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Reaction of 4-Aryl-1-(4-oxo-3,4-dihydrothieno-[2,3-*d*]pyrimidin-2-yl)thiosemicarbazides with Dimethyl Acetylenedicarboxylate

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Abstract—4-Aryl-1-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)thiosemicarbazides react with dimethyl acetylenedicarboxylate in methanol to give the corresponding methyl {3-aryl-4-oxo-2-[(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)hydrazono]-1,3-thiazolidin-5-ylidene}acetates, whereas in dioxane methyl 5-arylamino-2-methoxycarbonylmethyl-3-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-2,3-dihydro-1,3,4-thiadiazole-2-carboxylates are mainly formed.

We previously showed that 1-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-4-phenylthiosemicarbazides substituted at positions *5* and *6* of the fused heterocyclic system react with alkyl halides to afford angular triazolothienopyrimidine derivatives [1]. The reaction begins with nucleophilic substitution of the halogen atom in alkyl halide by the thiosemicarbazide sulfur atom, and the subsequent intramolecular ring closure is accompanied by elimination of thiolic fragment. Taking into account that dimethyl acetylenedicarboxylate tends to participate in nucleophilic addition processes, in the present work we examined its reaction with 4-aryl-1-(5,6-dimethyl- and 5,6-tetramethylene-4-oxo-3,4-dihydrotieno[2,3-*d*]pyrimidin-2-yl)thiosemicarbazides **I**–**III**.

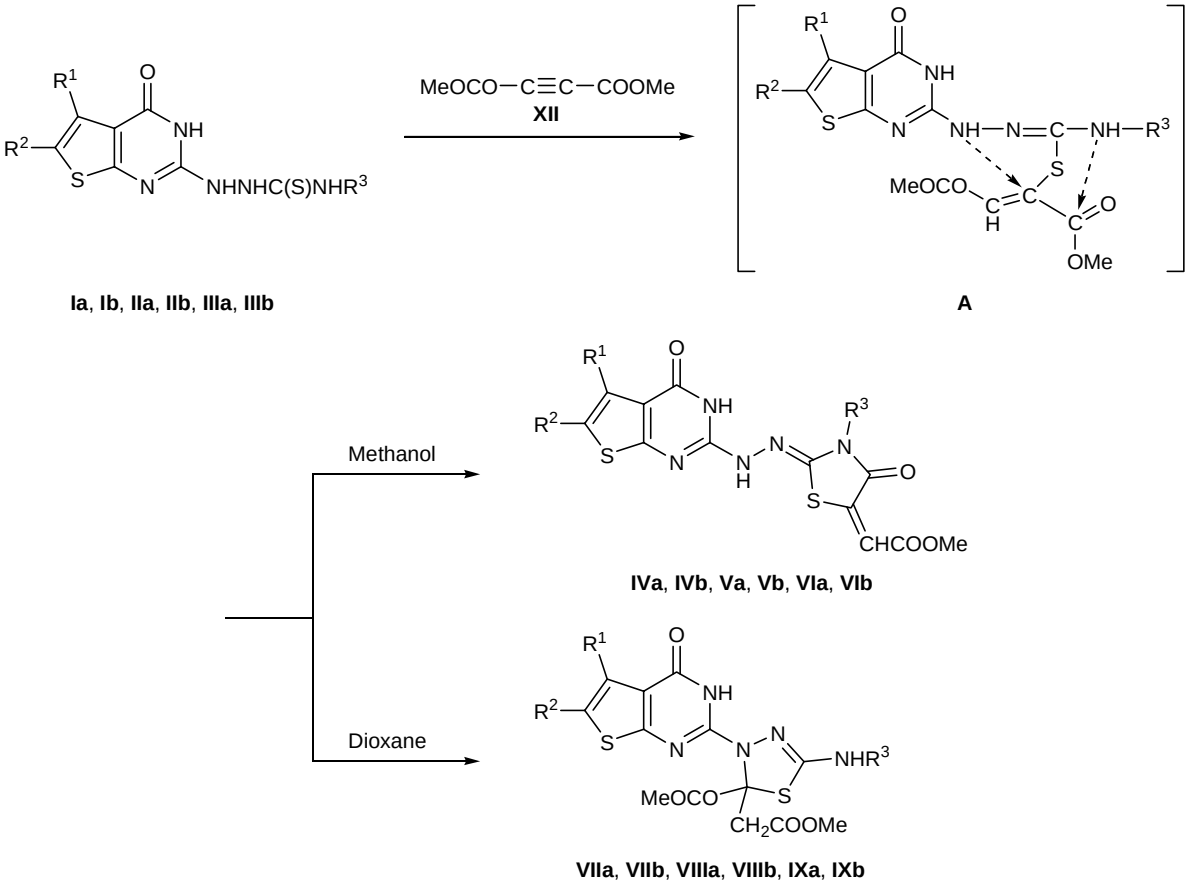
We have found that compounds **I**–**III** react with dimethyl acetylenedicarboxylate in methanol to afford thiazolidine derivatives **IV**–**VI**, which is well consistent with published data [2]. However, when dioxane was used as solvent, we isolated dihydrothiadiazole derivatives **VII**–**IX**. Here, the nature of substituent in the benzene ring of the thiosemicarbazide fragment exerted a strong effect on the cyclization direction. *para*-Methoxy-substituted compounds gave rise to mixtures of products **V** and **VIII**, while from *para*-ethoxycarbonyl analogs, as well as from unsubstituted derivatives, dihydrothiadiazoles **VII** and **IX** were formed exclusively (Scheme 1).

These results led us to presume that the initial reaction step is nucleophilic addition of the thiosemicarbazide sulfur atom at the triple bond of dimethyl acetylenedicarboxylate (**XII**) to give intermediate **A**; the subsequent intramolecular cyclization involves one of the two possible nucleophilic centers, N^1 or N^4 atoms of the thiosemicarbazide fragment. In methanol, nucleophilic attack by the N^4 atom is directed at the carbonyl carbon atom of the α-methoxycarbonyl group, resulting in formation of thiazolidines **IV**–**VI**. The presence of protons in the reaction medium favors elimination of methoxy group in the final (rate-determining) stage.

The intramolecular cyclization of intermediate **A** in dioxane via addition of N^1 at the double carbon–carbon bond follows the Markownikoff rule. In this case, the major products are thiadiazole derivatives **VII**–**IX**. Dioxane is an aprotic solvent which is more basic than methanol, and it favors just that reaction direction. However, introduction of a methoxy group into the *para* position of the benzene ring considerably increases the nucleophilicity of N^4; therefore, the cyclization of **II** can take both paths simultaneously.

The structure of the products was confirmed by elemental analysis and ^{1}H and IR spectra. The structure of **VIIb** was unambiguously proved by the X-ray diffraction method. The principal bond lengths and bond angles are given in table, and Figure 1 shows the general view of the molecule. The bicyclic system $S^1C^1C^2C^3C^4N^1C^5N^2C^6$ is almost planar: deviations of atoms from the mean-square plane do not exceed 0.056 Å, and the dihedral angle between the $S^1C^1C^2C^3C^4$ and $C^3C^4N^1C^5N^2C^6$ rings is

Scheme 1.



$R^1R^2 = (CH_2)_4$ (**a**), $R^1 = R^2 = Me$ (**b**); **I**, **IV**, **VII**, R^3 = Ph; **II**, **V**, **VIII**, R^3 = 4-$MeOC_6H_4$; **III**, **VI**, **IX**, R^3 = 4-$EtOCOC_6H_4$.

as small as 4.3°. The five-membered ring $S^2C^9N^4N^3C^{10}$ is not planar: it has an *envelope* conformation. The bond system S^2–C^9=N^4–N^3 is almost ideally planar; the C^{10} atom deviates from that plane by –0.423 Å; and the $S^2C^{10}N^3$ fragment with the S^2–C^9=N^4–N^3 plane forms an angle of 24.0°. The $C^{16}C^{17}C^{18}C^{19}C^{20}C^{21}$ benzene ring is almost coplanar to the $S^2C^9N^4N^3$ fragment: the corresponding dihedral angle is 2.3°. The N^2 and N^5 atoms have planar–trigonal bond configuration, and the N^3 atom is slightly pyramidal; the sum of the bond angles at these atoms is 360.0, 359.9, and 349.2°, respectively. The N^5–C^9 bond is shortened to 1.365(4) Å against the standard N(sp^2)–C(sp^2) bond length (1.43–1.45 Å [3, 4]) due to effective $n(N^5)$–$\pi(C^9{=}N^4)$ conjugation. Likewise, the $n(N^3)$–$\pi(C^5{=}N^1)$ interaction makes the N^3–C^5 bond shorter [to 1.394(4) Å], and the N^2–C^6 bond is shortened to 1.404(4) Å as a result of $n(N^2)$–$\pi(C^6{=}O^1)$ conjugation. Repulsion between the spatially close N^4 and C^{17} atoms [the N^4–C^{17} distance is 2.974 (4) Å which is considerably shorter than the sum of the corresponding van der Waals radii, 3.20 Å] leads to increase of the $N^5C^{16}C^{17}$ bond angle to 124.3(3)° relative to the $N^5C^{16}C^{21}$ bond angle [116.3(3)°].

Molecules of **VIIb** in crystal give rise to centrosymmetric dimers (Fig. 2) via medium-strength hydrogen bonds N^2–$H^2\cdots O^1$ [5] with the following parameters: $N^2\cdots O^1$ 2.927(4), $H^2\cdots O^1$ 2.09(4), N^2–H^2 0.85(4) Å; $\angle N^2H^2O^1$ 164(2)°. The dimers are linked through hydrogen bonds N^5–$H^5\cdots O^4$ [$N^5\cdots O^4$ 2.918(4), $H^5\cdots O^4$ 2.06(3), N^5–H^5 0.86(3) Å, $\angle N^5H^5O^4$ 179(2)°] to form an infinite network.

The ^{1}H NMR spectra of **IV**–**VI** contain a singlet at δ 3.76–3.78 ppm from the methoxy group and a singlet at δ 6.93–6.99 ppm typical of the C^5=CH proton. The positions of other signals insignificantly differ from those present in the spectra of the initial compounds. Compounds **VII**–**IX** characteristically give rise to two singlets from the ester methoxy groups at δ 3.61–3.63 and 3.66–3.67 ppm and two doublets from the C^2–CH_2 protons at δ 3.43–3.48 and 3.96–4.00 ppm.

EXPERIMENTAL

The IR spectra were measured on a UR-20 spectrometer from samples prepared as KBr pellets. The ^{1}H NMR spectra were recorded on a Varian VXR-300 instrument (300 MHz) in DMSO-d_6 using TMS as internal reference.

The X-ray diffraction data for a single crystal of **VIIb** (0.22×0.34×0.37 mm) were acquired at room temperature on an Enraf–Nonius CAD-4 automatic four-circle diffractometer (MoK_α irradiation, λ = 0.71069 Å, scan rate ratio 2θ/ω = 1.2, θ_{max} = 25°, spherical segment $0 \le h \le 11$, $0 \le k \le 23$, $-11 \le l \le 11$). Total of 4358 reflections were measured, 3804 of which were symmetry-independent (R_{int} = 0.026). Monoclinic crystal system with the following unit cell parameters: a = 8.224(2), b = 9.183(3), c = 30.439(11) Å; β = 90.47(2)°; V = 2299(1) Å^3; M = 487.5; Z = 4; d_{calc} = 1.41 g/cm^3; μ = 2.62 cm^{-1}; F(000) = 1017.1; space group $P2_1/c$. 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]; 2187 reflections with $I > 3(I)$ were used in the refinement (306 parameters, number of reflections per parameter 7.1). All hydrogen atoms were visualized from the difference synthesis of electron density and were included into the calculation with fixed positional and thermal parameters (only the H^2 and H^5 atoms involved in hydrogen bonding were refined in isotropic approximation). The Chebyshev weight scheme [7] with five parameters: 0.86, 0.74, 0.82, 0.25, and 0.21 was applied. The final divergence factors were R = 0.041 and R_W = 0.041, GOF = 1.153. The residual electron density from the Fourier difference series was 0.24 and –0.21 e/Å^3. Absorption by the crystal was taken into account using the azimuthal scanning technique [8]. The complete set of crystallographic data for compound **VIIb** was deposited to the Cambridge Structural Database (entry no. CCDC 205977).

Initial 1-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-4-phenylthiosemicarbazides (**I**) were described previously [1].

4-(*p*-Methoxyphenyl)- and 4-(*p*-ethoxycarbonylphenyl)-1-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)thiosemicarbazides II and III (*general procedure*). A solution of 0.015 mol of *p*-methoxyphenyl or *p*-ethoxycarbonylphenyl isothiocyanate in 20 ml of ethanol was added to a suspension of 0.01 mol of 4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-ylhydrazine in 50 ml of ethanol. The mixture was heated for 2 h under reflux and cooled, and the precipitate was filtered off and washed with ethanol and diethyl ether.

Principal bond lengths (d, Å) and bond angles (ω, deg) in the molecule of (**VIIb**)

Bond	d	Angle	ω
S^1–C^1	1.752(4)	$C^1S^1C^4$	91.12(17)
S^1–C^4	1.714(4)	$C^9S^2C^{10}$	89.38(15)
S^2–C^9	1.779(4)	$C^4N^1C^5$	114.0(3)
S^2–C^{10}	1.840(3)	$C^5N^2C^6$	23.1(3)
N^1–C^4	1.374(4)	$N^4N^3C^5$	114.8(3)
N^1–C^5	1.296(4)	$N^4N^3C^{10}$	116.4(2)
N^2–C^5	1.367(4)	$C^5N^3C^{10}$	118.0(3)
N^2–C^6	1.404(4)	$N^3N^4C^9$	109.4(3)
N^3–N^4	1.419(4)	$C^9N^5C^{16}$	128.9(3)
N^3–C^5	1.394(4)	$S^1C^1C^2$	12.8(3)
N^3–C^{10}	1.489(4)	$C^1C^2C^3$	111.9(3)
N^4–C^9	1.283(4)	$C^2C^3C^4$	112.2(3)
N^5–C^9	1.365(4)	$C^4C^3C^6$	118.1(3)
N^5–C^{16}	1.410(5)	$S^1C^4C^3$	12.0(2)
C^1–C^2	1.340(5)	$N^1C^4C^3$	126.5(3)
C^2–C^3	1.454(4)	$N^1C^5N^2$	125.1(3)
C^3–C^4	1.382(4)	$N^2C^6C^3$	113.1(3)
C^3–C^6	1.441(5)	$S^2C^9N^4$	117.3(3)
		$S^2C^{10}N^3$	101.2(2)

4-(*p*-Methoxyphenyl)-1-(4-oxo-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl)thiosemicarbazide (IIa). Yield 3.97 g (99%), mp >350°C. IR spectrum, ν, cm^{-1}: 3340, 3285, 3160, 2950 (NH); 1660 (C=O); 1610 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.75 m (4H, CH_2), 2.64–2.79 m (4H, CH_2), 3.74 s (3H, CH_3), 6.89 d (2H, H_{arom}, J = 8.7 Hz), 7.35 d (2H, H_{arom}, J = 9.0 Hz), 8.61 br.s (1H, NH), 9.51 s (1H, NH), 9.77 s (1H, NH), 11.15 br.s (1H, NH). Found, %: C 53.69; H 4.63; N 17.39; S 15.91. $C_{18}H_{19}N_5O_2S_2$. Calculated, %: C 53.85; H 4.77; N 17.44; S 15.97.

1-(5,6-Dimethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]-pyrimidin-2-yl)-4-(*p*-methoxyphenyl)thiosemicarbazide (IIb). Yield 3.49 g (93%), mp >330°C. IR spectrum, ν, cm^{-1}: 3340, 3160, 2980 (NH); 1660 (C=O); 1605 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.26 s and 2.31 s (6H, CH_3), 3.74 s (3H, CH_3O), 6.89 d (2H, H_{arom}, J = 9.0 Hz), 7.34 d (2H, H_{arom}, J = 8.7 Hz), 8.62 br.s (1H, NH), 9.53 s (1H, NH), 9.79 s (1H, NH),

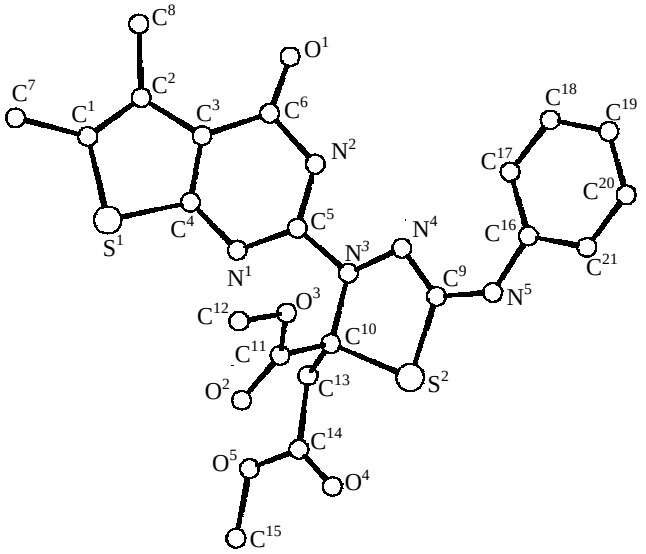


Fig. 1. Structure of the molecule of methyl 3-(5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)-2-methoxycarbonylmethyl-5-phenylamino-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (**VIIb**) according to the X-ray diffraction data (hydrogen atoms are not shown).

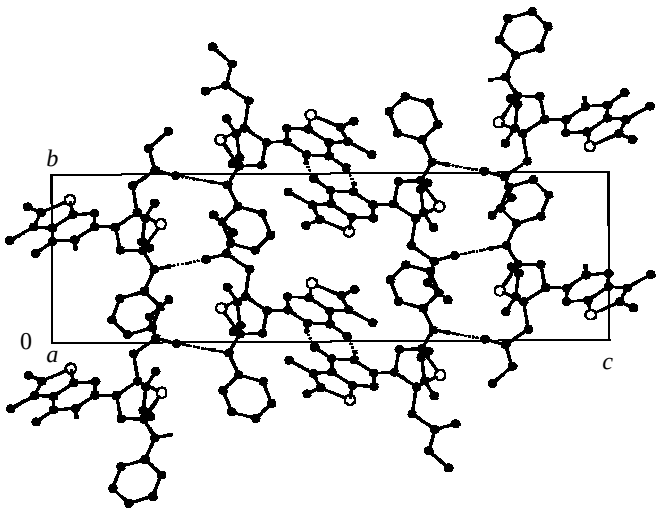


Fig. 2. Packing of molecules **VIIb** in crystal (projection onto the *ac* plane). Intermolecular hydrogen bonds are shown as dotted lines.

11.21 br.s (1H, NH). Found, %: C 51.03; H 4.49; N 18.57; S 17.05. $C_{16}H_{17}N_5O_2S_2$. Calculated, %: C 51.18; H 4.56; N 18.65; S 17.08.

4-(*p*-Ethoxycarbonylphenyl)-1-(4-oxo-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl)-thiosemicarbazide (IIIa). Yield 3.19 g (72%), mp >330°C. IR spectrum, ν, cm^{-1}: 3330, 3300, 3170 (NH); 1710, 1665 (C=O); 1610 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.31 t (3H, CH_3, J = 7.2 Hz), 1.76 m (4H, CH_2), 2.64–2.79 m (4H, CH_2), 4.30 q (2H, CH_2O, J = 7.2 Hz), 7.80 d (2H, H_{arom}, J = 8.7 Hz), 7.91 d (2H, H_{arom}, J = 8.7 Hz), 8.73 br.s (1H, NH), 9.84 br.s (1H, NH), 10.13 s (1H, NH), 11.31 br.s (1H, NH). Found, %: C 54.06; H 4.01; N 15.63; S 14.38. $C_{20}H_{21}N_5O_3S_2$. Calculated, %: C 54.16; H 4.77; N 15.79; S 14.46.

1-(5,6-Dimethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]-pyrimidin-2-yl)-4-(*p*-ethoxycarbonylphenyl)thiosemicarbazide (IIIb). Yield 2.96 g (71%), mp >330°C. IR spectrum, ν, cm^{-1}: 3280, 3150, 2900 (NH); 1710, 1665 (C=O); 1615 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, CH_3, J = 7.2 Hz), 2.27 s and 2.32 s (6H, CH_3), 4.30 q (2H, CH_2O, J = 7.2 Hz), 7.80 d (2H, H_{arom}, J = 8.7 Hz), 7.91 d (2H, H_{arom}, J = 8.7 Hz), 8.72 br.s (1H, NH), 9.87 br.s (1H, NH), 10.14 s (1H, NH), 11.33 br.s (1H, NH). Found, %: C 51.67; H 4.48; N 16.61; S 15.23. $C_{18}H_{19}N_5O_3S_2$. Calculated, %: C 51.78; H 4.59; N 16.77; S 15.36.

Methyl {3-aryl-4-oxo-2-[(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)hydrazono]-1,3-thiazolidin-5-ylidene}acetates IV–VI (*general procedure*). A mixture of 2 mmol of compound **I–III** and 0.37 ml (3 mmol) of dimethyl acetylenedicarboxylate (**XII**) in 30 ml of methanol was heated for 1 h under reflux and was left to stand for crystallization. The precipitate was filtered off and washed on a filter with methanol and diethyl ether.

Methyl {4-oxo-2-[(4-oxo-3,4,5,6,7,8-hexahydro-[1]benzothieno[2,3-*d*]pyrimidin-2-yl)hydrazono]-3-phenyl-1,3-thiazolidin-5-ylidene}acetate (IVa). Yield 0.73 g (76%), mp 258–260°C (from metanol). IR spectrum, ν, cm^{-1}: 3340, 3085 (NH); 1730, 1660 (C=O); 1600 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.75 m (4H, CH_2), 2.65–2.80 m (4H, CH_2), 3.77 s (3H, CH_3O), 6.92 d (2H, H_{arom}, J = 7.5 Hz), 6.95 s (1H, CH), 7.22 t (1H, H_{arom}, J = 7.5 Hz), 7.43 t (2H, H_{arom}, J = 8.1 Hz), 9.92 br.s (1H, NH), 12.10 br.s (1H, NH). Found, %: C 54.77; H 3.81; N 14.47; S 13.26. $C_{22}H_{19}N_5O_4S_2$. Calculated, %: C 54.87; H 3.98; N 14.54; S 13.32.

Methyl {2-[(5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)hydrazono]-4-oxo-3-phenyl-1,3-thiazolidin-5-ylidene}acetate (IVb). Yield 0.65 g (71%), mp 269–271°C (from methanol). IR spectrum, ν, cm^{-1}: 3340, 3080 (NH); 1720, 1660 (C=O); 1600 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.27 s and 2.32 s (6H, CH_3), 3.77 s (3H, CH_3O), 6.92 d (2H, H_{arom}, J = 7.8 Hz), 6.95 s (1H, CH), 7.22 t (1H, H_{arom}, J = 7.2 Hz), 7.43 t (2H, H_{arom}, J = 7.8 Hz), 9.88 br.s (1H, NH), 12.10 br.s (1H, NH). Found, %: C 52.68; H 3.75; N 15.32; S 14.05. $C_{20}H_{17}N_5O_4S_2$. Calculated, %: C 52.74; H 3.76; N 15.37; S 14.08.

Methyl {3-(*p*-methoxyphenyl)-4-oxo-2-[(4-oxo-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl)hydrazono]-1,3-thiazolidin-5-ylidene} acetate (Va). Yield 0.74 g (72%), mp 222–224°C (from methanol–dioxane). IR spectrum, ν, cm^{-1}: 3330, 2940 (NH); 1730, 1660 (C=O); 1600 (C=N). ^1H NMR spectrum, δ, ppm: 1.74 m (4H, CH_2), 2.64–2.79 m (4H, CH_2), 3.76 s (3H, CH_3O), 3.77 s (3H, CH_3), 6.88 d (2H, H_{arom}, J = 8.4 Hz), 6.93 s (1H, CH), 6.99 d (2H, H_{arom}, J = 8.7 Hz), 9.88 br.s (1H, NH), 12.07 br.s (1H, NH). Found, %: C 53.89; H 4.02; N 13.56; S 12.47. $C_{23}H_{21}N_5O_5S_2$. Calculated, %: C 54.00; H 4.14; N 13.69; S 12.54.

Methyl {2-[(5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)hydrazono]-3-(*p*-methoxyphenyl)-4-oxo-1,3-thiazolidin-5-ylidene}acetate (Vb). Yield 0.74 g (76%), mp 254–256°C (from methanol–dioxane). IR spectrum, ν, cm^{-1}: 3340, 3070 (NH); 1720, 1660 (C=O); 1600 (C=N). ^1H NMR spectrum, δ, ppm: 2.27 s and 2.32 s (6H, CH_3), 3.76 s (3H, CH_3O), 3.78 s (3H, CH_3O), 6.88 d (2H, H_{arom}, J = 9.0 Hz), 6.92 s (1H, CH), 6.99 d (2H, H_{arom}, J = 9.0 Hz), 9.81 br.s (1H, NH), 12.01 br.s (1H, NH). Found, %: C 51.86; H 3.89; N 14.35; S 13.20. $C_{21}H_{19}N_5O_5S_2$. Calculated, %: C 51.95; H 3.94; N 14.42; S 13.21.

Methyl {3-(*p*-ethoxycarbonylphenyl)-4-oxo-2-[(4-oxo-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]-pyrimidin-2-yl)hydrazono]-1,3-thiazolidin-5-ylidene}acetate (VIa). Yield 0.69 g (62%), mp 253–255°C (from methanol). IR spectrum, ν, cm^{-1}: 3330, 3065, 2950, 2860 (NH); 1745, 1720, 1660 (C=O); 1600 (C=N). ^1H NMR spectrum, δ, ppm: 1.32 t (3H, CH_3, J = 7.2 Hz), 1.79 m (4H, CH_2), 2.65–2.80 m (4H, CH_2), 3.77 s (3H, CH_3), 4.31 q (2H, CH_2, J = 7.2 Hz), 6.99 s (1H, CH), 7.05 d (2H, H_{arom}, J = 8.4 Hz), 8.02 d (2H, H_{arom}, J = 8.4 Hz), 9.96 br.s (1H, NH), 12.12 br.s (1H, NH). Found, %: C 54.14; H 4.17; N 15.13; S 11.47. $C_{25}H_{23}N_5O_6S_2$. Calculated, %: C 54.24; H 4.19; N 15.18; S 11.58.

Methyl {2-[(5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)hydrazono]-3-(*p*-ethoxycarbonylphenyl)-4-oxo-1,3-thiazolidin-5-ylidene} acetate (VIb). Yield 0.61 g (58%), mp 227–229°C (from methanol). IR spectrum, ν, cm^{-1}: 3340, 3070 (NH); 1720, 1660 (C=O); 1590 (C=N). ^1H NMR spectrum, δ, ppm: 1.33 t (3H, CH_3, J = 7.2 Hz), 2.27 s and 2.32 s (6H, CH_3), 3.78 s (3H, CH_3O), 4.32 q (2H, CH_2, J = 7.2 Hz), 6.99 s (1H, CH), 7.06 d (2H, H_{arom}, J = 8.4 Hz), 8.02 d (2H, H_{arom}, J = 8.4 Hz), 9.93 br.s (1H, NH), 12.11 br.s (1H, NH). Found, %: C 53.30; H 3.98; N 13.19; S 12.09. $C_{23}H_{21}N_5O_6S_2$. Calculated, %: C 53.36; H 4.01; N 13.27; S 12.16.

Reaction of 4-aryl-1-(4-oxo-3,4-dihydrothieno-[2,3-*d*]pyrimidin-2-yl)thiosemicarbazides (I–III) with dimethyl acetylenedicarboxylate (XII) in dioxane (*general procedure*). A mixture of 2 mmol of compound **I–III** and 3 mmol (0.37 ml) of compound **XII** in 30 ml of dioxane was heated for 20 min. The resulting solution was evaporated under reduced pressure, the residue was dissolved in 50–75 ml of acetone (if an undissolved material remained, it was separated), and the solvent was allowed to evaporate. The residue was treated with diethyl ether, and the precipitate was filtered off. The product was additionally purified by recrystallization from methanol. In the reaction of compounds **IIa** and **IIb** with dimethyl acetylenedicarboxylate, apart from thiadiazolidine derivatives **VIIIa** and **VIIIb**, we also isolated compounds **Va** (yield 0.39 g, 38%) and **Vb** (yield 0.20 g, 21%). For this purpose, the reaction mixture was evaporated by 2/3, and the precipitate (**Va** or **Vb**) was filtered off.

Methyl 2-methoxycarbonylmethyl-3-(4-oxo-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl)-5-phenylamino-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (VIIa). Yield 0.43 g (42%), mp 182–184°C (from methanol). IR spectrum, ν, cm^{-1}: 3380, 3290, 2950 (NH); 1730, 1680, 1650 (C=O); 1600 (C=N). ^1H NMR spectrum, δ, ppm: 1.76 m (4H, CH_2), 2.63–2.80 m (4H, CH_2), 3.44 d (1H, CH, J = 16.5 Hz), 3.61 s and 3.67 s (6H, CH_3O), 3.98 d (1H, CH, J = 16.5 Hz), 7.02 t (1H, H_{arom}, J = 7.8 Hz), 7.34 t (2H, H_{arom}, J = 7.8 Hz), 7.61 d (2H, H_{arom}, J = 8.1 Hz), 9.70 s (1H, NH), 10.88 s (1H, NH). Found, %: C 53.64; H 4.41; N 13.56; S 12.39. $C_{23}H_{23}N_5O_5S_2$. Calculated, %: C 53.79; H 4.51; N 13.64; S 12.49.

Methyl 3-(5,6-dimethyl-4-oxo-3,4-dihydrothieno-[2,3-*d*]pyrimidin-2-yl)-2-methoxycarbonylmethyl-5-phenylamino-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (VIIb). Yield 0.26 g (27%), mp 202–204°C (from methanol). IR spectrum, ν, cm^{-1}: 3345 (NH): 1730, 1700, 1660 (C=O); 1595 (C=N). ^1H NMR spectrum, δ, ppm: 2.26 s and 2.32 s (6H, CH_3), 3.44 d (1H, CH, J = 16.5 Hz), 3.61 s and 3.67 s (6H, CH_3O), 3.98 d (1H, CH, J = 16.8 Hz), 7.02 t (1H, H_{arom}, J = 7.5 Hz), 7.34 t (2H, H_{arom}, J = 7.8 Hz), 7.62 d (2H, H_{arom}, J = 8.1 Hz), 9.70 s (1H, NH), 10.89 s (1H, NH). Found, %: C 51.67; H 4.31; N 14.32; S 13.03. $C_{21}H_{21}N_5O_5S_2$. Calculated, %: C 51.73; H 4.34; N 14.36; S 13.15.

Methyl 2-methoxycarbonylmethyl-5-(*p*-methoxyphenylamino)-3-(4-oxo-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl)-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (VIIIa). Yield 0.32 g (29%), mp 227–228°C (from methanol). IR spectrum, ν, cm^{-1}: 3380, 2940 (NH); 1735, 1670 (C=O). ^1H NMR spectrum, δ, ppm: 1.75 m (4H, CH_2); 2.62–2.80 m (4H, CH_2); 3.44 d (1H, CH, *J* = 16.5 Hz); 3.62 s, 3.66 s, and 3.74 s (9H, CH_3); 3.96 d (1H, CH, *J* = 16.2 Hz), 6.91 d (2H, H_{arom}, *J* = 9.0 Hz), 7.53 d (2H, H_{arom}, *J* = 8.4 Hz), 9.53 s (1H, NH), 10.62 s (1H, NH). Found, %: C 52.97; H 4.53; N 12.78; S 11.67. $C_{24}H_{25}N_5O_6S_2$. Calculated, %: C 53.03; H 4.64; N 12.88; S 11.80.

Methyl 3-(5,6-dimethyl-4-oxo-3,4-dihydrothieno-[2,3-*d*]pyrimidin-2-yl)-2-methoxycarbonylmethyl-5-(*p*-methoxyphenylamino)-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (VIIIb). Yield 0.30 g (29%), mp 116–118°C (from methanol). IR spectrum, ν, cm^{-1}: 3300 (NH); 1735, 1660 (C=O). ^1H NMR spectrum, δ, ppm: 2.26 s and 2.32 s (6H, CH_3); 3.43 d (1H, CH, *J* = 16.5 Hz); 3.62 s, 3.66 s, and 3.74 s (9H, CH_3O); 3.97 d (1H, CH, *J* = 16.8 Hz); 6.91 d (2H, H_{arom}, *J* = 9.0 Hz); 7.53 d (2H, H_{arom}, *J* = 9.0 Hz); 9.54 s (1H, NH); 10.65 s (1H, NH). Found, %: C 50.97; H 4.37; N 13.47; S 12.26. $C_{22}H_{23}N_5O_6S_2$. Calculated, %: C 51.05; H 4.48; N 13.53; S 12.39.

Methyl 5-(*p*-ethoxycarbonylphenylamino)-2-methoxycarbonylmethyl-3-(4-oxo-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl)-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (IXa). Yield 0.41 g (35%), mp 192–195°C (from methanol). IR spectrum, ν, cm^{-1}: 3320, 2940 (NH); 1735, 1670 (C=O); 1590 (C=N). ^1H NMR spectrum, δ, ppm: 1.33 t (3H, CH_3, *J* = 7.2 Hz), 1.77 m (4H, CH_2), 2.63–2.81 m (4H, CH_2), 3.48 d (1H, CH, *J* = 16.5 Hz), 3.63 s and 3.67 s (6H, CH_3O), 3.99 d (1H, CH, *J* = 16.5 Hz), 4.30 q (2H, CH_2O, *J* = 7.2 Hz), 7.74 d (2H, H_{arom}, *J* = 9.0 Hz), 7.94 d (2H, H_{arom}, *J* = 8.4 Hz), 10.12 s (1H, NH), 11.02 s (1H, NH). Found, %: C 53.23; H 4.56; N 11.81; S 10.87. $C_{26}H_{27}N_5O_7S_2$. Calculated, %: C 53.32; H 4.65; N 11.96; S 10.95.

Methyl 3-(5,6-dimethyl-4-oxo-3,4-dihydrothieno-[2,3-*d*]pyrimidin-2-yl)-5-(*p*-ethoxycarbonylphenylamino)-2-methoxycarbonylmethyl-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (IXb). Yield 0.35 g (31%), mp 147–149°C (from methanol). IR spectrum, ν, cm^{-1}: 3310 (NH); 1730–1710, 1680–1650 (C=O); 1600 (C=N). ^1H NMR spectrum, δ, ppm: 1.33 t (3H, CH_3, *J* = 7.2 Hz), 2.27 s and 2.33 s (6H, CH_3), 3.48 d (1H, CH, *J* = 16.5 Hz), 3.62 s and 3.67 s (6H, CH_3O), 4.00 d (1H, CH, *J* = 16.5 Hz), 4.29 q (2H, CH_2O, *J* = 6.9 Hz), 7.75 d (2H, H_{arom}, *J* = 8.7 Hz), 7.86 d (2H, H_{arom}, *J* = 8.7 Hz), 10.12 s (1H, NH), 11.07 s (1H, NH). Found, %: C 51.46; H 4.46; N 12.49; S 11.39. $C_{24}H_{25}N_5O_7S_2$. Calculated, %: C 51.51; H 4.50; N 12.51; S 11.46.

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