DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

SYNTHESIS OF 3-(N-ALKYLAMINOMETHYL)CARBAZOLES CONTAINING FUNCTIONAL GROUPS IN THE ALKYL PART OF THE MOLECULE

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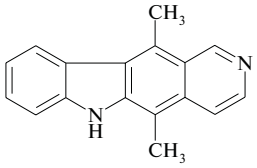
Drugs used for the treatment of oncological disorders differ in the mechanism of action on tumor cells. In particular, the antitumor activity of alkaloid ellipticine is based on the intercalation effect [1], whereby plane molecules of the drug penetrate between polynucleotide chains of the DNA double helix, thus violating the matrix activity and inhibiting the growth of pathogenic cells.



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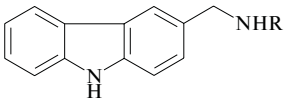

Ia – If

R = CH_2CH_2OH (a); $CH_2CH_2CH_2OH$ (b); $CH_2CH(OH)CH_2OH$ (c); $CH_2CH_2N(C_2H_5)_2$ (d); $CH_2CH_2CH_2N(CH_3)_2$ (e); $CH_2CH_2NHCH_2CH_2OH$ (f).

All synthetic drugs acting by the intercalation mechanism possess common structural features: a plane polycyclic fragment and a flexible atomic chain carrying functional groups [2, 3]. According to this principle, we have synthesized a series of tricyclic analogs of ellipticine (Ia – If). The initial reagents were 1,2,3,4-tetrahydrocarbazole-6-carboxylic acid (II) [4] and related ester III [5]. Acid II was obtained from 4-hydrazinebenzoic acid and cyclohexanone using a modified method of Burtner et al. [4].

The target aminomethylcarbazoles Ia – If were obtained by reducing the corresponding carbazolecarboxamides, which can be synthesized from acid II by two pathways. Both these pathways were tried in order to synthesize 3-carbazolecarboxylic acid N-(2-hydroxyethyl)amide VIa.

By dehydrating tetrahydrocarbazole-6-carboxylic acid derivatives III and V, we obtained aromatic compounds IV and VIa, respectively. The dehydration was catalyzed by palladium on carbon [6] in boiling xylene. Under these conditions, ester III leads (with a nearly quantitative yield) to aromatic ester IV. At the same time, amide V directly leads to aromatic amide VIa with a yield of 38%. Eventually, the pathway from acid II to amide VIa via 3-carbazolecarboxylic acid ester (IV) was proved to be more effective (total yield, 55%) as compared to the pathway via 1,2,3,4-tetrahydrocarbazole-6-carboxylic acid N-(2-hydroxyethyl)amide (V), where the total yield amounted to only 27%. For this reason, the other amides (VIb – VIe) were also synthesized via ester IV.

The synthesis of carbazole If containing a polyfunctional side chain was performed using carboxylic acid VII [7], which acylated glycine ethylate in the presence of dicyclohexylcarbodiimide [8]. The resulting N-(carbazolyl-3-carbonyl)glycine ester VIII was converted into diamide IX, the reduction of which led to compound If. The reduction of 3-carbazolecarboxamides VIa – VIe and diamide IX was performed by lithium aluminum hydride in tetrahydrofuran (THF). Amines Ib – If were obtained with a yield of 50 – 75%, whereas the yield of amine Ia was much lower, probably, because of the poor solubility of the initial amide VIa and its complex with lithium aluminum hydride. The target amides were converted into the corresponding salts – hydrochlorides, which rendered the compounds water-soluble and ensured additional purification. Almost all amine hydrochlorides are hygroscopic and exhibit no clear melting points (Table 1). The mass spectra of these compounds contain no peaks of molecular ions. The proposed structures of the synthesized compounds were confirmed by ^{1}H NMR data, mass spectra, and elemental analyses. The yields and physicoche-

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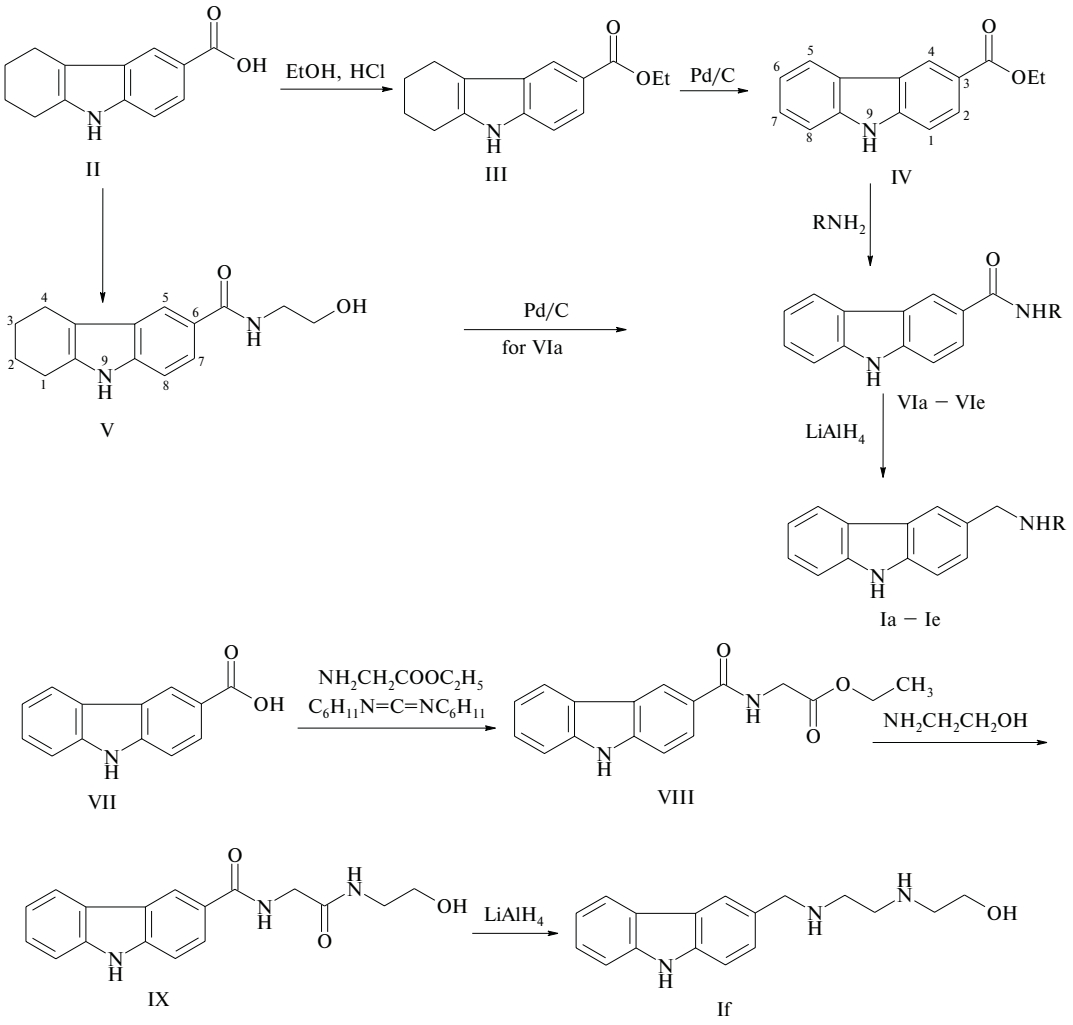

mical characteristics of newly synthesized compounds are listed in Table 1.

Some of the synthesized compounds were submitted for biological testing with respect to antitumor activity at the Research Institute of Experimental Diagnostics and Therapy of Tumors (Blokhin Oncological Research Center, Moscow).

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were measured on a Bruker AC-200 spectrometer with a working frequency of 200 MHz. The chemical shifts are listed in Tables 2 and 3. Thin-layer chromatography (TLC) was performed on Silufol UV-254 plates (Czech Republic); the spots were revealed by exposure to UV radiation or by treatment with a chloranyl solution in benzene. The TLC plates were eluted in the following systems of solvents: (A) chloroform – methanol (10 : 1); (B) chloroform – methanol (5 : 1); (C) chloroform – methanol – 20% aqueous ammonia (20 : 20 : 1); (B). The mass spectra were obtained on a Finnigan SSQ-710 mass spectrometer using 70-eV electron impact ionization and direct injection of samples into the ion source.

The data of elemental analyses agree with the results of analytical calculations using the empirical formulas (Table 1).

1,2,3,4-Tetrahydrocarbazole-6-carboxylic acid (II). To 7 g (46 mmole) of 4-hydrazinebenzoic acid (Lancaster) was added 6.32 g (64 mmole) of cyclohexanone. The reaction mass exhibits self-heating and caking. The resulting hydrazone was ground into a homogeneous mass and heated with stirring on a boiling water bath. To this product was added 75 ml of a 25% aqueous sulfuric acid and the reaction mixture was heated for 30 min with stirring on a boiling water bath and cooled. The precipitated 1,2,3,4-tetrahydrocarbazole-6-carboxylic acid (II) was filtered, washed sequentially with water (30 ml) and 50% aqueous ethanol (30 ml), and dried to constant weight at 105°C. The residual water was removed by additional drying over phosphorus pentaoxide. Acid II was obtained in the form of light-pink crystals; yield, 9.2 g (92.7%); m.p., 280 – 282°C (published m.p., 282°C [4]); R_f, 0.42 (system A).

1,2,3,4-Tetrahydrocarbazole-6-carboxylic acid ethyl ester (III). A suspension of 28 g (130 mmole) of 1,2,3,4-tetrahydrocarbazole-6-carboxylic acid (II) in 260 ml of anhydrous ethanol, containing 26 g of dry hydrogen chloride, was boiled for ~7 h until consumption of the initial acid (TLC monitoring). The solvent was distilled off and the residue crystallized from anhydrous ethanol to obtain 28.9 g (91%) of ester III; m.p., 115 – 117°C (published m.p., 117 – 119°C [5]); R_f, 0.80 (system A).

3-Carbazolecarboxylic acid ethyl ester (IV). 1,2,3,4-Tetrahydrocarbazole-6-carboxylic acid ethyl ester III (15 g) was dissolved on heating in 90 ml of xylene purified from sulfurous compounds. To this solution was added 3 g of a dehydrogenation catalyst (5% palladium on carbon [6]) and the mixture was boiled for 40 h, with 1 g portions of the fresh catalyst added every 10 h. Then the reaction mixture was cooled and xylene was decanted. The residue was extracted with boiling THF (3 × 70 ml) to obtain 13.6 g of 3-carbazolecarboxylic acid ethyl ester (IV); an additional 0.8 g of ester IV was extracted with THF from the catalyst in a Sohxlet apparatus. Total yield of ester IV, 14.4 g (97.6%); m.p., 154 – 157°C (published m.p., 156 – 157°C [7]); R_f, 0.75 (system A).

N-(2-Hydroxyethyl)-1,2,3,4-tetrahydrocarbazole-6-carboxamide (V). A suspension of 3.0 g (14 mmole) of acid II and 2.9 g (14 mmole) of phosphorus pentaoxide in 60 ml of anhydrous diethyl ether was stirred for 2,5 h at 5 – 10°C. Then the residual solvent and phosphorus oxychloride were distilled off and the residue was dissolved in 100 ml of dry benzene. The resulting chloroanhydride solution was gradually (over 1 h) added with stirring to a solution of 2.6 g (42 mmole) of ethanolamine in 150 ml of dry benzene and the emulsion was boiled with stirring for 3 h and cooled. The solvent (benzene) was decanted to leave an oily product, which was dissolved in 30 ml of isopropyl alcohol. This solution was boiled with activated carbon (grade B) and filtered. The filtrate was poured into 150 ml of ice-cold water and the mixture was allowed to stand for 3 h. The precipitated product was separated by filtration and recrystallized from isopropyl alcohol, which yielded 2.6 g (71%) of colorless crystals of amide V; ^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 1.84 (bm, 4H, 2-CH_3, 3-CH_2), 2.69 (bm, 4H, 1-CH_2, 4-CH_2), 3.36 (q, 2H, $J_1 = J_2$ 5.4 Hz, J_{NH,CH_2} 5.4 Hz, NCH_2), 3.54 (bq, 2H, $J_1 = J_2$ 5.4 Hz, J_{OH,CH_2} 5.4 H, CH_2O), 4.65 (bt, 1H, J_{OH,CH_2} 5.4 Hz, OH), 7.25 (d, 1H, J_{ortho} 8.8 Hz, 8-H), 7.56 (dd, 1H, J_{ortho} 8.8, J_{meta} 1.7 Hz, 7-H), 7.95 (bs, 1H, 5-H), 8.12 (t, 1H, J_{NH,CH_2} 5.4 Hz, CONH), 10.80 (bs, 1H, 9-NH); mass spectrum, m/z (I_{rel}, %): 258 (88), 212 (61), 198 (100), 170 (77), 142 (61).

N-(2-Hydroxyethyl)carbazole-3-carboxamide (VIa). *Method A*. A suspension of 2.0 g (8.3 mmole) of ester IV in a mixture of 1 ml (16.6 mmole) aminoethanol and 5 ml ethylene glycol was heated for ~8 h at 160 – 165°C until the initial ester was consumed (TLC monitoring). The reaction mass was cooled, diluted by ice-cold water, and allowed to stand for 2 h. The precipitated colorless crystals of amide VIa were separated by filtration; yield, 1.3 g (62%); mass spectrum, m/z (I_{rel}, %): 254 (98), 236 (73), 194 (100), 166 (94).

Method B. To 4 g (15.5 mmole) of amide V, dissolved on boiling in 600 ml of xylene, was added 1.5 g of a dehydrogenation catalyst (5% palladium on carbon [6]) and the mixture was boiled for ~18 h until the initial ester was consumed (TLC monitoring). The catalyst was separated from boiling xylene by filtration and washed with 20 ml of

TABLE 1. Yields and Characteristics of Newly Synthesized Compounds

Compound	Yield, %	M.p., °C	Solvent for crystallization	R_f (system)	Empirical formula
Ia	30	139 – 142	2-Propanol	0.21 (B)	$C_{15}H_{16}N_2O$
Ia · HCl	84*	162 – 165	Ether	0.21 (B)	$C_{15}H_{16}N_2O \cdot HCl$
Ib · HCl	52	110 – 112	Acetone – ethanol	0.20 (B)	$C_{16}H_{18}N_2O \cdot HCl \cdot 0.5H_2O$
Ic · HCl	66	195 – 200	Ether	0.17 (B)	$C_{16}H_{18}N_2O_2 \cdot HCl$
Id · 2HCl	67	75 – 80	Ether – ethanol	0.69 (C)	$C_{19}H_{25}N_3 \cdot 2HCl \cdot H_2O$
Ie · 2HCl	75	60 – 70	Ether – ethanol	0.17 (C)	$C_{18}H_{23}N_3 \cdot 2HCl \cdot H_2O$
If · 2HCl	54	190 – 200	Acetone – ethanol	0.30 (C)	$C_{17}H_{21}N_3O \cdot 2HCl \cdot H_2O$
V	71	179 – 182	2-Propanol	0.29 (C)	$C_{15}H_{18}N_2O_2$
VIa	62	208 – 210	2-Propanol	0.22 (C)	$C_{15}H_{14}N_2O_2$
VIb	68	208 – 209	2-Propanol	0.22 (A)	$C_{16}H_{16}N_2O_2$
VIc	65	210 – 215	2-Propanol	0.06 (A)	$C_{16}H_{16}N_2O_3$
VId · HCl	57	50 decomp	Ether – ethanol	0.44 (C)	$C_{19}H_{23}N_3O \cdot HCl$
VIe	68	132 – 135	Acetone	0.60 (C)	$C_{18}H_{21}N_3O$
VIII	58	176 – 180	Ethanol	0.36 (A)	$C_{17}H_{16}N_2O_3$
IX	89	182 – 188	Water	0.32 (A)	$C_{17}H_{17}N_3O_3$

* Yield for base Ia.

TABLE 2. Proton Chemical Shifts in the ^{1}H NMR Spectra of N-Substituted 3-Carbazolecarboxylic Acid Amides in DMSO-d_6; δ, ppm (J, Hz)

Compound	1-H, 8-H (2H)	2-H dd (1H)	4-H (1H)	5-H d (1H)	6-H (1H)	7-H (1H)	9-NH bs	CONH t, (1H)	R at N of amide
VIa	7.47 – 7.54 m	7.93, J_{orhto} 8.5, J_{meta} 1.2	8.68 d, J_{meta} 1.2	8.13, J_{orhto} 7.5	7.21 m	7.42 m	11.43	8.29, J 5.8	3.34 – 3.61 (m, 4H, CH_2CH_2)
VIb	7.50 – 7.55 m	7.95, bd, J_{orhto} 8.5	8.69 bs	8.15, J_{orhto} 7.5	7.22 t J_{orhto} 7.5	7.43 t J_{orhto} 7.5	11.44	8.34, J 5.8	1.77 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.42 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}$), 4.47 (bs, 1H, OH)
VIc	7.50 – 7.55 m	7.96 J_{orhto} 8.5, J_{meta} 1.2	8.71 bs	8.15 J_{orhto} 7.5	7.22 t J_{orhto} 7.5	7.43 t J_{orhto} 7.5	11.38	8.20 J 5.5	3.46 (m, 4H, $N\underline{CH_2} \cdot \underline{CH_2}OH$), 3.74 (m, 1H, CHOH), 4.48 (bs, 1H, OH), 4.74 (bs, 1H, OH)
VId · HCl	7.52 – 7.55 m	7.92, J_{orhto} 8.2, J_{meta} 1.2	8.69 bs	8.13 J_{orhto} 7.5	7.21 m	7.42 m	11.49	8.76 J 5.5	1.22 (t, 6H, J 6.2, $CH_2\underline{CH_2}$), 3.16 (q, 4H, $\underline{CH_2}CH_3$), 3.25 (t, 2H, J 6.0, CH_2)*
VIe	7.44 – 7.54 m	7.89 J_{orhto} 8.4, J_{meta} 1.2	8.63 d, J_{meta} 1.2	8.10 J_{orhto} 7.5	7.19 m	7.40 m	11.41	8.38 J 5.8	1.68 (m, 2H $CH_2\underline{CH_2}CH_2$), 2.20 (s, 6H, $N(CH_3)_2$), 2.29 (t, 2H, J 5.8, $\underline{CH_2}$ $N(CH_3)_2$), 3.40 (q, 2H, J 5.8, $CONH\underline{CH_2}$)
VIII	7.55 sd, J_{orhto} 8.4	7.98 bd J_{orhto} 8.4	8.74 bs	8.15 J_{orhto} 7.4	7.23 t, J_{orhto} 7.4	7.44 t J_{orhto} 7.4	11.53	8.85 J 5.5	1.23 (t, 3H, J 7.0, $CH_2\underline{CH_2}$), 4.09 (t, 2H, J 6.0, $\underline{CH_2}CON$), 4.15 (q, 2H, $\underline{CH_2}CH_3$)
IX	7.50 – 7.54 m	7.96 J_{orhto} 8.5 J_{meta} 1.3	8.72 bs	8.14 J_{orhto} 7.5	7.22 m	7.43 m	11.45	8.56 J 5.8	3.19 (q, 2H, J 5.4, $CONH\underline{CH_2}$), 3.44 (q, 2H, J 5.4, $\underline{CH_2}OH$), 3.93 (d, $\underline{2H}$, J 5.4, $CONH\underline{CH_2}$), 4.58 (t, 1H J 5.4 $CH_2\underline{CH}$), 7.79 (bt, 1H, J 5.4 $CO\underline{CH}CH_2$), 8.56 (bt, 1H, $ArCH_2\underline{CH}CO$, J 5.8)

* Signal from the other CH_2 group overlaps with the signal from water (in DMSO-d_6).

TABLE 3. Proton Chemical Shifts in the ^{1}H NMR Spectra of N-Substituted 3-(Aminomethyl)carbazoles in DMSO-d_6; δ, pp(m, J, Hz)

Compound	1-H, 8-H (2H)	2-H	4-H (1H)	5-H d (1H)	6-H (1H)	7-H (1H)	9-NH bs (1H)	NH_2^+ bs	$Ar\underline{CH_2}NH_2^+$ (2H)	R
I a · HCl	7.53 bd, J 8.4	7.61 dd, J_{ortho} 8.4, J_{meta} 1.2	8.33 bs	8.06 J_{ortho} 7.5	7.1 8 t J_{ortho} 7.5	7.41 t J_{ortho} 7.5	11.50	9.26	4.30 s	2.99 (t, 2H, J 6.0, $N+H_2$ $\underline{CH_2}$),3.74 (t, 2H, J 6.0, $\underline{CH_2}OH$), 5.25 (bs, 1H, OH)
Ib · HCl	7.52 bd, J 8.5	7.58 dd, J_{ortho} 8.4, J_{meta} 1.2	8.29 bs	8.08 J_{ortho} 7.5	7.20 m	7.42 m	11.43	9.13	4.27 bt J 5.3	1.84 (m, 2H, $CH_2\underline{CH_2}CH_2$), 2.99 (m, 2H, $\underline{CH_2}N$ +), 3.50 (t, 2H, J 5.8, $\underline{CH_2}OH$), 4.65 (bs, 1H, OH)
Ic · HCl*	7.40 bd, J 8.5	7.50 dd, J_{ortho} 8.4, J_{meta} 1.2	8.19 bs	7.95 J_{ortho} 7.5	7.07 t J 7.5	7.29 t J 7.5	11, 35	8.90	4.19 s	2.82 (m, 2H $\underline{CH_2}N$ +), 3.16 – 3.36** (m, 2H, $\underline{CH_2}OH$), 3.78 (m, 1H, $\underline{CH}OH$), 5.32 (bs, 1H, OH)
Id · 2HCl	7.52 bd, J 8.5	7.62 dd, J_{ortho} 8.4, J_{meta} 2.5	8.32 bs	8.05 d J_{ortho} 7.4	7.18 m	7.41 m	11.49	…	4.29 s	1.17 (t, 6H, J 7.0, $2CH_2\underline{CH_2}$), 2.96 (q, 4H, $2\underline{CH_2}CH_3$), 3.29 (bs, 4H, $N+H_2\underline{CH_2}\underline{CH_2}N + H_2$)
Ie · 2HCl	7.52 bd, J 8.5	7.60 dd, J_{ortho} 8.5, J_{meta} 1.2	8.30 bs	8.06 d J_{ortho} 7.5	7.19 m	7.41 m	11.39	…	4.26 s	2.08 (m, 2H, $CH_2\underline{CH_2}CH_2$), 2.59 (6H, N + $(CH_3)_2$), 2.97, 3.02 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}$)
If · 2HCl*	7.39 bd, J 8.5	7.49 bd, J_{ortho} 8.2	8.22 bs	7.92 J_{ortho} 7.5	7.06 t, J 7.5	7.28 t J 7.5	11.39	9.50	4.21 s	2.93 (t, 2H J 5.3, $NH\underline{CH_2}CH_2OH$), 3.29 (s, 4H, $N + H_2\underline{CH_2}\underline{CH_2}N$ + H2), 3.59 (t, 2H, J 5.3, $NHCH_2\underline{CH_2}OH$)

* Solvent, DMSO-d_6 + CCl_4.
** Signal partly overlaps with the signal from water (in DMSO-d_6).

boiling isopropyl alcohol, after which the filtrates were evaporated. The residues were combined and recrystallized from 25 ml of isopropyl alcohol to obtain 1.5 g (38%) of amide VIa identical to that synthesized by method A.

N-(2-Hydroxypropyl)carbazole-3-carboxamide (VIb). A suspension of 6.0 g (25 mmole) of ester IV in a mixture of 5.7 ml (75 mmole) of 1,3-aminopropanol and 10 ml of ethylene glycol was heated for ~3 h at 160 – 165°C until the initial ester was consumed (TLC monitoring). The solvent and excess 1,3-aminopropanol were distilled off in vacuum, after which the residue was dissolved in isopropyl alcohol. The solution was poured into ice-cold water and the mixture was allowed to stand for 2 h. The precipitated product (5.3 g) was separated by filtration and recrystallized from isopropyl alcohol to obtain colorless crystals of amide VIb; yield, 4.6 g (68%); mass spectrum, m/z (I_{rel}, %): 268 (20), 223 (30), 194 (100), 166 (33).

N-(2,3-Dihydroxypropyl)carbazole-3-carboxamide (VIc). A suspension of 1.7 g (7 mmole) of ester IV and 1.2 g (14 mmole) of 1-amino-2,3-dioxypropane in 5 ml of ethylene glycol was heated for 4 h at 160°C and diluted with 10 ml of isopropyl alcohol. The precipitated product was separated and dried to obtain 1.3 g (65%) of light-yellow crystals of amide VIc; mass spectrum, m/z (I_{rel}, %): 284 (10), 266 (16), 194 (100), 166 (40).

N-[2-Diethylamino)ethyl]carbazole-3-carboxamide hydrochloride (VId · HCl). A suspension of 2.4 g (10 mmole) of ester IV in a mixture of 3.5 ml (30 mmole) of N,N-diethylethylenediamine and 5 ml of ethylene glycol was heated for ~20 h at 190°C until the initial ester was consumed (TLC monitoring). The solvent and excess diamine were distilled off in vacuum, after which the residue was dissolved in chloroform. The chloroform solution was treated with diluted hydrochloric acid and the aqueous acid extract was alkalized with sodium carbonate. The subsequent extraction with chloroform yielded 2.8 g of base VId. Chloroform was distilled off and the residue of base VI was dissolved in ethanol. Finally, a solution of hydrogen chloride in ethanol was added to pH 4 and hydrochloride VId · HCl was precipitated with diethyl ether. The oily product was dried in vacuum until solidification; yield, 2.0 g (57%); mass spectrum, m/z (I_{rel}, %): 309 (2), 307 (17), 194 (60), 166 (60), 86 (100).

N-[3-Dimethylamino)propyl]carbazole-3-carboxamide hydrochloride (VIe). A suspension of 2.4 g (10 mmole) of ester IV in a mixture of 3.1 ml (30 mmole) of N,N-dimethyl-1,3-diaminopropane and 5 ml of ethylene glycol was heated for ~16 h at 190°C until the initial ester was consumed (TLC monitoring). The solvent and excess diamine were distilled off in vacuum, after which the residue was dissolved in chloroform. The chloroform solution was treated with diluted hydrochloric acid to extract hydrochloride VIe · HCl (0.5 g of acid VII remained in the chloroform). The aqueous acid extract was alkalized with sodium carbonate and amide VIe was extracted with chloroform and dried. The chloroform was distilled off and the residue was crystallized from acetone to obtain cream-colored crystals of amide VIe; yield, 2.0 g (68%); mass spectrum, m/z (I_{rel}, %): 295 (16), 194 (63), 166 (55), 58 (100).

3-Carbazolecarboxylic acid (VII). To a solution of 12 g (51 mmole) of 3-carbazolecarboxylic acid ethyl ester (IV) in 150 ml of ethanol was added a solution of 4.4 g (79 mmole) of KOH in 20 ml of water and the mixture was boiled for ~5 h until consumption of the initial ester (TLC monitoring). The solution was cooled and acidified with hydrochloric acid to pH 2. The precipitated colorless crystals were separated by filtration to obtain 9.8 g (92%) of acid VII m.p., 270 – 274°C (published m.p., 274 – 276°C [7]); R_f 0.29 (system A).

N-(Carbazolyl-3-carbonyl)glycine ethyl ester (VIII). A suspension of 3.0 g (14 mmole) of 3-carbazolecarboxylic acid (VII), 2.0 g (14 mmole) of glycine hydrochloride ethylate [9], and 2.93 g (14 mmole) of dicyclohexylcarbodiimide in 20 ml of pyridine was stirred for 2 h at 0°C and allowed to stand overnight in a refrigerator. Then, the precipitate of dicyclohexylurea was separated by filtration, pyridine was distilled off in vacuum, and the residue (containing initial acid VII and the product VIII) was dissolved in ethanol. The solution was poured into 150 ml of saturated aqueous sodium carbonate solution. The precipitate was separated by filtration to obtain 3.2 g of a technical-purity product VIII. Recrystallization from ethanol yields 2.4 g (58%) of compound VIII in the form of colorless crystals; mass spectrum, m/z (I_{rel}, %): 296 (100), 250 (16), 194 (93), 166 (13).

The aqueous solution was acidified to isolate 0.4 g of the initial acid VII (13%).

N_{α}-(Carbazolyl-3-carbonyl)glycine N-(2-hydroxyethyl)amide (IX). A mixture of 3.5 g (12 mmole) ester VIII and 3.0 ml (50 mmole) ethanolamine in 70 ml of ethylene glycol was heated for ~3 h on a bath at 140 – 150°C until termination of the reaction (TLC monitoring). The solvent and excess ethanolamine were distilled in vacuum. The residue was cooled and poured into an ice-cold sodium carbonate solution, after which the mixture was allowed to stand for 2 h. Then the precipitate was separated by filtration, washed with water, and dried to obtain 3.3 g (89%) of compound IX in the form of pink crystals; mass spectrum, m/z (I_{rel}, %): 311 (13), 250 (13), 194 (100).

3-[N-(3-Hydroxypropyl)aminomethyl]carbazole hydrochloride (Ib · HCl). To a suspension of 0.4 g of lithium aluminum hydride in 50 ml of anhydrous THF was gradually (over 1.5 h) added with stirring and boiling a solution of 2.5 g (9 mmole) of amide VIb in 250 ml of the same solvent. Every 0.5 h, additional 0.4 g portions of lithium aluminum hydride were added to a total amount of 1.6 g (42 mmole) $LiAlH_4$, after which the mixture was boiled for 5 h with TLC monitoring. Then the reaction mass was decomposed by treating sequentially with 1.6 ml of water, 1.6 ml of a 15% aqueous NaOH solution, and 4.8 ml of water [10] and stirred for 2 h. The inorganic precipitate was separated by filtration. The filtrate was washed with THF. THF was distilled off and

the residue (2.7 g) was dissolved in chloroform. The chloroform solution was extracted by water acidified with 1 ml of concentrated hydrochloric acid. The aqueous extract was alkalized with sodium carbonate to pH 10. The precipitate was separated by filtration to obtain 1.5 g (65%) of amine Ib in the form of light-yellow crystals possessing no clear melting point. To a suspension of 0.4 g of base Ib in anhydrous ether was added with stirring an equimolar amount of HCl dissolved in ethanol. After reprecipitation, the residue was separated by filtration and dried in vacuum over phosphorus pentaoxide to obtain semihydrate Ib $HCl \cdot 0.5H_2O$ in the form of light-yellow crystals; yield, 0.38 g (80%); mass spectrum, m/z (I_{rel}, %): 223 [M-CH_2OH] (27), 207 (100), 180 (72).

Using an analogous procedure, compounds Ia and Ia · HCl were obtained from amide VIa, and hydrochlorides Ic · HCl, Id · 2HCl, and Ie · 2HCl, from amides IVc and IVd (Table 1).

2-[2-[(Carbazol-3-yl)methylamino)ethylamino]ethanol dihydrochloride (If · 2HCl). To a suspension of 0.7 g of lithium aluminum hydride in 50 ml of anhydrous THF was gradually (over 3 h) added with stirring and boiling a solution of 2.5 g (8 mmole) of diamide IX in 800 ml of the same solvent. Every 0.5 h, additional 0.5 g portions of lithium aluminum hydride were added to a total amount of 3.7 g (97 mmole) $LiAlH_4$, after which the mixture was boiled for 5 h with TLC monitoring. Then the reaction mass was decomposed by treating sequentially with 3.7 ml of water, 3.7 ml of a 15% aqueous NaOH solution, and 11.1 ml of water [10]. The inorganic precipitate was separated by filtration. The filtrate was distilled to remove the solvent, and the residue was dissolved in 30 ml of acetone and acidified with an HCl solution in ethanol. The precipitated amine dihydrochloride was separated by filtration and dried in vacuum over phosphorus pentoxide to obtain 1.54 g (54%) of light-yellow crystals of dihydrochloride If · 2HCl; mass spectrum, m/z (I_{rel}, %): 265 [M-H_2O] (38), 253 (39), 208 (55), 180 (100).

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