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Reactions of *N*-(1-Chloro-2-oxo-2-phenylethyl) Carboxamides with Thiosemicarbazide and Its Derivatives

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Abstract—*N*-(1-Chloro-2-oxo-2-phenylethyl)acet-, -benz-, and -4-methylbenzamides reacted with thiosemicarbazides and aromatic aldehyde thiosemicarbazones to give derivatives of 5-amino-2-hydrazino-1,3-thiazole. The latter underwent recyclization and acid hydrolysis on heating with hydrochloric acid to produce substituted 3-amino-2-thiohydantoins.

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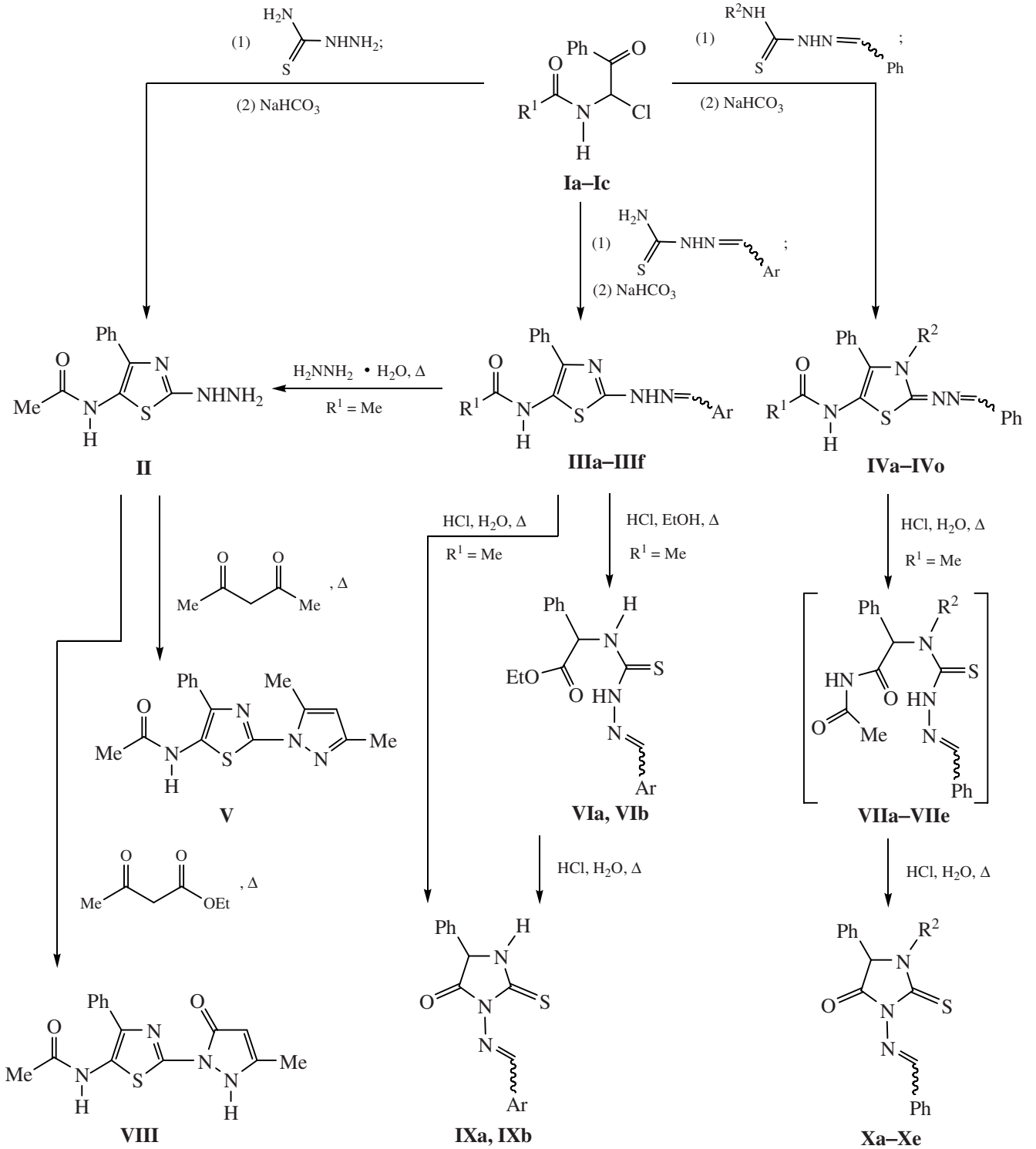
We previously found that accessible *N*-(1-chloro-2-oxo-2-phenylethyl) carboxamides **I** (Scheme 1) react with various thioamides and thiourea in a selective fashion, following the general Hantzsch cyclocondensation pattern [1–3]. In the present work we found that reactions of compounds **I** with thiosemicarbazide are not selective. As a result, complex mixtures of products are formed. Although expected 5-acylamino-2-hydrazino-4-phenyl-1,3-thiazoles **II** were detected in the product mixtures, we succeeded in isolating them as individual substances by repeated recrystallizations only in a few cases. On the other hand, reactions of N^1-benzylidene derivatives of thiosemicarbazide and its analogs with α-chloro amides **I** were quite selective, and the products were the corresponding substituted 1,3-thiazoles **III** or 2,3-dihydro-1,3-thiazoles **IV** (Table 1). Some compounds **III** and **IV** turned out to be suitable for further transformations of preparative interest (see structures **III**–**X** in Scheme 1). For instance, by heating compound **IIIb** (Ar = 4-$MeOC_6H_4$, R^1 = Me) with hydrazine hydrate we obtained 5-acetylamino-2-hydrazino-1,3-thiazole **II** which was isolated as analytically pure substance, so that we were able to identify it in the product mixture formed in the reaction of compound **Ia** with thiosemicarbazide. The presence in molecule **II** of an unsubstituted hydrazino group was proved by its condensation with acetylacetone and ethyl acetoacetate according to Knorr, which afforded the expected products, 5-acetylamino-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-phenyl-1,3-thiazole (**V**) and 5-acetylamino-2-(3-methyl-5-oxo-2,5-dihydro-1*H*-pyrazol-1-yl)-4-phenyl-1,3-thiazole (**VIII**), respectively. The structure of compounds **V** and **VIII** is beyond doubt, for such reactions were studied in detail using other substituted 2-hydrazino-1,3-thiazoles, and the product structure was determined unambiguously [4, 5].

Some consecutive transformations of compounds **III** and **IV** having an acetylamino group on C^5 were also important. Treatment of these compounds with hydrochloric acid in ethanol at heating is likely to involve opening of nonaromatic dihydrothiazole ring with formation of intermediate products **VI** and **VII** which are capable of undergoing recyclization to give new 3-amino-2-thiohydantoin derivatives **IX** and **X**. Analogous compounds were also obtained by other methods [6–8]; nevertheless, the described recyclizations **III** → **IX** and **IV** → **X** seem to be valuable from the preparative viewpoint, for they ensure synthesis of difficultly accessible substituted 2-thiohydantoins.

We succeeded in isolating with satisfactory yields intermediate products **VI** in the transformation **III** → **IX** (see Experimental). Compounds **VI**, as well as **III**, were smoothly converted into the corresponding substituted 3-amino-2-thiohydantoins **IX** on prolonged heating in a more concentrated solution of hydrochloric acid in ethanol. The structure of **VI** was determined on the basis of the IR, ^{1}H NMR (Table 2), and mass spectra. The structure of compound **VIb** was unambiguously proved using various two-dimensional

Scheme 1.



IIIa, **IIIc**, **IIIe**, **VIa**, **IXa**, Ar = Ph; **IIIb**, **IIId**, **IIIf**, **VIb**, **IXb**, Ar = 4-$MeOC_6H_4$; **Ia**, **IIIa**, **IIIb**, **IVa–IVe**, R^1 = Me; **Ib**, **IIIc**, **IIId**, **IVf–IVj**, R^1 = Ph; **Ic**, **IIIe**, **IIIf**, **IVk–IVo,** R^1 = 4-MeC_6H_4; **IVa**, **IVf**, **IVk**, **VIIa**, **Xa**, R^2 = Me; **IVb**, **IVg**, **IVl**;, **VIIb**, **Xb**, R^2 = CH_2=$CHCH_2$; **IVc**, **IVh**, **IVm**, **VIIc**, **Xc**, R^2 = $PhCH_2$; **IVd**, **IVi**, **IVn**, **VIId**, **Xd**, R^2 = Ph; **IVe**, **IVj**, **IVo**, **VIIe**, **Xe**, R^2 = 4-MeC_6H_4.

Table 1. Yields, melting points, and elemental analyses of compounds **II–VI** and **VIII–X**

Comp. no.	Yield,[a] %	mp, °C (solvent)	Found, %		Formula	Calculated, %	
			N	S		N	S
II	25 (70)	184–186 (MeCN)	22.38	12.79	$C_{11}H_{12}N_4OS$	22.56	12.91
IIIa	77	201–203 (MeCN–DMF)	16.49	9.43	$C_{18}H_{16}N_4OS$	16.65	9.53
IIIb	81	215–217 (MeCN–DMF)	15.29	8.73	$C_{19}H_{14}N_4O_2S$	15.45	8.84
IIIc	71	246–247 (MeCN–DMF)	13.89	7.93	$C_{23}H_{18}N_4OS$	14.06	8.04
IIId	78	231–233 (MeCN–DMF)	12.93	7.41	$C_{24}H_{20}N_4O_2S$	13.07	7.48
IIIe	69	239–240 (MeCN–DMF)	13.41	7.69	$C_{24}H_{20}N_4OS$	13.58	7.77
IIIf	75	233–234 (MeCN–DMF)	12.51	7.17	$C_{25}H_{22}N_4O_2S$	12.66	7.24
IVa	72	226–228 (MeCN)	15.83	9.05	$C_{19}H_{18}N_4OS$	15.99	9.15
IVb	76	183–185 (EtOH)	14.71	8.42	$C_{21}H_{20}N_4OS$	14.88	8.51
IVc	81	185–187 (MeCN)	13.05	7.39	$C_{25}H_{22}N_4OS$	13.13	7.51
IVd	86	253–255 (MeCN–DMF)	13.41	7.63	$C_{24}H_{20}N_4OS$	13.58	7.77
IVe	91	251–252 (MeCN–DMF)	13.03	7.45	$C_{25}H_{22}N_4OS$	13.13	7.51
IVf	81	191–192 (MeCN–DMF)	13.41	7.61	$C_{24}H_{20}N_4OS$	13.58	7.77
IVg	79	165–167 (EtOH)	12.63	7.19	$C_{25}H_{22}N_4OS$	12.77	7.31
IVh	87	235–237 (MeCN–DMF)	11.31	6.41	$C_{30}H_{24}N_4OS$	11.46	6.56
IVi	83	243–245 (AcOH)	11.63	6.63	$C_{29}H_{22}N_4OS$	11.80	6.75
IVj	90	242–243 (MeCN)	11.29	6.49	$C_{30}H_{24}N_4OS$	11.46	6.56
IVk	79	247–249 (MeCN–DMF)	13.01	7.39	$C_{25}H_{22}N_4OS$	13.13	7.51
IVl	85	139–141 (EtOH)	12.21	7.01	$C_{27}H_{24}N_4OS$	12.38	7.08
IVm	91	226–228 (MeCN–DMF)	11.05	6.21	$C_{31}H_{26}N_4OS$	11.14	6.38
IVn	78	207–209 (AcOH)	11.27	6.41	$C_{30}H_{24}N_4OS$	11.46	6.56
IVo	81	191–193 (MeCN)	11.02	6.23	$C_{31}H_{26}N_4OS$	11.14	6.38
V	68	199–201 (AcOH)	17.79	10.21	$C_{16}H_{16}N_4OS$	17.93	10.26
VIa	58	161–163 (EtOH)	12.16	9.30	$C_{18}H_{19}N_3O_2S$	12.30	9.39
VIb	54	159–160 (EtOH)	11.16	8.49	$C_{19}H_{21}N_3O_3S$	11.31	8.63
VIII	56	234–236 (AcOH)	17.65	10.11	$C_{15}H_{14}N_4O_2S$	17.82	10.20
IXa	57 (61)	196–198 (EtOH)	14.06	10.77	$C_{16}H_{13}N_3OS$	14.22	10.85
IXb	53 (59)	163–165 (EtOH)	12.79	9.71	$C_{17}H_{15}N_3O_2S$	12.91	9.85
Xa	85	142–144 (MeCN)	13.41	10.25	$C_{17}H_{15}N_3OS$	13.58	10.36
Xb	79	102–103 (EtOH)	12.39	9.38	$C_{19}H_{17}N_3OS$	12.52	9.56
Xc	93	192–193 (MeCN)	10.73	8.19	$C_{23}H_{19}N_3OS$	10.90	8.31
Xd	87	221–223 (MeCN)	11.19	8.51	$C_{22}H_{17}N_3OS$	11.31	8.63
Xe	88	218–219 (MeCN)	10.79	8.25	$C_{23}H_{19}N_3OS$	10.90	8.31

[a] The yield according to method *b* is given in parentheses.

Table 2. IR and ^{1}H NMR spectra of compounds **II**–**VI** and **VIII**–**X**[a]

Compound no.	^{1}H NMR spectrum (DMSO-d_6), δ, ppm
II[b]	2.00 s (3H, CH_3), 4.73 br.s (2H, NH_2), 7.24–7.73 m (5H_{arom}), 8.28 s (1H, NH), 9.74 s (1H, NH)
IIIa	2.07 s (3H, CH_3), 7.28–7.73 m (10H_{arom}), 7.99 s (1H, CH), 10.13 s (1H, NH), 11.97 br.s (1H, NH)
IIIb[b]	2.06 s (3H, CH_3), 3.80 s (3H, CH_3), 6.91–7.74 m (9H_{arom}), 7.90 s (1H, CH), 9.96 s (1H, NH), 11.67 br.s (1H, NH)
IIId[b]	3.81 s (3H, CH_3), 6.95–7.97 m (15H, 14H_{arom}, NH), 8.20 s (1H, CH), 10.71 s (1H, NH)
IVb[b]	1.88 s (3H, CH_3), 4.26 d (2H, CH_2), 4.89–5.08 m (2H, CH_2), 5.73 m (1H, CH), 7.32–7.70 m (10H_{arom}), 8.21 s (1H, CH), 9.52 s (1H, NH)
IVc	1.91 s (3H, CH_3), 4.93 s (2H, CH_2), 6.93–7.72 m (15H_{arom}), 8.23 s (1H, CH), 9.66 s (1H, NH)
IVd	1.96 s (3H, CH_3), 7.17–7.70 m (15H_{arom}), 8.14 s (1H, CH), 9.79 s (1H, NH)
IVe	1.95 s (3H, CH_3), 2.25 s (3H, CH_3), 7.10–7.69 m (14H_{arom}), 8.13 s (1H, CH), 9.75 s (1H, NH)
IVf	3.27 s (3H, CH_3), 7.39–7.79 m (15H_{arom}), 8.34 s (1H, CH), 10.02 s (1H, NH)
IVg	4.37 d (2H, CH_2), 4.89–5.13 m (2H, CH_2), 5,72 m (1H, CH), 7.38–7.77 m (15H_{arom}), 8.32 s (1H, CH), 10.00 s (1H, NH)
IVi	7.24–7.83 m (20H_{arom}), 8.20 s (1H, CH), 10.19 s (1H, NH)
IVk	2.36 s (3H, CH_3), 3.46 c (3H, CH_3), 7.29–7.79 m (14H_{arom}), 8.68 s (1H, CH), 10.56 s (1H, NH)
IVl	2.34 s (3H, CH_3), 4.37 d (2H, CH_2), 4.89–5.13 m (2H, CH_2), 5.71 m (1H, CH), 7.25–7.75 m (14H_{arom}), 8.31 s (1H, CH), 9.90 s (1H, NH)
IVo	2.27 s (3H, CH_3), 2.36 s (3H, CH_3), 7.14–7.73 m (18H_{arom}), 8.18 s (1H, CH), 10.05 s (1H, NH)
V	2.15 s (3H, CH_3), 2.20 s (3H, CH_3), 2.64 s (3H, CH_3), 6.18 s (1H, CH_{pir}), 7.35–7.79 m (5H_{arom}), 10.65 s (1H, NH)
VIa[c]	1.17 t (3H, CH_3), 4.18 m (2H, CH_2), 6.18 d, 8.72 d (2H, CH, NH, J = 8.0 Hz), 7.35–7.79 m (10H_{arom}), 8.15 s (1H, CH), 11.94 s (1H,NH)
VIb[d]	1.16 t (3H, CH_3), 3.80 s (3H, CH_3), 4.17 m (2H, CH_2), 6.17 d, 8.62 d (2H, CH, NH, J = 8.0 Hz), 7.00–7.72 m (9N_{arom}), 8.09 s (1H, CH), 11.82 s (1H, NH)
VIII[b]	2.11 s (3H, CH_3), 2.21 s (3H, CH_3), 5.14 s (1H, CH_{pir}), 7.31–7.78 m (5H_{arom}), 10.34 s (1H, NH), 12.16 br.s (1H, NH)
IXa	5.59 s (1H, CH), 7.37–7.90 m (10H_{arom}), 9.07 s (1H, CH), 11.04 s (1H, NH)
IXb	3.84 s (3H, CH_3), 5.57 s (1H, CH), 7.00–7.85 m (9H_{arom}), 9.00 s (1H, CH), 10.99 s (1H, NH)
Xa	3.13 s (3H, CH_3), 5.59 s (1H, CH), 7.34–7.91 m (10H_{arom}), 9.10 s (1H, CH)
Xb[b]	3.70 m (2H, CH_2), 5.16 m (2H, CH_2), 5.49 s (1H, CH), 5.75 m (1H, CH), 7.31–7.91 m (10H_{arom}), 9.08 s (1H, CH)
Xc	4.29 d and 5.43 d (1H each, CH_2, J = 15.2 Hz), 5.47 s (1H, CH), 7.24–7.93 m (15H_{arom}), 9.13 s (1H, CH)
Xd	6.27 s (1H, CH), 7.35–7.95 m (15H_{arom}), 9.14 s (1H, NH)
Xe	2.26 s (3H, CH_3), 6.22 s (1H, CH), 7.17–7.95 m (14H_{arom}), 9.13 s (1H, CH)

[a] IR spectra, ν, cm^{-1}: **II**, **IIIb**: 3100–3400 (NH_{as}), 1660 (C=O); **IVc**: 3100–3400 (NH_{as}), 1660 (C=O), 1600 (C=N); **IVd**: 3100–3400 (NH_{as}), 1640 (C=O), 1600 (C=N); **IVf**: 3100–3400 (NH_{as}), 1650 (C=O), 1600 (C=N); **IVi**: 3100–3400 (NH_{as}), 1670 (C=O), 1590 (C=N); **V**: 3100–3400 (NH_{as}), 1660 (C=O); **VIa**: 3100–3400 (NH_{as}), 1730 (C=O); **VIb**: 3100–3400 (NH_{as}), 1730 (C=O), 1610 (C=N); **VIII**: 3100–3300 (NH_{as}), 1660 (C=O), 1640 (C=O); **IXa**: 3100–3300 (NH_{as}), 1740 (C=O); **Xa**: 1740 (C=O, band with a shoulder); **Xd**: 1730 (C=O, band with a shoulder). [b] The ^{1}H NMR spectra were recorded on a Varian VXR-300 instrument. [c] Mass spectrum: m/z 341 $[M]^+$. [d] Mass spectrum: m/z 371 $[M]^+$.

NMR techniques (COSY, NOESY, HMQC, HMBC), which allowed us to assign all ^{1}H and ^{13}C signals. Figure shows principal homo- and heteronuclear correlations in molecule **VIb**, and the complete list of correlations is given in Table 3. Acyclic structure of compounds **VI** provides one more support to the proposed mechanism of the transformations **III** → **IX** and **IV** → **X**.

The structure of compounds **IX** and **X** is consistent with the IR and ^{1}H NMR data (Table 2). Their IR spectra contained a strong absorption band at 1720–1740 cm^{-1}, which was assigned to stretching vibrations of the carbonyl group in the 2-thiohydantoin system (cf. [6]). Singlets at δ 5.4–6.3 and 9.0–9.2 ppm in the ^{1}H NMR spectra of **IX** and **X** are typical of 5-H and benzylidene N=CH protons. The IR and ^{1}H NMR data clearly demonstrate disappearance of the *N*-acetyl group during the transformations **III** → **IX** and **IV** → **X** and of the ethoxy group (δ 1.1–4.2 ppm) in the transformation **VI** → **IX**.

Finally, it should be noted that recyclization analogous to the transformation **III** → **IX** was recently reported for the condensation products of compounds like **I** with *N*,*N*′-disubstituted thioureas [9], which may be regarded as an additional proof for the structure of new 2-thiohydantoin derivatives **IX** and **X**.

EXPERIMENTAL

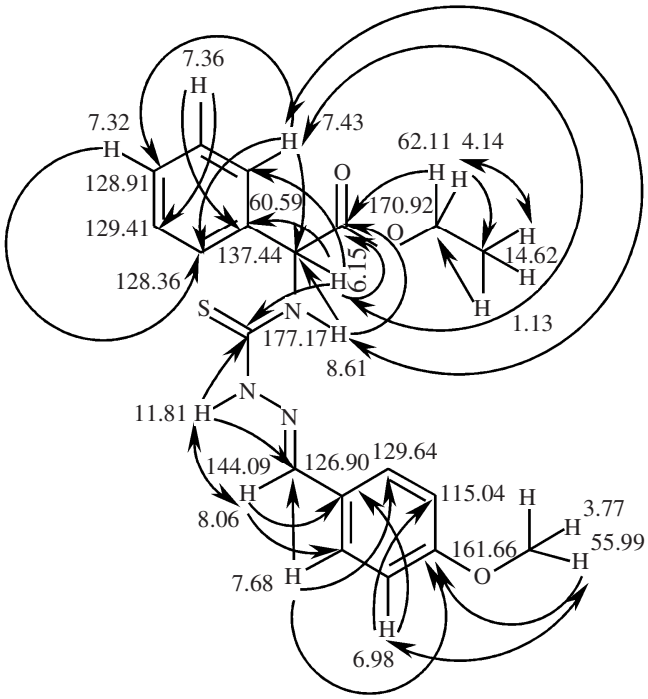
The IR spectra were recorded in KBr on a Specord M-80 spectrometer. The ^{1}H NMR spectra were measured on Varian Mercury-400 and Varian VXR-300 instruments, and the ^{1}H–^{13}C heteronuclear correlation spectra were obtained on a Varian Mercury-400 spectrometer; DMSO-d_6 was used as solvent, and tetramethylsilane, as internal reference. The mass spectra were recorded on a Varian MAT-311A mass spectrometer.

***N*-(1-Chloro-2-oxo-2-phenyl) carboxamides Ia–Ic** were synthesized according to the procedure described in [1].

***N*-(2-Hydrazino-4-phenyl-1,3-thiazol-5-yl)acetamide (II).** *a*. Compound **Ia**, 0.008 mol, was added to a suspension of 0.008 mol of thiosemicarbazide in 25 ml of anhydrous tetrahydrofuran. The mixture was stirred for 24 h at 20–25°C, the precipitate was filtered off and treated with 100 ml of a saturated aqueous solution of sodium hydrogen carbonate, and the precipitate was filtered off, washed with water, and purified by recrystallization from acetonitrile.

The reactions of compounds **Ib** and **Ic** with thiosemicarbazide resulted in the formation of mixtures of products, and we failed to isolate the corresponding thiazoles as individual substances.

b. The synthesis was performed according to the procedure described in [10]. A mixture of 0.011 mol of compound **IIIb**, 4 ml of hydrazine hydrate, and 40 ml



Principal correlations (shown with arrows) and signal assignment (δ, δ_C, ppm) in the ^{1}H and ^{13}C NMR spectra of compound **VIb**.

Table 3. Correlations in the COSY, NOESY, HMQC, and HMBC spectra for compound **VIb**[a]

^{1}H, δ, ppm	^{13}C, δ_C, ppm			
	COSY	NOESY	HMQC	HMBC
7.32	–	–	128.91	128.36
7.36	–	–	129.41	137.44; 129.41
7.43	–	6.15; 8.61	128.36	128.91; 60.59; 128.36
6.15	8.61	7.43; 8.61	60.59	128.36; 137.44; 170.92; 177.17
8.61	6.15	7.43; 6.15	–	60.59; 170.92
4.14	1.13	1.13	62.11	170.92; 14.62
1.13	4.14	4.14	14.62	62.11
11.81	–	8.06	–	177.17; 144.09
8.06	–	11.81	144.09	126.90; 129.64
7.68	6.98	6.98; 3.77	129.64	144.09; 129.64; 161.66
6.98	7.68	7.68	115.04	126.90; 115.04; 55.99
3.77	–	6.98	55.99	161.66

[a] For signal assignment, see figure.

of ethanol was heated for 6 h under reflux. The mixture was then left to stand overnight in a refrigerator, and the precipitate was filtered off, washed with cold ethanol, and recrystallized from acetonitrile. Samples of compound **II** prepared as described in *a* and *b* showed no depression of the melting point on mixing, and their IR and ^{1}H NMR spectra were identical.

2-[2-(Arylmethylidene)hydrazino]-5-acylamino-4-phenyl-1,3-thiazoles IIIa–IIIf *(general procedure).* Compound **Ia–Ic**, 0.01 mol, was added to a suspension of 0.01 mol of 1-(arylmethylidene)thiosemicarbazide in 25 ml of anhydrous THF, and the mixture was stirred for 24 h at 20–25°C. The precipitate was filtered off and dissolved in 30 ml of anhydrous methanol, and the solution was heated for 1 h under reflux. The solvent was removed under reduced pressure, the residue was treated with 100 ml of a saturated aqueous solution of sodium hydrogen carbonate, and the precipitate was filtered off, washed with water, and recrystallized from an appropriate solvent.

3-Alkyl(aryl)-5-acylamino-2-(2-benzylidenehydrazono)-4-phenyl-2,3-dihydro-1,3-thiazoles IVa–IVo *(general procedure).* Compound **Ia–Ic**, 0.002 mol, was added to a suspension of 0.002 mol of 4-alkyl(aryl)-1-benzylidenethiosemicarbazide in 20 ml of anhydrous THF, and the mixture was stirred for 24 h at 20–25°C. The solvent was removed under reduced pressure, 20 ml of anhydrous methanol was added to the residue, and the mixture was heated for 1 h under reflux. The solvent was removed under reduced pressure, the residue was treated with 100 ml of a saturated aqueous solution of sodium hydrogen carbonate, and the precipitate was filtered off, washed with water, and purified by recrystallization.

***N*-[2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-4-phenyl-1,3-thiazol-5-yl]acetamide (V).** A mixture of 0.004 mol of compound **II**, 0.004 mol of acetylacetone, and 10 ml of glacial acetic acid was heated for 2 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with ethanol, and dried.

Ethyl 2-[1-(arylmethylidene)thiosemicarbazido]-2-phenylacetates VIa and VIb *(general procedure).* Concentrated hydrochloric acid, 15 ml, was added to a solution of 0.006 mol of compound **IIIa** or **IIIb** in 40 ml of ethanol, the mixture was heated for 2 h under reflux, cooled, and treated with 100 ml of a saturated aqueous solution of sodium hydrogen carbonate, and the precipitate was filtered off and purified by recrystallization.

***N*-[2-(3-Methyl-5-oxo-2,5-dihydro-1*H*-pyrazol-1-yl)-4-phenyl-1,3-thiazol-5-yl]acetamide (VIII).** A mixture of 0.004 mol of compound **II**, 0.004 mol of ethyl acetoacetate, and 10 ml of glacial acetic acid was heated for 7 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with ethanol, and dried.

3-(Arylmethylideneamino)-2-thioxo-5-phenylimidazolidin-4-ones IXa and IXb *(general procedure). a*. Concentrated hydrochloric acid, 40 ml, was added to a solution of 0.004 mol of compound **IIIa** or **IIIb** in 25 ml of ethanol, and the mixture was heated for 6 h under reflux. The mixture was cooled, 150 ml of a saturated aqueous solution of sodium hydrogen carbonate was added, and the precipitate was filtered off and purified by recrystallization.

b. Concentrated hydrochloric acid, 40 ml, was added to a solution of 0.004 mol of compound **VIa** or **VIb** in 25 ml of ethanol, and the mixture was heated for 6 h under reflux. The mixture was cooled, 150 ml of a saturated aqueous solution of sodium hydrogen carbonate was added, and the precipitate was filtered off and purified by recrystallization. Samples of compounds **IXa** and **IXb** prepared as described in *a* and *b* showed no depression of the melting point on mixing, and their IR and ^{1}H NMR spectra were identical.

1-Alkyl(aryl)-3-(benzylideneamino)-2-thioxo-5-phenylimidazolidin-4-ones Xa–Xe *(general procedure).* Concentrated hydrochloric acid, 15 ml, was added to a solution of 0.006 mol of compound **IVa–IVe** in 40 ml of ethanol, and the mixture was heated for 2 h under reflux. The mixture was cooled, 100 ml of a saturated aqueous solution of sodium hydrogen carbonate was added, and the precipitate was filtered off and purified by recrystallization.

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