FORMATION OF DERIVATIVES OF THIAZOLINE BY THE REACTION OF THIOUREA WITH 2-BROMO-3-AMINOPROPIONIC ACID

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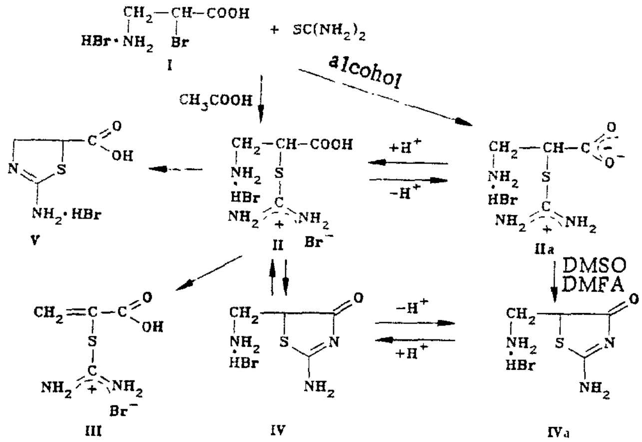
Depending on the conditions employed, thiourea reacts with the hydrobromide of 2-bromo-3-aminopropionic acid to give a dihydrobromide or an internal salt S-(2-amino-1-carboxyethyl)isothiourea. This compound can also lose ammonia to give a thiazoline derivative.

Many aminoalkylisothioureas can cyclize to give dihydrothiazine or thiazoline derivatives [1, 2]. Thus, S-(1-carboxyalkyl)isothioureas are starting materials for the preparatio of 2-amino-4-oxo-5-alkyl-2-thiazolines [3-5]. To obtain new aminoalkylisothiourea derivatives and compounds which can be prepared from them, we have studied the reaction of thiourea with 2-bromo-3-aminopropionic acid (I).

It was found that carrying out the reaction in glacial acetic acid at 20° gave the dihydrobromide S-(2-amino-1-carboxyethyl)isothiourea (II), but when alcohol was used as solvent, an internal salt II was obtained. Prlonged boiling of the dihydrobromide II in glacial acetic acid gave S-(1-carboxyvinyl)isothiourea hydrobromide (III), with simultaneous loss of ammonia. In water and in alcohols, compound II can react in several different ways to give the isothiourea III, 2-amino-4-oxo-5-aminomethyl-2-thiazoline dihydrobromide (IV), and 2-amino-5-carboxy-2-thiazoline hydrobromide (V). When the reaction is carried out in alcohol, esters of the isothiourea II and III are also formed.

In aprotic solvents (DMSO, DMFA), the dihydrobromide II is stable when heated to 60°, but the internal salt IIa quickly cyclizes to 4-oxothiazoline IV.

Compounds IV and IVa in aqueous solution ($T \leq 40°$, $3 < pH < 5$) are converted to 2-amino-5-carboxy-2-thiazoline; moreover, the intermediate isothiourea II was also isolated.



The 4-oxothiazoline IV can be obtained in preparative amounts by refluxing a solution of II in n-butanol and benzene solution containing hydrobromic acid, and carboxythiazoline V from the reaction of 2-bromo-3-aminopropionic acid hydrobromide with potassium thiocyanate.

At 60°, compounds II and IV, in either water or alcohol, lost ammonia, and isothiourea III was isolated as a final reaction product. The rate of loss of ammonia from compounds

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TABLE 1. Data for Synthesized Compounds

Compound	mp, °C	IR spectra, cm^{-1}								Mass spectra, m/z (relative intensity, %)	Yield, %
		C=N	C—O$^-$	C—N	ring	C=C	C=O	NH	C—S—C		
IIa	248 (decomp.)	—	1370	1240	—	—	1600	1700	629	163 (M+, 20), 147 (100), 119 (9), 91 (100)	84
III	186	—	1360	1260	—	1630	1690	—	640	146 (M+, 23), 130 (100), 129 (31), 102 (18)	80
IV*	152 (decomp.)	1590	—	1160	1040	—	1760	1690	730	146 (M+, 7), 130 (21), 117 (12), 114 (100)	76
V	204	1645	1370	1150	1035	—	1670	—	730	146 (M+, 41), 129 (11), 104 (44), 91 (27), 55 (100) 55 (100)	95

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*Picrate IV, mp 201°.

II and IV increases with increasing pH of the solution. It was found experimentally that the reactions of compounds II-IV and IVa were reversible.

EXPERIMENTAL

Mass spectra were obtained on a Varian MAT-III with direct introduction of the sample into the ionization chamber at 70 eV. Infrared spectra were recorded on a Perkin—Elmer 457 (KBr pellets). The course of the reaction and the purity of the products were checked by TLC using Silufol UV-254 plates and the following solvent systems: 1) n-C_4H_9OH—CH_3COOH—H_2O (4:1:5); 2) n-C_4H_9OH, saturated with 12% HBr; 3) n-C_4H_9OH, saturated with water.

Data for the compounds are given in Table 1.

Hydrobromide of 2-Bromo-3-aminopropionic Acid (I). A mixture of 10 g (0.1 mole) of β-alanine and 14.8 g (0.1 mole) of phthalic anhydride was maintained at 160° until no more water was formed. The reaction product was cooled and recrystallized from water. mp 150°; literature value [6], mp 150-151°. Yield 80%. The N-(β-phthalimidopropionic) acid was brominated with 13.2 ml (0.25 mole) of bromine and 0.1 g (0.03 mole) of red phosphorus. The reaction mixture was heated on a water bath until no more hydrogen bromide was given off. The reaction product was treated with 160 ml of hot water, and when cool, filtered. The phthalyl protecting group was removed by refluxing with 48% aqueous hydrobromic acid for 10 h. After cooling, the phthalic acid was removed by filtration, the filtrate evaporated to dryness, and the residue recrystallized from acetic acid. mp 187°; literature value [6], mp 188-189°, Rf 0.5 (system 1), 0.65 (2), 0.5 (3). Yield 70%.

Internal Salt of S-(2-Amino-1-carboxyethyl)isothiourea (IIa). To a solution of 7.6 g (0.1 mole) of thiourea in 100 ml of n-butanol was added a solution of 2.5 g (0.1 mole) of the hydrobromide I in 100 ml of n-butanol, and the reaction mixture kept in a thermostated bath at 100° for 3 h. The precipitated material was filtered off, washed with hot ethanol, and recrystallized from a 1:10 water—acetone mixture. mp 248° (with decomp.), Rf 0.27 (system 1), 0.31 (2), 0.15 (3). Yield 84%. Found, %: C 20.0, H 3.7, Br 32.7, N 17.7. $C_4H_{10}BrN_3O_2S$. Calculated, %: C 19.9, H 3.7, Br 32.9, N 17.3.

Hydrobromide of S-(2-Amino-1-carboxyethyl)isothiourea (II). A solution of 2.5 g (0.01 mole) of compound I and 0.76 g (0.01 mole) of thiourea in 100 ml of acetic acid was maintaine at 20° for 72 h. The material which precipitated was filtered off and washed with hot isopropanol, mp 192°, Rf 0.27 (system 1), 0.31 (2). Yield 53%. Found, %: C 13.9, H 3.9, Br 49.3. $C_4H_{11}Br_2N_3O_2S$. Calculated, %: C 14.7, H 3.2, Br 49.4. Picrate, mp 213°. Found, %: C 30.9, H 2.7, N 20.7, S 5.6. $C_{10}H_{15}N_9O_6S$. Calculated, %: C 30.9, H 2.4, N 20.3, S 5.2.

S-(1-Carboxyvinyl)isothiourea (III). A mixture of 12.5 g (0.05 mole) of compound I and 3.8 g (0.05 mole) of thiourea in 30 ml of acetic acid was refluxed for 48 h, the precipitate material filtered off, washed with water, and recrystallized from a 4:1 mixture of DMFA and isopropanol. mp 186°. Rf 0.05 (system 2). Yield 80%. Found, %: C 33.0, H 4.1, N 19. S 21.8. $C_4H_6N_2O_2S$. Calculated, %: C 32.9, H 4.1, N 19.2, S 22.0.

Dihydrobromide of 2-Amino-4-oxo-5-aminomethyl-2-thiazoline (IV). A solution of 33 g (0.1 mole) of the dihydrobromide II in a minimum quantity of 48% hydrobromic acid was added dropwise to 500 ml of a 1:20 mixture of n-butanol and benzene. The solution was brought to boiling and refluxed until compound II had dissolved. After cooling, the precipitated material was filtered off. Concentration of the mother liquors yielded additional product. The combined portions were recrystallized from a 10:1 mixture of n-butanol and 48% hydrobromic acid. mp 152° (decomp.). Rf 0.46 (system 1), 0.45 (2), 0.26 (3). Yield 76%. Found, %: C 26.9, H 2.3, Br 52.2. $C_4H_9Br_2N_3OS$. Calculated, %: C 16.2, H 2.9, Br 52.1. Dipicrate, mp 201°. Found, %: C 31.8, H 2.2, N 20.4, S 5.6. $C_{16}H_{13}N_9O_{15}S$. Calculated, %: C 31.8, H 2.2, N 20.9, S 5.3.

2-Amino-5-carboxy-2-thiazoline (V). A. A solution of 25 g (0.1 mole) of compound I in 100 ml of H_2O was neutralized to pH 7 with a NaH_2PO_4 solution (0.2 mole/liter), and 7.6 g (0.1 mole) of potassium thiocyanate in 50 ml of H_2O added. After refluxing for 3 h, the solution was concentrated to half volume and 75 ml of ethanol added. The precipitated material was filtered off and recrystallized from a 2:3 mixture of water and ethanol. mp 171°. Rf 0.52 (system 1), 0.54 (2), 0.51 (3). Yield 93%. The product was converted to the hydrobromide V, mp 204°, using 48% HBr. Yield 95%. Found, %: C 21.1, H 2.6, Br 35.5, N 12.6, S 13.9. $C_4H_8BrN_3OS$. Calculated, %: C 21.2, H 2.6, Br 35.2, N 12.3, S 14.1.

B. A solution of 3 g (0.01 mole) of compound IV in 100 ml of H_2O was brought to pH 7 by the addition of a solution of NaH_2PO_4, kept at 35° for 28 h, and then neutralized to pH 7. The solution was filtered and the filtrate evaporated to half volume. The product was precipitated by the addition of 75 ml of ethanol, filtered off, and recrystallized from a 2:3 mixture of water and ethanol. mp 171°. Yield 76%. Absence of melting point depression, together with identical Rf values in different solvent systems, and IR and mass spectra showed that the material was identical with compound V prepared as in A.

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