3. V. G. Zubenko, Farm. Zh. (Kiev), No. 5, 11 (1971).
4. Yu. G. Basova, Master's Dissertation, Leningrad (1980).
5. R. Silverstein, G. Bassler, and T. Morril, Spectrometric Identification of Organic Compounds, Wiley (1974).
6. S. A. Shevelev, Usp. Khim., 39, 1773 (1970).
7. I. I. Chizhevskaya and N. M. Yatsevich, Vestsi Akad. Nauk BSSR, Ser. Khim. N., No. 1, 85 (1971).
8. S. Yu. Solov'eva-Yavits, S. M. Ramsh, and A. I. Ginak, Khim. Geterotsikl. Soedin., No. 4, 477 (1981).

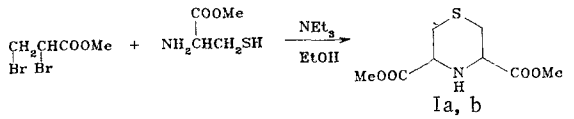
SYNTHESIS AND SEPARATION OF DIASTEREOMERS OF THIOMORPHOLINE-CARBOXYLIC ACID ESTERS

A. V. Eremeev, R. Nurdinov,
É. É. Liepin'sh, and F. D. Polyak

UDC 547.869.2

It is shown that the reaction of methyl 2,3-dibromopropionate with aminoethanethiol and L-cysteine methyl ester leads to the formation of esters of thiomorpholine-3-carboxylic and thiomorpholine-3,5-dicarboxylic acids; the latter ester was separated into individual diastereomers.

It has been previously shown that the reaction of methyl 2,3-dibromopropionate with methyl esters of natural amino acids, including S-substituted cysteine methyl ester, leads to the formation of aziridine-2-carboxylic acid derivatives [1]. In order to obtain aziridines that contain an SH group we attempted to study the reaction of methyl 2,3-dibromopropionate with L-cysteine methyl ester. As a result of the study we showed that the reaction leads to the formation of dimethylthiomorpholine-3,5-dicarboxylates rather than aziridine-2-carboxylic acid derivatives.

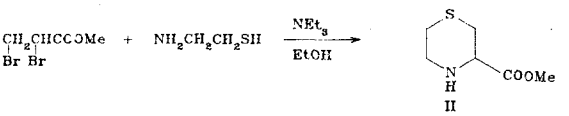


Ia, b

Analysis of the final products by high-performance liquid chromatography (HPLC) makes it possible to conclude that two compounds (in a ratio of 7:3), which were separated by preparative HPLC, are present in the product.

Data from the PMR and mass spectra prove unambiguously that these compounds are diastereomers that differ with respect to the configuration of the C_3 atom.

In order to confirm the general character of the reaction of 2,3-dibromopropionic acid with 2-mercapto-substituted amines we investigated the reaction with 2-mercaptoethylamine, in which the formation of methyl thiomorpholine-3-carboxylate (II) and the formation of methyl thiomorpholine-2-carboxylate are equally likely. The literature data, which are based only on the results of elementary analysis [2], do not make it possible to solve this problem unambiguously.



II

The product of the reaction of 2,3-dibromopropionic acid with 2-mercaptoethylamine was isolated by preparative gas–liquid chromatography (GLC). According to the PMR and mass-spectral data, the final product is methyl thiomorpholine-3-carboxylate.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1357-1358, October, 1983. Original article submitted January 3, 1983.

 0009-3122/83/1910-1080$07.50

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with Brucker WH-90 and WM-360 spectrometers (90 and 360 MHz) with hexamethyldisiloxane as the internal standard. The IR spectra of thin layers of the compounds were obtained with a UR-20 spectrometer. The mass spectra were recorded with an MS-50 AEI spectrometer. Preparative GLC was accomplished with a Pye-Unicam chromatograph with a flame-ionization detector; the column was packed with E-302 on Chromaton N-AW-HMDS as the stationary phase, the temperature was 180°C, and the carrier gas was helium. Preparative HPLC was accomplished with an EAK chromatograph (Special Design Office, Academy of Sciences of the Estonian SSR) with a CHROMPACK column (250 by 24.5) and a UV detector (254 nm) by elution with isopropyl alcohol–hexane (1:2).

Dimethyl Thiomorpholine-3,5-dicarboxylate (I). A 7-ml (0.05 mole) sample of triethylamine was added at 5°C to 12.3 g (0.05 mole) of methyl 2,3-dibromopropionate in 100 ml of absolute ethanol, and the mixture was maintained at the same temperature for 30 min. A solution of 8.6 g (0.05 mole) of L-cysteine methyl ester hydrochloride and 14 ml (0.1 mole) of triethylamine in 150 ml of absolute ethanol was added, and the mixture was heated at 70°C for 8 h. The solvent was evaporated, and the residue was washed with water and extracted with two 150-ml portions of ethyl acetate. The extract was passed through a column packed with silica gel (40 by 100 μm), the solvent was evaporated, and the residue was distilled *in vacuo* (10^{-3} mm) to give 5.2 g (48%) of ester I.

IR spectrum: 1732 (νCO) and 3238 cm^{-1} (νNH). Mass spectrum, m/z (relative intensities, %): 219 (7.8), 187 (2.1), 162 (5.2), 161 (7.4), 160 (100), 158 (2.0), 149 (1.5), 141 (3.5), 132 (11.0), 126 (2.3), 114 (6.5), 102 (4.2), 101 (4.5), 100 (79.9), 87 (9.6), 74 (10.3), 73 (4.6), 67 (7.5), 61 (2.9), 59 (7.3), 58 (3.3), 56 (4.2), 55 (11.5), 54 (17.6), 46 (56.1), 45 (13.1), 44 (3.9), 43 (5.1), 42 (4.9), 41 (5.8). Found: C 43.4; H 6.0; N 6.2%. $C_8H_{13}NO_4S$. Calculated: C 43.8; H 5.8; N 6.4%.

Isomers Ia, b were isolated after separation by preparative HPLC.

Ester Ia: $[\alpha]_D^{20} = -8.3°$ (c 1.0, methanol). PMR spectrum (90 MHz, $CDCl_3$): 2.50 (1H, broad s, NH), 2.60 (2H, dd, J = 10.6 and 13.4 Hz, 2- and 6-H_a), 2.79 (2H, dd, J = 2.4 and 13.4 Hz, 2- and 6-H_e), 3.70 (2H, dd, J = 2.4 and 10.6 Hz, 3- and 5-H), and 3.76 ppm (6H, s, CH_3).

Ester Ib: $[\alpha]_D^{20} = -70.2°$ (c 1.0. methanol). PMR spectrum (90 MHz, $CDCl_3$): 2.60 (1H, broad s, NH), 2.85 (2H, dd, J = 6.8 and 13.2 Hz, 2- and 6-H_a), 2.90 (2H, dd, J = 3.6 and 13.2 Hz, 2- and 6-H_e), 4.00 (2H, dd, J = 3.6 and 6.8 Hz, 3- and 5-H), 3.76 ppm (6H, s, CH_3).

Methyl Thiomorpholine-3-carboxylate (II). A 7-ml (0.05 mole) sample of triethylamine was added at 5°C to 12.3 g (0.05 mole) of methyl 2,3-dibromopropionate in 100 ml of absolute ethanol, and the mixture was maintained at the same temperature for 30 min. A mixture of 5.7 g (0.05 mole) of aminoethanethiol hydrochloride and 14 ml (0.1 mole) of triethylamine in 150 ml of absolute ethanol was added, and the mixture was treated as in the synthesis of I to give 3.85 g (48%) of ester II. An analytically pure sample was isolated by preparative GLC. IR spectrum: 1750 (νCO) and 3324 cm^{-1} (νNH). Mass spectrum, m/z (relative intensities, %): 161 (5.4), 117 (1.6), 104 (6.0), 103 (6.1), 102 (100), 100 (4.8), 87 (5.0), 75 (13.6), 56 (27.4), 55 (27.4), 46 (6.8), 45 (6.5), 44 (7.0), 43 (4.0), 42 (7.6), 41 (10.7). PMR spectrum (360 MHz, $CDCl_3$): 2.15 (1H, broad s, NH), 2.44 (1H, m, J = 1.3, 2.6, 4.8, and 13.3 Hz, 2-H_e), 2.67 (1H, m, J = 2.9, 9.8, and 13.3 Hz, 2-H_a), and 3.03 (1H, m, J = 2.6, 9.8, and 12.4 Hz, 3-H_a), 3.37 (1H, m, J = 2.9, 4.8, and 12.4 Hz, 3-H_e), 2.82 (1H, m, J = 1.3, 3.3, and 13.2 Hz, 6-H_e), 2.86 (1H, dd, J = 8.8 and 13.2 Hz, 6-H_a), 3.68 (1H, dd, J = 3.3 and 8.8 Hz, 5-H), and 3.74 ppm (3H, s, CH_3). Found: C 44.2; H 6.9; N 8.9%. $C_6H_{11}NO_2S$. Calculated: C 44.7; H 6.6; N 8.7%.

LITERATURE CITED

1. A. V. Eremeev, F. D. Polyak, A. F. Mishnev, Ya. Ya. Bleidelis, É. É. Liepin'sh, Sh. S. Nasibov, I. I. Chervin, and R. G. Kostyanovskii, Khim. Geterotsikl. Soedin., No. 11, 1495 (1982).
2. B. Belleau, J. Med. Pharm. Chem., 2, 553 (1960).