SYNTHESIS AND CONVERSIONS OF PIPERAZINE-2-CARBOXYLIC ACID

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A method has been developed for the synthesis of methyl piperazinium-2-carboxylate dihydrochloride (overall yield 46%) and piperazinium-2-carboxylic acid dihydrochloride (overall yield 36%), from ethylene diamine through N,N'-di(trifluoroacetyl)ethylenediamine and methyl N,N'-di(trifluoroacetyl)piperazine-2-carboxylate. The N,N'-dinitroso derivatives were synthesized.

Piperazine-2-carboxylic acid, (I), like other 1-azacycloalkanecarboxylic acids, is of considerable interest for the synthesis of biologically active compounds [1].

The synthesis of I from N,N'-ditosyl- [2], dibenzyl- [3], or di(benzenesulfo)- [4] ethylenediamines and α,β-dibromopropionic esters through the N,N'-disubstituted piperazine-2-carboxylic esters followed by removal of the N,N'-protecting groups and hydrolysis of the ester groups has been described. A great deal of difficulty was encountered in the removal of the tosyl or benzenesulfo groups from the piperazine nitrogen. Even prolonged heating in sealed tubes with concentrated hydrochloric acid, or boiling with fortified hydrobromic acid or its mixture with acetic acid did not complete the reaction, and the overall yield of I, calculated on N,N'-disubstituted ethylenediamine, was about 20% [3]. Similar results were obtained in our tests with methyl N,N'-ditosyl- (IIIa) and N,N'-di(benzylsulfo)- (IIIb) piperazine-2-carboxylates with either acid (conc. HCl or HBr) or alkaline (NaOH) hydrolysis or treatment of IIIb with Raney nickel in dimethylformamide in the presence of sodium hydroxide, or in treatment of IIIa with excess lithium aluminum hydride (18 h in boiling tetrahydrofurane). In the latter two tests, mainly only one of the N-protective groups is split off, and the mono-N-substituted piperazine derivative (IV, V) is formed (we have not firmly established the positions of the H atoma and the SO_2R group). The ester group is completely reduced to hydroxymethyl by lithium aluminum hydride.

These results forced us to give up the aryl- and aralkylsulfo - protective groups, and to use in the synthesis of piperazine-2-carboxylic acid I the more easily removable trifluoroacetyl group that is so widely used in peptide synthesis.

Treatment of ethylenediamine with an excess of trifluoroacetic anhydride gave the hitherto undescribed N,N'-di(trifluoroacetyl)ethylenediamine (VII) in 91% yield. The general procedure of Weigand and Geiger [5] for trifluoroacetylation of amines by reacting them with trifluoroacetic anhydride in trifluoroacetic acid was not well suited for the synthesis of VII; ethylenediamine gave a mixture of VII with mono-N-(trifluoroacetyl)ethylenediamine trifluoroacetate.

The reaction of VII with methyl α-β-dibromopropionate (VI) was carried out under various conditions: in the presence of sodium hydroxide, potassium hydroxide, and sodium hydride at various proportions, in various solvents, and at various temperatures and reaction times. The best results were obtained with sodium hydride in dimethylformamide at 1:1:2 molar proportions of VII:VI:NaH (3 h at room temperature). When sodium hydroxide was used instead, or when the amount of hydride was increased 1.5 times and the temperature was raised to 70°, the yield of VIII decreased from 59 to 13-15%.

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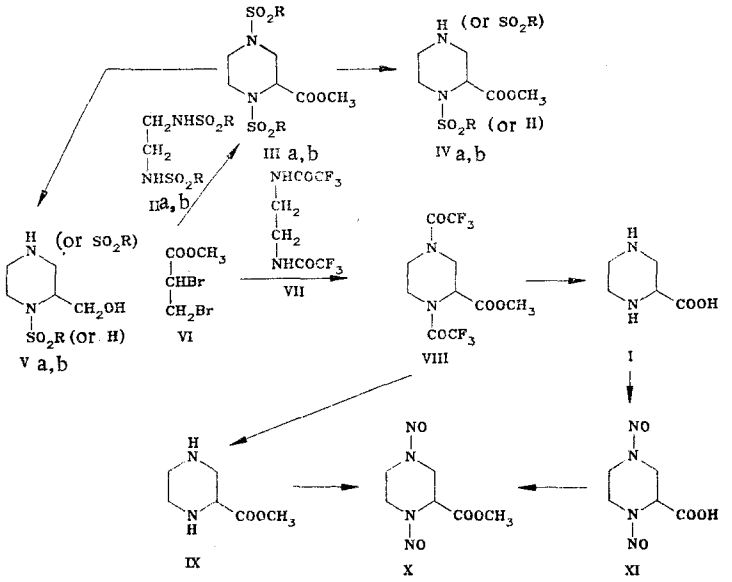

II—V a R = $-C_6H_4-CH_3$-*p*; b R = $-CH_2C_6H_5$

Removal of the trifluoroacetyl protective groups with simultaneous hydrolysis of the ester went quite smoothly by boiling VIII for 1.5 h with concentrated hydrochloric acid. It is more expedient not to subject VIII to additional purification, but to hydrolyze the technical porduct. Piperazine-2-carboxylic acid I separates as the dihydrochloride in 36% overall yield, based on the amount of N,N'-di(trifluoroacetyl)ethylenediamine VII that reacted. When VIII is treated with a boiling methanol solution of hydrogen chloride, only the two N,N'trifluoroacetyl groups are removed, and the dihydrochloride of methyl piperazine-2-carboxylate (IX) forms in 86% yield.

The corresponding N,N'-dinitroso derivative of IX (X) was synthesized by treating IX in aqueous medium with sodium nitrite. It was also obtained by a counter synthesis from I, via the N,N'-dinitroso derivative XI and esterification with diazomethane.

EXPERIMENTAL

Mass spectra were obtained on a Varian MAT-112 chromatomass spectrometer, electron ionization energy 70 eV, with direct introduction of sample into the source. Sample VIII was also studied by introduction into the mass spectrometer through a Varian 1440 chromatograph: column 3% E-30 on Chromosorb W 80/100, *l* 2m, d 1 mm, He rate 20 ml/min, t_{evap} 250°, t_{col} 140-250°, v = 20°/min, t_{sep} 260°.

N,N'-Di(benzylsulfo)ethylenediamine (IIb). To a mixture of 5.3 g (88.3 mmole) of ethylenediamine and 70 ml of 10% sodium hydroxide solution was added 35 g (183 mmole) of benzylsulfonyl chloride in 100 ml of dioxane dropwise with stirring so that the temperature of the reaction mixture did not exceed 15°. After the mixture was kept overnight, the precipitated crystals were filtered off and washed with water (3 × 50 ml). There was obtained 20 g (62%) of IIb as white crystals, mp 207-208° (from acetonitrile). The material was poorly soluble in the usual organic solvents and in water. Found: C 52.4; H 5.3; N 7.9; S 17.2%. $C_{16}H_{20}N_2O_4S_2$. Calculated: C 52.2; H 5.5; N 7.6; S 17.4%.

Methyl-N,N-'di(benzylsulfo)piperazine-2-carboxylate (IIIb). To a mixture of 13.68 g (37.1 mmole) of N,N'-di(benzylsulfo)ethylenediamine IIb, 4.2 g (100 mmole) of crushed sodium hydroxide, and 50 ml of dry dimethylformamide was added 5 ml of methyl α,β-dibromopropionate VI in 10 ml of dry dimethylformamide dropwise over 0.5 h. The mixture was heated for 3 h at 80°, cooled, and diluted with 200 ml of chloroform. The precipitate of sodium bromide was filtered off and washed with chloroform. The combined filtrate and washings were evaporated, and the residue was placed in a chromatographic column of 150 g of silica gel and eluted with 700 ml of chloroform. Evaporation of the chloroform solution gave 5 g (30%) of white crystals of IIIb, mp 168-169° (from methanol). The material had good solubility in DMFA, poor in alcohols, chloroform; insoluble in ether, benzene, water. Mass spectrum, m/z (%): 452 (<1) M^+, 393 (6) $[M - COOCH_3]^+$, 329 (26) $[M - COOCH_3 - SO_2]^+$, 297 (28) $[M - SO_2CH_2C_6H_5]^+$, 266 (4) $[M - SO_2CH_2C_6H_5 - OCH_3]^+$, 233 (31) $[M - SO_2CH_2C_6H_5 - SO_2]^+$, 174 (14) $[M - SO_2CH_2C_6H_5 - COOCH_3 - SO_2]^+$, 91 (100) $[CH_2C_6H_5]^+$. Found: C 53.2; H 5.4; N 6.3; S 13.9%. $C_{20}H_{24}N_2O_6S_2$. Calculated: C 53.1; H 5.4; N 6.2; S 14.2%.

N,N'-Di(trifluoroacetyl)ethylenediamine (VII). To 168 g (800 mmole) of trifluoroacetic anhydride cooled to -5° was added 19.2 g (319 mmole) of ethylenediamine dropwise slowly so that the temperature of the mixture did not rise above 5°. Toward the end of the addition the reaction mass thickened and became hard to stir; 150 ml of benzene was added and stirring was continued for 1.5 h at not more than 5°. Then the mixture was left at the same temperature for 12 h without stirring. The mixture was then evaporated to dryness and the residue was washed with benzene. There was obtained 72 g (91%) of diamide VII, mp 202-203°, which could be used in the next synthesis without purification. Recrystallization from isopropyl alcohol gave VII as colorless crystals, mp 203-204°; good solubility in acetone, methanol, ethanol, ethyl acetate, insoluble in ether, chloroform, benzene, water. Found: C 28.6; H 3.0; N 11.1%. $C_6H_6F_6N_2O_2$. Calculated: C 28.6; H 2.4; N 11.1%.

Methyl N,N'-di(trifluoroacetyl)piperazine-2-carboxylate (VIII). To a solution of 20 g (79.3 mmole) of VII in 120 ml of dry dimethylformamide was added 4.7 g (196 mmole) of sodium hydride in small protions. The mixture was cooled to 5° and 22.7 g (89.4 mmole) of VI was added dropwise over 40 min, then the mixture was stirred 3 h at room temperature and diluted with 300 ml of benzene. The sodium bromide precipitate was filtered off and washed with benzene. The combined filtrate and washing were evaporated, the remaining dimethylformamide was distilled off at 1-2 mm Hg, and 200 ml of benzene was added. The precipitate was filtered off and washed with benzene (3 × 50 ml). There was obtained 9 g of VII. The benzene solution containing VIII was evaporated; the residue (22.4 g) was dissolved in 50 ml of benzene and passed through 200 g of silica gel, and the silica gel was washed with 2000 ml of benzene. The combined benzene solutions were evaporated and the residue was triturated with heptane. There was obtained 7.6 g of VIII (59% based on diamide VII taken and 29% based on reacted), as white crystals, mp 41-43° (bp 122-125° at 2-3 mm Hg). The material had good solubility in most of the usual organic solvents, poorer in heptane and hexane, and insoluble in water. Mass spectrum, m/z (%): 336 (12) M^+, 304 (2) $[M - CH_3OH]^+$, 277 (100) $[M - COOCH_3]^+$, 239 (10) $[M - COCF_3]^+$, 180 (39) $[M - COCF_3 - COOCH_3]^+$, 152 (25) $[M - COCF_3 - COOCH_3 - CH_2N]^+$, 142 (8) $[M - 2COCF_3]^+$, 139 (11) $[M - COCF_3 - COOCH_3 - C_2H_3N]^+$, 83 (9) $[M - 2\ COCF_3 - COOCH_3]^+$, 69 (36) $COCF_3^+$, 56 (48) $C_3H_6^+$, 55 (20) $C_3H_5N^+$. Found: C 36.1; H 3.1; N 8.3%. $C_{10}H_{10}F_6N_2O_4$. Calculated: C 35.7; H 3.0; N 8.3%.

Piperazine-2-carboxylic Acid (I) Dihydrochloride. A. A solution of 5.45 g (16.2 mmole) of VIII in 40 ml of conc. hydrochloric acid was boiled 1.5 h. After cooling the precipitate was filtered off and washed with isopropyl alcohol. There was obtained 2.8 g (85%) of I dihydrochloride as colorless crystals, mp 264-265° (decomposes, from 90% isopropyl alcohol), good solubility in water, poor in alcohols, insoluble in other usual organic solvents. Mass spectrum, m/z (%): 130 (15) M^+, 101 (8) $[M - NHCH_2]^+$, 88 (40) $[M - C_2H_4N]^+$, 85 (63) $[M - COOH]^+$, 57 (52) $C_3H_7N^+$, 56 (77) $C_3H_6N^+$, 44 (100) CO_2^+. Found: C 29.2; H 6.1; N 14.0% $C_5H_{10}N_2O_2 \cdot 2HCl$. Calculated: C 29.6; H 6.0; N 14.0%.

B. A mixture of technical VIII, 22.4 g, obtained as described above from 20 g (79.3 mmole) of VII and 22 g (89.4 mmole) of methyl α,β-dibromopropionate and 50 ml of conc. HCL was boiled for 1.5 h. After cooling the precipitate was filtered off and washed with isopropyl alcohol. There was obtained 5.83 g (36% based on reacted VIII) of I, identical with that obtained by method A.

N,N'-Dinitrosopiperazine-2-carboxylic Acid (XI). To a solution of I dihydrochloride in 30 ml of water was added a solution of 2.3 g (33 mmoles) of sodium nitrite in 10 ml of water, dropwise at 20°. The mixture was heated for 1.5 h at 40-50°, then left at 20° for 12 h. The solution was evaporated to dryness in vacuum, the residual water was removed by azeotropic distillation with benzene, then in a vacuum desiccator over calcium chloride. The material was extracted with dry ether in an extractor. The ether was evaporated to give 1.9 g (69%) of light yellow crystals of XI, mp 121° (decomposes, from ether). The material has good solubility in alcohols, water, ethyl acetate, acetone; poor solubility in ether, is insoluble in benzene. R_f 0.66 (on Silufol UV-254, methanol mobile phase); under the same conditions R_f for I is zero. Mass spectrum, m/z (%): 188 (<1) M^+, 158 (8) $[M - NO]^+$, 128 (21) $[M - 2NO]^+$, 84 (11) $[M - 2NO - CO]_2^+$, 83 (47) $[M - 2NO - COOH]^+$, 56 (53) $C_3H_6N^+$, 42 (100) $C_2H_4N^+$. Found: C 32.0; H 4.5; N 30.1%. $C_5H_8N_4O_4$. Calculated: C 31.9; H 4.3; N 29.8%.

Methyl Piperazine-2-carboxylate (IX) Dihydrochloride. Compound VIII, 7.6 g (22.6 mmole) was boiled with 40 ml of methanolic hydrogen chloride for 1.5 h. The substance dissolved, and then a precipitate formed. After cooling the precipitate was filtered off and washed with dry acetone. There was obtained 4.2 g (86%) of colorless crystals of ester IX di-

hydrochloride, mp 226-228° (decomposes). The material has good solubility in water, poor solubility in alcohols, and is insoluble in the other common organic solvents. Mass spectrum, m/z (%): 144 (16) M^+, 115 (4) $[M - CH_2NH]^+$, 102 (6) $[M - C_2H_4N]^+$, 85 (100) $[M - COOCH_3]^+$, 56 (42) $C_3H_6N^+$, 42 (17) $C_2H_4N^+$. Found: C 32.9; H 6.9; Cl 32.7; N 12.6%. $C_6H_{12}N_2O_2 \cdot 2HCl$. Calculated: C 33.2; H 6.5; Cl 32.7; N 12.9%.

Methyl N,N'-dinitrosopiperazine-2-carboxylate (X). A. To a solution of 6.5 g (29.0 mmole) of methyl piperazine-2-carboxylate dihydrochloride (IX) in 110 ml of water was added a solution of 4.55 (66 mmole) sodium nitrite in 25 ml of water dropwise at 5° over 1.5 h; at the end of the reaction the pH of the solution varied from 1 to 4. The mixture was left at 20° for 12 h and extracted with ether (6 × 50 ml). The extract was dried with magnesium sulfate and passed through a silica gel column. There was obtained 4.8 g (79%) of light yellow crystals of X. The material has good solubility in water, alcohols, benzene, chloroform, and ether. Mass spectrum, m/z (%): 202 (5) M^+, 172 (97) $[M - NO]^+$, 171 (12) $[M - OCH_3]^+$, 143 (22) $[M - COOCH_3]^+$, 142 (69) $[M - 2NO]^+$, 113 (75) $[M - NO - COOCH_3]^+$, 83 (69) $[M - 2NO - COOCH_3]^+$, 56 (97) $C_3H_6N^+$, 42 (100) $C_2H_4N^+$. Found: C 35.7; H 5.1; N 27.5%. $C_6H_{10}N_4O_4$. Calculated: C 35.6; H 5.0; N 27.7%.

B. To 4.1 g (21.8 mmole) of XI was added 500 ml of dry ether, then with cooling to 5°, a solution of 2.8 g (66 mmole) of diazomethane in 200 ml of ether portionwise. During the reaction XI gradually dissolved. After 3 h the excess diazomethane was decomposed with five drops of acetic acid. The ether solution was washed with sodium bicarbonate, dried with magnesium sulfate, and evaporated. There was obtained 4.2 g (96%) of X, identical with the material synthesized according to A.

LITERATURE CITED

1. L. I. Mastafanova, K. F. Turchin, M. I. Evstratova, Yu. N. Sheinker, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 3, 367 (1985).
2. F. L. Bach, S. Kushner, and J. H. Williams, J. Am. Chem. Soc., 77, 6049 (1955).
3. E. Jucker and E. Rissi, Helv. Chim. Acta, 45, 2383 (1962).
4. Tsai Chun-Chao and Kao J-Sheng, Yao Hsueh Pao, 12, 11 (1965); Chem. Abstr., 63, 8361 (1966).
5. F. Weugand and R. Geiger, Chem. Ber., 89, 647 (1956).