ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 3, pp. 402–406. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © P.V. Savitskii, R.I. Vas'kevich, Yu.L. Zborovskii, V.I. Staninets, S.A. But, A.N. Chernega, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 3, pp. 407–410.

Heterocyclizations of 1-(Benzothiazol-2-yl)-4-phenylthiosemicarbazide

P. V. Savitskii, R. I. Vas'kevich, Yu. L. Zborovskii, V. I. Staninets, S. A. But, and A. N. Chernega

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 5, Kiev, 02660 Ukraine
e-mail: savitsky@bpci.kiev.ua

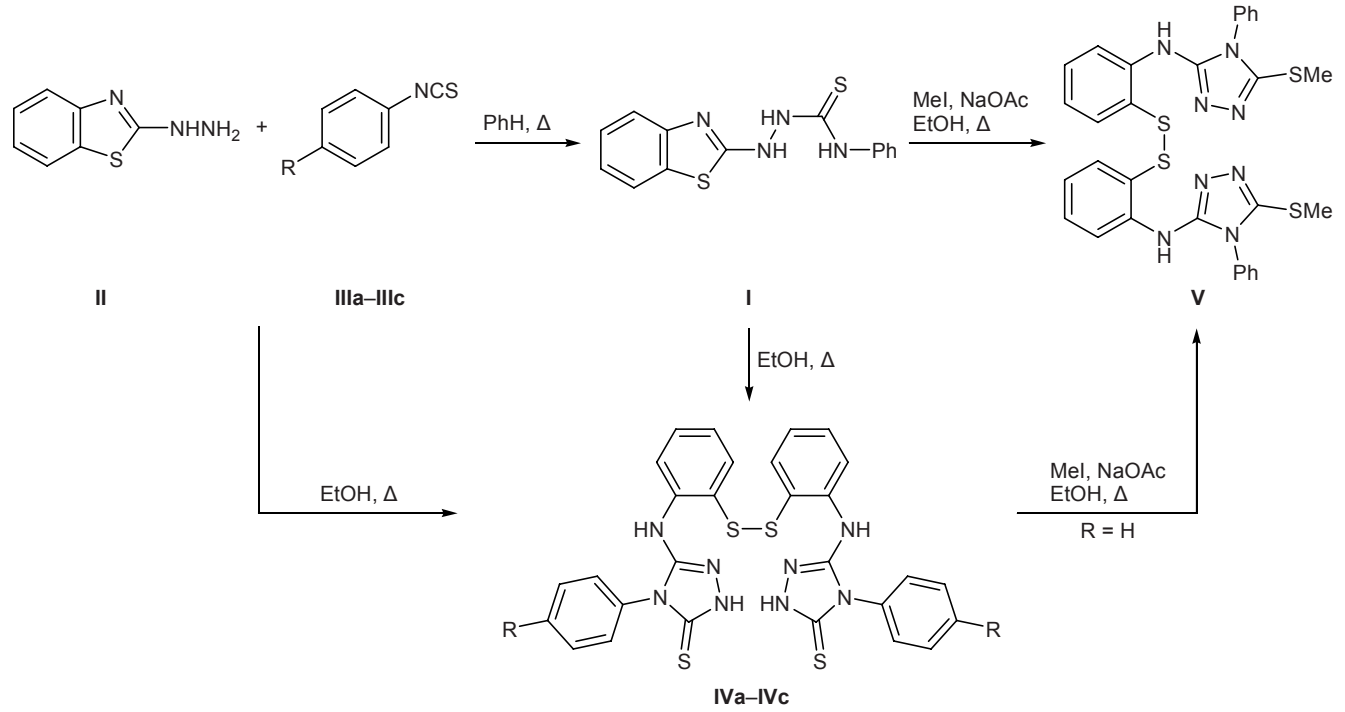
Received July 19, 2007

Abstract—1-(Benzothiazol-2-yl)-4-phenylthiosemicarbazide reacted with methyl iodide in the presence of sodium acetate in boiling ethanol to give 2,2′-dithiobis[*N*-(5-methylsulfanyl-4-phenyl-4*H*-1,2,4-triazol-3-yl)-benzenamine]. The reaction of the title compound with dimethyl acetylenedicarboxylate in dioxane led to the formation of methyl 3-(benzothiazol-2-yl)-2-(2-methoxy-2-oxoethyl)-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate.

DOI: 10.1134/S1070428008030159

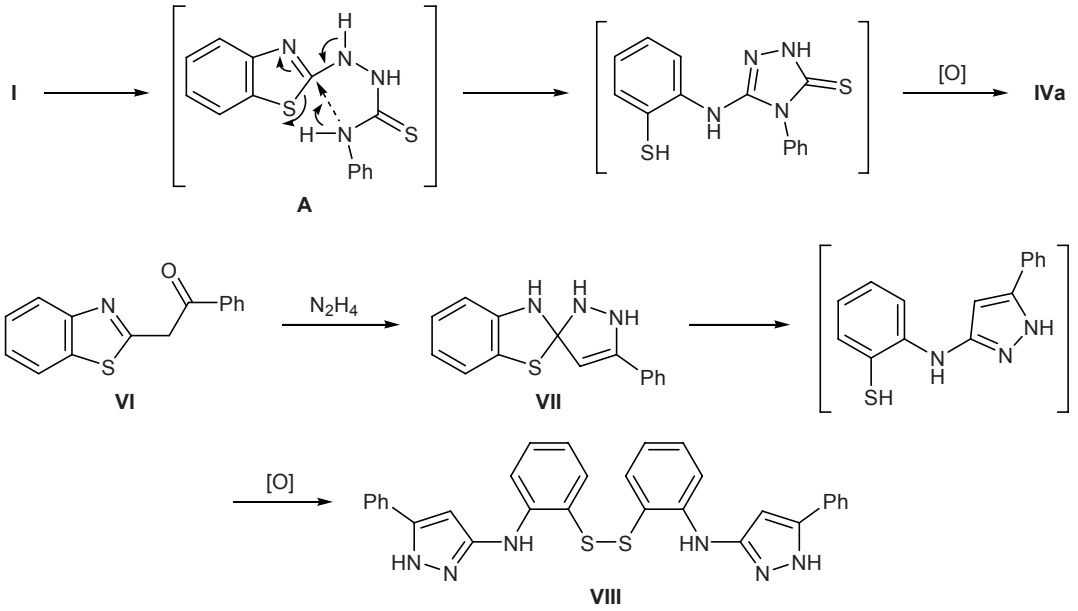
Thiosemicarbazides possess nitrogen and sulfur atoms that are capable of being involved in heterocyclization processes; therefore, they can be used in syntheses of nitrogen- and sulfur-containing heterocycles. We previously showed [1] that 1-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-4-arylthiosemicarbazides react with dimethyl acetylenedicarboxylate in dioxane to give derivatives of 2-(2-arylamino-4,5-dihydro-1,3,4-thiadiazol-4-yl)-3,4-dihydrothieno-[2,3-*d*]pyrimidin-4-ones and that an analogous reaction

Scheme 1.



R = H (**a**), MeO (**b**), EtOCO (**c**).

Scheme 2.



in methanol leads to the formation of *N*′-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-3-aryl-5-methoxycarbonylmethylidene-4-oxo-1,3-thiazolidin-2-one hydrazones. Cyclization of 4-aryl-1-(pyrimidin-2-yl)thiosemicarbazides by the action of methyl iodide [2, 3] provides a synthetic route to arylamino-substituted [1,2,4]triazolo[1,5-*a*]- or [1,2,4]triazolo[4,3-*a*]-pyrimidines.

In the present work we used as substrate for heterocyclization 1-(benzothiazol-2-yl)-4-phenylthiosemicarbazide (**I**) which was prepared by heating benzothiazol-2-ylhydrazine (**II**) with phenyl isothiocyanate (**IIIa**) in benzene. Our attempts to synthesize thiosemicarbazide **I**, as well as its analogs having a substituent in the *para* position of the benzene ring, by reaction of hydrazine **II** with the corresponding aryl isothiocyanates **IIIa**–**IIIc** in boiling ethanol according to the procedure described in [4] resulted in the formation of 2,2′-dithiobis[*N*-(4-aryl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)anilines] **IVa**–**IVc** instead of the expected thiosemicarbazides (Scheme 1).

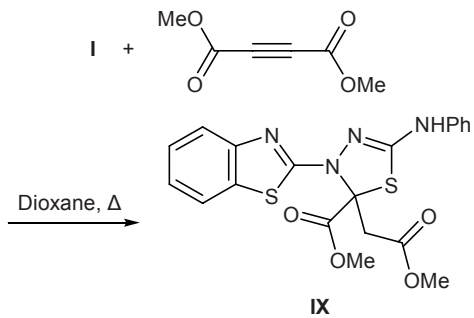
Thiosemicarbazide **I** reacted with methyl iodide and sodium acetate in boiling ethanol to give substituted 1,2,4-triazole **V**. Analogous thiosemicarbazides of the pyrimidine series were converted into triazolopyrimidine derivatives under similar conditions [2, 3]. Compound **V** was also obtained by treatment of **IVa** with methyl iodide in the presence of sodium acetate.

Taking into account that hydrolysis of the thiazole ring in benzothiazole derivatives with formation of 2-sulfanylanilines requires strongly alkaline medium and elevated temperature, we presumed that in our case mild cleavage of the thiazole ring occurs as recyclization of **I** according to synchronous donor–acceptor mechanism through intermediate spirocyclic complex **A** (Scheme 2). This assumption is consistent with the data of [5] where hydrazinolysis of 2-phenacylbenzothiazole (**VI**) was shown to involve intermediate formation of unstable spiro structure **VII**; the latter was also converted into disulfide derivative of 2-sulfanylaniline (compound **VIII**) in dioxane at room temperature.

Although compound **I** tends to undergo recyclization, it reacts with dimethyl acetylenedicarboxylate in a way similar to thiosemicarbazides of the pyrimidine series [1] with formation of dihydrothiadiazole derivative **IX** (Scheme 3).

The structure of the isolated compounds was confirmed by the analytical and ^{1}H NMR data. In addition,

Scheme 3.



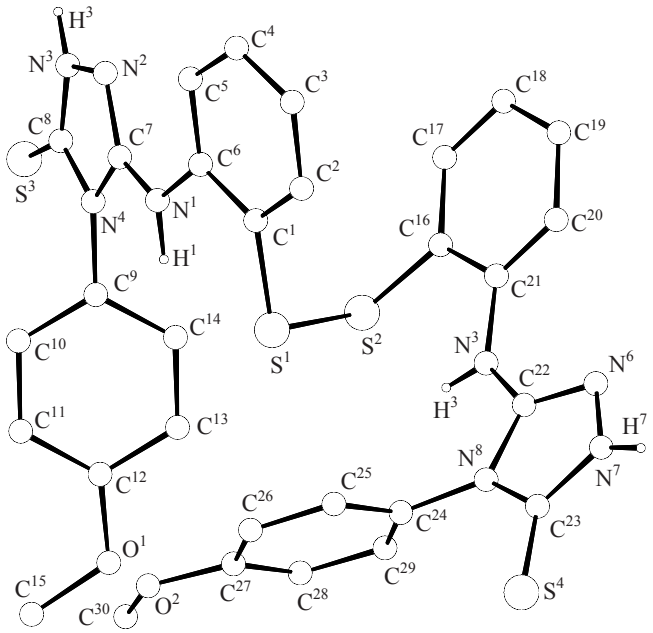


Fig. 1. Structure of the molecule of 2,2′-dithiobis{*N*-[4-(4-methoxyphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]aniline} (**IVb**) according to the X-ray diffraction data. Principal bond lengths (Å) and bond angles (deg): S^1–S^2 2.102(1), S^1–C^1 1.764(3), S^2–C^{16} 1.761(3), N^1–C^6 1.401(3), N^1–C^7 1.350(3), N^2–N^3 1.395(3), N^2–C^7 1.306(3), N^3–C^8 1.333(3), N^4–C^7 1.384(3), N^4–C^8 1.379(3), N^5–C^{21} 1.395(3), N^5–C^{22} 1.357(3), N^6–N^7 1.386(3), N^6–C^{22} 1.304(3), N^7–C^{23} 1.328(3), N^8–C^{22} 1.385(3), N^8–C^{23} 1.383(3); $S^2S^1C^1$ 100.31(9), $S^1S^2C^{16}$ 101.28(9).

the structure of **IVb** was unambiguously proved by X-ray analysis (Fig. 1). Molecule **IVb** is essentially nonplanar: the torsion angle $C^1S^1S^2C^{16}$ reaches 50.2°, the dihedral angle between the C^1–C^6 and C^{16}–C^{21} ring planes is 29.5°, the dihedral angles between the C^1–C^6 and $N^2N^3N^4C^7C^8$ planes is 16.6°, and the C^{16}–C^{21} benzene ring with the $N^6N^7N^8C^{22}C^{23}$ plane forms a dihedral angle of 21.6°. The C^1–C^6 and C^{16}–C^{21} rings are turned relative to the $N^2N^3N^4C^7C^8$ and $N^6N^7N^8C^{22}C^{23}$ heterorings, respectively, through dihedral angles of 65.6 and 65.9°. The $N^2N^3N^4C^7C^8$ and $N^6N^7N^8C^{22}C^{23}$ heterorings are planar within 0.009 and 0.006 Å, respectively. Their geometric parameters indicate considerable delocalization of electron density therein. The N^1 and N^5 atoms are characterized by planar–trigonal bond configuration within the experimental error: the sums of the bond angles at these atoms are equal to 360°. Effective conjugation of lone electron pairs on the N^1 and N^5 atoms with π systems of the $N^2N^3N^4C^7C^8$ and $N^6N^7N^8C^{22}C^{23}$ heterorings makes the N^1–C^7 [1.350(3) Å] and N^5–C^{22} bonds [1.357(3) Å] considerably shorter than the distance 1.43–1.45 Å typical of standard single N(sp^2)–C(sp^2) bond [6, 7].

Molecules **IVb** in crystal are linked to centrosymmetric dimers through fairly strong [8] hydrogen bonds N^3–$H^3\cdots S^{3'}$ [N–H 0.93(4), N···S 3.225(3), H···S 2.31(4) Å; ∠NHS 169(2)°]. Analogous dimers are also formed through N^7–$H^7\cdots S^{4'}$ hydrogen bonds with participation of the other half of the molecule [N–H 0.83(4), N···S 3.253(3), H···S 2.44(4) Å; ∠NHS 166(2)°]. As a result, infinite zigzag chains are formed (Fig. 2).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz) from solutions in DMSO-d_6 using TMS as internal reference.

The X-diffraction data for a 0.38×0.39×0.49-mm single crystal of compound **IVb** were acquired at room temperature on an Enraf–Nonius CAD-4 automatic diffractometer (CuK_α irradiation, λ = 1.54178 Å, θ_{max} = 65°, $0 \le h \le 16$, $0 \le k \le 16$, $-20 \le l \le 19$). Total of 5942 reflections were measured, 5430 of which were independent (R_{int} = 0.014). Monoclinic crystals with the following unit cell parameters: a = 13.754(4), b = 14.033(6), c = 17.137(3) Å; β = 104.9(2)°; V = 3195 Å^3; M 658.9; Z = 4; d_{calc} = 1.37 g/cm^3; μ = 30.77 cm^{-1}; F(000) = 1368; space group $P2_1/c$ (no. 14). The structure was solved by the direct method and was refined by the least-squares procedure in full-matrix anisotropic approximation using CRYSTALS software package [9]; 4035 reflections with $I > 3\sigma(I)$ were used in the refinement (413 refined parameters, 9.8 reflections per parameter). All hydrogen atoms were visualized from the difference synthesis of electron density and were involved in the refinement procedure with fixed positional and thermal factors (only the H^1, H^3, H^5, and H^7 atoms were refined in isotropic approximation). Chebyshev's weight scheme [10] was applied with the following five parameters: 1.28, –0.78, 0.42, –0.05, and –0.21. The final divergence factors were R = 0.042 and R_W = 0.046; goodness of fit 1.004. The final electron density from the Fourier difference series was –0.25 and 0.23 e/Å^3. Absorption by the crystal was taken into account by the azimuthal scanning technique [11]. The complete set of crystallographic data for compound **IVb** was deposited to the Cambridge Crystallographic Data Center (entry no. CCDC 651601).

1-(Benzothiazol-2-yl)-4-phenylthiosemicarbazide (I). Phenyl isothiocyanate, 2.0 ml (0.017 mol), was added to a suspension of 2.30 g (0.014 mol) of

compound **II** in 100 ml of benzene. The mixture was stirred for 1.5 h on heating on a water bath at a bath temperature of 70–75°C. The precipitate was filtered off from the hot mixture and washed first with benzene and then with diethyl ether. Yield 2.96 g (71%), mp 171–172°C. ^{1}H NMR spectrum, δ, ppm: 7.15 m (2H, H_{arom}), 7.33 m (3H, H_{arom}), 7.51 m (3H, H_{arom}), 7.82 m (1H, H_{arom}), 10.11 br.s (1H, NH), 10.24 br.s (2H, NH). Found, %: C 56.22; H 3.88; N 18.42; S 21.24. $C_{14}H_{12}N_4S_2$. Calculated, %: C 55.98; H 4.03; N 18.65; S 21.35.

2,2′-Dithiobis[*N*-(4-aryl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)anilines] IVa–IVc (*general procedure***).** Compound **II**, 1.00 g (6 mmol), was dissolved in 75 ml of ethanol on heating, a solution of 9 mmol of aryl isothiocyanate **IIIa**–**IIIc** in 15 ml of ethanol was added, and the mixture was heated for 1 h under reflux. After cooling, the finely crystalline product was filtered off, washed with diethyl ether, and dried at 70–80°C.

2,2′-Dithiobis[*N*-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)aniline] (IVa). Yield 1.46 g (81%), mp 265–268°C. ^{1}H NMR spectrum, δ, ppm: 6.96 m (1H, H_{arom}), 7.19 m (1H, H_{arom}), 7.36 m (1H, H_{arom}), 7.43 m (2H, H_{arom}), 7.59 m (4H, H_{arom}), 7.80 s (1H, NH), 13.49 s (1H, NH). Found, %: C 55.98; H 3.81; N 18.83; S 21.49. $C_{28}H_{22}N_8S_4$. Calculated, %: C 56.16; H 3.70; N 18.71; S 21.42.

2,2′-Dithiobis{*N*-[4-(4-methoxyphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]aniline} (IVb). Yield 1.17 g (59%), mp 252–254°C. ^{1}H NMR spectrum, δ, ppm: 3.85 s (3H, CH_3), 6.95 m (1H, H_{arom}), 7.10 d (2H, H_{arom}, J = 8.9 Hz), 7.22 m (1H, H_{arom}), 7.30 d (2H, H_{arom}, J = 8.9 Hz), 7.36 m (1H, H_{arom}), 7.62 m (1H, H_{arom}), 7.71 s (1H, NH), 13.43 s (1H, NH). Found, %: C 54.51; H 4.14; N 17.17; S 19.55. $C_{30}H_{26}N_8O_2S_4$. Calculated, %: C 54.69; H 3.98; N 17.01; S 19.47.

2,2′-Dithiobis{*N*-[4-(4-ethoxycarbonylphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]aniline} (IVc). Yield 1.16 g (52%), mp 153–155°C. ^{1}H NMR spectrum, δ, ppm: 1.33 t (3H, CH_3, J = 7.2 Hz), 4.36 q (2H, CH_2, J = 7.2 Hz), 6.95 m (1H, H_{arom}), 7.20 m (1H, H_{arom}), 7.28 m (1H, H_{arom}), 7.40 m (1H, H_{arom}), 7.60 d (2H, H_{arom}, J = 8.6 Hz), 8.04 s (1H, NH), 8.10 d (2H, H_{arom}, J = 8.6 Hz), 13.50 s (1H, NH). Found, %: C 55.21; H 4.26; N 15.03; S 17.18. $C_{34}H_{30}N_8O_4S_4$. Calculated, %: C 54.97; H 4.07; N 15.08; S 17.26.

2,2′-Dithiobis[*N*-(5-methylsulfanyl-4-phenyl-4*H*-1,2,4-triazol-5-yl)aniline] (V). *a*. A mixture of 0.30 g (1 mmol) of compound **I**, 0.12 g (1.5 mmol) of sodium acetate, 0.1 ml (1.5 mmol) of methyl iodide, and 25 ml of ethanol was heated for 1 h under reflux. After cooling, the precipitate was filtered off and washed in succession with water, ethanol, and diethyl ether. Yield 0.115 g (19%), mp 229–231°C (from DMF–ethanol). ^{1}H NMR spectrum, δ, ppm: 2.56 s (3H, CH_3), 6.82 m (1H, H_{arom}), 7.03 m (1H, H_{arom}), 7.35 m (1H, H_{arom}), 7.43 m (2H, H_{arom}), 7.58 m (3H, H_{arom}), 7.68 s (1H, NH), 7.76 m (1H, H_{arom}). Found, %: C 57.61; H 4.29; N 17.66; S 20.38. $C_{30}H_{26}N_8S_4$. Calculated, %: C 57.48; H 4.18; N 17.88; S 20.46.

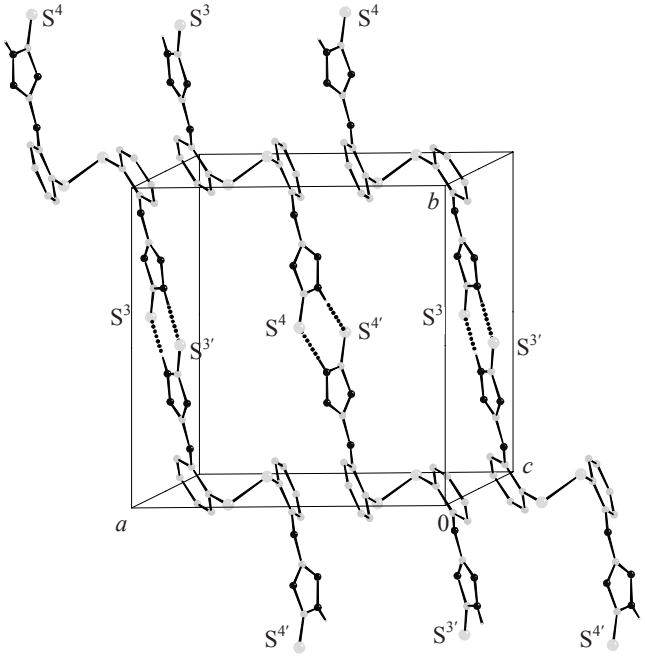


Fig. 2. Packing of 2,2′-dithiobis{*N*-[4-(4-methoxyphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]aniline} (**IVb**) molecules in crystal (the *p*-methoxyphenyl substituents are not shown). Intermolecular hydrogen bonds N–H···S are shown with dotted lines.

b. A mixture of 0.96 g (1.6 mmol) of compound **IVa**, 0.4 g (4.9 mmol) of sodium acetate, 0.3 ml (4.8 mmol) of methyl iodide, and 50 ml of ethanol was heated for 1.5 h under reflux. After cooling, the finely crystalline product was filtered off and washed with water and ethanol. Yield 0.27 g (26%). The product was identical to a sample prepared from compound **I** as described above in *a*.

Methyl 3-(benzothiazol-2-yl)-2-(2-methoxy-2-oxoethyl)-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (IX). A mixture of 0.3 g (1 mmol) of compound **I** and 0.15 ml (1.2 mmol) of dimethyl acetylenedicarboxylate in 20 ml of dioxane was stirred for 25 h at

18–25°C. The solvent was removed under reduced pressure (15–20 mm), the residue was ground with a small amount of acetone, and the finely crystalline product was filtered off and washed on a filter with acetone and hexane. Yield 0.31 g (70%), mp 186–188°C (MeOH). ^{1}H NMR spectrum, δ, ppm: 3.63 s and 3.70 s (3H each, OCH_3), 3.62 d and 4.29 d (1H each, CH_2, J = 16.5 Hz), 7.04 m (1H, H_{arom}), 7.15 m (1H, H_{arom}), 7.30–7.41 m (3H, H_{arom}), 7.53 m (3H, H_{arom}), 7.87 m (1H, H_{arom}), 9.86 s (1H, NH). Found, %: C 54.16; H 4.21; N 12.53; S 14.58. $C_{20}H_{18}N_4O_4S_2$. Calculated, %: C 54.28; H 4.10; N 12.66; S 14.49.

REFERENCES

1. Vas'kevich, R.I., Zborovskii, Yu.L., Staninets, V.I., and Chernega, A.N., *Russ. J. Org. Chem*., 2004, vol. 40, p. 1047.
2. Vas'kevich, R.I., Savitskii, P.V., Zborovskii, Yu.L., Staninets, V.I., Turov, A.V., and Chernega, A.N., *Russ. J. Org. Chem*., 2006, vol. 42, p. 1396.
3. Vas'kevich, R.I., Savitskii, P.V., Zborovskii, Yu.L., Staninets, V.I., Rusanov, E.B., and Chernega, A.N., *Russ. J. Org. Chem*., 2006, vol. 42, p. 1403.
4. Kossowska, B., Prelicz, D., Utko, K., and Wyzgowska, L., *Polish J. Chem*., 1983, vol. 57, p. 341.
5. Dzvinchuk, I.B., Vypirailenko, A.V., and Lozinskii, M.O., *Izv. Ross. Akad. Nauk, Ser. Khim*., 2005, p. 735.
6. Burke-Laing, M. and Laing, M., *Acta Crystallogr., Sect. B*, 1976, vol. 32, p. 3216.
7. Allen, F.H., Kennard, O., Watson, D.G., Brammer, L., Orpen, A.G., and Taylor, R., *J. Chem. Soc., Perkin Trans. 2*, 1987, p. S1.
8. Kuleshova, L.N. and Zorkii, P.M., *Acta Crystallogr., Sect. B*, 1981, vol. 37, p. 1363.
9. Watkin, D.J., Prout, C.K., Carruthers, J.R., and Betteridge, P.W., *CRYSTALS, Issue 10*, Chemical Crystallography Laboratory, Univ. of Oxford, 1996.
10. Carruthers, J.R. and Watkin, D.J., *Acta Crystallogr., Sect. A*, 1979, vol. 35, p. 698.
11. North, A.C.T., Phillips, D.C., and Mathews, F.S., *Acta Crystallogr., Sect. A*, 1968, vol. 24, p. 351.