DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

SYNTHESIS OF 3,5-DISUBSTITUTED 10,11-DIHYDRO-5H-DIBENZ[b,f]AZEPINES[1]

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Previously we have demonstrated that some 5-aminoacyl iminodibenzyl derivatives possess a pronounced antiarrhythmic activity [1, 2]. Similar properties were observed for the corresponding derivatives in the related tricyclic systems of iminostilbene [3] and dibenzodiazepine [4]. We have thoroughly investigated in this respect a series of 3-alkoxycarbonylamino-5-aminoacyl iminodibenzyl derivatives [5], where special attention was drawn to 3-ethoxycarbonylamino-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine(bonnecor) [6].

It was also of interest to synthesize and study compounds containing some other aminoacyl substituents in positions 3 and 5 of the tricyclic iminodibenzyl system. For this purpose, we have used 3-aminoiminodibenzyl (I) as the initial compound whose reactions with chloroacetyl chloride and β-chloropropionyl chloride led to the corresponding chloroacyl derivatives (IIa, IIb). The subsequent interaction of compounds II with chloroacetyl chloride leads to bischloroacyl derivatives (IIIa, IIIb). In the presence of excess chloroacetyl chloride, the system also yields a trischloroacetyl derivative (IV). Interactions of bischlorides IIIa, IIIb with secondary amines under the Schotten – Baumann reaction conditions led to the isolation of 3,5-bisdialkylaminoacyl derivatives (Va – Vd) differing by the length of their aminoacyl chains and the type of substituents at the nitrogen atoms. Under the same conditions, the reactions of compound IIa led to 3-aminoacetylamino derivatives (VIa – VIc) without substituents at a nitrogen atom in the cycle.

3-(Chloroacetylamino)iminodibenzyl (IIa) was also converted into 5-acyl derivatives (VIIa, VIIb). Aminolysis of these compounds led to the corresponding amino derivatives (VIIIa, VIIIb). Acylation of 3-amino-5-dimethylaminoacetylaminodibenzyl (IX) [6] yields a series of 3-acylamino derivatives (Xa – Xe) of aliphatic and aromatic acids, as well as carbamoyl and thiocarbamoyl derivatives (Xf, Xg). The amino derivatives were isolated as hydrochlorides; in some cases, they exhibited crystallization with attachment of a water molecule.[3]

EXPERIMENTAL PART

Purity of the synthesized compounds was checked by TLC on Kieselgel-60 F_{254} (Merck) plates eluted in the toluene – ethanol – acetone – ammonia 70 : 5.5 : 4.5 : 2.5 (A) and dioxin – benzene – concentrated aqueous ammonia 10 : 2 : 1 (B) systems. The data of elemental analyses coincide with the results of calculations according to the empirical formulas.

3-Chloroacetylamino-10,11-dihydro-5H-dibenz[b,f]-azepine (IIa). Under the Schotten – Baumann reaction conditions, a mixture of 7.88 g (0.04 mole) of 3-amino-10,11-dihydro-5H-dibenz[b,f]azepine (I) [6], 7.6 g (0.06 mole) of chloroacetyl chloride, and 8 g (0.04 mole) of sodium carbonate in 20 ml water and 100 ml ethanol at 8 – 12°C yields 7 g (60.9%) of compound IIa; m.p., 182 – 183°C (from propanol); $C_{16}H_{15}ClN_2O$.

3-(β-Chloropropionylamino)-10,11-dihydro-5H-dibenz-[b,f]azepine (IIb) was obtained by analogous procedure; m.p., 162 – 164°C (from toluene); R_f, 0.56 (A); $C_{17}H_{17}ClN_2O$.

3-Chloroacetylamino-5-chloroacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (IIIa). A mixture of 4.3 g (0.015 mole) of compound IIa, 1.93 g (0.017 mole) of chloroacetyl chloride, and 70 ml toluene was boiled for 4 h. To this reaction

[1] For brevity, compounds of this series are referred to in the general part as iminodibenzyl derivatives.

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[3] The results of pharmacological characterization of these compounds will be reported in a separate paper.

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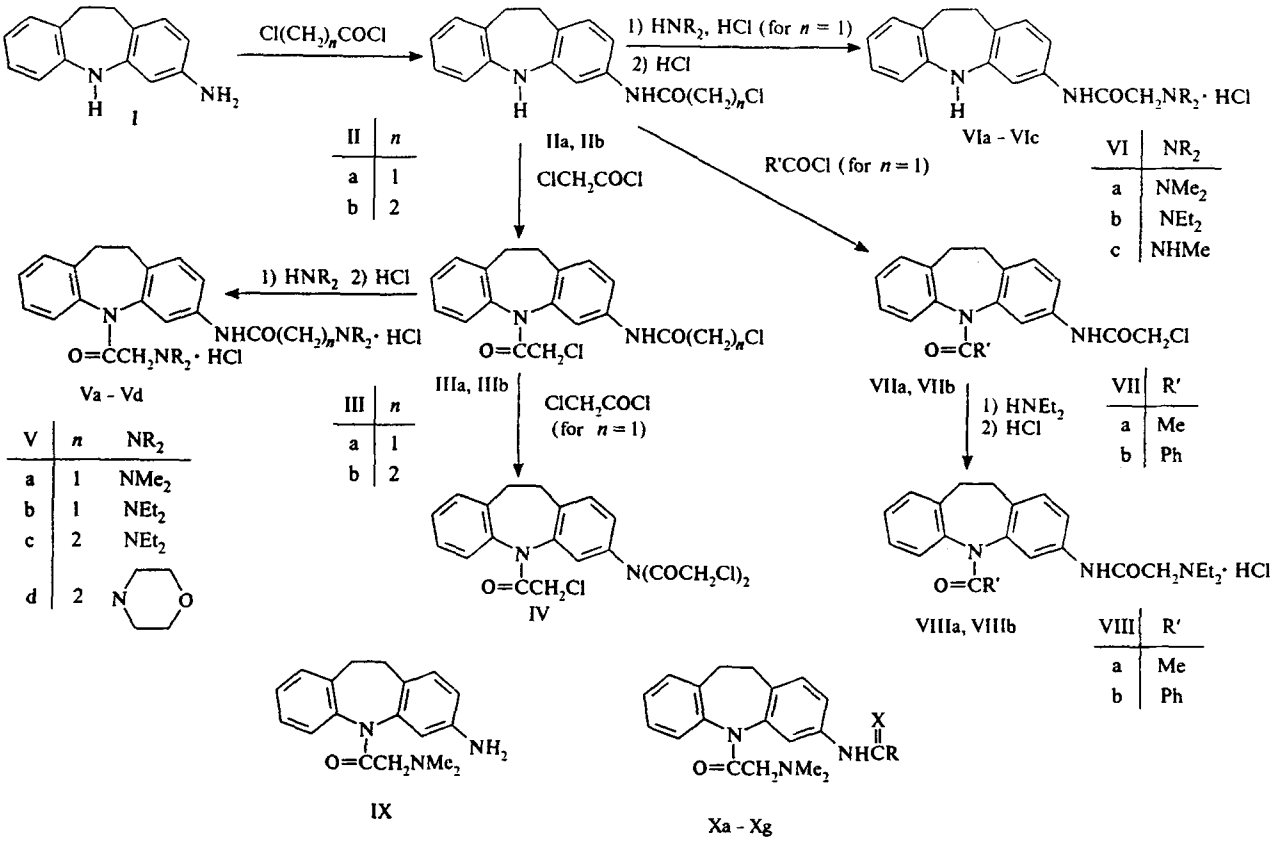

X: C(X)R = COMe (a), COPh (b), $COC_6H_4NO_2$-4 (c), $COC_6H_4NH_2$-4 (d), COC_6H_4NHAc-4 (e), $CONH_2$ (f),$CSNH_2$ (g).

mass was added activated charcoal and the mixture was heated for 10 min and filtered. Toluene was distilled off and the oily residue was crystallized from 2-propanol. Yield of compound IIIa, 2.9 g (60%); m.p., 153 – 155°C (from ethyl acetate); $C_{18}H_{16}Cl_2N_2O_2$.

3-(β-Chloropropionylamino)-5-chloroacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (IIIb) was obtained by an analogous procedure from 24 g (0.08 mole) of compound IIb, 9.94 g (0.088 mole) of chloroacetyl chloride, and 200 ml toluene; yield, 22 g (80%); m.p., 187 – 188°C (from butanol); $C_{19}H_{18}Cl_2N_2O_2$.

3-[Bis(chloroacetyl)amino]-5-chloroacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (IV). Compound IV was obtained from 2.86 g (0.01 mole) of compound IIIa, 2.64 g (0.022 mole) of chloroacetyl chloride, and 50 ml toluene; yield upon recrystallization, 2.2 g (50%); m.p., 176 – 177°C (from methanol); $C_{20}H_{17}Cl_3N_2O_3$.

3-Dimethylaminoacetylamino-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine dihydrochloride (Va). To a solution of 1.9 g (5 mmole) of compound IIIa in 20 ml toluene was added a solution of 4.5 g (50 mmole) of dimethylamine in toluene, and the mixture was heated for 6 h at 60 – 70°C. Upon cooling, the precipitated dimethylamine hydrochloride was filtered, toluene distilled off, and the residue was dissolved in 2-propanol. Dihydrochloride Va was precipitated by adding an ethanol solution of HCl; yield, 1.8 g (75%); m.p., 212 – 214°C; R_f, 0.50 (B); $C_{22}H_{28}N_4O_2 \cdot 2HCl \cdot 2H_2O$.

3-Diethylaminoacetylamino-5-diethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine dihydrochloride (Vb) was obtained by analogous procedure from 9.0 g (0.25 mole) of compound IIIa, and 8.6 g (0.12 mole) of diethylamine in 100 ml toluene; yield, 10 g (70%); m.p., 190 – 195°C (hygroscopic); R_f, 0.60 (A); $C_{26}H_{36}N_4O_2 \cdot 2HCl \cdot H_2O$.

3-(β-Diethylaminopropionylamino)-5-diethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine dihydrochloride (Vc) was obtained from 7.4 g (0.02 mole) of compound IIIb, and 8 g (0.088 mole) of diethylamine in 100 ml toluene; yield, 7 g (70%); m.p., 110 – 112°C (with decomp.); R_f, 0.3 (B); $C_{27}H_{40}N_4O_2 \cdot 2HCl \cdot H_2O$.

3-(β-Morpholinopropionylamino-5-morpholinoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine dihydrochloride (Vd) was obtained similarly to Va from 7.4 g (0.02 mole) of compound IIIb, and 8.7 g (0.1 mole) of morpholine in 100 ml toluene; yield, 7.8 g (70%); m.p., 212°C (with decomp., from DMF); R_f, 0.4 (B); $C_{27}H_{34}N_4O_4 \cdot 2HCl \cdot H_2O$.

3-Dimethylaminoacetylamino-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride (VIa). To a solution of 5.72 g (0.02 mole) of compound IIa in 150 ml toluene was added a solution of 3 g (0.066 mole) of dimethylamine in toluene and the mixture was stirred for 6 h at 50 – 60°C. Upon cooling, the precipitated dimethylamine hydrochloride

was filtered, toluene distilled off, and the residue was dissolved in 2-propanol. Dihydrochloride VIa was precipitated by adding ethanol saturated with HCl; yield, 6.0 g (85%); m.p., 230°C; m.p., 270°C (with decomp.) after single recrystallization from water; $C_{18}H_{21}N_3O \cdot HCl \cdot H_2O$.

3-Diethylaminoacetylamino-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride (VIb) was obtained similarly to Va from 5.72 g (0.02 mole) of compound IIa and 3.2 g (0.045 mole) of diethylamine in 100 ml toluene; yield, 5 g (69%); m.p., 222 – 225°C; R_f, 0.74 (A); $C_{20}H_{25}N_3O \cdot HCl$.

3-Methylaminoacetylamino-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride (VIc). A mixture of 8.7 g (0.03 mole) of compound IIa and 12 ml of 23% aqueous methylamine was heated in 100 ml DMF at 65 – 70°C for 6 h. The solvent was distilled off in vacuum and the residue dissolved on heating in water. Upon adding HCl and activated charcoal, the solution was filtered and cooled to precipitate hydrochloride VIc; yield, 6.0 g (62%); m.p., 250 – 252°C; R_f, 0.60 (B); $C_{17}H_{19}N_3O \cdot HCl$.

5-Acetyl-3-chloroacetylamino-10,11-dihydro-5H-dibenz[b,f]azepine (VIIa). A mixture of 5.6 g (0.02 mole) of compound IIa and 2.4 g (0.025 mole) of acetyl chloride in 50 ml benzene was boiled for 4 h. The solvent was distilled off and the residue recrystallized from 2-propanol with activated charcoal. Yield of compound VIIa, 5 g (87%); m.p., 156 – 158°C; R_f, 0.52 (A); $C_{18}H_{17}ClN_2O_2$.

5-Benzoyl-3-chloroacetylamino-10,11-dihydro-5H-dibenz[b,f]azepine (VIIb) was obtained by analogous procedure; yield, 69%; m.p., 183 – 184°C (from ethanol); $C_{23}H_{19}ClN_2O_2$.

5-Acetyl-3-diethylaminoacetylamino-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride (VIIIa). A mixture of 1.3 g (4 mmole) of compound VIIa and 0.73 g (10 mmole) of diethylamine in 30 ml benzene was boiled for 3 h. The precipitated dimethylamine hydrochloride was filtered, benzene distilled off, and the residue was dissolved in 2-propanol and treated with activated charcoal. Then was added a solution of hydrogen chloride in isopropyl alcohol, the solution evaporated to dryness, and the hydrochloride residue dried for a prolonged time in vacuum at 80°C. Yield of compound VIIIa, 0.9 g (60%); m.p., 90 – 92°C (with decomp.); $C_{22}H_{27}N_3O_2 \cdot HCl$.

5-Benzoyl-3-diethylaminoacetylamino-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride (VIIIb) was obtained by analogous procedure; yield, 60%; m.p., 215 – 216°C (with decomp., from 2-propanol); R_f, 0.56 (A); $C_{27}H_{29}N_3O_2 \cdot HCl$.

3-Acetylamino-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (Xa) was obtained Under Schotten – Baumann reaction conditions from a mixture of 2.95 g (0.01 mole) 3-aminoazepine IX [6], 1.2 g (0.12 mole) acetyl chloride, and 2 g sodium carbonate in 5 ml water and 20 ml ethanol. Upon ethanol distillation, the base was extracted with toluene to obtain 2.6 g (76%) of compound Xa; m.p., 136 – 137°C; R_f, 0.48 (B); $C_{20}H_{23}N_3O_2$.

To the base dissolved in toluene was added an ether solution of hydrogen chloride to precipitate hydrochloride Xa · HCl; m.p., 125 – 127°C (from propanol); $C_{20}H_{23}N_3O_2 \cdot HCl$.

3-Benzoylamino-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f] azepine (Xb) was obtained similarly to Xa from a mixture of 5.9 g (0.02 mole) of compound IX, 4.2 g (0.03 mole) benzoyl chloride, and 4.0 g sodium carbonate in 7 ml water and 60 ml ethanol. The precipitated base was recrystallized from 2-propanol. Yield of compound Xb, 6 g (75%) ; m.p., 171 – 172°C; R_f, 0.40 (B). Hydrochloride Xb · HCl: m.p., 338 – 340°C (from 2-propanol); $C_{25}H_{25}N_3O_2 \cdot HCl$.

5-Dimethylaminoacetyl-3-(4-nitrobenzoylamino)-10,11-dihydro-5H-dibenz[b,f]azepine (Xc). To a solution of 9 g (0.03 mole) of compound IX, in 150 ml ethanol was gradually added with stirring at 10 – 12°C a solution of 5.6 g (0.032 mole) of *p*-nitrobenzoic acid chloroanhydride in acetone. After adding half of the acetone solution, simultaneously dropwise was added 5 g of sodium carbonate in 12 ml water. The mixture was kept for 1 h and then the precipitate was filtered, washed with water and isopropyl alcohol. Yield of compound Xc, 12 g (80%) ; m.p., 142 – 143°C (from ethanol); R_f, 0.71 (B); $C_{25}H_{24}N_4O_4 \cdot H_2O$.

3-(4-Aminobenzoylamino)-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (Xd). To a suspension of 13.2 g (0.03 mole) of compound Xc in 500 ml ethanol was added 10 g moisturized Raney nickel catalyst. To this mixture was added dropwise with stirring and heating to 40 – 50°C a solution of 7.5 g (0.15 mole) of hydrazine hydrate in 25 ml acetone (this leads to dissolution of the precipitate and discoloration of the reaction mass). The mixture was stirred for 1 h at 40 – 45°C, then another 1 h with boiling, and filtered hot from the catalyst. On cooling, the crystalline product precipitates from the ethanol filtrate. Yield of compound Xd, 9.5 g (73%) ; m.p., 246 – 248°C (from butanol); R_f, 0.52 (B); $C_{25}H_{26}N_4O_2$.

3-(4-Acetylaminobenzoylamino)-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (Xe). A mixture of 8.28 g (0.02 mole) of compound Xd and 30 ml acetic anhydride was stirred for 1.5 h at 65 – 70°C, poured into water, and clarified with activated charcoal. To this mixture was added a NaOH solution to pH 8 – 9. The precipitated base has m.p. 151 – 153°C. To the base dissolved in 2-propanol and treated with activated charcoal was added an ethanol solution of HCl to precipitate hydrochloride Xe · HCl. Yield, 6.5 g (65%); m.p., 223 – 225°C (hygroscopic); R_f, 0.35 (B); $C_{27}H_{28}N_4O_3 \cdot HCl \cdot H_2O$.

3-Aminocarbonyl-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride (Xf). To a solution of 2.95 g (0.01 mole) of compound IX in a mixture of 4 ml of concentrated hydrochloric acid and 18 ml water was added by portions 3 g sodium cyanate (0.03 mole) and the mixture was heated for 3 h at 80°C. Upon cooling, the oily precipitate was dissolved in 2-propanol. Hydrochloride was precipitated by adding ether saturated with hydrogen chlo-

ride; yield of compound Xf · HCl, 1.58 g (42%); upon recrystallization from 2-propanol and drying in vacuum with heating: m.p., 178°C (with decomp); R_f, 0.18 (B); $C_{19}H_{22}N_4O_2 \cdot HCl$.

3-Aminothiocarbonylamino-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride (Xg). A mixture of 8.85 g (0.03 mole) of compound IX, 4.5 g (0.072 mole) of ammonium thiocyanate, and 8 ml of concentrated hydrochloric acid was boiled with stirring for 6 h. To the oily precipitate formed upon cooling was added 10 ml of water, the mixture was stirred, and the acid aqueous solution decanted. The residue was dissolved on heating in 0.4 liter water and the base precipitated by adding ammonia. Yield of compound Xg, 5 g (50%); m.p., 180 – 181°C (from 2-propanol). To the ethanol solution of the base was added a solution of hydrogen chloride in isopropyl alcohol to precipitate hydrochloride Xg · HCl; yield, 2.8 g; m.p., 175 – 177°C (with decomp.); R_f, 0.20 (A) (hygroscopic); $C_{19}H_{22}N_4OS \cdot HCl \cdot H_2O$.

REFERENCES

1. H. Wunderlich, A. Stark, E. Carstens, et al., *Pharmazie*, **40**(12), 827 – 830 (1985).
2. N. V. Kaverina, Z. P. Senova, V. V. Lyskovzev, et al., *Pharmazie*, **40**(12), 830 – 832 (1985).
3. A. P. Skoldinov, N. V. Kaverina, A. N. Gritsenko, et al., *Khim.-Farm. Zh.*, **30**(3), 26 – 30 (1996).
4. E. K. Grigor'eva, N. V. Kaverina, A. M. Likhosherstov, et al., RF Patent No. 2026862; *Byull. Izobret.*, No. 2 (1995).
5. A. P. Skoldinov, N. V. Kaverina, A. N. Gritsenko, et al., *Khim.-Farm. Zh.*, **30**(3), 23 – 25 (1996).
6. A. P. Skoldinov, A. N. Gritsenko, H. Wunderlich, et al., *Khim.-Farm. Zh.*, **24**(12), 51 – 53 (1990).