SYNTHESIS OF A NEW ANTIARRHYTHMIC AGENT — BONNECOR

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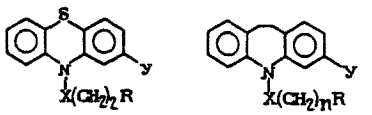
The structural feature ensuring neuroleptic activity in phenothiazine derivatives is the presence of a γ-amino alkyl group at the 10-position and an electron-acceptor substituent at the 2-position of the tricyclic phenothiazine system. Aminazine (Ia), and the trifluoromethyl derivatives triphthasine (Ib) and fluorophenazine (Ic) satisfy these requirements, and at the present time are considered as the most powerful neuroleptics. It was further shown that a directed change in the structure of these compounds makes it possible to change the spectrum of their pharmacological activity substantially. Thus, by substituting the α-methylene unit of the side chain by a carbonyl group, or in other words, with transition from γ-aminopropyl to β-aminoacyl derivatives, the adrenolytic properties become considerably weakened and the adrenopositive effect increases, and as a result the neuroleptic action disappears, and a set of properties is provided which are important for their action on various functions of the cardiovascular system. The cardiotropic properties of these compounds become considerably intensified when the electron acceptor substituent at the 2-position of the ring is replaced by an electron donor substituent. The result of these investigations was the provision of effective antiarrhythmic agents etmosine (Id) and etacisine (Ie) containing carbalkoxyamino groupings in the 2-position [2, 3].

Attention is drawn to the structural relationship between the phenothiazine neuroleptics and the psychotropic derivatives of dibenzazepine, among which the best known are the active antidepressants imipramine (IIa), chlorimipramine (IIb), and desimipramine (IIc), in the



Ia-e IIa-e

R = $N(CH_3)_2$ (Ia, e; IIa, b, e), N-(4-methylpiperazinyl) (Ib), N-(4-hydroxyethylpiperazinyl) (Ic), morpholino (Id), $NHCH_3$ (IIc), NR^1R^2 (IId); X = CH_2 (Ia-c; IIa-c) CO (Id, e; IId, e); Y = Cl (Ia; IIb); CF_3 (Ib, c) $NHCOOC_2H_5$ (Id, e; IId, e), H (IIa, c); n = 2 (IIa-c), 1-3 (IId), 1 (IIe).

structure of which γ-aminopropyl groups also occur. It was of interest to find out how those changes which led to the inversion of the activity spectrum in the series of phenothiazine derivatives will be reflected in the spectrum of activity of similar compounds. Investigations in this direction were carried out by our Institute in cooperation with the Arzneimittelwerk, Dresden. To solve the set-up problem, it was necessary to obtain the previously unknown 10, 11-dihydro-5H-dibenz[b,f]-azepin derivatives containing 3-aminoacyl substituents at the 3-position. The solution of this problem was facilitated by the fact that the Arzneimittelwerk produces chlorimipramine industrially, one of the intermediates for which 3-nitro-5-acetylamino-10,11-dihydro-5H-dibenz[b,f]azepine may serve as the starting compound for the planned syntheses. From this compound a large series of substituted dibenzazepines of the assigned structure IId were obtained by a four-stage synthesis. These compounds contain a carbalkoxyamino group with C_1–C_3 alkyls at the 3-position of the cyclic system and at the 5-position ω-aminoacyl chains of variable length (n = 1-3) having various R_2N groups including cyclic groups at the ω-position [1, 7]. Most of the synthesized compounds showed a pronounced antiarrhythmic activity experimentally. A detailed comparative pharmacological investigation made

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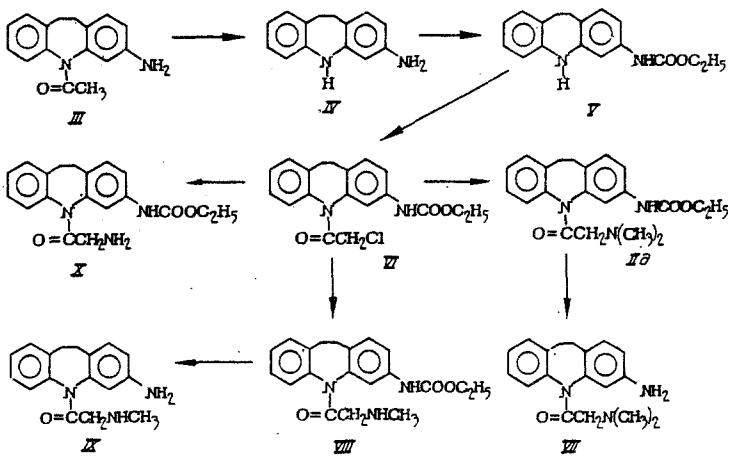
it possible to select the most promising compound, the hydrochloride of 3-carbethoxyamino-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine named "bonnecor" (IIe·HCl) [4]. Its synthesis was carried out as follows.



3-Amino-5-acetyldibenzazepine III is saponified by heating with a propanolic solution of potassium hydroxide. The 3-aminodibenzazepine (IV) formed is converted by the action of ethyl formate into 3-carbethoxyaminodibenzazepine (V). Heating a toluene solution of V with chloroacetyl chloride in the absence of hydrogen chloride acceptor led to 3-carbethoxyamino-5-chloroacetyl-dibenzazepine (VI). The action of an excess of dimethylamine on the toluene solution of VI gave the base of bonnecor IIe, which after purification was converted into bonnecor by treatment with an isopropanolic solution of HCl.

Unlike phenothiazine cardiotropic agents Id and Ie, bonnecor is stable to the action of light and is not oxidized in air. Moreover, the presence in it of an α-dimethylaminoacetyl group instead of the β-aminopropionyl group, eliminates the possibility of β-elimination reactions occurring readily both with respect to the compound itself during the preparation of medicinal forms, as well as with the intermediate β-chloropropionyl compound in the synthesis process.

The pharmacological examination of bonnecor on animals and humans showed that its metabolism proceeds mainly according to a stepwise demethylation of the dimethylamino group and saponification of the urethane group. The metabolites are pharmacologically active and, because of their long half-dissociation period, prolong the action of bonnecor. To identify the metabolites, a countersynthesis was carried out. Saponification of bonnecor with an aqueous-alcoholic solution of an alkali gave 3-amino-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]-azepine (VII). Other metabolites were synthesized from the 5-chloroacetyl derivative VI, which was converted with an excess of methylamine into a monodemethylation product of bonnecor (VIII), and which was further saponified into 3-amino-5-N-methylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (IX). Ammonolysis of the 5-chloroacetyl derivative VI leads to a product which is a completely demethylated bonnecor (X).

Bonnecor was subjected to an extensive clinical investigation in 10 clinics of the USSR and GDR and showed high effectiveness in the treatment of various forms of arrhythmia; the preparation also exhibits an antifibrillatory action. Bonnecor was authorized for use in cardiology in the USSR and GDR; it is produced in the form of tablets and in an ampule form.

EXPERIMENTAL

The data of the elemental analysis of the compounds correspond to the calculated values.

3-Amino-10,11-dihydro-5H-dibenz[b,f]azepine (IV). A mixture of 252 g (1 mole) of 3-amino-5-acetyl-10,11-dihydro-5H-dibenz[b,f]azepine (III), 167 g (3 moles) of ground potassium hydroxide and 1000 ml of n-propanol was heated for 5 h with boiling on an oil bath. After a slight foaming, the reagents were gradually dissolved and crystals of potassium acetate precipitated on the walls of the flask. A still hot reaction mixture was poured with stirring into 2-3 liters of water, whereby the saponification product formed separated in the form of an oil, which crystallized after overnight standing in a refrigerator. The crystals were fil-

tered off, washed with water from the alkali and dried in air, and then at 60-70°C. Yield, 206.4 g of IV (98% of theoretical), mp 98-102°C (a Koffler block), $C_{14}H_{14}N_2$.

3-Carbethoxyamino-10,11-dihydro-5H-dibenz[b,f]azepine (V). A 120 g portion (1.1 mole) of ethyl chloroformate was added slowly over a period of 40 min with cooling on a water bath to a mixture of 210 g (1 mmole) of IV, 200 ml of a 20% solution of potassium hydroxide (1 mole) and 625 ml of acetone. The reaction mixture was heated for 1 h with slight boiling, and then was cooled and poured with stirring into 2.5 liters of water. On the next day, the precipitate was filtered, washed with water from the alkali, and after drying (first in air and then at 80-90°C), 280 g of a crude product was obtained, mp 118-122°C. After recrystallization from 1 liter of toluene with the addition of carbon, the yield of V was 253 g (91% of theoretical), mp 123-124°C. $C_{17}H_{18}N_2O_2$.

3-Carbethoxyamino-5-chloroacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (VI). A 125 g portion (1.1 mole) of chloroacetyl chloride was added with stirring over a period of 1 h, to a hot solution of 282 g (1 mole) of V in 1700 ml of toluene, and then the reaction mixture was heated for 2 h under reflux (temperature of the oil bath 130-140°C). The abundant evolution of hydrogen chloride which took place at the beginning thereby almost ceased. The mixture was cooled slightly, 15 g of active carbon was added, and the mixture was heated again with stirring for 30 min. The solution was filtered while hot and it crystallized on stirring. The precipitate was filtered and washed with a small amount of toluene. Yield 349 g of VI (97% of theoretical), mp 172-174°C. $C_{19}H_{19}N_2O_3Cl$.

3-Carbethoxyamino-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (IIe-base). A 530 g portion (about 4.1 moles) of a 35% aqueous solution of dimethylamine was added dropwise rapidly with stirring to a mixture of 358 g (1 mmole) of VI and 1700 ml of toluene, and the mixture was heated on a boiling water bath for 1.5 h. After cooling, the toluene layer was separated and washed with water in a separatory funnel to remove excess dimethylamine. After being freed from the unreacted starting material, the base obtained was extracted from the toluene layer by shaking it with 1500 ml, and then with 150 ml of 2 N HCl. A 700 ml portion of butyl acetate was added to the hydrochloric acid solution, and the mixture was made alkaline with a 20% solution of NaOH. On cooling crystals separated out, which were filtered off, washed with alkali and dried, first in air and then at 90°C. The yield of the crude base IIe was 346 g, mp 132-135°C. After recrystallization from 1000 ml of isopropanol, 279.3 g of IIe-base was obtained (76% of theoretical), mp 135-137°C. M^+ 367, $C_{21}H_{25}N_3O_3$ M 367.4.

3-Carbethoxyamino-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride (bonnecor, IIe·HCl). A 367 g portion (1 mole) of IIe base was dissolved with heating to 60-70°C in 5500 ml of butyl acetate and 160 ml of an isopropanolic solution of HCl (HCl content 23.4%) was added dropwise to the filtered solution over a period of 15-20 min with stirring and cooling. To complete the crystallization, the stirring was continued for two more hours, the precipitate was filtered and dried, and then, to remove the water of hydration, it was boiled for 30 min with 2000 ml of acetone, the crystals were filtered without cooling, washed with a small amount of acetone and dried. Yield 367 g of IIe·HCl, (91% of theoretical mp 226-228°C. $C_{21}H_{25}N_3O_3 \cdot HCl$. UV spectrum: λ_{shelf}, nm (log ε) in C_2H_5OH 235 (41.00). IR spectrum, KBr, ν_{max}, cm^{-1}: 1720 and 1220 ($\nu_{C=O}$ and ν_{C-O} of the urethane group), 1680 ($\nu_{C=O}$ of the acetate group), 1620, 1590 (ν of the aromatic system).

Bonnecor is a colorless or slightly yellowish fine-crystalline powder. It is soluble in water and in chloroform, and moderately soluble in alcohol. It is stable on storage under normal conditions.

3-Amino-5-N-methylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (IX). A 3.5 g portion (0.01 mole) of base VIII was dissolved with heating and stirring in 40 ml of ethanol, a solution of 1.6 g (0.04 mole) of NaOH in 8 ml of water and 8 ml of ethanol was added and the mixture was heated for 4 h with boiling under reflux. The precipitate of sodium carbonate that separated out was filtered and the solution was poured into 200 ml of water. The mixture was acidified with 2 N HCl to pH 8, and after distilling 50 ml of water and alcohol in vacuo, it was filtered, and an ammonia solution was added to the filtrate, until a distinctly alkaline reaction was obtained. The oil that separated out was extracted with 45 ml of chloroform, the chloroform layer was separated and evaporated to dryness. Base IX remained in the form of a viscous oil (2.7 g). To separate the impurities, the oil was dissolved in 20 ml of 1 N HCl, the solution was filtered, and the filtrate was again made alkaline by adding ammonia. The oily base that separated out was extracted with 30 ml of chloroform. The organic layer was dried

over Na_2SO_4 and the solvent was evaporated again to dryness. The residue was dissolved with heating in 30 ml of toluene and the solution was allowed to stand in a refrigerator until it crystallized. The crystals that separated out were filtered off, washed with toluene and dried. Yield, 2.1 g (74.7% of theoretical), mp 160.5-162°C. $C_{17}H_{19}N_3O$.

3-Carbethoxy-5-aminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (X). A mixture of 17.6 g (0.05 mole) of VI and a solution of 17 g (1 mole) of ammonia in 500 ml of alcohol was heated in a closed steel container with periodic shaking for 3 h at the bath temperature of 55-60°C and then for 4 h at 140-150°C. After cooling the reaction mixture, the solution was evaporated, and the residue was dissolved in 1.2 liter of 5% HCl. The acid solution was clarified by carbon, and the base was separated by adding a dilute solution of sodium hydroxide. Yield, 11.2 g (68%) of X, mp 158-159°C (from toluene). $C_{29}H_{21}N_3O$.

Hydrochloride, mp 242-244°C (from ethanol). $C_{19}H_{21}N_3O \cdot HCl$.

3-Amino-5-dimethylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (VII). A mixture of 16.1 g (0.04 mole) of bonnecor, 40 ml of a 4 N aqueous solution of NaOH and 140 ml of ethanol was heated at the boiling point and stirred for 2 h. After cooling the reaction mixture, a precipitate of inorganic salts was filtered off, and washed with alcohol. The alcoholic filtrate was evaporated, the residue was dissolved in 50 ml of toluene, and filtered with charcoal. After cooling, the precipitate of the base separated out, yield, 10 g (85%) of VII, mp 126-128°C (from toluene). $C_{18}H_{21}N_3O$.

Dihydrochloride. The base obtained was dissolved in 50 ml of chloroform, and an ether solution of hydrogen chloride was added with stirring, the precipitate was filtered off, and washed with acetone. Yield 10.2 g (85% of theoretical), mp 220°C (dec., from isopropanol). $C_{18}H_{21}N_3O \cdot 2HCl \cdot 1.5H_2O$.

3-Carbethoxyamino-5N-methylaminoacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (VIII). A 70 g portion of a 38% aqueous solution of methylamine (0.85 mole) was added with stirring at room temperature to a suspension of 10.8 g (0.003 mole) of VI in 150 ml of ethanol. The reaction mixture was heated over a period of 30 min to 50°C, and stirred at this temperature for 5 h and for 1 h at 60°C. It was then cooled to 30°C, 190 ml of water was added, and the mixture was stirred with water cooling for 3 h. The precipitate that separated out was filtered, washed with water from the amine, and dried. Yield, 9.8 g of VIII (83% of theoretical), mp 167-168°C (from acetone). $C_{20}H_{23}N_3O_3$.

Hydrochloride. An isopropanol solution of HCl was added to the solution of the base in acetone. The precipitate that separated out was filtered off, and recrystallized from methanol, mp 265-270°C. $C_{20}H_{23}N_3 \cdot HCl$.

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