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Reaction of 3-Oxo-*N*-phenylbutanethioamide with 5-Amino-1*H*-1,2,4-triazoles

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Abstract—Reactions of 3-oxo-*N*-phenylbutanethioamide with 3-substituted 5-amino-1*H*-1,2,4-triazoles in acetic acid led to the formation of 5-methyl-7,8-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-thiones, 7-methyl-5,8-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-5-thiones and 7-methyl-5-phenylamino[1,2,4]triazolo[1,5-*a*]pyrimidines. The structure of the products was proved by the ^{1}H and ^{13}C NMR spectra, X-ray diffraction data, and chemical transformations.

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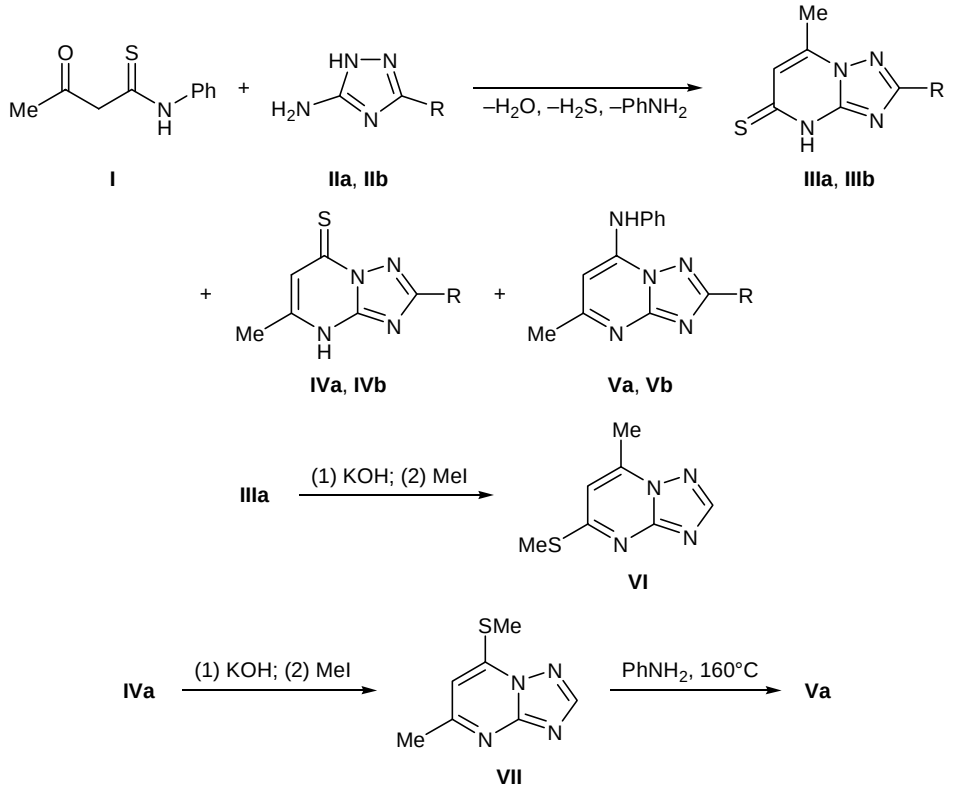
We previously showed that 3-oxo-*N*-phenylbutanethioamide (**I**) possessing several reaction centers can be used to synthesize various heterocyclic compounds, such as thiazole [1], 1,2,4-dithiazolidine [2], pyrazole [3], 1,3-thiazin-4-one, 6-thioxopiperidin-2-one, and thiopyran-4-one derivatives [4]. In the present work we examined reactions of 3-oxo-*N*-phenylbutanethioamide (**I**) with 5-amino-1*H*-1,2,4-triazoles **IIa** and **IIb**, which followed the [3+3]-cyclocondensation pattern. It should be noted that each of the reactants (**I** and **IIa** or **IIb**) possesses several potential reaction centers; therefore, the reaction could give rise to four compounds of the [1,2,4]triazolo[1,5-*a*]pyrimidine series and four compounds of the [1,2,4]triazolo[4,3-*a*]pyrimidine series. Thus the main difficulty was to separate and identify the products.

We found that three types of triazolopyrimidines **III**–**V** were formed in the reactions of 3-oxo-*N*-phenylbutanethioamide (**I**) with 5-amino-1*H*-1,2,4-triazoles **IIa** and **IIb** in acetic acid at 100°C (Scheme 1). A mixture of compounds **III** and **IV** separated from the solution on cooling to room temperature, and triazolopyrimidines **Va** and **Vb** were isolated as individual substances by treatment of the reaction mixture with an aqueous solution of sodium hydrogen carbonate.

Mixtures **IIIa**/**IVa** and **IIIb**/**IVb** cannot be separated by recrystallization from water or organic solvents. According to the ^{1}H NMR data, their ratio did not change after recrystallization. It was also difficult to use chromatographic methods because of poor solubility of these compounds. Therefore, we have developed a procedure for the separation of mixtures **IIIa**/**IVa** and **IIIb**/**IVb**, taking advantage of the better solubility of compounds **IIIa** and **IIIb** in aqueous potassium hydroxide. According to the developed procedure, mixture **IIIa**/**IVa** or **IIIb**/**IVb** was treated with an aqueous solution of potassium hydroxide whose amount was equimolar to the amount of compound **IIIa** or **IIIb** in the mixture, the undissolved material (compound **IVa** or **IVb**) was filtered off, and the filtrate was acidified to precipitate triazolopyrimidine **IIIa** or **IIIb**. The procedure is characterized by a good efficiency and minimal losses of products **III** and **IV**.

The structure of triazolopyrimidines **III**–**V** cannot be determined unambiguously on the basis of their ^{1}H NMR spectra and elemental analyses. Therefore, the structure of compound **Vb** was stidued by the X-ray diffraction method. The results showed that compound **Vb** is 7-methyl-2-methylsulfanyl-*N*-phenyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-amine. The general view of molecule **Vb** is shown in figure. The $N^{1-4}C^{1-5}$ bicyclic system is planar within 0.009 Å. The $C^{7-}C^{12}$ benzene ring with that system forms a dihedral angle of 49.3°. The bond length distribution in the bicyclic fragment suggests essential delocalization of electron density. The N^{5} atom has a planar–trigonal bond configuration (the sum of the bond angles at that atom is 358.9°). Conjugation between the unshared electron pair on the N^{5} atom and π-system of the bicyclic fragment leads to a considerable shortening of the formally

Scheme 1.



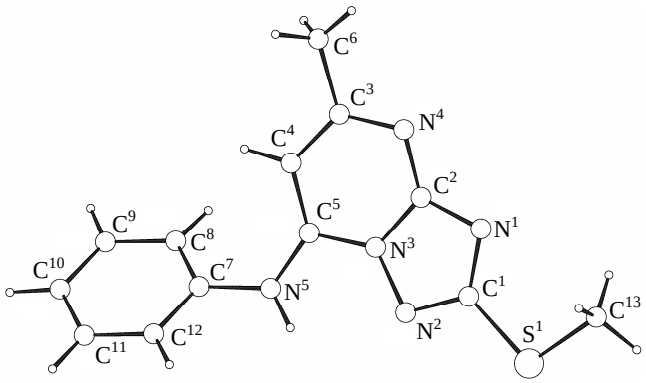
IIa–**Va**, R = H; **IIb**–**Vb**, R = MeS.

single N^5–C^5 bond [1.350(2) Å] against the standard length of a single N_{sp^2}–C_{sp^2} bond (1.43–1.45 Å) [5, 6].

According to the ^{1}H NMR data, triazolopyrimidines **III** and **IV** in neutral medium exist mainly in the thione form. Their ^{1}H NMR spectra contained broadened singlets in a weak field (δ 14.06–14.95 ppm), which should be assigned to NH rather than SH proton; the latter is known [7] to appear in the δ region 3.5–5.0 ppm.

Compounds **IIIa** and **IVa** were subjected to alkylation by treatment with methyl iodide in alkaline medium. Methylation products **VI** and **VII** showed in the ^{1}H NMR spectra singlets at δ 2.72–2.79 ppm from the SCH_3 protons, which were absent in the spectra of the initial compounds. Heating of triazolopyrimidine **VII** with aniline at 160°C was accompanied by liberation of methanethiol, and 5-phenylamino[1,2,4]triazolo[1,5-*a*]pyrimidine (**Va**) was isolated. These data unambiguously indicate that initial compounds **IVa** and **IVb** are 7-methyl-5,8-dihydro[1,2,4]triazolo-[1,5-*a*]pyrimidine-5-thiones.

According to published data [8, 9], the C^2–S signal in the ^{13}C NMR spectra of [1,2,4]triazolo[1,5-*a*]pyrimidines is located at δ_C 163–165 ppm, and that belonging to C^3–S in [1,2,4]triazolo[4,3-*a*]pyrimidines, at δ_C ~143 ppm. We showed in [10, 11] that the C^2 signals of methyl 7-oxo-2-phenyl-7*H*-[1,2,4]triazolo-[5,1-*b*][1,3]thiazine-5-carboxylate and 5-phenyl-5,6-dihydro-7*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-one appear in the ^{13}C NMR spectra in region δ_C 152–153 ppm. We recorded the ^{13}C NMR spectra of triazolopyrimidines **IIIa**, **IIIb**, **Va**, and **Vb**. In the spectra of **Va** and **Vb** (whose structure was proved by X-ray



Structure of the molecule of 7-methyl-2-methylsulfanyl-*N*-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidin-5-amine (**Vb**).

analysis), signals from the C^2 atom were observed at δ_C 154.4 (C–H) and 163.6 ppm (C–S), respectively, which was consistent with the data of [6–9]. Taking into account that the corresponding signals in the spectra of triazolopyrimidines **IIIa** and **IIIb** were located at δ_C 151.8 and 165.1 ppm, respectively, these compounds were assigned the structure of 5-methyl-7,8-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-thiones.

Thus 3-oxo-*N*-phenylbutanethioamide (**I**) reacts with 5-amino-1*H*-1,2,4-triazoles **IIa** and **IIb** in acetic acid to give mixtures of 5-methyl-7,8-dihydro[1,2,4]-triazolo[1,5-*a*]pyrimidine-7-thiones **III**, 7-methyl-5,8-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-5-thiones **IV**, and 7-methyl-*N*-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidin-5-amines **V**. Two reaction centers in triazoles **IIa** and **IIb** (exocyclic amino group and the N^1 atom) are involved in this process, and their reactivities are approximately similar. 3-Oxo-*N*-phenylbutanethioamide (**I**) reacts at the ketone carbonyl carbon atom and carbon atom of the thioamide group; in the first case, the departing molecule is only water, and in the second, aniline and hydrogen sulfide are released.

The ratio of [1,2,4]triazolo[1,5-*a*]pyrimidines **III**, **IV**, and **V** is 1.0:3.0:1.2 in the reaction with triazole **IIa** and 2.8:1.4:1.0 in the reaction with **IIb**. This means that the contribution of the cyclocondensation pathway leading to the formation of [1,2,4]triazolo-[1,5-*a*]pyrimidinethiones **III** and **IV** with elimination of water and aniline is approximately twice as large as that of the pathway leading to 7-methyl-5-phenylamino[1,2,4]triazolo[1,5-*a*]pyrimidines **V** with elimination of water and hydrogen sulfide. Unlike the first reaction, the second pathway is regioselective. Therefore, transamination of the thioamide group in compound **I** with elimination of aniline occurs more readily than its amination accompanied by elimination of hydrogen sulfide. A probable reason is that the double $S{=}C^1$ bond is stronger than the single $N{-}C^1$ bond, which is consistent with the energies of the corresponding bonds reported in [12] (530 and 285 kJ/mol, respectively).

EXPERIMENTAL

The X-ray diffraction data for a single crystal of compound **Vb** (0.28×0.37×0.43 mm) were acquired at room temperature on an Enraf–Nonius CAD-4 automatic four-circle diffractometer (CuK_α irradiation, λ = 1.54178 Å; scan rates ratio $2\theta/\omega = 1.2$, $\theta_{max} = 70°$; spherical segment $0 \le h \le 7$, $0 \le k \le 13$, $-21 \le l \le 21$). Total of 2746 reflections were measured. Monoclinic crystals with the following unit cell parameters: a = 6.921(5), b = 10.718(5), c = 17.622(9) Å; β = 95.25(7)°; V = 1301.6 $Å^3$; M = 271.3; Z = 4; d_{calc} = 1.38 g/cm^3; μ = 21.1 cm^{-1}; $F(000)$ = 570.6; space group $P2_1/n$ (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 [6]. The structure refinement was performed using 2385 reflections with $I > 3\sigma(I)$ (225 refined parameters, 10.6 reflections per parameter). All hydrogen atoms were visualized from the difference synthesis of electron density, and their positions were refined in isotropic approximation. Chebyshev's weight scheme [13] with five parameters (0.72, –1.26, 0.08, –0.69, –0.02) was applied. The final divergence factors were R = 0.037 and R_W = 0.035, GOF 1.142. The residual electron density from the Fourier difference series was 0.18 and –0.22 $e/Å^3$. Absorption by the crystal was taken into account using the azimuthal scanning technique [14]. The complete set of crystallographic data for compound **Vb** was deposited to the Cambridge Crystallographic Data Center (entry no. CCDC 275142).

The NMR spectra were recorded from solutions in DMSO-d_6 on a Varian-300 spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C; the chemical shifts were measured relative to TMS as internal reference.

5-Methyl-7,8-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-thiones IIIa and IIIb, 7-methyl-5,8-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-5-thiones IVa and IVb, and 7-methyl-*N*-phenyl-[1,2,4]triazolo-[1,5-*a*]pyrimidin-5-amines Va and Vb (*general procedure***).** A solution of 1 g (5.2 mmol) of 3-oxo-*N*-phenylbutanethioamide (**I**) and 6.0 mmol of 1*H*-1,2,4-triazol-5-amine (**IIa**) or 3-methylsulfanyl-1*H*-1,2,4-triazol-5-amine (**IIb**) in 5 ml of acetic acid was heated for 5 h at 100°C. The mixture was cooled, and the yellow precipitate containing compounds **III** and **IV** was filtered off, washed on a filter with propan-2-ol (2×3 ml), and dried. Yield of mixture **IIIa/IVa** 0.51 g, ratio **IIIa**:**IVa** = 1:3 (according to the ^1H NMR data). Yield of **IIIb/IVb** 0.67 g, ratio **IIIb**:**IVb** = 2:1.

The filtrate was adjusted to a weakly alkaline reaction by adding 10% aqueous sodium hydrogen carbonate, and the precipitate of compound **Va** or **Vb** was filtered off, washed with water (2×5 ml), and dried. Yield of **Va** 0.21 g (18%), mp 183–185°C (from propan-2-ol). ^1H NMR spectrum, δ, ppm: 2.42 s (3H, 7-CH_3), 6.39 s (1H, 6-H), 7.31 m (1H, H_{arom}), 7.48 m (4H, H_{arom}), 8.51 s (1H, 2-H), 10.21 s (1H, NH).

^{13}C NMR spectrum, δ_C, ppm: 24.6 (7-CH_3), 89.1 (C^6), 124.3 (C_{arom}), 126.1 (C_{arom}), 129.5 (C_{arom}), 136.9 (C_{arom}), 145.9 (C^5), 154.4 (C^2), 155.6 (C^{8a}), 164.2 (C^7). Found, %: C 63.87; H 4.93; N 30.82. $C_{12}H_{11}N_5$. Calculated, %: C 63.99; H 4.92; N 31.09. Yield of **Vb** 0.20 g (14%), mp 178–180°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 2.39 s (3H, 7-CH_3), 2.68 s (3H, SCH_3), 6.31 s (1H, 6-H), 7.28 m (1H, H_{arom}), 7.43 m (4H, H_{arom}), 10.00 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.4 (SCH_3), 24.6 (7-CH_3), 89.0 (C^6), 124.2 (C_{arom}), 125.8 (C_{arom}), 129.3 (C_{arom}), 136.8 (C_{arom}), 144.9 (C^5), 155.9 (C^{8a}), 163.6 (C^2), 165.6 (C^7). Found, %: C 57.82; H 5.02; N 25.62; S 12.03. $C_{13}H_{13}N_5S$. Calculated, %: C 57.55; H 4.83; N 25.81; S 11.82.

Mixture **IIIa**/**IVa**, 0.51 g, was treated with a solution of 0.043 g (0.77 mmol) of potassium hydroxide in 8 ml of water, and the undissolved material (compound **IVa**) was filtered off and dried. Yield 0.33 g (38%), mp 295–297°C (from water). ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, 7-CH_3), 6.91 s (1H, 6-H), 9.30 s (1H, 2-H), 14.95 br.s (1H, N^{8}H). Found, %: C 43.40; H 3.71; N 33.90; S 19.19. $C_6H_6N_4S$. Calculated, %: C 43.36; H 3.64; N 33.71; S 19.29.

The filtrate was acidified with acetic acid, and the precipitate was filtered off and dried. Yield of **IIIa** 0.10 g (12%), mp 323–325°C (from water). ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, 5-CH_3), 6.89 s (1H, 6-H), 8.48 s (1H, 2-H), 14.24 br.s (1H, N^{8}H). ^{13}C NMR spectrum, δ_C, ppm: 18.8 (5-CH_3), 114.7 (C^6), 146.9 (C^{8a}), 147.9 (C^5), 151.8 (C^2), 177.9 (C^7). Found, %: C 43.13; H 3.50; N 33.62; S 19.06. $C_6H_6N_4S$. Calculated, %: C 43.36; H 3.64; N 33.71; S 19.29.

Mixture **IIIb**/**IVb** was separated in a similar way. Yield of **IVb** 0.17 g (16%), mp 265–267°C (from AcOH). ^{1}H NMR spectrum, δ, ppm: 2.24 s (3H, 7-CH_3), 2.49 s (3H, SCH_3) 6.66 s (1H, 6-H), 14.32 br.s (1H, N^{8}H). ^{13}C NMR spectrum, δ_C, ppm: 15.1 (SCH_3), 22.5 (7-CH_3), 115.5 (C^6), 146.9 (C^{8a}), 150.0 (C^7), 160.7 (C^2), 174.1 (C^5). Found, %: C 39.83; H 3.66; N 26.48; S 30.05. $C_7H_8N_4S_2$. Calculated, %: C 39.61; H 3.80; N 26.39; S 30.20. Yield of **IIIb** 0.39 g (35%), mp 274–275°C (from AcOH). ^{1}H NMR spectrum, δ, ppm: 2.31 s (3H, 5-CH_3), 2.63 s (3H, SCH_3), 6.79 s (1H, 6-H), 14.06 br.s (1H, N^{8}H). ^{13}C NMR spectrum, δ_C, ppm: 13.6 (SCH_3), 18.0 (7-CH_3), 114.0 (C^6), 145.0 (C^{8a}), 147.6 (C^5), 165.1 (C^2), 176.8 (C^7). Found, %: C 39.52; H 3.85; N 26.19; S 30.29. $C_7H_8N_4S_2$. Calculated, %: C 39.61; H 3.80; N 26.39; S 30.20.

5-Methyl-7-methylsulfanyl[1,2,4]triazolo[1,5-*a*]-pyrimidine (VI). Methyl iodide, 0.8 g (5.6 mmol), was added dropwise to a solution of 0.83 g (5.0 mmol) of compound **IIIa** and 0.28 g (5.0 mmol) of KOH in 5 ml of ethanol and 3 ml of water. The mixture was stirred for 1 h at 30°C and evaporated to a volume of 3 ml, and the precipitate was filtered off. Yield 0.7 g (78%), mp 187–190°C (from 75% ethanol). ^{1}H NMR spectrum, δ, ppm: 2.62 s (3H, 5-CH_3), 2.72 s (3H, SCH_3), 7.19 s (1H, 6-H), 8.49 s (1H, 2-H). Found, %: C 46.52; H 4.22; N 30.82; S 18.04. $C_7H_8N_4S$. Calculated, %: C 46.65; H 4.47; N 31.09; S 17.79.

7-Methyl-5-methylsulfanyl[1,2,4]triazolo[1,5-*a*]-pyrimidine (VI) was synthesized in a similar way from compound **IVa**. Yield 0.73 g (81%), mp 220–222°C (from 75% ethanol). ^{1}H NMR spectrum, δ, ppm: 2.58 s (3H, 7-CH_3), 2.79 s (3H, SCH_3), 6.99 s (1H, 6-H), 9.12 s (1H, 2-H). Found, %: C 46.73; H 4.33; N 31.19; S 17.94. $C_7H_8N_4S$. Calculated, %: C 46.65; H 4.47; N 31.09; S 17.79.

Aminolysis of 7-methyl-5-methylsulfanyl[1,2,4]-triazolo[1,5-*a*]pyrimidine (VII). A mixture of 0.45 g (2.5 mmol) of compound **VII** and 0.31 g (3.3 mmol) of aniline was heated for 1 h at 160°C. The mixture was cooled and diluted with 5 ml of diethyl ether, and the precipitate was filtered off and dried. Yield of **Va** 0.47 g (84%), mp 183–185°C (from propan-2-ol). Found, %: C 64.12; H 5.07; N 30.93. $C_{12}H_{11}N_5$. Calculated, %: C 63.99; H 4.92; N 31.09. The ^{1}H NMR spectra of samples of **Va** obtained in the reaction of 3-oxobutanethioamide **I** with aminotriazole **IIa** and by aminolysis of [1,2,4]triazolo[1,5-*a*]pyrimidine **VIIa** were fully identical, and their mixture showed no depression of the melting point.

REFERENCES

1. Borisevich, A.N., Samoilenko, L.S., Lozinskii, M.O., Rusanov, E.B., and Chernega, A.N., *Russ. J. Gen. Chem*., 2001, vol. 71, p. 1767.
2. Borisevich, A.N. and Pel'kis, P.S., *Khim. Geterotsikl. Soedin*., 1979, no. 11, p. 1479.
3. Britsun, V.N., Bazavova, I.M., Bodnar, V.N., Chernega, A.N., and Lozinskii, M.O., *Khim. Geterotsikl. Soedin*., 2005, no. 1, p. 120.
4. Britsun, V.N., Borisevich, A.N., Samoilenko, L.S., and Lozinskii, M.O., *Russ. J. Org. Chem*., 2005, vol. 41, p. 283.
5. Burke-Laing, M. and Laing, M., *Acta Crystallogr., Sect. B*., 1976, vol. 32, no. 12, p. 3216.
6. Allen, F.H., Kennard, O., Watson, D.G., Brammer, L., Orpen, A.G., and Taylor, R., *J. Chem. Soc., Perkin Trans. 2*, 1987, no. 12, p. S1.

7. Gordon, A.J. and Ford, R.A., *The Chemist's Companion*, New York: Wiley, 1972. Translated under the title *Sputnik khimika*, Moscow: Mir, 1976, p. 278.
8. Reiter, J., Pongo, L., Somorai, T., and Pallagi, I., *Monatsh. Chem*., 1990, vol. 121, p. 173.
9. Reiter, J., Pongo, L., and Dvortsak, P., *Tetrahedron*, 1987, vol. 43, p. 2497.
10. Britsun, V.N., Esipenko, A.N., Chernega, A.N., and Lozinskii, M.O., *Russ. J. Org. Chem*., 2005, vol. 41, p. 108.
11. Britsun, V.N. and Lozinskii, M.O., *Khim. Geterotsikl. Soedin*., 2004, no. 8, p. 1256.
12. Gauptman, Z., Grefe, Yu., and Remane, Kh., *Organicheskaya khimiya* (Organic Chemistry), Moscow: Khimiya, 1979, p. 52.
13. Watkin, D.J., Prout, C.K., Carruthers, J.R., and Betteridge, P.W., *CRYSTALS, Issue 10*, Chemical Crystallography Laboratory, Univ. of Oxford, 1996.
14. Carruthers, J.R. and Watkin, D.J., *Acta Crystallogr., Sect. A*, 1979, vol. 35, no. 3, p. 698.