Chemistry of Heterocyclic Compounds, Vol. 42, No. 2, 2006

REACTION OF 2-AMINOTHIOPHENOL WITH ACRYLIC ACID AND CONVERSION OF THE RESULTANT ADDUCTS

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The reaction of acrylic acid with 2-aminothiophenol gives 5-carboxyethyl-2,3-dihydro-5H-benzo[b][1,4]-thiazepin-4-one and N-[2-(carboxyethylthio)phenyl]-β-alanine, while the reaction of acrylic acid with bis(2-aminophenyl) disulfide gives bis[2-(carboxyethylamino)phenyl] disulfide. The action of potassium thiocyanate in acid medium on the carboxyethylamino derivatives yields 1-[2-carboxyethylthio)phenyl]dihydro-4(1H,3H)-pyrimidinone-2-thione, bis-{2-[dihydro-4(1H,3H)-pyrimidinone-2-thion-1-yl]phenyl} disulfide, and 3-(2-mercaptobenzothiazol-3-yl)propanoic acid.

Keywords: acrylic acid, β-alanine, 2-aminothiophenol, hydrobenzothiazepinone disulfide, mercaptobenzothiazole, phenyldihydropyrimidinonethione.

The products of the reaction of aromatic amines with acrylic acid and its homologs, namely, N-substituted β-alanines, are starting compounds for the synthesis of derivatives of hexahydropyrimidine, quinolinone, quinolizidinedione, and other heterocyclic systems [1-3]. In most cases, the preparation of such N-substituted β-alanines does not pose special difficulties and the reaction course is clearcut. However, in the case of anilines with reactive groups in the *ortho* position, the direct preparation of the corresponding alanines is not always possible.

Mills and Whitworth [4] described the reaction of 2-aminothiophenol (**1**) with a series of unsaturated compounds, including acrylic acid, and found that, upon increasing the reaction temperature, 2,3-dihydro-5H-benzo[*b*][1,4]-thiazepin-4-one (**2**) is formed in about 25% yield, i.e., the mercapto group undergoes nucleophilic addition to the unsaturated α,β-bond in acrylic acid, while the amino group undergoes intramolecular acylation.

In a continuation of a study of the transformations of N-substituted β-alanines to give heterocyclic products, we have thoroughly examined the reaction of 2-aminothiophenol with acrylic acid. Bicyclic thiazepinone **2** is the major product isolated when the ratio of thiophenol **1** to acrylic acid is 1:1 both at room temperature in toluene and upon heating. Increasing the amount of acrylic acid leads to the formation of N-(2-carboxyethylthiophenyl)-β-alanine (**3**), which crystallizes out of the reaction mixture during the reaction both at room temperature in toluene and upon heating. When the molar ratio of thiophenol **1** to acrylic acid is 1:3, the yield of β-alanine **3** reaches 65%, while bicyclic thiazepinone **2** separates out of the reaction mixture by crystallization. The ^{1}H NMR spectrum of **3** shows a set of four methylene group triplets. The NCH_2 group protons appear at lower field than the SCH_2 group protons.

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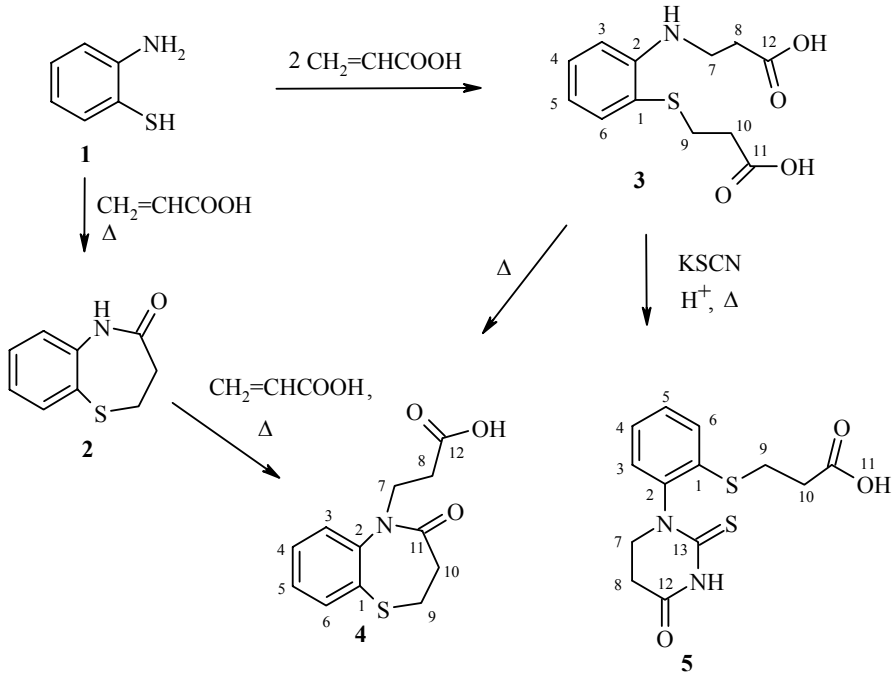
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 256-261, February, 2006. Original article submitted December 12, 2004.

Heating **2** with acrylic acid in toluene gives 5-carboxyethyl-2,3-dihydro-5H-benzo[*b*][1,4]thiazepin-4-one (**4**). The intramolecular acylation of dicarboxy derivative **3** upon heating in toluene at reflux until water is no longer released also gives thiazepinone **4**. The ^{1}H NMR spectrum of **4** lacks the amide group proton at 5.51 ppm, while its ^{13}C NMR spectrum lacks the signal for the carboxyl group carbon at 172.78 ppm but shows a C=O group signal at 170.73 ppm.

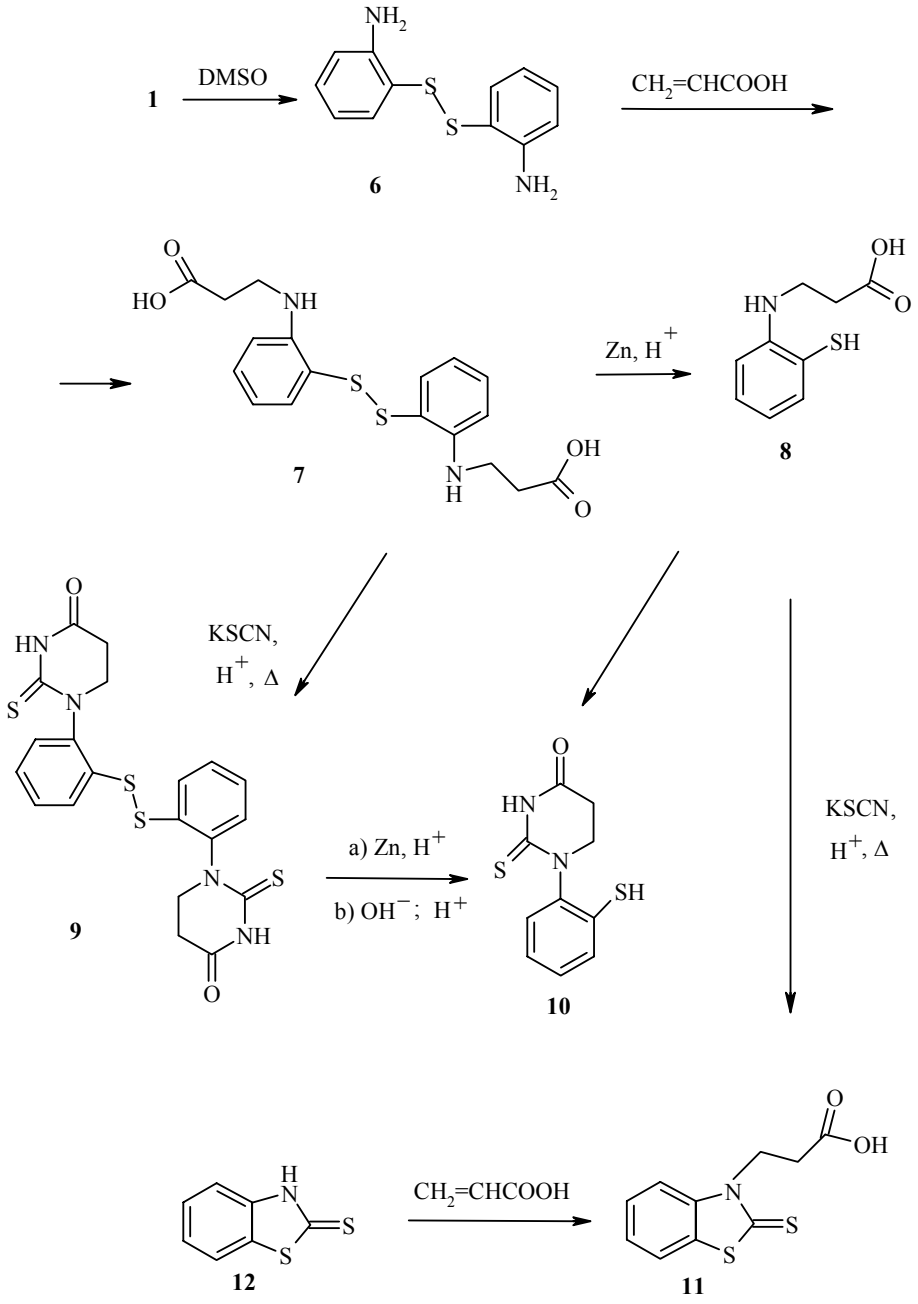


Heating dicarboxylic acid **3** with potassium thiocyanate in acetic acid with the subsequent addition of hydrochloric acid gives 1-[2-(carboxyethylthio)phenyl]dihydro-4(1H,3H)-pyrimidinone-2-thione (**5**). The ^{13}C NMR spectrum of **5**, in comparison with the spectrum of **3**, lacks the carboxyl group signal for the carboxyethylamino fragment at 173.28 ppm but shows new signals for heterocyclic C=S and C=O groups at 179.02 and 166.86 ppm, respectively. The signal for the SCH_2 group at 33.78 ppm and signal for the methylene group carbon of the CH_2CO_2H fragment at 28 ppm remain unchanged, while the other two signals for methylene group carbons are shifted from 33.36 to 30.55 ppm and from 38.72 to 47.63 ppm. The ^{1}H NMR signal for the secondary amino group found at 5.51 ppm in starting **3** is lacking and a new heterocyclic amide group signal is seen at 12.31 ppm. The hydrogen atoms of the heterocyclic methylene groups become nonequivalent, probably due to hindered rotation about the nitrogen–carbon bond such that the NCH_2 group protons give two doublet of doublets of doublets with coupling constants 7.5 and 13.5 Hz, while the CH_2CO group protons appear as multiplets at 3.10-3.26 ppm (Scheme 1).

Since N-(2-mercaptophenyl)-β-alanine (**8**) cannot be obtained directly from 2-aminothiophenol, this product was synthesized by the reductive cleavage of the disulfide bridge of bis[(2-carboxyethylamino)phenyl] disulfide (**7**) obtained in the reaction of diaminodiphenyl disulfide **6** with acrylic acid in toluene. In turn, diamine **6** was synthesized by the oxidation of aminothiophenol (**1)** upon heating in DMSO.

Bis{2-[dihydro-4(1H,3H)-pyrimidinone-2-thion-1-yl]phenyl} disulfide (**9**) was synthesized from diacid **7** and potassium thiocyanate analogously to the synthesis of dihydropyrimidinonethione **5**. The action of zinc powder in a mixture of hydrochloric acid and 2-propanol on disulfide **9** leads to the reductive cleavage of the disulfide bond to give 1-(2-mercaptophenyl)dihydro-4(1H,3H)-pyrimidinone-2-thione (**10**), which also may be obtained directly from diacid **7** without isolation of disulfide **9**. Bispyrimidinonethione **9** is converted to **10** also

Scheme 1



by the action of aq. NaOH with subsequent heating at reflux with hydrochloric acid. Opening of the dihydrouracil ring can also occur upon the action of alkali solutions with renewed formation of this ring upon the heating with strong acids [1, 2].

N-Phenyl-β-alanines with *o*-hydroxy or *o*-amino groups react with urea to form derivatives of benzoxazole [5] or benzimidazole [6]. In our case, the action of potassium thiocyanate on N-(2-mercaptophenyl)-β-alanine (**6**) gave 3-(2-mercaptobenzothiazol-3-yl)propanoic acid (**11**), which was also obtained by heating mercaptobenzothiazole (**12**) with acrylic acid in toluene.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were taken on a JOEL FX-100 spectrometer at 100 MHz and Varian 300 spectrometer at 300 MHz using TMS or HMDS (δ 0.05 ppm) as the internal standard and DMSO-d_6 as the solvent (acetone-d_6 for **11**). The mass spectra were taken on a Waters (micromas) ZQ 2000 mass spectrometer with chemical ionization and 20 eV ionizing voltage. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol 254 and Silufol UV-254 plates.

2,3-Dihydro-5H-benzo[*b*][1,4]thiazepin-4-one (2). A mixture of 2-aminothiophenol (6.25 g, 50 mmol), acrylic acid (3.4 ml, 50 mmol), and toluene (20 ml) was heated at reflux for 2 h and then cooled. The crystalline precipitate was filtered off and washed with ether to give 3.5 g (39.5%) **2**; mp 220-221°C (2-propanol–water, 1:1; mp 220-221°C [4]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.73 (1H, s, NH); 7.51 (1H, d, *J* = 7.3, ArH); 7.34 (1H, d, *J* = 7.3, ArH); 7.12 (2H, t, *J* = 7.3, ArH); 3.37 (2H, t, *J* = 6.9, SCH_2); 2.43 (2H, t, *J* = 6.9, $COCH_2$). Mass spectrum, *m/z* (I_{rel}, %): 179.3 $[M]^+$ (40). Found, %: C 59.80; H 5.60; N 7.90. C_9H_9NOS. Calculated, %: C 60.31; H 5.06; N 7.81.

N-[2-(Carboxyethylthio)phenyl]-β-alanine (3). A. A mixture of aminothiophenol **2** (8.8 g, 70 mmol), acrylic acid (10.2 ml, 15 mmol), and toluene (20 ml) was heated at reflux for 5 h. The solvent was decanted off and remaining solid was crystallized from 1:1 2-propanol–water to give 5.6 g (29.5%) **3**; mp 129-130°C.

B. A mixture of 2-aminothiophenol (1.25 g, 10 mmol) and acrylic acid (2.1 ml, 30 mmol) in toluene (10 ml) was maintained at room temperature for 72 h. The light-greenish crystalline precipitate was filtered off, washed with ether, and crystallized from 1:1 2-propanol–water to give 1.76 g (65.4%) **3**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.31 (2H, s, 2OH); 7.31 (1H, d, *J* = 7.5, ArH); 7.19 (1H, t, *J* = 7.5, ArH); 6.67 (1H, d, *J* = 7.5, ArH); 6.58 (1H, t, *J* = 7.5, ArH); 5.51 (1H, s, NH); 3.38 (2H, t, *J* = 6.8, NCH_2); 2.84 (2H, t, *J* = 6.8, SCH_2); 2.55 (2H, t, *J* = 6.8, $COCH_2$); 2.40 (2H, *t*, *J* = 6.8, $COCH_2$). ^{13}C NMR spectrum, δ, ppm: 173.8 ($C_{(12)}$); 172.78 ($C_{(11)}$); 148.55 ($C_{(2)}$); 135.77 ($C_{(3)}$); 130.12 ($C_{(4)}$); 116.24 ($C_{(5)}$); 116.05 ($C_{(6)}$); 109.96 ($C_{(1)}$); 38.72 ($C_{(7)}$); 33.77 ($C_{(10)}$); 33.36 ($C_{(8)}$); 29.04 ($C_{(9)}$). Mass spectrum, *m/z* (I_{rel}, %): 270.3 $[M]^+$ (100), 252 $[M - H_2O]^+$ (5). Found, %: C 53.91; H 5.63; N 5.40. $C_{12}H_{15}NO_4S$. Calculated, %: C 53.56; H 5.57; N 5.20.

5-Carboxyethyl-2,3-dihydro-5H-benzo[*b*][1,4]thiazepin-4-one (4). A solution of alanine **3** (1.39 g, 5.2 mmol) in toluene (30 ml) was heated at reflux with a Dean–Stark trap for 10 h. The solvent was distilled off to give 0.35 g (27%) **4**; mp 105-106°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.71-12.72 (1H, br. s, OH); 7.30 (1H, d, *J* = 15, H-6 Ar); 7.20 (1H, t, *J* = 15, H-4 Ar); 6.62 (1H, t, *J* = 15, H-5 Ar); 6.56 (1H, d, *J* = 15, H-3 Ar); 3.37 (2H, t, *J* = 6.6, NCH_2); 2.84 (2H, t, *J* = 6.6, $COCH_2$); 2.55 (2H, t, *J* = 7.2, $COCH_2$); 2.40 (2H, t, *J* = 7.2, SCH_2). ^{13}C NMR spectrum, δ, ppm: 173.4 ($C_{(12)}$); 170.7 ($C_{(11)}$); 145.2 ($C_{(2)}$); 135.2 ($C_{(6)}$); 130.1 ($C_{(5)}$); 127.2 ($C_{(3)}$); 127.12 ($C_{(4)}$); 109.9 ($C_{(1)}$); 44.5 ($C_{(7)}$); 39.2 ($C_{(9)}$); 33.4 ($C_{(8)}$); 29.1 ($C_{(10)}$). Found, %: C 57.52; H 5.41; N 5.62. $C_{12}H_{13}NO_3S$. Calculated, %: C 57.36; H 5.21; N 5.57.

1-[2-(Carboxyethylthio)phenyl]dihydro-4(1H,3H)-pyrimidinone-2-thione (5). A mixture of diacid **3** (1.35 g, 5 mmol), potassium thiocyanate (2.5 g, 25 mmol), and glacial acetic acid (10 ml) was heated at reflux for 8 h. Then, concentrated hydrochloric acid (5 ml) was added and heating at reflux was continued for additional 30 min. Water (100 ml) was added to the reaction mixture. The precipitate formed was filtered, washed with water and ethanol, and dried to give 0.7 g (23%) **5**; mp 181-182°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.36 (1H, s, NH); 7.55 (1H, d, *J* = 7.5, ArH); 7.31-7.37 (3H, m, ArH); 3.88 (1H, ddd, *J* = 7.5, *J* = 13.5, NCH)); 3.71 (1H, ddd, *J* = 7.5, *J* = 13.5, NCH); 3.26-3.10 (2H, m, *J* = 7.5, $COCH_2$); 2.82 (2H, t, *J* = 7.5, $COCH_2$); 2.54 (2H, t, *J* = 7.5, SCH_2). ^{13}C NMR spectrum, δ, ppm: 179.21 ($C_{(12)}$); 172.62 ($C_{(11)}$); 166.86 ($C_{(13)}$); 143.59 ($C_{(2)}$); 133.98 ($C_{(3)}$); 129.31 ($C_{(4)}$); 128.68 ($C_{(6)}$); 128.45 ($C_{(5)}$); 127.12 ($C_{(1)}$); 47.63 ($C_{(7)}$); 33.78 ($C_{(8)}$); 30.54 ($C_{(10)}$); 27.49 ($C_{(9)}$). Found, %: C 50.83; H 5.62; N 9.11. $C_{13}H_{14}N_2O_3S_2$. Calculated, %: C 50.33; H 5.55; N 9.03.

Bis(2-aminophenyl) Disulfide (6) was obtained in 77% yield according to Karabinos [7] from 2-aminothiophenol by heating in DMSO at 80-90°C for 8 h.

Bis[2-(carboxyethylamino)phenyl] Disulfide (7). A mixture of disulfide **6** (4.96 g, 20 mmol), acrylic acid (2.9 g, 40 mmol), and toluene (30 ml) was heated for 5 h at 70-80°C. The liquid fractions were distilled off in vacuum. The remaining thick mass was washed with water, dissolved in 10% aq. NaOH, and extracted with three 20-ml ether portions. The alkaline solution was treated with activated charcoal, filtered, and brought to pH 4-5 by adding acetic acid. The precipitate formed was filtered off to give 1.95 g (25%) **7**; mp 98-99.5°C (2-propanol–water, 1:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.74 (2H, s, 2NH); 7.05-7.60 (8H, m, ArH); 2.43 (4H, t, *J* = 7.2, $2NCH_2$); 3.4 (4H, t, *J* = 7.2, $2COCH_2$). Mass spectrum, *m/z* (I_{rel}, %): 393.4 $[M]^+$ (20). Found, %: C 55.42; H 5.34; N 7.28. $C_{18}H_{20}N_2O_4S_2$. Calculated, %: C 55.10; H 5.10; N 7.14.

N-(2-Mercaptophenyl)-β-alanine (8). Disulfide **7** (3.92 g, 10 mmol) was dissolved in 2-propanol (15 ml). Then, 10% hydrochloric acid (20 ml) and zinc powder (3 g) were added and the mixture was heated for 15 min. The solution was cooled and the precipitate formed was filtered off to give 3.75 g (90%) **8**; mp 132-133.5°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.27 (1H, d, *J* = 9.4, ArH); 7.03 (1H, d, *J* = 9.4, ArH); 6.85-6.89 (2H, m, ArH); 5.47 (1H, s, 1NH); 4.95 (1H, s, SH); 2.49 (2H, t, *J* = 5.5, $NHCH_2$); 2.43 (2H, t, *J* = 5.5, $COCH_2$). Mass spectrum, *m/z* (I_{rel}, %): 198.3 $[M]^+$ (100), 180.3 $[M - 18]^+$ (35). Found, %: C 54.98; H 5.81; N 7.22. $C_9H_{11}NO_2S$. Calculated, %: C 54.80; H 5.62; N 7.10.

Bis{2-[dihydro-2(1H,3H)-pyrimidinone-2-thion-1-yl]phenyl} Disulfide (9). A mixture of diacid **7** (3.7 g, 10 mmol), potassium thiocyanate (7.8 g, 80 mmol), and acetic acid (20 ml) was heated at reflux for 18 h. Then, concentrated hydrochloric acid (5 ml) was added and the mixture was heated for an additional 15 min. After cooling, the thick mass precipitated was crystallized from 2-propanol to give 5.7 g (60%) **9**; mp 286-287.5°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.2 (2H, s, 2NH); 7.30-7.62 (8H, m, ArH); 3.5 (4H, t, *J* = 7.1, $2NCH_2$); 2.54 (4H, t, *J* = 7.1, $2COCH_2$). Mass spectrum, *m/z* (I_{rel}, %): 465.7 $[M]^+$ (20). Found, %: C 50.41; H 4.02; N 12.05. $C_{20}H_{18}N_4O_2S_4$. Calculated, %: C 50.61; H 3.82; N 11.80.

1-(2-Mercaptophenyl)dihydro-2(1H,3H)-pyrimidinone-2-thione (10). A. Disulfide **9** (2.37 g, 50 mmol) was heated at reflux in 10% aq. NaOH (30 ml) for 10 min. The reaction mixture was filtered and the filtrate was brought to pH 3 by adding hydrochloric acid and then heated at reflux for 10 min to give 1.6 g (67.2%) **10**; mp 241-242.5°C.

B. Disulfide **9** (2.37 g, 50 mmol) was dissolved in 2-propanol (10 ml) and 10% hydrochloric acid (15 ml) was added. Then, zinc powder (3 g) was added to the stirred solution heated to 60-70°C. Heating was continued until the brown color disappeared. The hot solution was filtered and cooled. The precipitate formed was filtered off to give 1.62 g (68%) **10**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.62 (1H, s, NH); 7.28-7.60 (4H, m, ArH); 3.2 (2H, t, *J* = 7.1, NCH_2); 2.51 (2H, t, *J* = 7.1, $COCH_2$). Mass spectrum, *m/z* (I_{rel}, %): 239.5 $[M]^+$ (20). Found, %: C 50.82; H 4.13; N 11.87. $C_{10}H_{10}N_2OS_2$. Calculated, %: C 50.40; H 4.23; N 11.75.

3-(2-Mercaptobenzothiazol-3-yl)propanoic Acid (11). A mixture of 2-mercaptobenzothiazole (**12**) (3.34 g, 20 mmol), acrylic acid (1.58 g, 22 mmol), and toluene (15 ml) was heated at reflux for 10 h. The reaction mixture was cooled and the precipitate formed was filtered off to give 2.2 g (45.8%) **11**; mp 141-142°C (2-propanol–water, 1:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.3-8.2 (4H, m, ArH); 3.54 (2H, t, *J* = 6.9, NCH_2); 2.92 (2H, t, *J* = 6.9, $COCH_2$). Found, %: C 50.71; H 3.93; N 5.98. $C_{10}H_9N_2O_2S_2$. Calculated, %: C 50.21; H 3.76; N 5.86.

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