITUTED 1-[(5*R*,8*S*,10*R*)-8-ERGOLINYL]--3,3-DIETHYLUREAS*

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6-Substituted 1-[(5*R*,8*S*,10*R*)-8-ergolinyl]-3,3-diethylureas *II*—*VII* were prepared from hydrazides of (5*R*,8*S*,10*R*)-6-alkyl-8-ergolinecarboxylic acids (*VIIIa*, *VIIIb*) *via* the corresponding azides *IXa* and *IXb* and isocyanates *Xa* and *Xb*, and/or from 1-[(5*R*,8*S*,10*R*)-6-methyl-8-ergolinyl]--3,3-diethylurea (*I*) *via* *XI* and *XII*. Two of the by-products arising in the latter route have been identified (*XIII*, *XIV*). Some of the ureas prepared, especially *II* and *III*, had strong inhibitory effects *in vivo* on the secretion of prolactin in rats.

Our preceding communications describe syntheses of some 6-substitution 8β-ergoline derivatives, of which 6-ethyl and 6-propyl derivatives of 8β-cyanomethylergoline[1] and 8β-ergolineacetamide[2] inhibited the secretion of prolactin with a much higher efficacy than did the corresponding 6-methyl derivatives, synthetized from natural ergot alkaloids. We were now interested to see how replacement of the 6-methyl group by higher alkyl groups would affect the efficacy of the clinically tested 1-[(5*R*,8*S*,10*R*)-6-methyl-8-ergolinyl]-3,3-diethylurea (*I*) (*trans*-9,10-dihydrolisuride, terguride[3,4]), pertaining to the series of 8α-substituted ergolines. For this purpose we synthetized the 6-substituted 1-[(5*R*,8*S*,10*R*)-8-ergolinyl]-3,3-diethylureas *II*—*VII*. After we had synthetized them[5] compounds of this type were described in the patent literature[6] being obtained by catalytic hydrogenation of 1-(9,10-didehydro-8α-ergolinyl)-3,3-diethylureas.

The compounds *II*—*VII* were synthetized in two ways. In one (method *A*), known hydrazides of (5*R*,8*S*,10*R*)-6-alkyl-8-ergolinecarboxylic acids[7] (*VIIIa*, *VIIIb*) were converted by the action of nitrous acid in an acid aqueous solution into the corresponding azides *IXa*, *IXb*, whose pyrolysis gave the isocyanates *Xa* and *Xb*; condensation of these with diethylamine *in situ* afforded good yields of the ureas *II* and *III* (Table I). In the other method the starting urea *I* was demethylated according to von Braun by the action of cyanogen bromide in dichloromethane[1,7,8] thus giving the 6-cyano derivative *XI* in good yield. The key step then was conversion of this

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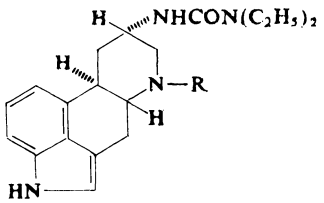
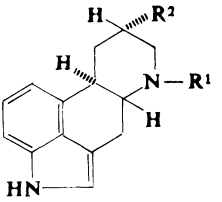
cyano derivative into the 6-nor derivative *XII*. Catalytic hydrogenation of *XI* in dimethyl formamide, in the presence of Raney nickel as catalyst[7,8], produced a mixture of compounds, *XII* being the main product; this was isolated by column chromatography in a yield of 58%. Of the concomitant substances, apart from the starting cyano derivative *XI*, we isolated and identified the 6-formyl derivative *XIII* (formed from an intermediary imino compound by hydrolysis with water present in the solvent) and the 6-methyl derivative *I*, arising from reduction of the formyl compound *XIII*.



I, R = CH_3
II – *VII*, *XI* – *XIV*
(R see Table I)



VIIIa – *Xa*, $R^1 = C_2H_5$
VIIIb – *Xb*, $R^1 = (CH_2)_2CH_3$
VIII, $R^2 = CONHNH_2$
IX, $R^2 = CON_3$
X, $R^2 = NCO$

In an attempt at decyanization of *XI* by reduction with zinc in boiling acetic acid[8] we obtained a mixture of several compounds, shown by TLC to contain the 6-nor derivative *XII* (about 50%), in addition to the starting *XI*, formyl derivative *XIII* and 6-methyl derivative *I*. Compound *XII* was obtained in good yield by reduction of *XI* with potassium in hexamethylphosphorictriamide. The reaction was very sensitive to quality of the solvent, mainly to the presence of water; at a water concentration of 0·1% the main product was the product of hydrolysis, 6-carboxyl derivative *XIV*. This was converted into *XII* by decarboxylation in boiling toluene containing acetic acid. The most rewarding route to *XII* proved to be hydrolytic removal of the cyano group from *XI* by its boiling in a 30% aqueous-ethanolic solution of potassium hydroxide; the yield of *XII* was 86%.

The 6-substituted ureas *II* – *VII* were prepared from *XII* by two methods. In one (method *B*), compounds *II*, *III*, *V* and *VI* were obtained by the action of alkyl halides (ethyl bromide, propyl bromide, butyl bromide) or allyl bromide on *XII* in dimethylformamide containing anhydrous potassium carbonate. This method is suitable for introducing primary alkyl groups or an allyl group; in attempts to use the method for the introduction of a secondary alkyl, competitive dehydrohalogenation of the alkyl halide occurred and the desired product was obtained in a negligible yield or not at all. In such cases we employed, with good results, reductive alkylation of *XII* with the corresponding carbonyl compounds in methanol in the presence

TABLE I

6-Substituted 1-[(5*R*,8*S*,10*R*)-8-ergolinyl]-3,3-diethylureas

Compound R	Yield, % (method)	M.p., °C (solvent)	$[\alpha]_D^{20}$ (*c*)	Formula (mol.mass)	Calculated/Found		
					% C	% H	% N
II[a]	70; 83[b]; 85	197–199	+24·9	$C_{21}H_{32}N_4O_2$[c]	67·71	8·65	15·04
C_2H_5	(*A*) (*B*) (*C*)	(ethanol)	(0·25)	(372·5)	68·01	8·25	15·48
III[d]	68; 76[e]	132–134	+36·8	$C_{22}H_{32}N_4O$	71·70	8·75	15·20
C_3H_7	(*A*) (*B*)	(ethanol)	(0·25)	(368·5)	71·20	8·98	14·90
IV[f]	33	104–106	+34·0	$C_{22}H_{32}N_4O$	71·70	8·75	15·20
$CH(CH_3)_2$	(*C*)	(S5)	(0·13)	(368·5)	70·90	9·07	14·97
V[g]	78[h]	95–98	+37·4	$C_{23}H_{34}N_4O$	72·21	8·96	14·64
C_4H_9	(*B*)	(S4)	(0·25)	(382·6)	72·00	9·54	14·24
VI[i]	82[j]	155–158	+23·8	$C_{22}H_{30}N_4O$	72·09	8·25	15·29
$CH_2CH{=}CH_2$	(*B*)	(S4)	(0·25)	(366·5)	71·65	8·69	15·22
VII[k]	30	157–159	+8·6	$C_{24}H_{34}N_4O$	73·06	8·69	14·20
C_5H_9, cyclo	(*C*)	(S5)	(0·20)	(394·6)	72·82	8·85	13·94
XI[l]	83	278–280	+102·7	$C_{20}H_{25}N_5O$	68·35	7·17	19·93
CN		(S3)	(0·15)	(351·5)	67·98	7·08	20·07
XII[m]	—	114–116	+67·4	$C_{19}H_{26}N_4O$	69·90	8·03	17·16
H		(ethanol)	(0·5)	(326·5)	70·03	8·22	17·28
XIII[n]	6	218–222	+220·6	$C_{20}H_{26}N_4O_2$	67·77	7·39	15·80
CHO		(ethanol)	(0·24)	(354·5)	67·46	7·61	15·84
XIV[o]	—	200–202	+61·9	$C_{20}H_{28}N_4O_4$[p]	61·83	7·27	14·42
COOH		(ethanol)	(0·5)	(388·5)	61·99	7·49	14·33

[a] UV spectrum, λ_{max} (log ε): 293 (3·74), 282 (3·81), 275 infl. (3·79), 234 (3·75) nm; IR spectrum: 1 630, 1 510 (NHCO), 3 150, 3 300 (NH), 1 610, 1 500 (arom. + double bonds) cm^{-1}; ^1H NMR spectrum: δ 6·60–7·30 (m, 4 H, ArH); 5·60 (bd, J = 8·0 Hz, 1 H, NHCO); 4·10 (bm, 1 H $C_{(8)}$—H_{eq}), 3·21 (q, 4 H, $N(CH_2CH_3)_2$), 1·02 (t, 6 H, $N(CH_2CH_3)_2$), 0·95 (t, 3 H, NCH_2CH_3); [b] 0·33 g (1 mmol) *XII*, 10 ml dimethylformamide, 0·83 g (6 mmol) K_2CO_3, 0·33 g (3 mmol) ethylbromide, 5 h at 60°C; [c] monohydrate; [d] UV spectrum, λ_{max} (log ε): 292 (3·72), 281 (3·80), 275 (3·79) nm; IR spectrum: 3 220, 3 360 (NH), 1 630 (NHCO), 1 510, 1 610 (arom. + double bonds) cm^{-1}; ^1H NMR spectrum: δ 8·55 (bs, indole NH), 6·60–7·10 (m, 3 H, ArH), 6·75 (bs, 1 H, $C_{(2)}$—H), 5·50 (bd, J = 8·0 Hz, 1 H, NHCO), 4·20 (bm, 1 H, $C_{(8)}$—H_{eq}), 3·20 (q, J = 7·0 Hz, 4 H, $N(CH_2CH_3)_2$), 1·50 (m, 3 H, $C_{(9)}$—H_{ax} + NCH_2CH_2), 1·05 (t, J = 7·0 Hz, 6 H, $N(CH_2.CH_3)_2$), 0·82 (t, J = 7·0 Hz, 3 H, $N(CH_2)_2CH_3$); [e] 0·66 g (2 mmol) *XII*, 20 ml dimethylformamide, 1·66 (12 mmol) K_2CO_3, 0·74 g (6 mmol) propyl bromide, 15 h at 60°C; [f] UV spectrum, λ_{max} (log ε): 291 (3·53), 281 (3·67), 275 infl. (3·65), 223 (4·35) nm; IR spectrum: 1 625, 1 510 (NHCO), 3 320, 3 160 (NH), 1 490, 1 500, 1 610 (arom. + double bonds) cm^{-1}; ^1H NMR spectrum: δ 8·20 (bs, 1 H, indole NH), 6·70–7·20 (m, 4 H, ArH), 5·59 (bd, 1 H, NHCO), 4·20 (bm, 1 H, $C_{(8)}$—H_{eq}), 3·25 (q, J = 7·0 Hz, 4 H, $N(CH_2CH_3)_2$), 1·60 (dt, J = 13·3, 4·8 Hz,

TABLE I
(*Continued*)

1 H, $C_{(7)}$—H_{eq}), 1·12 (t, J = 7·0 Hz, 6 H, $N(CH_2CH_3)_2$), 1·12 (d, J = 6·5 Hz, 3 H, CH). .$(CH_3)_2$), 0·86 (d, J = 6·5 Hz, 3 H, $CH(CH_3)_2$), [g] UV spectrum, λ_{max} (log ε): 293 (3·74), 282 (3·82), 277 infl. (3·80), 225 (4·48) nm; IR spectrum: 1 625, 1 510 (NHCO), 3 180, 3 300 (NH), 1 500, 1 610 (arom. + double bonds) cm^{-1}; ^1H NMR spectrum: δ 10·65 (bs, 1 H, indole NH), 6·50 to 7·10 (m, 4 H, ArH), 5·52 (d, J = 7·0 Hz, 1 H, NHCO), 4·00 (bm, 1 H, $C_{(8)}$—H_{eq}); 3·20 (q, J = 7·0 Hz, 4 H, $N(CH_2CH_3)_2$), 1·05 (t, J = 7·0 Hz, 6 H, $N(CH_2CH_3)_2$), 0·98 (bt, 3 H, alif. CH_3); [h] 0·66 g (1 mmol) *XII*, 20 ml dimethylformamide, 1·66 g (12 mmol) K_2CO_3, 1·10 g (6 mmol) n-butyl iodide, 5 h at 60°C, [i] UV spectrum, λ_{max} (log ε): 293 (3·75), 282 (3·83), 277 infl. (3·81), 234 (3·77) nm; IR spectrum: 1 625, 1 510 (NHCO), 3 160, 3 320 (NH), 1 500, 1 605, 1 610 (arom. + double bonds) cm^{-1}; ^1H NMR spectrum: δ 10·65 (bs, 1 H, indole NH), 6·50 to 7·10 (m, 4 H, ArH), 5·85 (m, 1 H, CH_2CH=CH_2), 5·55 (d, J = 7·0 Hz, 1 H, NHCO), 5·22 (bd, J = 17·0 Hz, 1 H, *trans* —CH=CH_2), 5·18 (bd, J = 10·0 Hz, 1 H, *cis* —CH=CH_2), 4·02 (bm, 1 H, $C_{(8)}$—H_{eq}), 3·20 (q, J = 7·0 Hz, 4 H, $N(CH_2CH_3)_2$), 1·05 (t, J = 7·0 Hz, 6 H, $N(CH_2CH_3)_2$); [j] 0·66 g (2 mmol) *XII*, 20 ml dimethylformamide, 1·66 g (12 mmol) K_2CO_3, 0·73 (6 mmol) allyl bromide, 5 h at room temp.; [k] UV spectrum, λ_{max} (log ε): 291 (3·74), 281 (3·82), 275 infl. (3·80), 223 (4·53) nm; IR spectrum: 1 625, 1 510 (NHCO), 3 310, 3 170 (NH), 1 500, 1 560, 1 610 (arom. + double bonds) cm^{-1}; ^1H NMR spectrum: δ 8·40 (bs, 1 H, indole NH); 6·80—7·20 (m, 3 H, ArH), 6·82 (bs, 1 H, $C_{(2)}$—H), 5·60 (bd, J = 8·0 Hz), 1 H, NHCO), 4·25 (bm, 1 H, $C_{(9)}$—H_{ax}), 3·80 (bm, 1 H, NCH), 3·26 (q, J = 7·0 Hz, 4 H, $N(CH_2CH_3)_2$), 1·50 (bm, 8 H, $(CH_2)_4$), 1·11 (t, J = 7·0 Hz, 6 H, $N(CH_2CH_3)_2$); [l] UV spectrum, λ_{max} (log ε): 292 (3·75), 281 (3·83), 277 infl. (3·81), 224 (4·51) nm; IR spectrum: 1 625, 1 510 (NHCO), 3 160, 3 280 (NH), 2 195 (CN), 1 500, 1 530, 1 610 (arom. + double bonds) cm^{-1}; ^1H NMR spectrum: δ 8·73 (bs, 1 H, indole NH), 6·60—7·30 (m, 4 H, ArH), 5·00 (bd, J = 8·0 Hz, 1 H, NHCO), 4·30 (bm, 1 H, $C_{(8)}$—H_{eq}), 3·30 (q, J = 7·0 Hz, 4 H, $N(CH_2CH_3)_2$; 1·60 (bt, J = 13·3 Hz, 1 H, $C_{(9)}$—H_{ax}), 1·15 (t, J = 7·0 Hz, 6 H, $N(CH_2CH_3)_2$); [m] UV spectrum, λ_{max} (log ε): 293 (3·75), 282 (3·83), 276 (infl. (3·81), 225 (4·50) nm; IR spectrum: 1 620, 1 510 (NHCO), 3 180, 3 310 (NH), 1 500, 1 610 (arom. + double bonds) cm^{-1}; ^1H NMR spectrum: δ 8·53 (bs, 1 H, $N_{(1)}$—H, 6·6—7·20 (m, 3 H, ArH), 6·75 (bs, 1 H, $C_{(2)}$—H), 5·53 (bd, J = 8·0 Hz, 1 H, NHCO), 4·20 (bm, 1 H, $C_{(8)}$—H_{eq}), 3·20 (q, J = 7·0 Hz, 4 H, NCH_2), 2·00 (bs, 1 H, $C_{(9)}$—H_{ax}), 1·58 (bt, J = 13·3 Hz, $N_{(6)}$—H), 1·07 (t, J = 7·0 Hz, 6 H, $N(CH_2CH_3)_2$; [n] ^1H NMR spectrum: δ 9·02 (bs, 1 H, indole NH), 8·60 (bs, 1 H, N—CHO), 6·70—7·30 (m, 4 H, ArH), 5·02 (d, 1 H, NHCO), 4·78 (bd, J = 10·0 Hz, 1 H, $C_{(5)}$—H_{ax}), 4·25 (bm, 1 H, $C_{(8)}$—H_{eq}), 3·25 (q, 4 H $N(CH_2CH_3)_2$), 1·15 (t, 6 H, $N(CH_3CH_3)_2$); [o] IR spectrum: 2 550 (COOH), 1 620 (CO) cm^{-1}; ^1H NMR spectrum (hexadeuteriodimethyl sulphoxide): δ 8·00 (bs, COOH, H_2O, indole NH), 6·80—7·30 (m, 3 H, ArH); 6·70 (bd, 1 H, $C_{(2)}$—H), 6·55 (bd, 1 H, NHCO), 4·20 (bm, 1 H, $C_{(8)}$—H_{eq}), 3·20 (q, J = 7·0 Hz, 4 H, CH_2CH_3), 1·58 (dt, J = 4·8 Hz, 13·3 Hz, 1 H, $C_{(9)}$—H_{ax}), 0·98 (t, J = 7·0 Hz, 6 H, CH_2CH_3); [p] monohydrate.

of sodium cyanoborohydride at pH 5 to 6 (ref.[9]). In the use of ketones (*e.g.* acetone or cyclopentanone) the reaction was very slow (taking days) and compounds *IV* and *VII* were obtained in yields of 30 to 33%. With aldehydes the reaction took a much faster course; in the use of acetaldehyde the reaction was complete within 1 h, compound *II* being the sole product.

Compounds *II*, *III*, *V* and *VI* were pharmacologically tested for their effect on the hypophyseal secretion of prolactin and gonadotropins and the results were compared with those obtained with terguride (*I*) and lisuride (1-[(5*R*,8*S*)-6-methyl--9,10-didehydro-8-ergolinyl]-3,3-diethylurea). The substances were administered as aqueous solutions of their hydrogen maleates (in doses referred to the base forms) with a stomach probe.

TABLE II

Biological activity of 6-substituted 1-[(5*R*,8*S*,10*R*)-8-ergolinyl]-3,3-diethylureas

Compound	Antilactation[a] mg/kg	Antinidation[b] mg/kg	Decrease of prolactinemia[c] mg/kg		Activation of ovary[d] mg/kg	Acute toxicity[e] mg/kg
			in 3 h	in 9 h		
Lisuride[f]	0·045 (0·018—0·105)	0·06—0·07	0·0084	0·054	—	14·4
I	0·22 (0·15—0·39)	~0·30	0·0089	0·045	0·2	75 (62—106)
II	0·009 (0·002—0·018)	0·010—0·015	0·0019	—	0·01	—
III	0·010 (0·006—0·018)	0·010—0·015	0·0008	0·0051	0·01	37 (31—48)
V	—	at 5 ineffectual	—	—	—	—
VI	0·08 (0·02—0·14)	0·350	—	—	—	—

[a] Calculated mean effective dose (ED_{50}), which if administered once daily to stomachs of lactating rats from 5th to 8th post-delivery day would reduce the daily weight increases of their 6 sucklings to 50%, compared to an unaffected control group. [b] Minimum dose preventing intrauterine nidation of fertilized ova in 100% of rats in a single-dose intragastric administration on the 5th day following copulation. [c] Calculated, interpolated, single intragastric dose reducing prolactinemia to a half of the control group in 3 or 9 h after administration to adult females castrated 13 days ago and oestrogenized (0·03 mg/kg estradiol dipropionate, Agofollin Spofa) two days ago. [d] Minimum intragastric dose whose administration once daily to lactating rats from 5the to 8th day after delivery induced the onset of oestral cycles with a fortnight after delivery. No oestral cycle appeared in the controls in this period. [e] Mean lethal dose (LD_{50}) in intravenous administration to female mice. [f] 1-[(5*R*,8*S*)-6-methyl-9,10-didehydro-8-ergolinyl]-3,3-diethylurea (Lysenyl Spofa).

The inhibitory effect on the secretion of prolactin was assessed by the extent to which a substance affected the prolactin-controlled physiological processes and by the degree by which it reduced the content of prolactin in blood. The physiological processes dependent on prolactin and used for the testing were lactation of rats[4,10,11,13] and nidation of fertilized ova in rats[10,14]. The effect on the secretion of prolactin was ascertained in adult castrated female rats the prolactinemia of which was increased by standard administration of oestrogen[15]. Prolactin was determined by a radioimmunoassay employing a kit for this purpose. The stimulating effect on the secretion of gonadotropins and the function of ovary was followed by onsets of oestral periods of lactating rats, where the oestral periods are physiologically discontinued[12]. Compound *III* also underwent two toxicological tests, *viz.* an acute toxicity test in intravenous application to mice and a foetal toxicity test on rats and rabbits. In assessing the effect on the development of foetuses the compound was administered in the form of hydrogen tartarate with a stomach probe to female rats from the 11th to the 19th day of their pregnancy, and to female rabbits from the 11th to the 27th day of their pregnancy, once daily in doses 0·005 and 0·020 mg/kg for the two animal species. The animals were killed one day before the end of the gestation. Dissection of the uteruses showed the state of pregnancy and morphology of the foetuses.

The results of pharmacological tests are given in Table II. It shows, in accordance with our previous findings, that replacement of the methyl group at the 6-position by an ethyl group (compound *II*) or propyl group (compound *III*) enhanced by an order of magnitude (5 to 24 times) the inhibition of the prolactin secretion and the associated stimulation (desinhibition) of the secretion of gonadotropins. Replacement by an allyl group (compound *VI*) raised this activity of compound *I* approximately three times. However, elongation of the substituent at the 6-position to a butyl group (compound *V*) resulted in a loss of influence on secretion of the investigated group of hormones. In toxicological tests the propyl substituent exhibited an increase of acute toxicity to about a two-fold value (Table II). As to the foetal development after nidation, however, this compound was as innoxious, in the dose used, as the starting compound *I* in daily doses 0·2 and 0·8 mg/kg in rats, and 0·2 and 0·6 mg/kg in rabbits.

EXPERIMENTAL

The melting points were determined on the Kofler block and are not corrected. The analytical samples were dried over P_2O_5 at about 30 Pa and 20 to 100°C to constant weight. The specific rotations in pyridine were determined using a polarimeter Perkin–Elmer 141 and correspond to solvent-free substances. The UV spectra were measured with a spectrophotometer Pye Unicam SP 8000 at concentrations 0·004 and 0·0008% (w/v) in methanol. The IR spectra were measured in KBr pellets with an apparatus Perkin–Elmer 577. The ^{1}H NMR spectra were measured employing a spectrophotometer Tesla BSC 487 (80 MHz) at a concentration of about

10% (w/v) in deuteriochloroform, with tetramethylsilane as internal standard; the values of δ are given in ppm. The usual solvents were removed in a rotary vacuum evaporator, using a water jet pump, at a bath temperature of 40°C, with dimethylformamide at 60–65°C. Purity of the substances was tested by TLC on reflex foils of silica gel with a luminiscent indicator (Silufol UV 254, Kavalier) in systems chloroform–ethanol–triethylamine 90 : 10 : 5 (S1) and/or benzene–dioxane–ethanol–triethylamine 50 : 40 : 10 : 5 (S2); the spots were detected under UV light of 254 nm or by a spray of the plate with 0·5% 4-dimethylaminobenzaldehyde in cyclohexane, followed by exposure to vapour of HCl. Column chromatography was carried out with silica gel Merck Kieselgel 60 or Silpearl Kavalier.

1-[(5*R*,8*S*,10*R*)-6-Cyano-8-ergolinyl]-3,3-diethylurea (*XI*)

To a solution of *I* (10·0 g, 0·0294 mol) in dichloromethane (800 ml) was added cyanogen bromide (5·95 g, 0·0506 mol). The mixture was stirred for 35 h at room temperature and diluted with dichloromethane (200 ml). The solution was washed with 1M tartaric acid and water, the organic layer was dried with Na_2SO_4 and the solvent was distilled off. The residue was chromatographed on a column of silica gel (300 g), with chloroform as eluant. The corresponding fractions were combined, the solvent was distilled off and the product was recrystallized (Table I).

1-[(5*R*,8*S*,10*R*)-8-Ergolinyl]-3,3-diethylurea (*XII*)

a) *By hydrogenation of* XI: To a solution of the cyano derivative *XI* (1·76 g, 5 mmol) in dimethylformamide (15 ml) was added Raney nickel (*c.* 0·6 g) suspended in dimethylformamide and the mixture was hydrogenated for 25 h at 25–30°C and a pressure of about 100 kPa. The catalyst was filtered off, the solvent was removed under reduced pressure and the residue was distributed between 1M tartaric acid and a system dichloromethane–methanol 9 : 1 (organic portion 1). The aqueous layer was brought with ammonia to *c.* pH 7·5 and the product was taken into a mixture of chloroform and ethanol 9 : 1. The extract was dried (Na_2SO_4), the solvents were distilled off and the residue was chromatographed on a column of silica gel, the eluant being chloroform with an increasing concentration of ethanol (0 to 10% v/v). The solvents were removed under reduced pressure and the product *XII* (0·86 g, 58%) was recrystallized (Table I). The organic portion 1 and the head fraction in the column chromatography of crude *XII* contained, apart from the starting compound *XI* and the product *XII*, small quantities of the 6-methyl derivative *I* and 6-formyl compound *XIII*. The mixture was resolved by column chromatography on a 30-fold weight of silica gel, with chloroform as eluant; the formyl derivative *XIII* (22 mg) was recrystallized (Table I).

b) *By reduction of* XI *with zinc in acetic acid*: A stirred mixture of the cyano derivative *XI* (0·7 g, 2 mmol), acetic acid (90 ml), water (1·6 ml) and zinc dust (5·0 g) was boiled for 7 h under a reflux condenser. The excess of zinc was filtered off, the solvent was removed under reduced pressure, the residue was dissolved in water and the solution was brought to *c.* pH 9 with ammonia. The product was taken into chloroform and the solvent was distilled off. TLC of the residue (0·9 g), using the system S2, gave the starting *XI* (*c.* 5%), 6-methyl derivative *I* (*c.* 10%), 6-formyl derivative *XIII* (*c.* 5%) and compound *XII* (*c.* 50%).

c) *By reduction of* XI *with potassium*: To a stirred solution of *XI* (0·351 g, 1 mmol) in hexamethylphosphorictriamide (10 ml, with less than 0·05% H_2O) under nitrogen at 20–25°C was added, in portions in the course of about 10 min, potassium (0·39 g, 10 mmol) and the blue solution was stirred for 3 more h at 25 to 30°C. The brown reaction mixture was treated with tert-butanol (1 ml), the solution was poured into ice water (150 ml) and the separated solid was

collected on a filter. The crude product, practically pure by TLC, (0·31 g, 95%) was recrystallized from ethanol to analytically pure *XII* (Table I). In repeating the experiment with a larger charge of *XI* (4·31 g, 12·26 mmol) in hexamethylphosphorictriamide containing 0·1% of water a small amount of *XII* (0·7 g, 17·5%) was filtered off, the aqueous layer was extracted with chloroform, the extract was washed with aqueous 10% tartaric acid and the aqueous extract was neutralized with ammonia to pH 7. During standing in a refrigerator product *XIV* separated (3·09 g, 65%); it was purified by recrystallization (Table I).

d) *By decarboxylation of* XIV: A solution of *XIV* (1·0 g) in a mixture of toluene (100 ml) and acetic acid (20 ml) was boiled for 1 h under a reflux condenser. The solvents were removed under reduced pressure, the residue was distributed between chloroform (100 ml) and dilute (1 : 9) ammonia (10 ml); the organic phase was dried (Na_2SO_4) and taken to dryness. The residue was recrystallized from ethanol; yield pure *XII* (0·6 g, 71%).

e) *By alkaline hydrolysis of* XI: A solution of *XI* (1·76 g, 5 mmol) in 30% (w/v) of aqueous–ethanolic (1 : 1) potassium hydroxide (42 ml) was boiled under nitrogen for 6 h under a reflux condenser. The ethanol was removed by distillation under reduced pressure, the aqueous mixture was diluted with water (60 ml) and the separated product *XII* (1·40 g, 86%) was collected on a filter and recrystallized from ethanol (Table I).

6-Substituted 1-[(5*R*,8*S*,10*R*)-8-ergolinyl]-3,3-diethylureas *II*—*VII*

Method A: To a stirred solution of hydrazide *VIIIa* (0·60 g, 2 mmol) or *VIIIb* (0·62 g, 2 mmol) in 0·1M hydrochloric acid (20 ml, 2 mmol) at 0 to 5°C was added 1M-$NaNO_2$ (2 ml, 2 mmol), then, at the same temperature in the course of about 5 min, 0·2M-HCl (11 ml, 2·2 mmol) was added dropwise. The mixture was stirred for 15 min at *c.* 0°C, and alkalinized with 1M-$NaHCO_3$ (4·4 ml, 4·4 mmol), the separated azide was taken into benzene (400 ml) and the extract was washed with water. The benzene solution was dried (Na_2SO_4, then Potasit 3A), boiled for 10 min in a nitrogen atmosphere under a reflux condenser (the escaping nitrogen prevented contact with aerial moisture). The solution of isocyanate *Xa* or *Xb* thus obtained was cooled to 20°C, diethylamine (1·01 g, 10 mmol) was added and the mixture was left standing overnight at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel (20-fold amount), with chloroform as eluant. The combined fractions (0·52 g of *II*, 0·47 g of *III*) were distilled under reduced pressure to remove the solvent and the substance *II* and/or *III* was recrystallized (Table I).

Method B: To a solution of *XII* (0·65 g, 2 mmol) in dimethylformamide (20 ml) was added anhydrous potassium carbonate (0·83 to 1·66 g, 6—12 mmol) and alkyl halide or allyl bromide (4—6 mmol) and the mixture was stirred at 20 to 70°C till the starting *XII* had disappeared (monitored by TLC in S2); the reaction conditions for the individual compounds prepared by this method (*II*, *III*, *V*, *VI*) are given in Table I. The solvent was removed under reduced pressure, the residue was stirred up with water (50 ml), the product was collected on a filter and chromatographed on a 30-fold amount of silica gel, with chloroform as eluant. The physico-chemical properties of the products are given in Table I. Systems for crystallization: S3 chloroform–ethanol 1 : 1, S4 ethanol–water, S5 acetone–hexane.

Method C: To a solution of *XII* (0·16 g, 0·5 mmol) in methanol (1·6 ml) was added acetaldehyde (0·048 g, 0·11 mmol) and sodium cyanoborohydride (0·063 g, 1·0 mmol), and pH of the mixture was brought with glacial acetic acid to 5·5. The solution was left standing for 2 h at room temperature, then diluted with chloroform (15 ml). The mixture was washed with dilute (1 : 9) ammonia and water, dried (Na_2SO_4), and solvents were removed under reduced pressure. The crude product was purified by crystallization (Table I).

To a solution of *XII* (0·16 g, 0·5 mmol) in methanol (1·6 ml) was added 10 mmol of a ketone (0·58 g of acetone or 0·84 g of cyclopentanone), 0·063 g, (1 mmol) of sodium cyanoborohydride and about 0·2 g of the molecular sieve Potasit 3A. The mixture was brought to pH 5·5 with acetic acid and left standing at room temperature for 24 h. Another 5 mmol of the ketone and 0·031 g (0·5 mmol) of sodium cyanoborohydride were added and pH was readjusted to 5·5 with acetic acid. After 72 hours' standing at room temperature the same amounts of the two components were added once again, and so was readjusted the pH. After another week's standing at room temperature the reaction mixture contained the starting and the desired compounds in the ratio of *c.* 1 : 1 (S2). The solution was decanted, the Potasit was extracted with chloroform (20 ml), the combined organic portions were washed with dilute ammonia (1 : 9) and water, and the solvents were removed under reduced pressure. The crude product was chromatographed on a column of silica gel (elution with chloroform) and the product *IV* or *VII* was recrystallized (Table I).

Hydrogen Maleate of 1-[(5*R*,8*S*,10*R*)-6-propyl-8-ergolinyl]-3,3-diethylurea

To a saturated solution of *III* (0·184 g, 0·5 mmol) in hot ethanol was added a solution of maleic acid (0·064 g, 0·55 mmol) in ethanol (0·5 ml) and the solution was left standing in a refrigerator to crystallize; the crop (0·15 g, 62%) was collected on a filter, m.p. 180—182°C, $[\alpha]_D^{20} = -15{\cdot}2°$ ($c = 0{\cdot}5$, methanol).

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