TETRAHYDROTHIAZINONES BASED ON AMINOTHIOLS AND α-CHLOROBUTYRIC ACID

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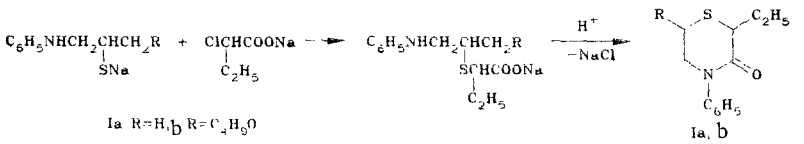
The reaction of aminothiols with α-chlorobutyric acid and its ethyl ester has been studied. It has been shown that the reaction of aminothiols with α-chlorobutyric acid results in the formation of thiazin-3-ones. Ethyl α-chlorobutyrate reacts with aminothiols under similar conditions to form the corresponding aminothioethers.

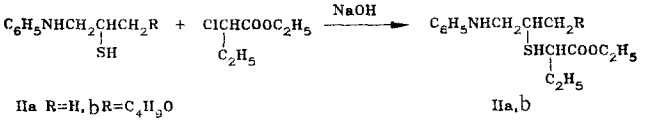
We previously [1, 2] reported the synthesis of derivatives of tetrahydro-1,4-thiazin-3-ones by reacting the corresponding aminothiols with monochloroacetic acid. Continuing the investigations in this area, we studied the reactions of aminothiols with α-chlorobutyric acid and its ethyl ester. When aminothiols I-II are reacted with α-chlorobutyric acid, as in the case of their reactions with chloroacetic acid, the corresponding thiazin-3-ones form; however, the reaction takes place under more severe conditions. This is probably due to the steric hindrances created by the ethyl radical to nucleophilic replacement of the chlorine atom. The reaction takes place according to the following scheme:



Ia R=H, b R=C$_4$H$_9$O — Ia, b

Apparently, the corresponding aminothio acids form first and are then converted into the thiazin-3-ones during vacuum distillation as a result of intramolecular cyclization [3]. This hypothesis is confirmed by the IR spectra of the compounds obtained before and after distillation. The IR spectra initially display absorption bands at 3340, 2600-2200, 1700, and 500 cm^{-1}, which are characteristic of the aminothio acids. The IR spectra recorded after distillation of the reaction products display intense absorption bands at 1650-1660 cm^{-1}, which are characteristic of the stretching vibrations of the amide carbonyl.

The reaction of aminothios with ethyl α-chlorobutyrate was studied under similar conditions. It was found that the reaction results in the formation of only aminothioethers IIa and b and that the formation of the corresponding thiazin-3-ones does not take place.



IIa R=H, b R=C$_4$H$_9$O — IIa, b

It should be noted that, according to the data in [4, 5], the reaction of aminoethyl mercaptan with esters of halocarboxylic acids results in the formation of the corresponding thiazinones. In out case, such a course of the reaction may be attributed to the fact that the aminothiols of types I and II investigated are less basic (the pK_a of aniline is 4.58) [6] than aminoethyl mercaptan (pK_a = 8.35) [7]; therefore, the esteric groups in aminothioethers IIa and b are not subject to nucleophilic attack by the amine, and a lactamization process does not take place.

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The thiazinones obtained (Ia and b) are viscous yellow products, whereas aminothioethers IIa and b are colorless liquids, which yellow slightly upon standing. They are highly soluble in acetone, ethanol, and benzene, but insoluble in water.

The structures of the compounds synthesized have been confirmed by spectral data and elemental analysis. The IR spectra of aminothioethers IIa and b show absorption bands at 3370 and 1725 cm^{-1}, which correspond to the stretching vibrations of the NH bond and the esteric carbonyl.

In the PMR spectrum of thiazinone Ia the signals of the protons in the two methyl groups are displayed in the form of a multiplet at 0.9-1.4 ppm, and the signals of the CH_2 group bonded to a CH group are displayed in the form of a multiplet at 1.8 ppm. The signals of the CH group bonded to the C=O group have low-field positions at 3.1-3.6 ppm and are superimposed on the signals of the CH_2 group bonded to the nitrogen atom. The signals of the protons of the aromatic ring are displayed at 6.8 ppm in the form of a singlet.

EXPERIMENTAL

The PMR spectra of compounds Ia, Ib, IIa, and IIb were recorded at room temperature on a Variant T-60 spectrometer in CCl_4 solutions (the concentration was 10%). The internal reference was TMS. The IR spectra were obtained on a UR-20 spectrometers in thin layers.

The original aminothiols I and II were synthesized according to the method described in [8, 9].

2-Ethyl-6-methyl-4-(N-phenyl)tetrahydro-1,4-thiazin-3-one (Ia). A mixture of 18.9 g (0.1 mole) of an aqueous solution of the sodium salt of 1-(N-phenylamino)propane-2-thiol and 14.8 g (0.1 mole) of an aqueous solution of sodium α-chlorobutyrate is heated at 60-70°C for 3 h. Then the reaction mixture is acidified by a 20% solution of hydrochloric acid to pH 4. The mixture is extracted with ether and dried over calcined sodium sulfate. The residue remaining after the solvent is driven off is vacuum-distilled. The yield of Ia is 16.5 g (70%), bp 165-167°C (0.1 mm Hg) n_D^{20} 1.5445. Found: C, 66.5; H, 7.0; N, 5.5; S, 13.8%. Calculated for $C_{13}H_{17}NOS$: C, 66.3; H, 7.3; N, 5.9; S, 13.6%. IR spectrum: 1650 (C=), 1600 cm^{-1} (C=C). PMR spectrum: 0.9-1.4 (6H, m, $2CH_3$), 1.8 (2H, m, CH_2—CH), 3.1-3.6 (3H, m, CH_2N—and CH), 6.8 pp, (5H, s, C_6H_5).

2-Ethyl-6-butoxymethyl-4-(N-phenyl)tetrahydro-1,4-thiazin-3-one (Ib). In analogy to the preceding method, the reaction of 26.1 g (0.1 mole) of an aqueous solution of the sodium salt of 1-(N-phenylamino-3-butoxypropane-2-thiol (II) and 14.8 g (0.1 mole) of an aqueous solution of sodium α-chlorobutyrate gives 17.6 g (57%) of compound Ib with bp 179-181°C (0.1 mm Hg) and n_D^{20} 1.5405. Found: C, 66.2; H, 8.5; N, 4.3; S, 10.7%. Calculated for $C_{17}H_{25}NO_2S$: C, 66.4; H, 8.2; N, 4.5; S, 10.4%. Ir spectrum: 1660 (C=O), 1605 cm^{-1} (C=C). PMR spectrum: 0.6-1.6 (10 H, m, C_3H_7 and CH_3), 1.8 (2H, m, CH_2—CH), 3-3.5 (3H, m, CH_2N—and CH), 3.6-4.2 (4H, m, $2CH_2O$), 7.2 ppm (5H, s, C_6H_5).

Ethyl 2-[1-(N-Phenylamino)-2-isopropylthio]butanoate (IIa). A mixture of 15.2 g (0.1 mole; of 1-(N-phenylamino)propane-2-thiol and 2.3 g (0.1 mole) of sodium hydroxide in 30 ml of water is given a dropwise addition of 15 g (0.1 mole) of ethyl α-chlorobutyrate with intense stirring, and the mixture is heated at 60-70°C for 3 h. Then the reaction mass is cooled, and the organic layer is separated from the aqueous layer by extraction with ether. The extract is dried over calcined sodium sulfate, the solvent is driven off, and the residue is subjected to vacuum distillation. This gives 22 g (78%) of compound IIa with bp 159-160°C (0.1 mm), n_D^{20} 1.5490, and d_4^{20} 1.1276. Found: C, 64.5; H, 8.1; N, 4.6; S, 11.2%. Calculated for $C_{15}H_{29}NO_2S$: C, 64.0; H, 8.2; N, 5.0; S, 11.4%. IR spectrum: 3370 (NH), 1725 cm^{-1} (C=O). PMR spectrum: 0.8-1.4 (9H, q, $3CH_3$), 1.8 (2H, m, CH_2CH), 3.1 (4H, m, CH_2N—, 2CH), 4 (2H, q, CH_2O), 4.5 (IH, broadened signal, NH), 6.1-7.1 ppm (5H, m, C_6H_5).

Ethyl 2-[1-(Phenylamino)-2-(butoxymethyl)ethylthio]butanoate (IIb). In analogy to the preceding method, a mixture of 24 g (0.1 mole) of 1-(N-phenylamino)-3-butoxypropane-2-thiol, 2.3 g (0.1 mole) of sodium hydroxide in 30 ml of water, and 15 g (0.1 mole) of ethyl α-chlorobutyrate gives 25 g (70%) of compound IIb with bp 170-171°C (0.08 mm Hg), N_D^{20} 1.5262, and d_4^{20} 1.0687. Found: C, 64.8; H, 8.6; N, 4.2; S. 9.3%. Calculated for $C_{19}H_{31}NO_3S$: C, 64.5; H, 8.8; N, 4.4; S, 9.1%. IR spectrum: 3365 (NH), 1720 cm^{-1} (C=O). PMR spectrum: 0.8-1.8 (13H, m, C_3H_7 and $2CH_3$), 2 (2H, m, CH_2CH), 2.8-3.75 (4H, m, CH_2N—, CH, and NH), 3.7-4.3 (4H, m, $2CH_2O$), 6.2-7.1 ppm (5H, m, C_6H_5).

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