SOLVOLYSIS OF SOME 1-(8α-ERGOLINYL)-3,3-DIETHYLUREAS AND THEIR SALTS*

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Nine salts of 1-(8α-ergolinyl)-3,3-diethylurea (*II*) were prepared and their solubility in water and the stability of the aqueous solutions at 60 a 100°C were studied. The main product of hydrolysis is 6-methyl-8α-aminoergoline *IV*. The urethan *VII* is formed in the ethanolic solution. Both decomposition products are also formed under long-term storage at +5°C. The course of hydrolysis of N-propyl homologue *III* is similar. The decomposition of 9,10-didehydro derivative *I* is much slower under the conditions used.

Some 1-(8α-ergolinyl)-3,3-diethylureas have significant dopaminergic effect, inhibit adenohypophysal secretion of prolactine and strongly stimulate the secretion of gonadotropine. 1-[(5*R*,8*S*)-6-Methyl-9,10-didehydro-8-ergolinyl]-3,3-diethylurea (*I*, lisuride)[1] is already used in the clinical practice as its hydrogen maleate (*Ia*, Lysenyl Spofa); 1-[(5*R*, 8*S*,10*R*)-6-methyl-8-ergolinyl]-3,3-diethylurea (*II*, terguride)[2] and 1-[(5*R*, 8*S*, 10*R*)-6-propyl-8-ergolinyl]-3,3-diethylurea (*III*, proterguride)[3] are being tested. Since the base *II* is nearly insoluble in water, we sought the suitable salts that can be used in the form of injections and drops. They were expected to be soluble in water, alcohols, and other physiologically acceptable media and their solutions ought to have sufficient stability during storage.

Chloride *IIa*, hydrogen sulfate *IIb*, dihydrogen phosphate *IIc*, methanesulfonate *IId*, hydrogen maleate *IIe* (ref.[2]), hydrogen tartarate *IIf*, dihydrogen citrate *IIg*, ascorbate *IIh*, and terebate (2,2-dimethyl-5-oxo-tetrahydro-3-furancarboxylate) *IIi* were prepared from the base *II* and corresponding acids by usual manner. Their physico-chemical properties are summarized in Table I. The best soluble in water are *IIa*, *IIc*, *IId*, *IIg*, and *IIi*. However, when stored, the solutions of these salts quickly change their colour to yellow or yellowish-brown what indicates a decomposition. The stability of selected salts was studied by heating of their solutions in sealed ampoules to the elevated temperatures. Colorimetric assay[4] established

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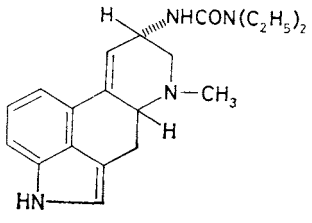
TABLE I

Physico-chemical properties of base *II* salts

Salt (acid)	M.p., °C (solvent)	Yield of salt, %	Solubility mg/ml[a]	$[\alpha]_D^{20}$ (c = 0·2, H_2O)	Formula (m. wt.)	Found/calculated		
						% C	% H	% N
IIa (HCl)	220—221 (methanol)	90·2	10·5	−16·3	$C_{20}H_{29}ClN_4O_2$. 0·5 H_2O (385·9)[b]	62·24 62·45	7·84 7·99	14·52 14·09
IIb (H_2SO_4)	>300 (CH_3OH–$(C_2H_5)_2O$)	95·7	4·18	−14·7	$C_{20}H_{30}N_4O_5S$. 0·5 H_2O (447·65)[c]	53·67 53·67	6·98 7·01	12·52 11·95
IIc (H_3PO_4)	>215 decompn. (methanol)	81·0	10·0	−13·7	$C_{20}H_{31}N_4O_5P$. 3 H_2O (492·5)	48·77 48·35	7·57 6·72	11·37 11·80
IId (CH_3SO_3H)	165—168 (acetone)	91·5	100·0	−15·1	$C_{21}H_{32}N_4O_4S$. H_2O (454·6)[d]	55·48 55·75	7·53 7·31	12·32 12·18
IIe ($C_4H_4O_4$)	152—153 (ethanol)	94·6	1·26	−15·0 (c = 0·1, H_2O)	$C_{24}H_{32}N_4O_5$. H_2O (474·6)[e]	60·74 60·51	7·22 7·40	11·81 11·90
IIf ($C_4H_6O_6$)	185—190 (methanol)	95·8	1·96	−3·7	$C_{24}H_{34}N_4O_7$ (490·7)	58·76 58·22	6·99 7·01	11·42 10·84
IIg ($C_6H_8O_7$)	187—188 (methanol)	88·2	4·55	−13·0	$C_{26}H_{36}N_4O_8$ (532·6)	58·63 59·30	6·81 7·13	10·32 10·25
IIh ($C_6H_8O_6$)	190—191 (methanol)	65·4	0·8	+16·8 (c = 0·1, CH_3OH)	$C_{26}H_{36}N_4O_7$. 0·5 H_2O (525·6)	59·41 59·29	7·10 7·10	10·66 10·75
IIi ($C_7H_{10}O_4$)	173—175 (ethanol)	84·2	7·8	−16·3	$C_{27}H_{38}N_4O_5$. 0·5 H_2O (507·7)	63·87 63·81	7·76 7·73	11·03 10·63

[a] In water at room temperature; [b] calculated 9·19% Cl, found 9·00% Cl; [c] calculated 7·16% S, found 7·47% S; [d] calculated 7·05% S, found 7·63% S; [e] from absolute ethanol was obtained the crystal solvent-free compound, m.p. 190—191°C (see ref.[2]).

that upon heating the aqueous solutions of salts *IIc*, *IId*, and *IIg* to 60°C, the most stable is dihydrogen citrate *IIg* (see Table II). On the other hand, the heating of aqueous solutions of salts *Ia*, *IIe*, and *IIg* or aqueous dioxane (1 : 1) solution of *II* to 100°C showed that the most stable is the base *II*, followed by *Ia* and *IIa*; the fastest reaction is the decomposition of dihydrogen citrate *IIg*. From the study of kinetics of solvolysis, it follows that the hydrolysis of *II* and *Ia* and the ethanolysis of *II* are reactions of pseudo-first order with rate constants ($k \cdot 10^5$, s^{-1}) 1·06 ± ± 0·04 (*II*), 2·02 ± 0·05 (*Ia*), and 1·22 ± 0·09 (ethanolysis of *II*), respectively. Hydrolysis of salts *IIe*, *IIg* and ethanolysis of *IIe* probably follow the second order kinetics with rate constants ($k \cdot 10^2$, 1 mol^{-1} s^{-1}) 5·91 ± 0·28 (*IIe*), 23·0 ± 0·93 (*IIg*), and 0·12 ± 0·02 (ethanolysis of *IIe*), respectively. The anion apparently participates on the reaction besides the solvent in these cases.



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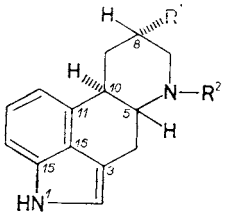

II, R^1 = $NHCON(C_2H_5)_2$; R^2 = CH_3
III, R^1 = $NHCON(C_2H_5)_2$; R^2 = $CH_2CH_2CH_3$
IV, R^1 = NH_2 ; R^2 = CH_3
V, R^1 = $NHCOCH_3$; R^2 = CH_3
VI, R^1 = NH_2 ; R^2 = $CH_2CH_2CH_3$
VII, R^1 = $NHCOOC_2H_5$; R^2 = CH_3
VIII, R^1 = $CONHNH_2$; R^2 = CH_3
IX, R^1 = CON_3 ; R^2 = CH_3
X, R^1 = NCO ; R^2 = CH_3

TABLE II
Stability of aqueous solutions of salts *IIc*, *IId*, and *IIg* at 60°C

Compound	Content of the starting compound upon heating, (%)	
	8 h	16 h
IIc	94·1	74·4
IId	90·9	68·2
IIg	92·8	83·9

The results of thin-layer chromatographic analysis of heated solutions of salts *IIe* and *IIg* were in variance with the colorimetric analysis. According to them, no parent compound was present upon 8 h heating of solutions to 100°C, only the products of decomposition having R_F 0·1 (major compound) and R_F 0·3 (minor compound) (system S2). With the salt *Ia*, about 30% of the starting material was present after 16 h heating, accompanied with series of decomposition products, three among them with greater mobility then *I* (in S1). No formation of less polar compounds was observed with salts of *II*.

The compound $C_{15}H_{19}N_3$ was isolated as the main product of hydrolysis in a preparative run. Its physical properties are identical to those of (5*R*, 8*S*, 10*R*)-6--methyl-8-aminoergoline[5] (*IV*). Mass, ^1H, and ^{13}C NMR spectra fully support this structure. Acetylation of *IV* afforded a crystalline acetyl derivative *V* that was characterized spectroscopically. We found that compound *V* is also formed by the reaction of urea *II* with boiling acetanhydride; this reaction documents the relatively low stability of diethylcarbamoyl group in *II*. Reaction of *IV* with N,N-diethylcarbamoyl chloride yields the starting urea *II*. Hydrolysis of solutions of *IIe* and *IIg* takes place even under storage at +5°C (see Experimental).

TLC evaluation (in S2) of aqueous solutions of dihydrogen citrate of base *III* heated 8 h to 100°C showed (by comparison with a standard) that the main product of the hydrolysis is the amino compound[6] *VI*. Therefore, the aqueous solutions of salts derived from the base *III* are hydrolyzed similarly to the salts of the base *II*.

TLC analysis of ethanolic solutions (in S5) of hydrogen maleate *IIe* stored in dark at room temperature also showed the presence of decomposition products, a minor one with R_F identical to that of *IV* and a major one with higher value (0·5). Preparative HPLC of these solutions afforded a compound of summary formula $C_{18}H_{23}N_3O_2$ (MS) corresponding to the urethan[7] *VII*. This compound contains one oxygen atom more and one C_2H_5N group less than *II*. The mass spectroscopic fragmentation did not differ from that of *II*. Also ^1H and ^{13}C NMR spectra (Table III) have many features in common. The main difference is in number of ethyl groups; compound *II* contains two whereas compound *VII* only one. Both methyl and methylene signals of the ethyl group are shifted donfield with respect to *II* (0·87 and 0·13 ppm; 19·5 and 0·8 ppm in ^1H and ^{13}C NMR spectra, respectively). That indicates that the ethyl group in *VII* is attached to oxygen instead to nitrogen, *i.e.* that the substituent at C-8 is $NHCO_2C_2H_5$. The accomplished synthesis of *VII* starting from hydrazide of (5*R*,8*S*,10*R*)-6-methyl-8-ergolinecarboxylic acid[8] (*VIII*) through the azide *IX* and isocyanate *X* (for details see ref.[7]), or from the aminoergoline *IV* by condensation with ethyl chloroformate or by ethanolysis of *IIe* at 140°C confirmed the above mentioned conclusion.

Solvolysis of urea and its simple N-substituted derivatives is known for a long time. The ethanolysis of urea producing an urethan made by Wöhler[9] is a classics; detailed information on alcoholysis of ureas to carbamates are contained in a review[10]. The

kinetics of hydrolysis of 1,1-dimethylurea under boiling in acidic or alkaline media leading to CO_2, NH_3, and dimethylamine was studied by Fawsitt[11]. It is surprising that with salts *IIe* and *IIg*, the solvolysis takes place already under very mild conditions, during storing of aqueous or alcoholic solutions at room temperature or even at +5°C.

EXPERIMENTAL

Melting points were determined in a Kofler apparatus and were not corrected. Samples for analysis were dried over phosphorus pentoxide at 30 Pa and 80 to 100°C. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. The reported values correspond to the solvent-free compounds. UV—VIS spectra were recorded in methanol using a Unicam SP-8000 spectrophotometer. Infrared spectra were measured in KBr pellets with a Perkin–Elmer 577 spectrometer. Mass spectra were taken on a Varian MAT-311 spectrometer (electron energy 70 eV, ion source temperature 200°C, direct inlet at 100—180°C). ^{1}H NMR spectra were measured on a Tesla BS 487C (80 MHz, CW) and Jeol FX-60 (59·797 MHz, FT) spectrometers in deuteriochloroform or hexadeuteriodimethyl sulfoxide. ^{13}C NMR spectra were taken on a Jeol FX-60 instrument (15·036 MHz). Tetramethylsilane was used as an internal standard. Chemical shifts

TABLE III
^{13}C Chemical shifts of compounds *II*, *IV*, *V*, and *VII*

Atom	Compound				
	II[a]	*IV*[b]	*V*[a]	*V*[b]	*VII*[a]
2	123·1	122·0	123·2	122·1	123·2
3	111·6	110·2	111·5	110·0	111·9
4	27·0	26·5	26·8	26·4	26·9
5	67·7	67·7	67·6	67·3	67·6
7	62·0	63·5	61·1	60·6	61·5
8	43·4	35·3	36·4	35·5	43·3
9	32·6	34·7	32·0	31·8	32·5
10	45·1	45·4	44·2	43·7	45·7
11	132·2	133·2	132·9	132·7	133·3
12	113·2	111·8	113·2	112·0	113·2
13	117·9	118·4	117·9	118·6	117·7
14	108·6	108·5	108·6	108·8	108·6
15	133·4	133·2	133·3	133·2	133·3
16	126·1	126·2	126·2	126·1	125·1
N—CH_3	36·7	43·1	43·3	43·0	36·3
C=O	156·7	—	169·5	168·8	156·0
1′	41·2[c]	—	23·5	22·9	60·7
2′	13·9[c]	—	—	—	14·7

[a] Deuteriochloroform; [b] hexadeuteriodimethyl sulfoxide; [c] 2 C.

are given in the δ-scale. The purity of isolated compounds was checked by HPLC on a LiChrosorb NH_2 column (25 × 0·4 cm, 5 μm, hexane–ethanol 4 : 1, 1 ml/min). Isolation of compound *VII* was performed on a semipreparative column LiChrosorb NH_2 (50 × 0·8 cm, 10 μm, diethyl ether–ethanol 4 : 1, 100 ml/h). Further checks of purity were made on silica gel TLC plates Merck Kieselgel 60 F_{254} in the systems chloroform–methanol 85 : 15 (S1), chloroform–methanol–acetic acid 60 : 35 : 5 (S2) or on Silufol UV 254 (Kavalier) in the systems chloroform–ethanol–triethylamine 90 : 10 : 5 (S3), benzene–dioxane–ethanol–triethylamine 50 : 40 : 10 : 5 (S4) or chloroform–benzene–ethanol 4 : 2 : 1 (S5). The spots were detected under UV light at 254 nm or by spraying with 0·5% cyclohexane solution of *p*-dimethylaminobenzaldehyde followed by exposure to hydrogen chloride vapours. Densitometric determination of *II* was made by evaluation of chromatograms performed on silica gel plates (Merck Kieselgel 60 F_{254}, sample amount 10 μg) developed in the system toluene–dioxane–ethanol–concentrated ammonia 12 : 8 : 4 : 1 (S6) on a Densitometr Opton PMQ II instrument in the UV region at 280 nm using the reflexion mode. Colorimetric assay of *II* was based on the measurement of the absorbance of the coloured product obtained by reaction with tropeoline 00 extracted into chloroform[4]. Silica gel Merck Kieselgel 60 or Silpearl Kavalier were used for column chromatography.

Preparation of Salts *IIa*—*IIi*

Hot solution of base *II* (0·34 g, 1 mmol) in minimal amount of solvent given in Table I was mixed with 1·05 ml (1·05 mmol) of the solution of the corresponding acid in the same solvent. If necessary, the volume of solution was slightly reduced by evaporation under reduced pressure and allowed to crystallize at +5 to −10°C. The solid salt was filtered off, washed with small amount of solvent and dried in an exsiccator over potassium hydroxide at room temperature and 2·7 kPa. The yields and physico-chemical properties of salts are given in Table I.

(5*R*,8*S*,10*R*)-6-Methyl-8-aminoergoline (*IV*)

Solution of dihydrogen citrate *IIg* (1·07 g, 2 mmol) in 0·1M solution of citric acid (250 ml) was refluxed for 14 h. The reaction mixture, not containing the starting compound according to TLC in S4, was alkalized with ammonia and extracted with chloroform–methanol 9 : 1 mixture (500 ml). Organic layers were combined, dried over Na_2SO_4, the solvents were removed and the residue (0·24 g, 50%) was crystallized from methanol. Compound *IV* — 0·16 g, m.p. 262—266°C (decompn.), $[\alpha]_D^{20}$ −64·2° (*c* 0·2, pyridine) was obtained; the properties are in agreement with literature[6]. Mass spectrum *m/z* (% of relative intensity, elemental composition, assignment): 241 (71, $C_{15}H_{19}N_3$, M^+), 223 (13, $C_{15}H_{15}N_2$, $M-NH_4$), 197 (46, $C_{13}H_{13}N_2$), 181 (46, $C_{13}H_{11}N$), 167 (30, $C_{12}H_9N$), 154 (100, $C_{11}H_8N$), 127 (28, $C_{10}H_7$). UV spectrum λ_{max} (log ε): 293 (3·70), 282 (3·79), 277 (3·77), 225 (4·47) nm. IR spectrum: 3 290, 3 230, 3 090 (NH_2, NH), 2 810 (NCH_3) cm^{-1}. ^1H NMR ($(C^2H_3)_2SO$): 1·49 td ($J_{8eq,9ax}$ = 3·7 Hz, $J_{9eq,9ax} = J_{9ax,10ax}$ = = 12·8 Hz, H-9 ax), 2·32 s (3 H, NCH_3), 4·35 mt (1 H), 6·62—7·19 mt (4 H, aromatic protons), 8·24 s (1 H, indole NH), 10·50 s (2 H, NH_2). ^{13}C NMR spectrum see Table III.

(5*R*,8*S*,10*R*)-6-Propyl-8-aminoergoline (*VI*)

Solution of *III* (5·0 mg) in 0·1M citric acid (1 ml) was heated 8 h in a sealed ampoule on a boiling water bath. The reaction mixture was alkalized with ammonia and analyzed by TLC in S2. No starting compound (R_F 0·78) was found, only the main reaction product with R_F 0·28 identical to that of amino compound[6] *VI* and small amount of two other decomposition products (R_F 0·4 and 0·0) were present. The main reaction product exhibited the R_F identical to that of *VI* also on Silufol in systems S3 and S4.

(5*R*,8*S*,10*R*)-6-Methyl-8-acetamidoergoline (*V*)

By acetylation of IV: Suspension of *IV* (0·12 g, 0·5 mmol) in acetanhydride (2·5 ml) was heated 3 min on a boiling water bath. The solution was left standing overnight. Acetanhydride was distilled off under reduced pressure at 60°C. The residue was extracted with mixture chloroform–aqueous ammonia 1 : 3. Solvent was removed and the residue was crystallized from ethanol. Compound *V* (0·10 g) was obtained in 85% yield, m.p. 112—115°C, $[\alpha]_D^{20}$ +12·3° (*c* 0·2, pyridine). For $C_{17}H_{21}N_3O$ (283·4) was calculated: 72·05% C, 7·47% H, 14·83% N, found: 71·67% C, 7·40% H, 14·96% N. UV spectrum λ_{max} (log ε): 292 (3·71), 281 (3·81), 275 (3·78), 225 (4·43) nm. IR spectrum: 3 250, 3 400 (NH), 2 790 (NCH_3), 1 650, 1 520 (amide), 1 360, 1 630 cm^{-1} (arom.). Mass spectrum *m/z* (% of relative intensity, elemental composition, assignment): 283 (32, $C_{17}H_{21}N_3O$, M^+), 266 (8, $C_{17}H_{18}N_2O$, M — NH_3), 252 (6, $C_{16}H_{16}N_2O$, M — CH_5N), 223 (96, $C_{15}H_{15}N_2$, M — C_2H_6NO), 167 (100, $C_{12}H_9N$), 154 (59, $C_{11}H_8N$), 127 (14, $C_{10}H_7$). Direct analysis of daughter ions (DADI) proved that ions *m/z* 266, 252 and 223 arise from the molecular ion. ^{1}H NMR (C^2HCl_3): 1·60 dt ($J_{8eq,9ax}$ = 3·7 Hz, $J_{9eq,9ax} = J_{9ax,10ax}$ = 13·8 Hz, H-9 ax), 2·02 s (3 H, $COCH_3$), 2·42 s (3 H, NCH_3), 4·35 mt (1 H, H-8), 6·64 d ($J_{8,NH}$ = 7·8 Hz, NH), 6·88—7·26 mt (4 H, aromatic protons), 8·16 s (1 H, indole NH). ^{1}H NMR ($(C^2H_3)_2SO$): 1·48 td ($J_{8eq,9ax}$ = 3·7 Hz, $J_{9eq,9ax} = J_{9ax,10ax}$ = 13·4 Hz, H-9 ax), 1·90 s (3 H, N—Ac), 2·28 (3 H, NCH_3), 4·10 mt (1 H), 6·59—7·31 mt (4 H, aromatic protons), 7·92 d ($J_{8,NH}$ = 7·3 Hz, NH), 10·62 s (1 H, indole NH). ^{13}C NMR spectra see Table III.

By reaction of II *with acetanhydride*: Solution of *II* (0·17 g, 0·5 mmol) in acetanhydride (2·5 ml) was refluxed 30 min and the reaction mixture was worked-up as described above. The crystalline product (0·13 g, 92%) had physico-chemical properties corresponding to those of *V*.

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

N-Ethyldiisopropylamine (0·142 g, 1·1 mmol) and then N,N-diethylcarbamoyl chloride (0·149 g, 1·1 mmol) were added to the stirred suspension of amino compound *IV* (0·24 g, 1 mmol) in dry dimethylformamide (5 ml) at 15 to 20°C. The reaction mixture was stirred 3 h at room temperature, allowed to stand overnight and then poured into ice-cold water (15 ml). The precipitate was filtered off, dried, dissolved in the mixture chloroform–ethanol 9 : 1 and subjected to column chromatography on silica gel (1 g). The obtained crude product (0·29 g, 85%) was recrystallized from ethanol, m.p. 205—207°C (decompn.), $[\alpha]_D^{20}$ +29·0° (*c* 0·2, pyridine), see ref.[2]. UV spectrum λ_{max} (log ε): 292 (3·72), 281 (3·81), 277 sh (3·79), 224 (4·42) nm. IR spectrum: 1 635, 1 520 (NHCO), 3 480, 3 220 (NH), 1 510, 1 620 (arom.) cm^{-1}. Mass spectrum *m/z* (% relative intensity, elemental composition): 341 (7), 340 (26, $C_{20}H_{28}N_4O$, M^+), 268 (9), 267 (29, $C_{16}H_{17}N_3O$), 224 (40, $C_{15}H_{16}N_2$), 223 (36, $C_{15}H_{15}N$), 209 (8), 197 (8), 180 (7), 168 (21), 167 (100, $C_{12}H_9N$), 155 (29, $C_{11}H_9N$), 154 (36, $C_{11}H_8N$), 127 (10), 100 (11). ^{1}H NMR (C^2HCl_3): 1·14 t (J = 7·3 Hz, 6 H, 2× NCH_2CH_3), 1·60 td ($J_{9eq,9ax} = J_{9ax,10ax}$ = 14·0 Hz, $J_{8eq,9ax}$ = 3·7 Hz, H-9 ax), 2·41 s (3 H, NCH_3), 3·29 q (J = 7·3 Hz, 4 H, 2 × NCH_2CH_3), 4·27 mt (1 H, H-8 eq), 5·52 d ($J_{8eq,NH}$ = 8·5 Hz, NHCO), 6·67—7·25 mt (4 H, aromatic protons), 8·29 s (1 H, indole NH). ^{1}H NMR ($(C^2H_3)_2SO$): 1·05 t (J = 7·0 Hz, 6 H, 2 × NCH_2CH_3), 1·50 dt ($J_{9eq,9ax} = J_{9ax,10ax}$ = 13·3 Hz, $J_{8eq,9ax}$ = 4·8 Hz, H-9 ax), 2·36 s (3 H, NCH_3), 3·20 q (J = 7·0 Hz, 4 H, 2 × NCH_2CH_3), 4·10 mt (1 H, H-8 eq), 5·65 d ($J_{8eq,NH}$ = 8·0 Hz, NHCO), 6·60—7·70 mt (4 H, aromatic protons), 10·65 s (1 H, indole NH). ^{13}C NMR spectrum see Table III.

Ethyl N-[(5*R*,8*S*,10*R*)-6-methyl-8-ergolinyl]carbamate (*VII*)

Isolation from the drop preparation: Experimental batch of the drop preparation containing 0·2 g of *IIe* in 1 ml of 50% ethanol was stored 30 days in dark at room temperature. TLC evalua-

tion in S5 detected besides the parent *II* the compound *VII* (R_F 0·5) as the main product of decomposition and small amount of *IV*. The solvents were removed by distillation at reduced pressure and the product was extracted with a mixture of chloroform and 5% aqueous ammonia 9 : 1. The chloroform layer was dried over Na_2SO_4, solvent removed under reduced pressure and the residue was subjected to preparative HPLC. Two compounds were isolated, one (88%) corresponding to the starting *II* and the other (11%) to the urethane *VII*. Mass spectrum *m/z* (% of relative intensity, elemental composition, assignment): 314 (15), 313 (87, $C_{18}H_{23}N_3O_2$, M^+), 268 (10), 267 (14, $C_{16}H_{17}N_3O$), 224 (52, $C_{15}H_{16}N_2$), 209 (10), 197 (12, $C_{13}H_{13}N_2$), 180 (13), 168 (15), 167 (57,$C_{12}H_9N$), 155 (33,$C_{11}H_9N$), 154 (62, $C_{11}H_8N$), 127 (14). ^{1}H NMR, (C^2HCl_3): 1·27 t (J = 6·8 Hz, 3 H, $CO_2CH_2CH_3$), 1·62 td ($J_{9eq,9ax} = J_{9ax,10ax}$ = 12·7 Hz, $J_{8eq,9ax}$ = 3·9 Hz, H-9 ax), 2·40 s (3 H, NCH_3), 4·10 mt (1 H, H-8 eq), 4·16 q (J = 6·8 Hz, 2 H, $CO_2CH_2CH_3$), 5·74 d ($J_{8eq,NH}$ = 8·3 Hz, NHCO), 6·89—7·41 mt (4 H, aromatic protons), 7·94 s (1 H, indole NH). For ^{13}C NMR spectrum see Table III.

By ethanolysis of IIe: The solution of *IIe* (0·5 g, 1·095 mmol) in 96% ethanol (10 ml) was heated in a glass-inlaid autoclave in a 140°C bath for 5 h. The reaction mixture was evaporated at reduced pressure and the residue was extracted with mixture of saturated aqueous solution of sodium hydrogen carbonate and chloroform. Organic layer was separated, dried over Na_2SO_4, solvent removed by distillation and the residue was subjected to column chromatography on silica gel (chloroform–ethanol 99 : 1). Homogeneous fractions were combined and the residue crystallized from the mixture ethanol–light petroleum. Compound *VII* (0·275 g, 80%), m.p. 100—102°C, $[\alpha]_D^{20}$ +23·8° (*c* 0·2, chloroform), $[\alpha]_D^{20}$ —25° (*c* 0·1, dimethylformamide) was obtained. The basic physical characteristics was in good agreement with literature[7]. UV spectrum λ_{max} (log ε): 292 (3·70), 281 (3·79), 276 sh (3·77), 224 (4·40) nm. IR spectrum: 3 410, 3 330 (NH), 2 790 (NCH_3), 1 710 (NHCOOR), 1 620, 1 510 (arom.) cm^{-1}.

From azide IX: Azide of (5*R*,8*S*,10*R*)-6-methyl-8-ergolinecarboxylic acid (*IX*) prepared[8] from 1 g (3·5 mmol) of hydrazide *VIII* was extracted into cold (5°C) mixture of ethyl acetate–1,2-dichloroethane (4 : 1, 150 ml). The solution was dried over sodium sulfate and then over molecular sieve M4A at 0°C. It was dropwise added to the boiling mixture of toluene (100 ml) and absolute ethanol (10 ml). The reaction mixture was boiled 15 min, volatile portions were distilled off under reduced pressure and worked-up as above. The yield of *VII* was 0·418 g (38%) with the same properties as already described.

From the amino compound IV: N-Ethyldiisopropylamine (0·13 g, 1 mmol) and the solution of ethyl chloroformate (0·12 g, 1·1 mmol) in dichloromethane (5 ml) were dropwise added to the stirred suspension of *IV* (0·241 g, 1 mmol) in dichloromethane (20 ml). Reaction mixture was stirred 2 h at room temperature. The volatile produts were distiled off under reduced pressure and the residue was worked up as described above. The yield of *VII* with the above reported physico-chemical properties was 0·226 g (72%).

Kinetics of Hydrolysis of Base II, its Salts *IIe* and *IIg*, and of Salt *Ia*

Solution of base *II* in 50% aqueous dioxane (1 mg/ml) or the solutions of salts *IIe*, *IIg* or *Ia* in water (1 mg of base in 1 ml) were divided into 5 ml portions into ampoules, sealed and heated on a boiling water bath. At time intervals 0·5, 1, 2, 4, 8, and 16 h the ampoules were taken away, cooled to the room temperature and the amount of the parent compound was determined by colorimetry. The following values were found: *Ia* (pH 5·05) 95·5, 91·3, 83·7, 76·4, 57·2, 30·6%; *II* (pH 8·28) 95·9, 92·8, 88·7, 81·63, 73·07, 52·88%; *IIe* (pH 5·47) 69·61, 53·98, 37·16, 25·66, 16·51, 11·99%; *IIg* (pH 3·87) 64·1, 32·05, 17·09, 9·61, 6·71, 5·18%.

Kinetics of Ethanolysis of Base *II* and Salt *IIe*

Ethanolic solutions of *II* or *IIe*, respectively, (concentration 10 mg/ml) were divided into 0·2 ml portions, transfered into ampoules and sealed. They were heated on a boilling water bath. At time intervals 0·5, 1, 2, 4, 8 and 16 h the ampoules were removed, cooled to the room temperature and the content of the starting compound was determined by densitometry. Following values were found: *II* 96·2, 91·6, 84·2, 75·9, 63·5, 49·0%; *IIe*: 76·0, 69·0, 59·8, 50·0, 46·7, 37·0%.

Stability of Injections of *IIe* and *IIg*

The experimental batch of injections based on hydrogen maleate *IIe*, containing 1 mg of *IIe*, 100 mg of glycerol and up to 1 ml of water for injections, pH 3·1, was stored 10 months at room temperature. Colorimetric determination found 66·6% of *IIe*. The main product of decomposition was *IV* (S2).

An analogous batch of dihydrogen citrate *IIg*, containing 1 mg of *IIg*, 200 mg of glycerol and up to 1 ml of water for injections, pH 3·11, was stored 2 years at + 5°C. Colorimetry had found 85% of *IIg*.

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