Hydrazones derived from thiooxamohydrazides and 3-formyl-4-hydroxycoumarin: synthesis, structures, and fragmentation

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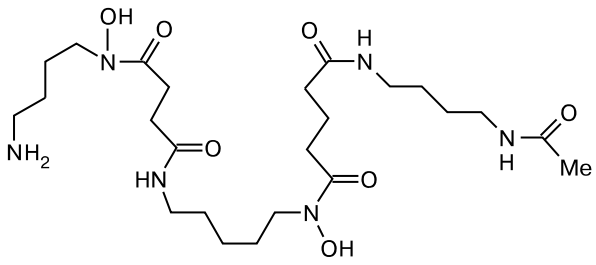
Novel hydrazones were obtained from thiooxamohydrazides and 3-formyl-4-hydroxycoumarin. According to data from NMR spectroscopy and X-ray diffraction, the coumarin fragment in the compounds obtained exists as 4-hydroxycoumarin or chromane-2,4-dione. When dissolved in dimethyl sulfoxide, these hydrazones undergo fragmentation into derivatives of 1,3,4-thiadiazole and 4-hydroxycoumarin.

Key words: 3-formyl-4-hydroxycoumarin, oxamic acids, thiohydrazides, 1,3,4-thiadiazole, tautomerism, NMR spectroscopy, X-ray diffraction.

Hydrazones, amides, and hydrazides, which are derivatives of aldehydes and carboxylic acids, exhibit high biological activity.[1—3] Hydrazones synthesized by reactions of benzohydrazide and pyridine-3-carbohydrazide with salicylaldehyde affect the virulence system of pathogenic bacteria.[4] To treat malaria infection, deferoxamine (**1**) is used in clinical practice. Its therapeutic activity against the infection is due to the ability to bind free iron(III) ions that abound in infected red blood cells.[5]



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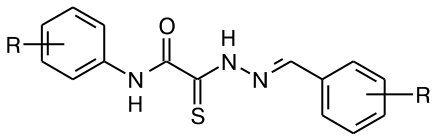
Aroylhydrazones of salicylaldehyde and its analogs are chelators of iron(III) ions that are comparable in efficiency with deferoxamine.[6,7] Hydrazones of thiooxamohydrazides with fluorine-containing substituents (**2**) possess low toxicity and a pronounced inhibitive effect on acute chlamydia infection.[8] It is significant that isomerizational transformations (including tautomerization) characteristic of this class of compounds can affect their tendency toward complex formation as well as the character of their biological activity.[9]

In this respect, hydrazones of thiooxamohydrazides containing the 3-formyl-4-hydroxycoumarin fragment (**3**) are of undoubted interest.



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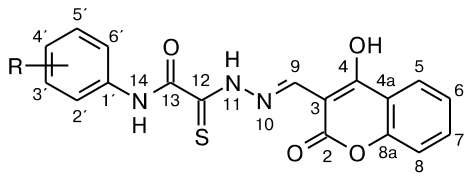

3

For instance, hydrazone derivatives (thiazolidinones **4** and thiadiazoles **5**) containing the coumarin fragment are known to exhibit antioxidant and antifungal effects, respectively,[10,11] and natural and synthetic coumarin derivatives generally show high biological activity.[12]

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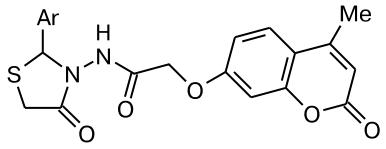

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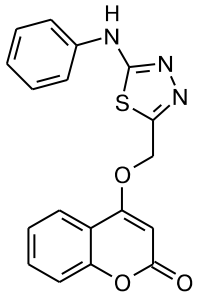

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In our continued search for novel biologically active compounds, we obtained a number of hydrazones **3** from thiohydrazides and 3-formyl-4-hydroxycoumarin **6** (Scheme 1)[8] and examined their structures by NMR spectroscopy and X-ray diffraction analysis.

The presence of the coumarin and thiohydrazide fragments in hydrazones **3** allows them to exist in several tautomeric forms.

Scheme 2 displays four tautomers of compounds **3a**—**g**: two of them contain the 4-hydroxycoumarin fragment (structures $\mathbf{A^1}$ and $\mathbf{A^2}$) and the other two contain the chromane-2,4-dione fragment (geometric isomers $\mathbf{B^1}$ and $\mathbf{B^2}$ stabilized by intramolecular hydrogen bonds). Earlier, in the study of the ratio of the isomers of arylimines of compound **6**, we have found[13] that keto enamines of the type $\mathbf{B^1}$ with a stronger intramolecular hydrogen bond between the N(10)H group and the fragment C(4)=O of coumarin predominate in mixtures with the corresponding keto enamines of the type $\mathbf{B^2}$.

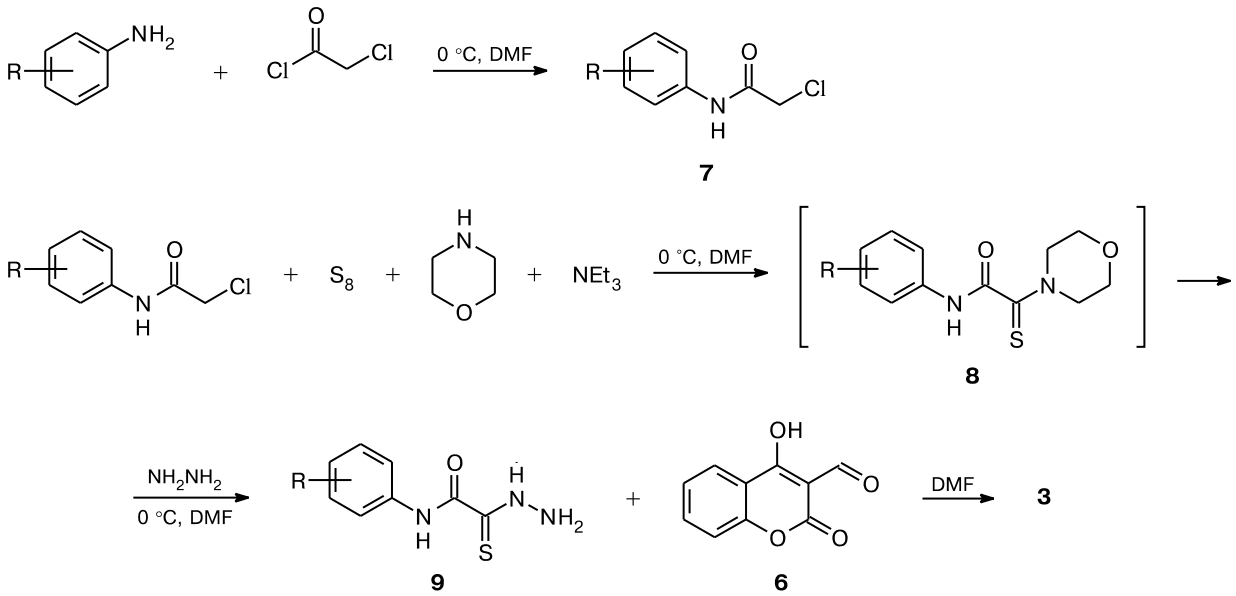
All the tautomeric forms depicted in Scheme 2 can be identified in the NMR spectra of hydrazones **3a**—**g**. In the ^{1}H NMR spectra of their freshly prepared solutions in DMSO-d_6 and DMSO-d_6—$CDCl_3$, the signals for the H(9) proton differ in multiplicity. In the spectrum of compound **3a**, this proton is manifested as two doublets at δ 8.68 ($^3J_{H(9),N(10)H}$ = 13.4 Hz) and 8.85 ($^3J_{H(9),N(10)H}$ = = 12.5 Hz), with an intensity ratio of 7 : 3. The low-field region of the spectrum shows doublets for the N(10)H protons at δ 14.23 ($^3J_{H(9),N(10)H}$ = 13.4 Hz) and 13.20 ($^3J_{H(9),N(10)H}$ = 12.5 Hz), which correspond to chromane-2,4-dione structures $\mathbf{B^1}$ and $\mathbf{B^2}$.

In the spectra of compounds **3b** and **3f** in DMSO-d_6—$CDCl_3$, a singlet for the H(9) proton appears at δ 9.17 (**3b**) and 9.21 (**3f**). These spectra contain strongly broadened low-field signals at δ 14.80 (**3b**) and 14.71 (**3f**), which correspond to the OH group of the coumarin ring in tautomer $\mathbf{A^1}$.

The ^{1}H NMR spectrum of a freshly prepared solution of compound **3c** in DMSO-d_6 exhibits a singlet at δ 8.71 for the H(9) proton and a strongly broadened signal at δ 14.29 for the proton of the OH group of the coumarin fragment; these signals belong to the major tautomer $\mathbf{A^1}$ (60%). The minor tautomer $\mathbf{B^1}$ (40%) in this spectrum is characterized by a doublet at δ 8.85 (H(9), $^3J_{H(9),N(10)H}$ = = 12.8 Hz) and a doublet at δ 13.20 (N(10)H).

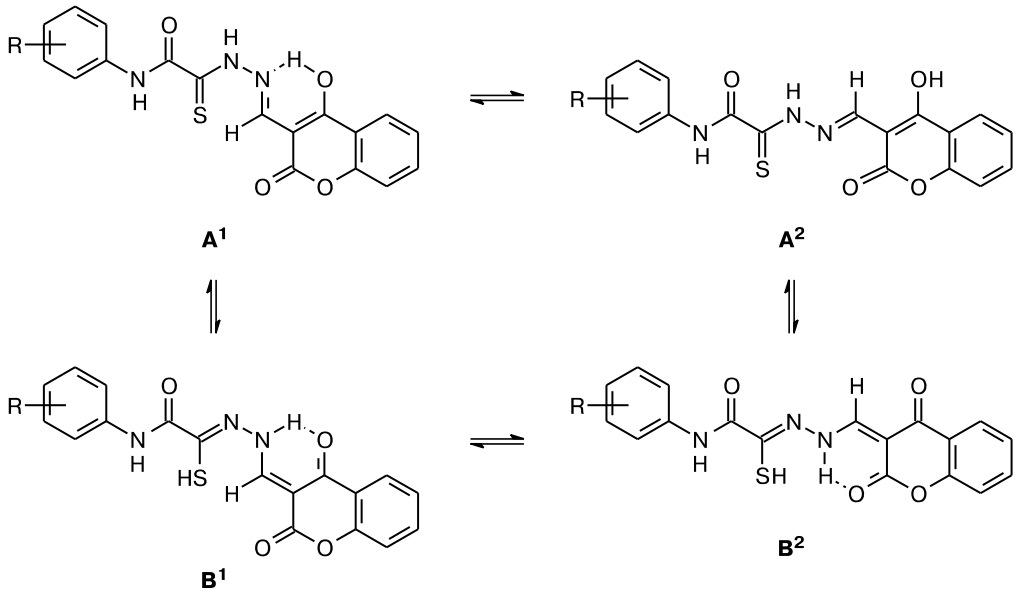
A similar spectral pattern is observed for compound **3d**. The major isomer (4-hydroxycoumarin $\mathbf{A^1}$, 60%) is represented by a singlet at δ 8.70 for the H(9) proton and a strongly broadened signal at δ 14.80 for the proton of the OH group of the coumarin fragment. For the minor tauto-

Scheme 1



R = H (**a**), 4-F (**b**), 4-Br (**c**), 4-NO_2 (**d**), 4-OCH_3 (**e**), 2-CF_3 (**f**), 3-CF_3 (**g**)

Scheme 2



mer (chromane-2,4-dione **B¹**, 40%), doublet signals appear at δ 8.86 (H(9), $^3J_{H(9),N(10)H}$ = 12.0 Hz) and 13.20 (N(10)H).

The spectrum of compound **3g** is most complicated. The spectrum of a freshly prepared solution of this compound in DMSO-d_6 shows signals for its four tautomers, **B¹** and **B²** being dominant. The signals for the H(9) proton and the corresponding signals for the N(10)H proton appear as doublets. For **B¹** (50%): δ 8.77 (d, H(9), $^3J_{H(9),N(10)H}$ = 12.0 Hz) and 14.23 (N(10)H); for **B²** (25%): δ 8.92 (d, H(9), $^3J_{H(9),N(10)H}$ = 12.0 Hz) and 13.20 (N(10)H). The minor tautomers **A¹** and **A²** are manifested by singlets for the H(9) protons at δ 9.00 and 9.04 with a total relative intensity of 25%.

The proposed signal assignment to the tautomers of compounds **3a**—**g** is confirmed by the ^{13}C NMR spectra. For instance, the ^{13}C NMR spectrum of compound **3a** in DMSO-d_6—$CDCl_3$ contains signals for the C(4)=O atoms at δ 177.1 and 177.4, which correspond to tautomers **B¹** and **B²**, respectively. The ^{13}C NMR spectrum of compound **3f** shows no signals for the C(4)=O atom in this region; instead, signals for the C(4)—OH atom appear at δ 161.5 and 161.8 (tautomers **A¹** and **A²**, respectively).

In contrast to solutions containing, in some or other amount, all the four isomers of hydrazones **3a**—**g** depicted in Scheme 2, these compounds in the solid state exist as chromane-2,4-dione **B¹** only, which was confirmed by X-ray powder diffraction data[14—16] for compounds **3a** and **3f**. The geometrical parameters of the molecules in the crystal structures **3a(I)** and **3a(II)** (these are two polymorphs of hydrazone **3a**) and **3f** (Fig. 1) have typical values in agreement with tautomeric structures **B**; they are

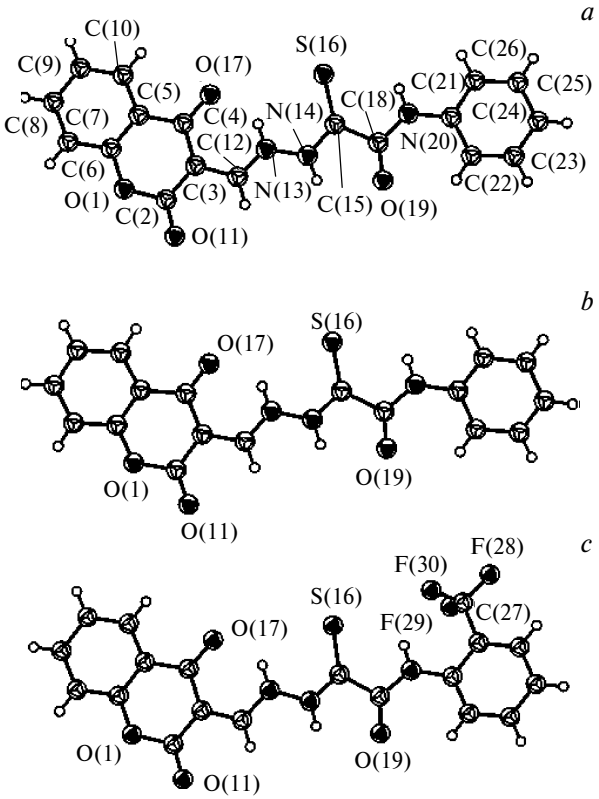


Fig. 1. Molecular structures of compounds **3a(I)** (*a*), **3a(II)** (*b*), and **3f** (*c*) with atomic numbering. The unnumbered atoms in structures **3a(II)** and **3f** correspond to the numbered ones in structure **3a(I)**. The non-hydrogen atoms are depicted as atomic displacement spheres (p = 50%).

also comparable with the parameters of related compounds retrieved from the Cambridge Structural Database.[17]

In structures **3a(I)** and **3a(II)**, the plane of the phenyl ring is nearly parallel to the mean-square plane of the coumarin fragment: the angle between them is 2(2)° and 4(2)° in **3a(I)** and **3a(II)**, respectively. In structure **3f**, the corresponding angle is 14(2)°.

The crystal packing in all the structures consists of centrosymmetric dimers formed by intermolecular hydrogen bonds N(14)—H(14)···O(11) (Table 1). A centrosymmetric dimer in the crystal structure of compound **3f** is shown in Fig. 2. The formation of these dimers in compounds **3a(II)** and **3f** is also contributed by nonclassic hydrogen bonds C(12)—H(12)···O(11) (see Table 1). In polymorphic crystals of **3a(I)** and **3a(II)**, weak intermolecular interactions C(9)—H(9)···S(16) (see Table 1) play an important role by uniting the centrosymmetric dimers into ribbons along the crystallographic axes [110] and [120], respectively.

Earlier,[8,18] cyclic tautomers of hydrazones derived from thiohydrazides, apart from their linear tautomers, have been detected. The predominance of linear (**A**) or cyclic (**C**) tautomers (Scheme 3) in an equilibrium mixture in solution depends on both the mutual effects of substituents in the aldehyde and thiohydrazide moieties and the polarity of the medium. It has been noted that an increase in the bulkiness and electronegativity of substituent R (see Scheme 3) stabilizes thiadiazoline structure **C**, while the presence of electron-donating and bulky substituents R^1 in the aldehyde moiety favors hydrazone structure **A**.

For thiobenzoylhydrazones of cyclic β-oxo esters, the major tautomer is thiadiazoline **C** in a mixture with the ene hydrazine tautomer;[19] for thiobenzoylhydrazones of aroylacetones and aroylacetaldehydes, three tautomers (ene hydrazine, 1,3,4-thiadiazoline, and 5-hydroxypyrazoline) are in equilibrium.[20]

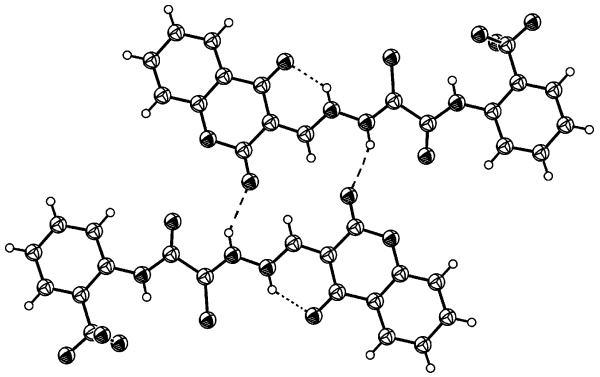
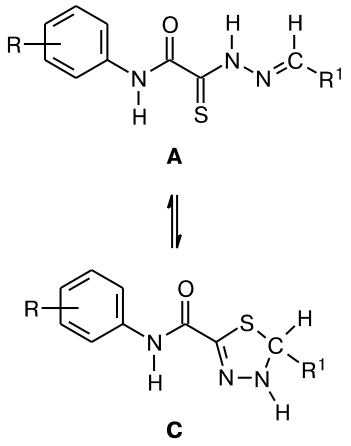


Fig. 2. Centrosymmetric dimer formed by intermolecular hydrogen bonds N—H···O (indicated with dashed lines) in the crystalline structure of compound **3f**. Intramolecular hydrogen bonds N—HsO are indicated with dotted lines.

Scheme 3



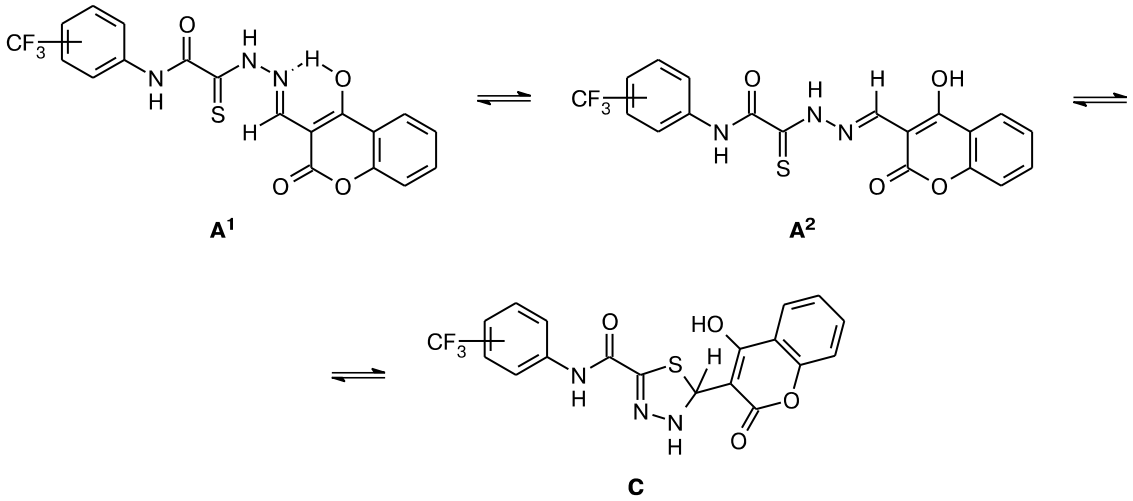
When analyzing the ^{1}H NMR spectra of hydrazones **3a**—**g**, we identified signals for cyclic tautomer **C** (Scheme 4) in compounds **3f** and **3g** soluble in acetone-d_6: a singlet

Table 1. Hydrogen bond parameters in the tautomeric structures **3a(I)**, **3a(II)**, and **3f***

Compound	D—H...A	D—H	H...A	D...A	D—H...A /deg
		Å			
3a(I) B	N(13)—H(13)...O(17)	0.86	1.82	2.534 (15)	139
	N(14)—H(14)...O(11)[a]	0.86	2.09	2.882 (14)	152
	C(9)—H(9)...S(16)[b]	0.93	2.68	3.511 (15)	149
3a(II) B	N(13)—H(13)...O(17)	0.86	1.87	2.54 (2)	133
	N(14)—H(14)...O(11)[c]	0.86	2.24	3.01 (3)	149
	C(12)—H(12)...O(11)[c]	0.93	2.28	3.08 (3)	145
	C(9)—H(9)...S(16)[d]	0.93	2.73	3.60 (2)	157
3f B	N(13)—H(13)...O(17)	0.86	1.85	2.515 (12)	132
	N(14)—H(14)...O(11)[b]	0.86	2.09	2.851 (13)	148
	C(12)—H(12)...O(11)[b]	0.93	2.01	2.833 (15)	147

* The symmetry operation codes are [a] $-x, -y, 1-z$; [b] $2-x, 1-y, 1-z$; [c] $-x, 2-y, 1-z$; [d] $1-x, 2-y, 1-z$.

Scheme 4



3f (2-CF_3), **3g** (3-CF_3)

for the methine proton of the thiadiazoline ring appears at δ 6.66 (**3f**) and 6.58 (**3g**), which agrees with the literature data (δ 6.50—7.10).[8,18] The low-field spectra contain signals for the NHC(O) proton of the cyclic tautomer. The content of the cyclic tautomer is ~10 (**3f**) and 20% (**3g**).

Cyclic tautomer **C** is not abundant and could be detected only in acetone-d_6 solutions. However, the cyclic tautomer of hydrazones derived from thiohydrazides and 3-formyl-4-hydroxycoumarin seems to play a considerable role in their structural transformations. Analysis of the ^{1}H NMR spectra revealed that the hydrazones under study are unstable in DMSO-d_6 and DMSO-d_6—$CDCl_3$. Even the spectra of freshly prepared solutions of all hydrazones, except for **3a** (R = H) and **3g** (R = 3-CF_3), show distinct low-intensity signals (≤10%): singlets at δ 5.60 and 9.66—9.91, broadened signals at δ 10.08—11.10, and strongly broadened signals at δ 12.20—12.55, all these signals being of equal intensity.

We studied in detail the behavior of hydrazone **3b**, which exists as 4-hydroxy-2-chromanone **A** in a freshly prepared solution in DMSO-d_6—$CDCl_3$. In the ^{1}H NMR spectra of this compound (Fig. 3), the signals for the N(14)H (δ 10.15) and H(9) protons (δ 9.15) gradually become less intense with time and finally vanish. Simultaneously, the originally minor signals (the singlets at δ 5.60 and 9.65 and the broadened signals at δ 11.10 and 12.20) become more intense and are predominant 48 h after the preparation of the solution. In about 15 days, these signals remain the only ones in the spectra.

The singlet at δ 5.60 ($^1J_{13C,H}$ = 167.0 Hz) and the strongly broadened signal at δ 12.20 were assigned to the H(3) proton and the proton of the C(4)—OH group, respectively, in 4-hydroxycoumarin (**10**). The correctness of this assignment was proved by analyzing the ^{1}H NMR spectra of both individual solutions of compounds **3b** and **10** and their mixture (Fig. 4).

To prove the fragmentation of hydrazone **3b** into compounds **10** and **11** (Scheme 5), we carried out a NOE experiment and recorded a ^{13}C NMR spectrum of the mixture under study. According to the NOE data, the signals at δ 5.58 (H(3)) and 12.14 (OH); 7.24 (H(6,8)) and 7.52 (H(7)); 7.24 (H(6,8)) and 7.78 (H(5)) for 4-hydroxycoumarin (**10**) as well as the signals at δ 11.10 (NH) and 7.84 (H(8′), H(12′)); 7.06 (H(9′), H(11′)) and 7.84 (H(8′), H(12′)) for compound (**11b**) show clear correlations. In the ^{13}C NMR spectrum, we identified the signals for 4-hydroxycoumarin (163.9 (C(2)), 160.5 (C(4)), 154.2 (C(8a)), 130.5 (C(7)), 121.8 (C(6))*, 121.4 (C(5))*, 114.4 (C(8)), 114.2 (C(4a)), 89.3 (C(3))) and *N*-(4-fluorophenyl)-1,3,4-thiadiazole-2-carboxamide (164.0 (C(6′)), 157.3 ($^1J_{13C,F}$ = 242.8 Hz, C(10′)), 155.8 ($^1J_{13C,H}$ = 214.3 Hz, C(5′)), 151.8 (C(2′)), 132.2 ($^4J_{13C,F}$ = 2.7 Hz, C(7′)), 120.8 ($^3J_{13C,F}$ = 8.0 Hz, C(8′), C(12′)), 113.4 ($^2J_{13C,F}$ = 22.2 Hz, C(9′), C(11′))), which confirms the above fragmentation of compound **3b**. The presence of the signal for the C(5′) atom at δ 155.8 with the characteristic coupling constant $^1J_{13C,H}$ = 214.3 Hz is conclusive evidence for the correctness of structure **11b**. 1,3,4-Thiadiazoles **11b**,**f** were isolated from the reaction mixtures and characterized by ^{1}H NMR and mass spectra.

Fragmentation of hydrazones **3c,d,e** into 4-hydroxycoumarin and the corresponding *N*-aryl-1,3,4-thiadiazole-2-carboxamides was proved by ^{1}H NMR spectroscopy without isolation of the amides. At the same time, hydr-

* The signals at δ 121.8 (C(5)) and 121.4 (C(6)) may be interchangeable.

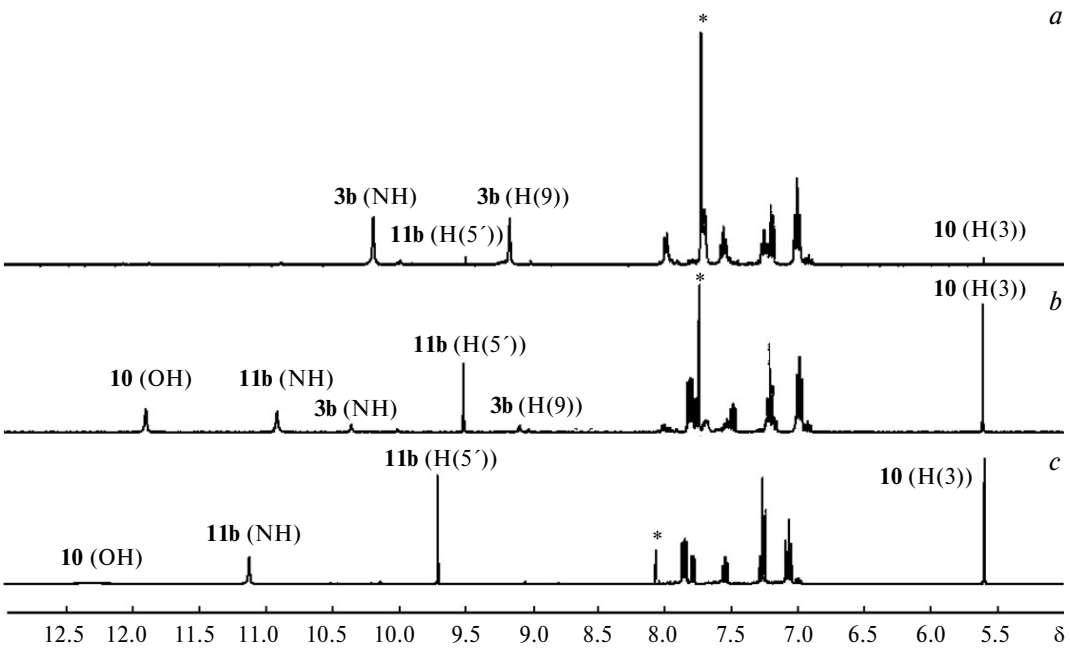


Fig. 3. ^{1}H NMR spectra of solutions of compounds **3b**, **10**, and **11b** in DMSO-d_6—$CDCl_3$: freshly prepared (*a*); after 48 h (*b*); after 15 days (*c*) (the signals of the solvent are asterisked; the structures of compounds **10** and **11b** are discussed in text).

azones **3a** and **3g** keep fairly stable in DMSO. No signals for 4-hydroxycoumarin and 1,3,4-thiadiazole-2-carboxanilide were detected in the ^{1}H NMR spectrum of hydrazone **3a** even upon prolonged storage of its solution. The fragmentation of compound **3g** in DMSO proceeds very slowly (for more than three months).

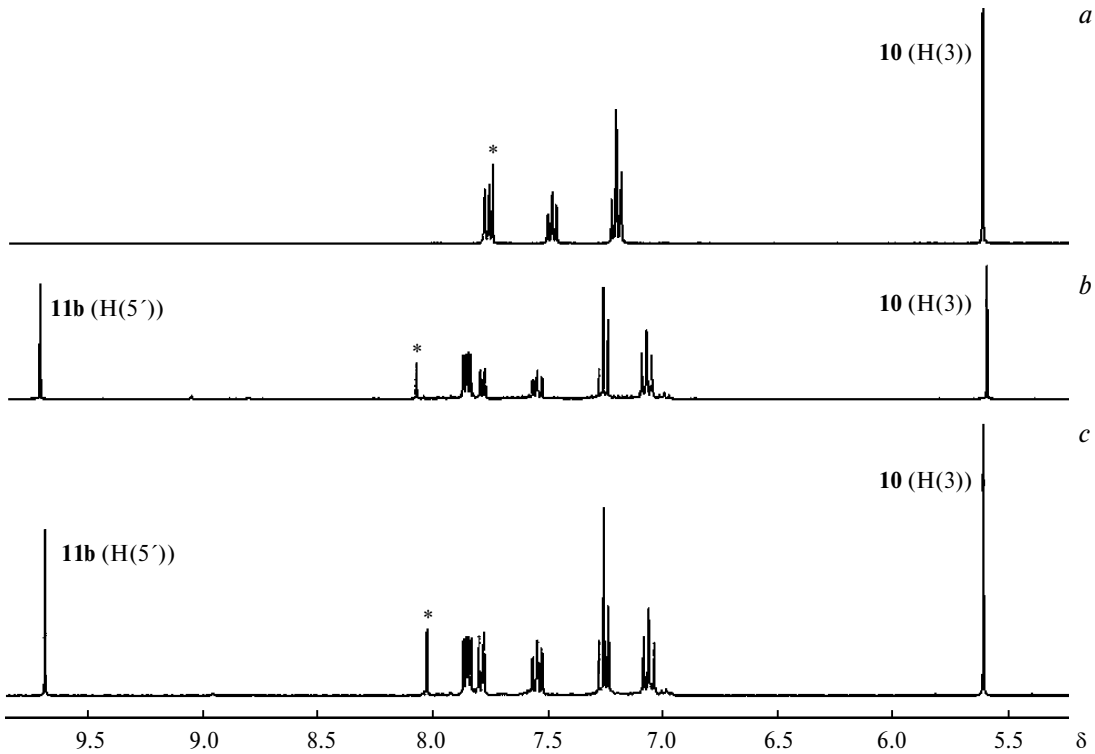
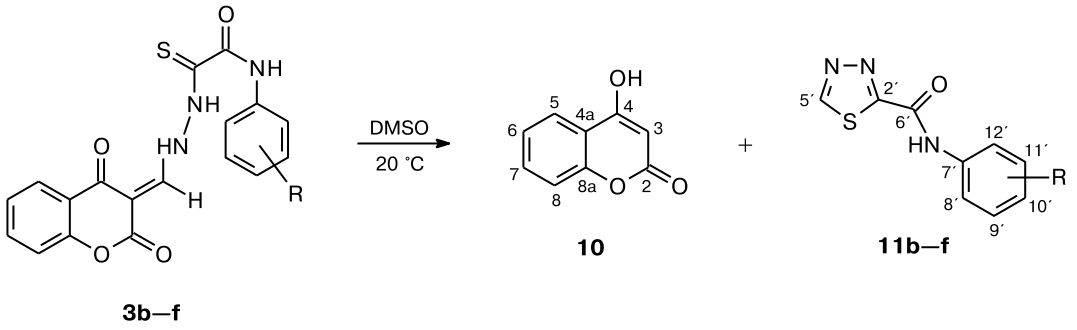


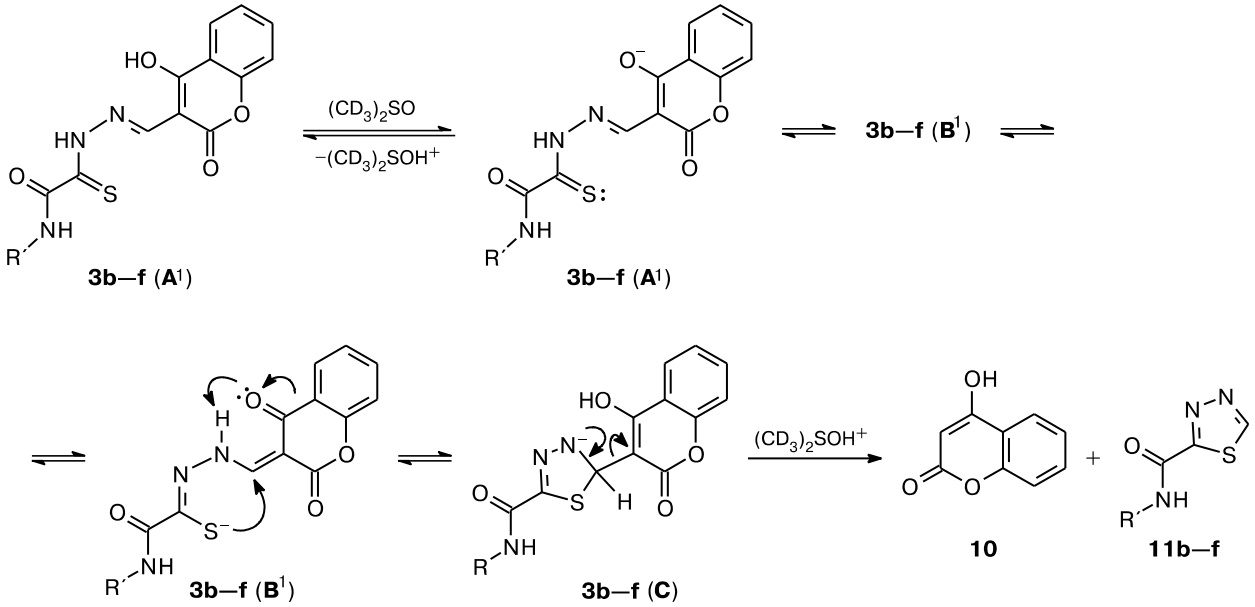
Fig. 4. ^{1}H NMR spectra of solutions of 4-hydroxycoumarin **10** (*a*), compound **3b** (*b*), and their mixture (*c*) in DMSO-d_6—$CDCl_3$ (the signals of the solvent are asterisked).

Scheme 5



R = 4-F (**b**), 4-Br (**c**), 4-NO_2 (**d**), 4-OMe (**e**), 2-CF_3 (**f**)

Scheme 6



R′ = 4-F-C_6H_4 (**b**); 4-Br-C_6H_4 (**c**), 4-NO_2-C_6H_4 (**d**), 4-OCH_3-C_6H_4 (**e**), 2-CF_3-C_6H_4 (**f**)

It should be noted that fragmentation of hydrazones derived from thiooxamohydrazides according to the pattern described above for compounds **3b—f** has not been reported hitherto.[8,18] A possible sequence of transformations of compound **3b** in DMSO is shown in Scheme 6. It is not improbable that this fragmentation is due to the domination of tautomer **A** (4-hydroxy-2-chromanone), which is characteristic of compounds **3b—f**.

In contrast, the stability of hydrazones **3a** and **3g** is probably due to the fact that these compounds both exist in solution either entirely as chromane-2,4-dione **B**[1] (**3a**) or with substantial domination of this tautomer. Apparently, strong intramolecular hydrogen bonding characteristic of tautomers **B**[1] and **B**[2] prevents fragmentation of these compounds.

Experimental

^{1}H NMR spectra were recorded on Bruker WP-200-SY and Varian Unity+ 400 spectrometers in DMSO-d_6, $CDCl_3$—DMSO-d_6, and acetone-d_6. The signals of the residual protons of the solvent (δ_H 2.50 for DMSO-d_6 and $CDCl_3$—DMSO-d_6 and δ_H 2.05 for acetone-d_6 with reference to Me_4Si) served as the internal standards. ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (600 MHz) in $CDCl_3$—DMSO-d_6. The signal for ^{13}C in DMSO-d_6 (δ_C 39.8 with reference to Me_4Si) was used as the internal standard. Low-resolution mass spectra were measured with a Kratos MS-30 instrument (UK) (EI, 70 eV, direct inlet probe, 200 °C). High-resolution mass spectra were recorded on a Bruker micrOTOF II instrument (ESI).[21] Measurements were performed in the positive ion (capillary voltage 4500 V) or negative ion modes (capillary voltage 3200 V); *m/z*

scan range was 50—3000 Da. The instrument was calibrated internally or externally using an Electrospray Calibrant Solution (Fluka). An analyte dissolved in methanol was syringed into the mass spectrometer at a flow rate of 3 μL min^{-1}. Nitrogen was employed as a spray gas (4 L min^{-1}); the interface temperature was 180 °C. Elemental analysis was carried out on a Euro Elemental analyzer.

3-Formyl-4-hydroxycoumarin[13] and thiohydrazides **9a—g** (see Ref. 8) were prepared as described earlier. Hydrazone samples for X-ray powder diffraction were additionally purified by repeated recrystallization from different solvents.

Synthesis of hydrazones 3a—g (general procedure). A solution of an appropriate thiohydrazide **9a—g** (1.1 mmol) in DMF (1—2.5 mL) was mixed with a solution of 3-formyl-4-hydroxycoumarin (**6**) (1.1 mmol) in DMF (2.5 mL). Methanol was added with stirring to the resulting mixture until a precipitate of hydrazone was formed. The precipitate was filtered off, washed on the filter with *n*-hexane, and dried with P_2O_5 *in vacuo* at 78 °C. The hydrazones obtained were analyzed without further purification.

2-{2-[(*E*/*Z*)-(2,4-Dioxo-2*H*-chromen-3(4*H*)-yl)methylidene]hydrazino}-2-thioxoacetanilide (3a). Yield 93%, m.p. 290 °C (decomp.). ^{1}H NMR (200 MHz, DMSO-d_6), δ: 14.23 (d, 0.7 H, N(10)H (**B^1**), ^3J = 13.4 Hz); 13.20 (d, 0.3 H, N(10)H (**B^2**), ^3J = 12.5 Hz); 10.17 (br.s, 1 H, NHCO); 8.85 (d, 0.3 H, H(9) (**B^2**), ^3J = 12.5 Hz); 8.68 (d, 0.7 H, H(9) (**B^1**), ^3J = 13.4 Hz); 7.99 (d, 1 H, H(5), ^3J = 7.4 Hz); 7.58—7.80 (m, 3 H, H(7), H(2′), H(6′)); 7.24—7.40 (m, 4 H, H(6), H(8), H(3′), H(5′)); 7.06 (t, 1 H, H(4′), ^3J = 7.3 Hz). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 276 [M − C_6H_5N]$^+$ (5), 173 [M − $C_8H_8N_3SO$]$^+$ (22), 163 [M − $C_{10}H_8O_3N_2$]$^+$ (6), 162 [M − $C_9H_7N_3SO$]$^+$ (43), 119 [M − $C_{11}H_8O_3N_2S$]$^+$ (89), 92 [M − $C_{12}H_7O_4N_2S$]$^+$ (100). HRMS. Found: *m*/*z* 366.0543 [M − H]$^-$. $C_{18}H_{13}N_3O_4S$. Calculated: M − H = 366.0543.

***N*-(4-Fluorophenyl)-2-{2-[(*E*/*Z*)-(2,4-dioxo-*2H*-chromen-3(4*H*)-yl)methylidene]hydrazino}-2-thioxoacetamide (3b).** Yield 32%, m.p. 170—173.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 14.80 (br.s, 1 H, OH); 10.20 (br.s, 1 H, NHCO); 9.18 (s, 1 H, H(9)); 8.00 (d, 1 H, H(5), ^3J = 8.1 Hz); 7.67—7.74 (m, 2 H, H(2′), H(6′)); 7.56 (t, 1 H, H(7), ^3J = 7.9 Hz); 7.17—7.29 (m, 2 H, H(6), H(8)); 6.97—7.05 (m, 2 H, H(3′), H(5′)). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 385 [M]$^+$ (4), 223 [M − $C_9H_6O_3$]$^+$ (49), 203 [M − C_8H_5FNOS]$^+$ (39), 181 [M − $C_{10}H_8N_2O_3$]$^+$ (39), 162 [M − $C_9H_6FN_3OS$]$^+$ (60), 137 [M − $C_{11}H_8N_2O_3S$]$^+$ (100), 121 [M − $C_9H_6FN_3OS$ − C_2HO]$^+$ (56), 110 [M − −$C_{12}H_7N_2O_4S$]$^+$ (29). HRMS. Found: *m*/*z* 384.0457. [M − H]$^-$. $C_{18}H_{12}FN_3O_4S$. Calculated: M − H = 384.0449.

***N*-(4-Bromophenyl)-2-{2-[(*E*/*Z*)-(2,4-dioxo-2*H*-chromen-3(4*H*)-yl)methylidene]hydrazino}-2-thioxoacetamide (3c).** Yield 33%, m.p. 208—209 °C. ^{1}H NMR (200 MHz, DMSO-d_6), δ: 14.29 (br.s, 0.6 H, OH); 13.20 (br.s, 0.4 H, N(10)H); 10.27 (br.s, 1 H, NHCO); 8.85 (d, 0.4 H, H(9), ^3J = 12.8 Hz); 8.71 (s, 0.6 H, H(9)); 7.99 (d, 1 H, H(5), ^3J = 7.9 Hz); 7.24—7.88 (m, 7 H, H(6), H(7), H(8), H(2′), H(3′), H(5′), H(6′)). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 447 [M{Br^{81}}]$^+$ (2), 445 [M{Br^{79}}]$^+$ (2), 285 [M{Br^{81}} − $C_6H_4OC(O)CHC(OH)$]$^+$ (63), 283 [M{Br^{79}} − $C_6H_4OC(O)CHC(OH)$]$^+$ (60), 243 [M{Br^{81}} − − $C_{10}H_7O_3N_2$ − H]$^+$ (30), 241 [M{Br^{79}} − $C_{10}H_7O_3N_2$ − H]$^+$ (33), 204 [M − C_8H_4NSOBr]$^+$ (91), 199 [M{Br^{81}} − − $C_{11}H_7O_3N_2S$ − H]$^+$ (93), 197 [M{Br^{79}} − $C_{11}H_7O_3N_2S$ − H]$^+$ (95), 189 [M − $C_8H_5N_2SOBr$]$^+$ (14), 173 [M − $C_8H_7N_3OBr$]$^+$ (23), 162 [M − $C_9H_6N_3OSBr$]$^+$ (100). HRMS. Found: *m*/*z* 443.9659. [M − H]$^-$. $C_{18}H_{12}BrN_3O_4S$. Calculated: M − H = = 443.9648.

Table 2. Crystallographic parameters and the data collection statistics for compounds **3a(I)**, **3a(II)**, and **3f**

Parameter	**3a(I)**	**3a(II)**	**3f**
Molecular formula	$C_{18}H_{13}N_3O_4S$	$C_{18}H_{13}N_3O_4S$	$C_{19}H_{12}F_3N_3O_4S$
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a/Å	5.1035(17)	10.081(4)	4.8391(18)
b/Å	10.238(2)	5.070(3)	20.620(3)
c/Å	32.196(4)	32.505(5)	18.978(3)
β/deg	90.925(18)	91.29(4)	95.27(2)
V/Å^3	1682.0(7)	1660.9(12)	1885.7(8)
M_{20}*	27	32	32
F_{30}*	32 (0.009, 53)	25 (0.011, 63)	37 (0.008, 54)
Z	4	4	4
ρ_{calc}/g cm^{-3}	1.451	1.469	1.534
Radiation	Cu-Kα_1 (λ = 1.5406 Å)		
Scan range: ($2\theta_{min}$—$2\theta_{max}$)/deg	3.00—80.00	3.00—70.00	4.00—80.00
Scan step/deg	0.01	0.01	0.01
R_p*	0.0270	0.0215	0.0214
R_{wp}*	0.0345	0.0271	0.0323
R_{exp}*	0.0164	0.0174	0.0116
χ^2*	3.990	2.309	7.102

* The figures of merit M_{20} (see Ref. 32) and F_{30} (see Ref. 33) were defined earlier; R_p, R_{wp}, R_{exp}, and χ^2 were calculated by the formulas cited in Ref. 34.

***N*-(4-Nitrophenyl)-2-{2-[(*E*/*Z*)-(2,4-dioxo-2*H*-chromen-3(4*H*)-yl)methylidene]hydrazino}-2-thioxoacetamide (3d).** Yield 31%, m.p. 218—219 °C. ^{1}H NMR (200 MHz, DMSO-d_6), δ: 14.80 (br.s, 0.6 H, OH); 13.20 (d, 0.4 H, N(10)H, ^3J = 12.0 Hz); 10.68 (s, 1 H, NHCO); 8.86 (d, 0.4 H, H(9), ^3J = 12.0 Hz); 8.70 (s, 0.6 H, H(9)); 8.14—8.30 (m, 2 H, H(3´), H(5´)); 7.91—8.09 (m, 3 H, H(2´), H(6´), H(5)); 7.66 (t, 1 H, H(7), ^3J = 7.7 Hz); 7.25—7.40 (m, 2 H, H(6), H(8)). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 412 $[M]^+$ (2), 395 $[M - OH]^+$ (6), 250 $[M - C_9H_6O_3]^+$ (42), 208 $[M - C_{10}H_8O_3N_2]^+$ (35), 204 $[M - C_8H_4N_2O_3S]^+$ (30), 162 $[M - C_9H_6O_3N_4S]^+$ (100). HRMS. Found: *m*/*z* 411.0405. $[M - H]^-$. $C_{18}H_{12}N_4O_6S$. Calculated: M − H = 411.0394.

***N*-(4-Methoxyphenyl)-2-{2-[(*E*/*Z*)-(2,4-dioxo-2*H*-chromen-3(4*H*)-yl)methylidene]hydrazino}-2-thioxoacetamide (3e).** Yield 38%, m.p. 181—182 °C. ^{1}H NMR (200 MHz, DMSO-d_6), δ: 10.09 (s, 1 H, NHCO); 8.76 (br.s, 1 H, H(9)); 7.92—8.04 (m, 1 H, H(5)); 7.59—7.81 (m, 3 H, H(7), H(2´), H(6´)); 7.27—7.45 (m, 2 H, H(6), H(8)); 6.85—7.02 (m, 2 H, H(3´), H(5´)). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 235 $[M - C_9H_6O_3]^+$ (23), 162 $[M - C_{10}H_9N_3O_2S]^+$ (42), 149 $[M - C_{11}H_8N_2O_3S]^+$ (97), 134 $[M - C_{11}H_8N_2O_3S - CH_3]^+$ (100), 121 $[M - C_{10}H_9N_3O_2S - C_2HO]^+$ (78), 108 $[M - C_{12}H_7N_3O_4S]^+$ (52). Found (%): C, 57.47; H, 3.88; N, 10.36; S, 7.93. $C_{19}H_{15}N_3O_5S$. Calculated (%): C, 57.43; H, 3.78; N, 10.58; S, 8.06.

***N*-[2-(Trifluoromethyl)phenyl]-2-{2-[(*E*/*Z*)-(2,4-dioxo-2*H*-chromen-3(4*H*)-yl)methylidene]hydrazino}-2-thioxoacetamide (3f).** Yield 84%, m.p. 242—244 °C. ^{1}H NMR (200 MHz, DMSO-d_6—$CDCl_3$), δ: 14.71 (br.s, 1 H, OH); 10.40 (br.s, 1 H, NHCO); 9.21 (s, 1 H, H(9)); 8.27 (d, 1 H, H(6´), ^3J = 8.3 Hz); 8.00 (d, 1 H, H(5), ^3J = 7.4 Hz); 7.51—7.69 (m, 3 H, H(7), H(3´), H(5´)); 7.30—7.50 (m, 3 H, H(6), H(8), H(4´)). Found (%): C, 52.07; H, 2.46; N, 9.54. $C_{19}H_{12}F_3N_3O_4S$. Calculated (%): C, 52.41; H, 2.76; N, 9.65.

***N*-[3-(Trifluoromethyl)phenyl]-2-{2-[(*E*/*Z*)-(2,4-dioxo-2*H*-chromen-3(4*H*)-yl)methylidene]hydrazino}-2-thioxoacetamide (3g).** Yield 78%, m.p. 310—312 °C. ^{1}H NMR (200 MHz, DMSO-d_6), δ: 14.23 (d, 0.5 H, N(10)H (**B**^{1}), ^3J = 12.0 Hz); 13.20 (d, 0.25 H, N(10)H (**B**^{2}), ^3J = 12.0 Hz); 10.48 (br.s, 1 H, NHCO); 9.04, 9.00 (both s, 0.25 H, H(9), (**A**^{2}, **A**^{1})); 8.92 (d, 0.25 H, H(9) (**B**^{2}), ^3J = 12.0 Hz); 8.77 (d, 0.5 H, H(9) (**B**^{1}), ^3J = 12.0 Hz); 8.27 (br.s, 1 H, H(2´)); 7.91—8.08 (m, 2 H, H(5), H(6´)); 7.50—7.75 (m, 2 H, H(7), H(5´)); 7.20—7.50 (m, 3 H, H(6), H(8), H(4´)). Found (%): C, 52.06; H, 2.54; N, 10.00. $C_{19}H_{12}F_3N_3O_4S$. Calculated (%): C, 52.41; H, 2.76; N, 9.65.

Transformations of hydrazones 3b,f into thiadiazoles 11b,f. Hydrazone **3b** or **3f** (0.2 mmol) was dissolved in DMSO (2—3 mL). The resulting solution was kept at ~20 °C until the starting compound was completely consumed (TLC, Silufol UV 254 plates, chloroform—acetone—methanol (30 : 5 : 2)) and two new spots appeared; one of them (R_f 0.5) corresponds to 4-hydroxycoumarin. Then the reaction mixture was poured into a 20-fold volume of water and the product was extracted with ethyl acetate (5×10 mL). The combined extracts were dried with $MgSO_4$, concentrated *in vacuo*, and separated into components by preparative TLC on Silufol UV 254 plates with chloroform—acetone—methanol (30 : 5 : 2) as an eluent. The bands with R_f 0.7—0.9 were cut out and cut into small pieces; the product was extracted with ethyl acetate. The solvent was removed to give a crystalline precipitate.

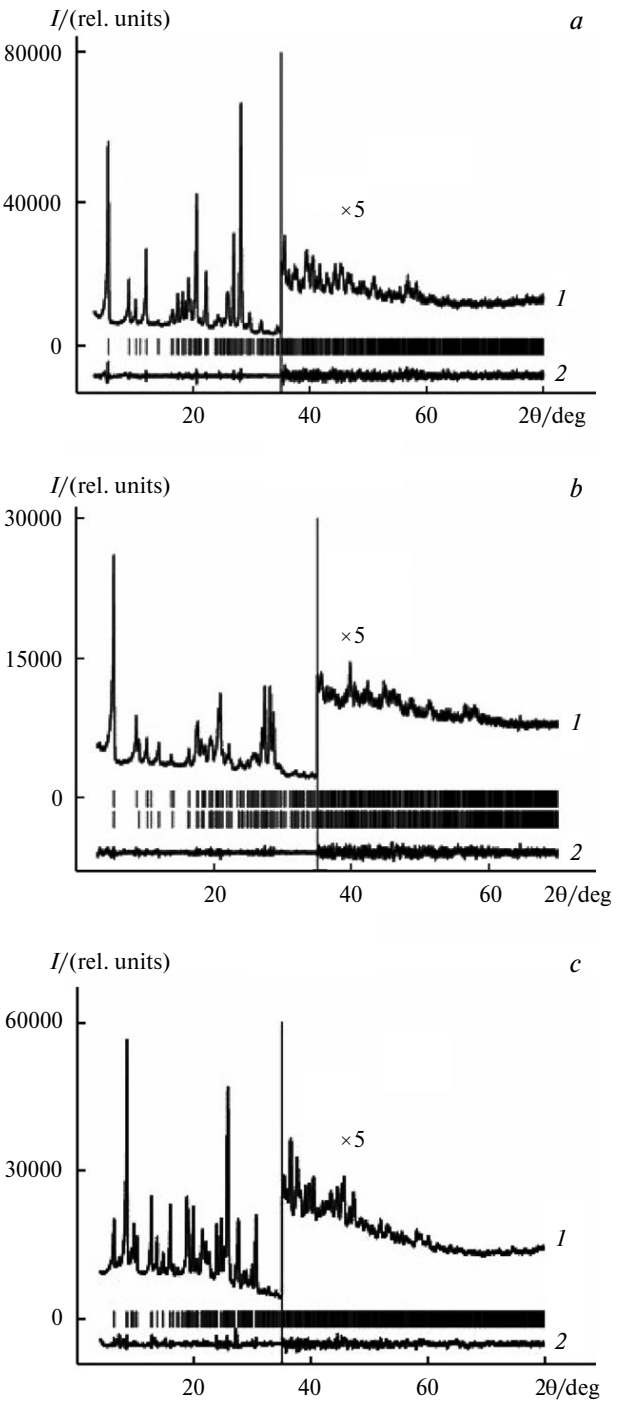


Fig. 5. The Rietveld refinement of the crystal structure of polymorph **3a(I)** (*a*), polymorph **3a(II)** (*b*), and compound **3f** (*c*): (*1*) the experimental curve and (*2*) the difference between the experimental curve and the calculated profile upon the refinement; the high-angle range (2θ > 35°) is shown with a 5x magnification. The calculated positions of the reflections are indicated with vertical strokes. For two-phase refinement (*b*), the upper and lower rows of the vertical strokes correspond to the reflections from polymorphs **3a(I)** and **3a(II)**, respectively.

***N*-(4-Fluorophenyl)-1,3,4-thiadiazole-2-carboxamide (11b).** Yield 13%, m.p. 181.5—184 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 9.34 (s, 1 H, H(5′); 9.23 (br.s, 1 H, NH); 7.66—7.73 (m, 2 H, H(8′), H(12′)); 7.07—7.16 (m, 2 H, H(9′), H(11′)). The ^{1}H NMR spectrum agrees with the literature data.[22] MS (EI, 70 eV), *m/z* (I_{rel} (%)): 223 $[M]^+$ (50), 203 $[M - HF]^+$ (27), 137 $[M - C_2H_2N_2S]^+$ (100).

***N*-[2-(Trifluoromethyl)phenyl]-1,3,4-thiadiazole-2-carboxamide (11f).** Yield 9%, m.p. 88—90 °C. ^{1}H NMR (200 MHz, DMSO-d_6), δ: 7.54—7.85 (m, 4 H, H(9′), H(10′), H(11′), H(12′); 9.88 (s, 1 H, H(5′)); 10.89 (br.s, 1 H, NH). HRMS. Found: *m/z* 296.0071. $[M + Na]^+$. $C_{10}H_6N_3F_3OS$. Calculated: M + Na = 296.0076.

Determination of the crystal structures of samples 3a(I), 3a(II), and 3f. The crystal structures of samples **3a(I)**, **3a(II)**, and **3f** were examined by X-ray powder diffraction[14—16] in a Guinier—Huber G670 camera with a curved germanium monochromator. The positions of the first 30 peaks on the X-ray diffraction patterns obtained were refined and used for indexing with the TREOR90,[23] ITO,[24] and AUTOX programs.[25,26] Sample **3a(II)** contained two polymorphs of compound **3a**. One of them was solved from the diffraction pattern of sample **3a(I)** and the other, from the diffraction pattern of sample **3a(II)**, with allowance for the presolved first polymorph. Compound **3f** contained a small amount of an unidentified impurity manifested by weak peaks with the interplanar spacings d = 12.969, 12.234, 6.702, 5.874, and 3.276 Å. The crystal structures were solved using the simulated annealing algorithm[27] for the centrosymmetric space group $P2_1/c$. In all three cases, molecular 3D models were constructed by DFT optimization with the Priroda program.[28] The structures were refined by the Rietveld method with the MRIA program.[29] The peak profiles were approximated with the modified Voigt function.[30] The effects of preferential orientation of crystallites (texture) were taken into account in terms of the March—Dollase formalism.[31] Refinement restrictions included tolerated deviations from the interatomic distances in the structures and the planar geometry of the rings. The thermal parameters for the non-hydrogen atoms in **3a(I)** and **3f** were refined isotropically. Structure **3a(II)** was refined using the diffraction pattern of its sample containing the crystalline phases of two polymorphs **3a(I)** and **3a(II)** in a ratio of 5 : 6. For this reason, only one isotropic thermal parameter common to all non-hydrogen atoms was refined for **3a(II)** and the previously determined structural parameters of **3a(I)** (atomic coordinates and isotropic thermal parameters) were fixed in the refinement of **3a(II)**. The hydrogen atoms were located geometrically and not refined. Selected crystallographic parameters and the data collection statistics for structures **3a(I)**, **3a(II)**, and **3f** are summarized in Table 2. The experimental powder diffraction patterns and the difference curves upon the Rietveld refinement are shown in Fig. 5. All crystallographic data have been deposited with the Cambridge Structural Database[17] (CCDC Nos 884249 (**3a(I)**), 884250 (**3a(II)**), and 884251 (**3f**)).

High- and low-resolution mass spectra were measured at the Section of Structural Studies of the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences. Elemental analysis was performed at the Laboratory for Microanalysis and Electrochemical Research of the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences.

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