BIS(β-CHLOROETHYL)AMINES OF DOUBLE-RING COMPOUNDS

IX.* SYNTHESIS OF 2,4-DIMETHYL-7-N-BIS(β-CHLOROETHYL)-AMINOMETHYL-1,5-BENZODIAZEPINE

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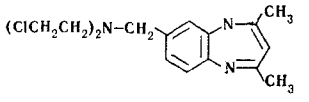
3-Nitro-4-acetamidobenzyl bromide, from which 2,4-dimethyl-7-N-bis(β-chloroethyl)aminomethyl-1,5-benzodiazepine was synthesized, was obtained by the bromination of 3-nitro-4-acetamidotoluene.

In a continuation of our study [1] to seek biologically active substances we undertook the synthesis of 2,4-dimethyl-7-N-bis(β-chloroethyl)aminomethyl-1,5-benzodiazepine (I). The starting material in the synthesis of I was 3-nitro-4-acetamidotoluene (II), the bromination of which yielded 3-nitro-4-acetamidobenzyl bromide (III) [2]. This reaction proceeds unambiguously without the formation of isomeric substances. The structure of III was confirmed by preparation from it of 3-nitro-4-acetamidobenzyl thiocyanate (IV) and N-(3-nitro-4-aminobenzyl)-N-bis(β-chloroethyl)amine (VII) as well as by IR and PMR spectral data. The IR spectrum of III contains the absorption bands of CO groups and amide NH groups, while the PMR spectrum contains signals from the protons of CH_2 groups and CH_3 groups, which is in agreement with structure III.



I

N-(3-Nitro-4-acetamidobenzyl)-N-bis(β-hydroxyethyl)amine (V), which was converted to N-(3-nitro-4-acetamidobenzyl)-N-bis(β-chloroethyl)amine (VI) by treatment with thionyl chloride, was isolated from the reaction of III with diethanolamine. Refluxing of VI with hydrochloric acid yielded VII, the structure of which was confirmed by the absence in its IR spectrum of an absorption for a CO group and by the presence of primary amino group bands.

An attempt was made to obtain VI from N-(4-aminobenzyl)-N-bis(β-hydroxyethyl)amine (VIII) [3]. Compound IX, which was converted to N-(4-acetamidobenzyl)-N-bis(β-chloroethyl)amine (X) by treatment with thionyl chloride, was prepared by acetylation of VIII. However, VI could not be obtained by nitration of X with nitric acid in acetic acid under various conditions.

Catalytic reduction of the nitro group in VII yielded N-(3,4-diaminobenzyl)-N-bis(β-chloroethyl)-amine (XI), which was condensed with acetylacetone without isolation. The reaction product obtained is, according to elementary analysis and determination of the moisture content by the Fischer electrometric titration method, the hydrochloride of I, which, depending on the drying time, contains different amounts of water of crystallization. The benzodiazepine structure of I was confirmed by the presence of an absorption maximum at 510 nm in its UV spectrum, which is characteristic for 1,5-benzodiazepine derivatives, and also by the violet-purple coloration peculiar to the 1,5-benzodiazepinium cation. In analogy with [1], one

*See [1] for communication VIII.

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cannot exclude the presence in I of the corresponding monoanil, which is not contradicted by the IR spectral data and the presence of moisture (according to Fischer) in the hydrochloride of I dried to constant weight.

Compound I is quite labile. On standing in a physiological solution it apparently isomerized to benzimidazole, as indicated by the decrease in the intensity of the absorption maximum at 510 nm.

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EXPERIMENTAL

The PMR spectra of carbon tetrachloride solutions were obtained with a JNM-4H-100 (100 MHz) spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions were obtained with a UR-10 spectrophotometer. The UV spectra in alcohol or in a phyiological solution were obtained with an EPS-3 recording spectrophotometer.

3-Nitro-4-acetamidobenzyl Bromide (III). A. An iodine crystal was added to 10 g (0.051 mole) of II in 350 ml of dry carbon tetrachloride. A solution of 2.5 ml (7.85 g) of bromine in 40 ml of carbon tetrachloride was slowly added at the boiling point of the mixture in the course of 3.5-4 h with stirring and illumination with UV light. The mixture was then refluxed until hydrogen bromide evolution ceased (2.5-3 h). The mixture was then cooled, and the excess bromine and solvent were removed in vacuo. The residue was repeatedly refluxed with petroleum ether (bp 40°) to extract unchanged II and thereby obtain 9.5 g (68%) of yellow crystals of III with mp 98-101° (benzene). The product was soluble in alcohol and ether and insoluble in petroleum ether. Found %: C 39.90; H 3.45; Br 29.21; N 10.03. $C_9H_9BrN_2O_3$. Calculated %: C 39.56; H 3.3; Br 29.26; N 10.25. IR spectrum (in mineral oil): 1710 and 3380 cm^{-1} (CO and NH in the $NHCOCH_3$ group).

B. N-Bromosuccinimide [5.7 g (0.0032 mole)] and 0.01 g of freshly purified benzoyl peroxide were added to 6 g (0.031 mole) of II in 200 ml of dry carbon tetrachloride, and the mixture was heated at 80-85° for 18 h. It was then filtered, the solvent was removed in vacuo, and the residue was treated as in method A to give 6.7 g (80%) of a product with mp 94-95°, which was identical to the I obtained by method A.

3-Nitro-4-acetamidobenzyl Thiocyanate (IV). A solution of 0.6 g (0.009 mole) of ammonium thiocyanate in 40 ml of glacial acetic acid was added to 2 g (0.0073 mole) of III in 100 ml of glacial acetic acid, and the mixture was stirred at room temperature for 2 h and allowed to stand for 12-15 h. The ammonium bromide precipitate was filtered, and the mother liquor was made alkaline with 10% sodium carbonate to give 1.6 g (87%) of a yellow, crystalline product with mp 134-135° (from benzene). The product was insoluble in water. Found %: C 47.52; H 3.59; N 16.61; S 12.69. $C_{10}H_9O_3S_3$. Calculated %: C 47.80; H 3.58; N 16.73; S 12.75. A viscous, dark-red substance which could not be crystallized from the usual organic solvents was obtained when IV was heated in concentrated hydrochloric acid.

N-(3-Nitro-4-acetamidobenzyl)-N-bis(β-hydroxyethyl)amine (V). A solution of 7.72 g (0.028 mole) of III in 20 ml of benzene was added in the course of 3-3.5 h to 8 g (0.076 mole) of diethanolamine in 30 ml of dry benzene at 80°, and the mixture was stirred at the same temperature for 1.5-2 h and allowed to stand for 12-15 h. The benzene layer was separated, and the lower layer was repeatedly extracted with benzene. The benzene extracts were combined, and the benzene was vacuum evaporated to give 5.92 g (71%) of a product with mp 73-74° (alcohol). Found %: C 52.41; H 6.48; N 14.45. $C_{13}H_{19}N_3O_5$. Calculated %: C 52.52; H 6.40; N 14.14. IR spectrum (in mineral oil): 1700 and 3380 cm^{-1} (CO and NH in the $NHCOCH_3$ group).

N-(3-Nitro-4-acetamidobenzyl)-N-bis(β-chloroethyl)amine (VI). A solution of 3.5 ml (0.049 mole) of thionyl chloride in 30 ml of dry chloroform was added gradually at 0° to 5.9 g (0.02 mole) of V in 70 ml of dry chloroform, and the mixture was stirred without heating for 2 h and allowed to stand for 12-15 h. The solvent was removed by decantation to give an oily residue which crystallized on trituration with ether to give 6.45 g (87.7%) of the hydrochloride of VI with mp 155-156°. Found %: C 41.51; H 4.94; Cl 29.0; N 11.24. $C_{13}H_{17}Cl_2N_3O_3 \cdot HCl$. Calculated %: C 42.10; H 4.86; Cl 28.79; N 11.33.

A solution of 6.45 g of the hydrochloride of VI in 100 ml of water was made alkaline with sodium bicarbonate and extracted with ether. The ether extract was dried with sodium sulfate, the ether was removed, and the residue was recrystallized from hexane–ethyl acetate to give 5.76 g (87%) of VI with mp 94-95°. Found %: C 46.96; H 5.05; Cl 21.15; N 12.54. $C_{13}H_{17}Cl_2N_3O_3$. Calculated %: C 46.7; H 5.05; Cl 21.28; N 12.54. IR spectrum: 1700 and 3380 cm^{-1} (CO and NH in the $NHCOCH_3$ group).

N-(3-Nitro-4-aminobenzyl)-N-bis(β-chloroethyl)amine (VII). A mixture of 1.1 g (0.0033 mole) of VI in 10 ml of concentrated HCl was heated on a boiling-water bath for 30 min, cooled, neutralized with sodium bicarbonate, and extracted repeatedly with ether. The ether extracts were dried with sodium sulfate, and the ether was removed to give 0.53 g (55.3%) of an oily substance which crystallized on trituration with petroleum ether to give a product with mp 49° (alcohol). Found %: C 45.43; H 5.18; Cl 24.54; N 14.29. $C_{11}H_{15}Cl_2N_3O_3$. Calculated %: C 45.20; H 5.14; Cl 24.31; N 14.38. IR spectrum: 1645 cm^{-1} (δ_{NH_2}) and a group of bands at 3200-3360-3480 cm^{-1} (ν_{NH_2}).

Hydrogenation of VII. A mixture of 2 g (0.0068 mole) of VII and 30 ml of 18% hydrochloric acid was shaken in a hydrogen atmosphere in the presence of 0.2 g of reduced Pd/C (5%). After 3 h, 460 ml of hydrogen had been absorbed (this corresponds to a ratio of 1:3). The catalyst was removed by filtration, and the solution of XI was used in the reaction with acetylacetone.

Condensation of XI with Acetylacetone. A solution of 1 ml (0.01 mole) of acetylacetone in 5 ml of alcohol was added to 1.79 g (0.0068 mole) of XI in 30 ml of 18% hydrochloric acid, and the mixture was then allowed to stand at room temperature for 20-25 min, shaken with ether to extract the unchanged acetylacetone, and made alkaline with 10% sodium bicarbonate with the simultaneous addition of ether to extract I. The ether extract was dried with sodium sulfate, and the ether was removed. The residue was dissolved in the minimum amount of alcohol and acidified with an ether solution of hydrogen chloride. A. The dihydrochloride of I with mp 62-66° (decomp.) was obtained on addition of ether to the point of complete precipitation. Found %: C 45.11; H 6.04; Cl 33.14; N 10.07; H_2O 6.76 (Fischer). $C_{16}H_{20}Cl_2N_3 \cdot 2HCl \cdot 1.6H_2O$. Calculated %: C 45.0; H 5.90; Cl 33.2; N 9.85.

B. A dihydrochloride of I with mp 147-149° (decomp.) was obtained on addition of ether until the major amount of product precipitated. Found %: C 46.28; H 6.17; Cl 34.43; N 9.60; H_2O 3.8. $C_{16}H_{20}Cl_2N_3 \cdot 2HCl \cdot 0.876H_2O$. Calculated %: C 46.3; H 5.75; Cl 34.25; N 10.10. A dihydrochloride of I with mp 150-152° (decomp.) was obtained after drying over P_2O_5 for 4 days. Found %: C 46.4; H 5.78; Cl 34.48; N 10.52; H_2O 2.5. $C_{16}H_{20}Cl_2N_3 \cdot 2HCl \cdot 0.577H_2O$. Calculated %: C 46.9; H 5.76; Cl 34.8; N 10.23. A dihydrochloride of I with mp 154-155° (decomp.) was obtained after drying over P_2O_5 for 15 days (to constant weight). Found %: C 48.0; H 5.9; Cl 34.46; N 10.4; H_2O 1.4. $C_{16}H_{20}Cl_2N_3 \cdot 2HCl \cdot 0.323H_2O$. Calculated %: C 47.7; H 5.65; Cl 35.2; N 10.4. IR spectrum: 1600, 1650, 1745, 2200-2600, and 3200-3400 cm^{-1} (δ_{NH_2}, C=C, C=N, CO, H_2O, N^+, ν_{NH_2}, ν_{NH}). UV spectrum (in alcohol): λ max 510 nm, log ε 2.813.

N-(4-Acetamidobenzyl)-N-bis(β-hydroxyethyl)amine (IX). Acetic anhydride [0.5 ml (0.005 mole)] was added to 1 g (0.005 mole) of VIII [3] in 3 ml of dry pyridine, the mixture was allowed to stand for 24 h, and the pyridine was removed in vacuo. The residue was an oily substance which began to solidify on successive trituration with petroleum ether, ether, and alcohol to give 0.8 g (66.5%) of IX with mp 121-123° (alcohol). Found %: C 61.96; H 8.00; N 10.84. $C_{13}H_{20}N_2O_3$. Calculated %: C 62.00; H 7.93; N 11.21. IR spectrum: 1655 cm^{-1} (CO in the $NHCOCH_3$ group) and a group of bands at 3070-3260 cm^{-1} (NH and OH groups).

N-(4-Acetamidobenzyl)-N-bis(β-chloroethyl)amine (X). Thionyl chloride [5.4 g (0.045 mole)] was added gradually at 80° to 1.9 g (0.0075 mole) of IX in 150 ml of dry dichloroethane, and the mixture was stirred and refluxed for 1 h. The excess thionyl chloride and solvent were removed in vacuo, and the residue was dissolved in the minimum amount of water. The aqueous solution was filtered, neutralized with sodium bicarbonate, and extracted with ether to give 8.95 g (41%) of X with mp 92-94° (petroleum ether). Found %: C 53.72; H 6.09; Cl 24.54; N 9.59. $C_{13}H_{18}Cl_2N_2O$. Calculated %: C 54.00; H 6.23; Cl 24.60; N 9.68. IR spectrum: 1700 and 3430 cm^{-1} (CO and NH in the $NHCOCH_3$ group).

Hydrochloride of X. This melted at 167-169.5° (benzene–alcohol). Found %: Cl 32.29; N 8.90. $C_{13}H_{18}Cl_2N_2O \cdot HCl$. Calculated %: Cl 32.70; N 8.61. IR spectrum: 1700, 3120-3250 cm^{-1} (CO and NH in the $NHCOCH_3$ group), 2480-2680 cm^{-1} (N^+).

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