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Synthesis of New 2,5-Diamino-1,3-thiazole and 2-Thiohydantoin Derivatives by Condensation of *N*-(2-Aryl-1-chloro-2-oxoethyl) Carboxamides with Thioureas

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Abstract—*N*-(2-Aryl-1-chloro-2-oxoethyl) carboxamides react under mild conditions with thiourea, *N*-alkyl- and *N*-arylthioureas, and various *N*,*N*′-disubstituted thioureas, following the Hantzsch reaction scheme. The reactions are selective, and the resulting 2,5-diamino-1,3-thiazole derivatives undergo recyclization acid followed by hydrolysis to give substituted 2-thiohydantoins on heating with hydrochloric acid in ethanol.

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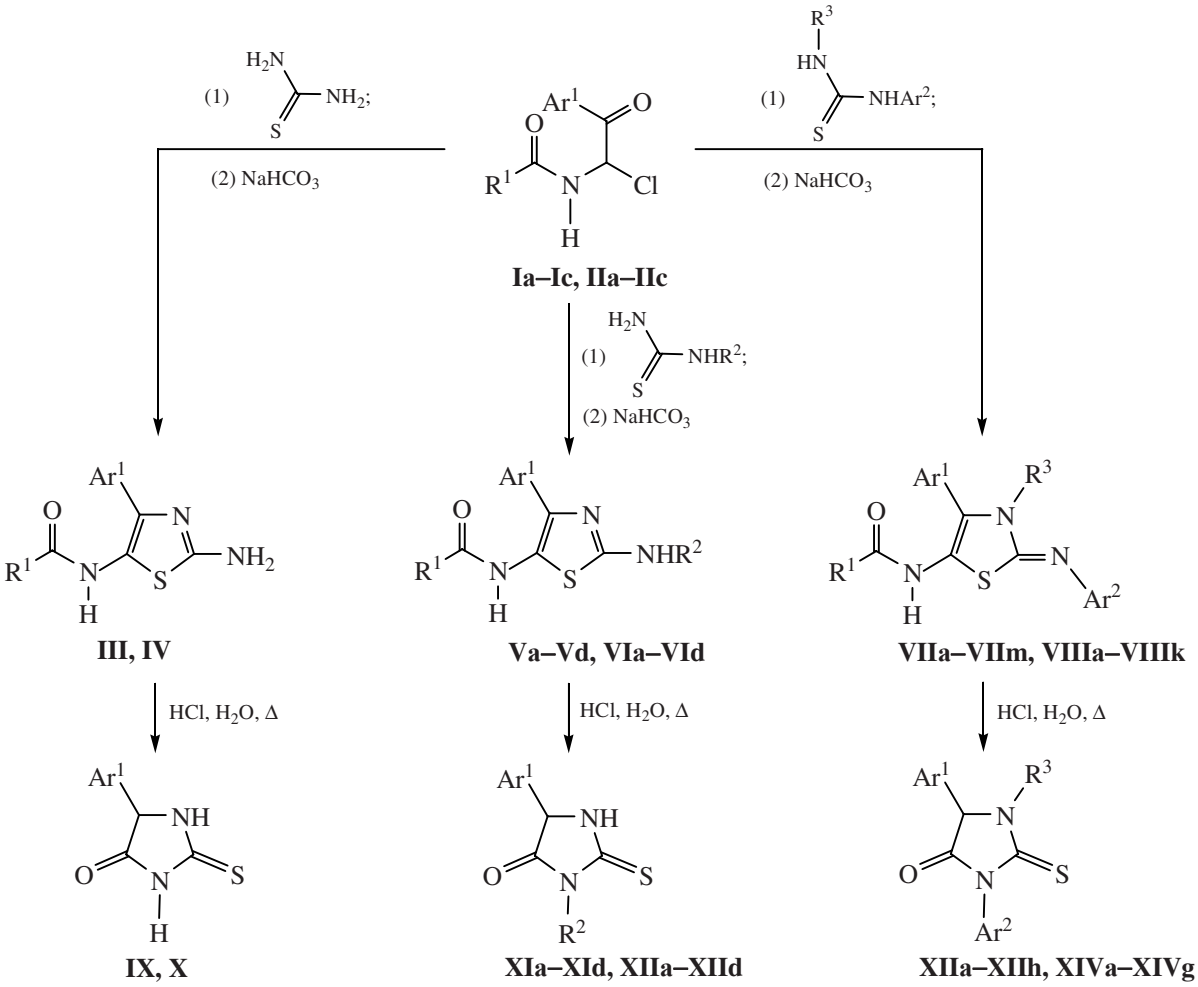
Accessible *N*-(2-aryl-1-chloro-2-oxoethyl) carboxamides of the general formula ArCOCHClNHCOR may be regarded as most reactive phenacylating agents; they are readily obtained from the addition products of carboxylic acid amides and aryl(oxo) acetaldehydes [1–5]. These compounds turned out to be suitable for the synthesis of a series of nitrogen-containing heterocycles [3, 6–10]; however, the scope of their application has been studied poorly. In the present work we examined in detail the possibility of using compounds **I** and **II** for the preparation of new derivatives of 2,5-diamino-1,3-thiazole (**III**–**VIII**) and 2-thiohydantoin (**IX**–**XIV**) (Scheme 1, Table 1).

Compounds **I** and **II** (Ar^1 = Ph, 4-MeC_6H_4) were brought into cyclocondensation with thiourea, *N*-alkyl- and *N*-arylthioureas, and various *N*,*N*′-disubstituted thioureas. The direction of such reactions with thiourea was determined previously [7, 11], while the regioselectivity in the condensation involving both electrophilic centers in the α-chloro carbonyl fragment of **I** and **II** and nitrogen and sulfur nucleophilic centers in unsymmetrically substituted thioureas was established only on the basis of a combination of spectral, X-ray diffraction, and chemical studies (Scheme 1, Table 2, Fig. 1). The IR and ^{1}H NMR data showed that the cyclization actually involves the COCHCl fragment in **I** and **II** and that the *N*-acyl moiety remains intact. The IR and ^{1}H NMR spectra of condensation products **III** and **IV** contained absorption bands and signals assignable to the amide bond and primary amino group. In the ^{1}H NMR spectra of **VII** and **VIII** we observed only one set of signals from ptotons in the R^1, R^3, Ar^1, and Ar^2 groups, which indicated high regioselectivity of the condensation of **I** and **II** with unsymmetrically substituted thioureas having an aryl group at one nitrogen atom and alkyl, aralkyl, or alkenyl group at the other nitrogen atom.

The structure of products **VII** and **VIII** was finally proved by X-ray analysis of a single crystal of compound **VIIIj** obtained by reaction of **IIc** (Ar^1 = 4-MeC_6H_4, R^1 = 2-furyl) with *N*-allyl-*N*′-(4-ethoxyphenyl)thiourea. The structure of molecule **VIIIj** is shown in Fig. 1. The central five-membered heteroring $S^1N^1C^1C^2C^3$ is planar within 0.009 Å. The benzene rings $C^{9-}C^{14}$ and $C^{19-}C^{24}$ with the $S^1N^1C^1C^2C^3$ ring plane form dihedral angles of 67.7 and 89.5°, respectively, and the dihedral angle between the thiazole and furan ($O^2C^5C^6C^7C^8$) rings is 29.5°. The N^3 atom has a planar–trigonal configuration: the sum of the bond angles at that atom is 360.0°. Conjugation between the unshared electron pair on the N^3 atom with the π-electron system of the thiazole ring and

Scheme 1.



I, **III**, **V**, **VII**, **IX**, **XI**, **XIII**, $Ar^1 = C_6H_5$; **II**, **IV**, **VI**, **VIII**, **X**, **XII**, **XIV**, Ar^1 = 4-$CH_3C_6H_4$; **Ia**, **IIa**, **III**, **IV**, **Va–Vd**, **VIa–VId**, **VIIa–VIIh**, **VIIIa–VIIIg**, $R^1 = CH_3$; **Ib**, **IIb**, **VIIi–VIIk**, **VIIIh**) $R^1 = C_6H_5$; **Ic**, **IIc**, **VIIl**, **VIIm**, **VIIIi–VIIIk**, R^1 = 2-furyl; **Va**, **VIa**, **XIa**, **XIIa**, $R^2 = CH_3$; **Vb**, **VIb**, **XIb**, **XIIb**, $R^2 = C_6H_5CH_2$; **Vc**, **VIc**, **XIc**, **XIIc**, $R^2 = C_6H_5$; **Vd**, **VId**, **XId**, **XIId,** R^2 = 4-$CH_3C_6H_4$; **VIIa**, **VIIIa**, **XIIIa**, **XIVa**, $R^3 = CH_3$; **VIIb**, **VIIi**, **VIIl**, **VIIIi**, **XIIIb**, $R^3 = CH_3OCH_2CH_2$; **VIIc**, **VIIj**, **VIIm**, **VIIIb**, **VIIIj**, **XIIIc**, **XIVb**, $R^3 = CH_2{=}CHCH_2$; **VIId**, **VIIIc**, **XIIId**, **XIVc**, $R^3 = C_6H_5CH_2$; **VIIe**, **VIIId**, **XIIIe**, **XIVd**, R^3 = 4-$CH_3OC_6H_4CH_2$; **VIIf**, **VIIk**, **VIIIe**, **VIIIh**, **VIIIk**, **XIIIf**, **XIVe**, R^3 = 2-furylmethyl; **VIIg**, **VIIIf**, **XIIIg**, **XIVf**, R^3 = 4-$CH_3C_6H_4$; **VIIh**, **VIIIg**, **XIIIh**, **XIVg,** R^3 = 4-$C_2H_5OC_6H_4$; **VIIa**, **VIIb**, **VIId–VIIf**, **VIIi**, **VIIk**, **VIIl**, **VIIIa**, **VIIIc–VIIIe**, **VIIIh**, **VIIIi**, **VIIIk**, **XIIIa**, **XIIIb**, **XIIId–XIIIf**, **XIVa**, **XIVc–XIVe**, $Ar^2 = C_6H_5$; **VIIg**, **VIIIf**, **XIIIg**, **XIVf**, Ar^2 = 4-$CH_3C_6H_4$; **VIIc**, **VIIh**, **VIIj**, **VIIm**, **VIIIb**, **VIIIg**, **VIIIj**, **XIIIc**, **XIIIh**, **XIVb**, **XIVg**, Ar^2 = 4-$C_2H_5OC_6H_4$.

C=O bond (the conformation of molecule **VIIIj** is favorable for this interaction) leads to shortening of the N^3–C^1 [1.400(5) Å] and N^3–C^4 bonds [1.349(2) Å] relative to a purely single N(sp^2)–C(sp^2) bond (1.43–1.45 Å) [19, 20].

Taking into account the above data, as well as the results of chemical transformations of compounds **III–VIII** (see below), we can state that the electrophilic C–Cl carbon atom in **I** and **II** interacts mainly with the sulfur center in the thiourea reagent and that the carbonyl group in the COCHClNH fragment preferentially interacts with either primary amino group or (if the latter is lacking) NHAlk, $NHCH_2CH{=}CH_2$, $NHCH_2Ar$, or $NHCH_2Ht$ group which is more nucleophilic than NHAr group. Thus the examined condensations occur under very mild conditions (THF, 20–25°C) in a regioselective fashion

Table 1. Yields, melting points, and elemental analyses of compounds **III–XIV**

Comp. no.	Yield, %[a]	mp, °C (solvent)	Found, %		Formula	Calculated, %	
			N	S		N	S
III	73	232–234 (AcOH)	17.93	13.63	$C_{11}H_{11}N_3OS$	18.01	13.74
IV	75	243–245 (EtOH)	16.83	12.79	$C_{12}H_{13}N_3OS$	16.99	12.96
Va	77	211–213 (EtOH)	16.79	12.87	$C_{12}H_{13}N_3OS$	16.99	12.96
Vb	84	158–160 (EtOH)	12.81	9.95	$C_{18}H_{17}N_3OS$	12.99	9.91
Vc	73	227–229 (EtOH)	13.39	10.29	$C_{17}H_{15}N_3OS$	13.58	10.36
Vd	60	181–183 (MeOH)	12.85	9.79	$C_{18}H_{17}N_3OS$	12.99	9.91
VIa	81	215–217 (EtOH)	15.99	12.19	$C_{13}H_{15}N_3OS$	16.07	12.26
VIb	80	167–169 (EtOH)	12.29	9.31	$C_{19}H_{19}N_3OS$	12.45	9.50
VIc	71	183–185 (EtOH)	12.78	9.78	$C_{18}H_{17}N_3OS$	12.99	9.91
VId	67	159–161 (EtOH)	12.29	9.36	$C_{19}H_{19}N_3OS$	12.45	9.50
VIIb	69	211–213 (*i*-PrOH)	10.26	7.84	$C_{20}H_{22}ClN_3O_2S$[b]	10.40	7.93
VIIc	81	125–126 (EtOH)	10.49	8.01	$C_{22}H_{23}N_3O_2S$	10.67	8.14
VIId	67	138–140 (*i*-PrOH)	10.53	7.95	$C_{24}H_{21}N_3OS$	10.51	8.02
VIIe	63	167–168 (*i*-PrOH)	9.59	7.29	$C_{25}H_{23}N_3O_2S$	9.78	7.46
VIIf	68	167–169 (EtOH)	9.73	7.39	$C_{22}H_{20}ClN_3O_2S$[c]	9.86	7.52
VIIg	56	166–168 (*i*-PrOH)	10.01	7.59	$C_{25}H_{23}N_3OS$	10.16	7.75
VIIh	61	107–109 (*i*-PrOH)	8.69	6.67	$C_{27}H_{27}N_3O_3S$	8.87	6.77
VIIi	77	173–174 (EtOH)	9.59	7.29	$C_{25}H_{23}N_3O_2S$	9.78	7.46
VIIj	80	169–171 (CH_3CN)	9.09	6.95	$C_{27}H_{25}N_3O_2S$	9.22	7.03
VIIk	74	164–166 (MeOH)	9.19	6.99	$C_{27}H_{21}N_3O_2S$	9.30	7.10
VIIl	81	137–139 (EtOH)	9.93	7.60	$C_{23}H_{21}N_3O_3S$	10.01	7.64
VIIm	71	103–105 (EtOH)	9.28	6.99	$C_{25}H_{23}N_3O_3S$	9.43	7.19
VIIIa	69	174–176 (*i*-PrOH)	12.29	9.41	$C_{19}H_{19}N_3OS$	12.45	9.50
VIIIb	73	110–112 (EtOH)	10.16	7.69	$C_{23}H_{25}N_3O_2S$	10.31	7.86
VIIIc	74	166–168 (*i*-PrOH)	10.03	7.62	$C_{25}H_{23}N_3OS$	10.16	7.75
VIIIe	79	201–202 (EtOH)	10.26	7.79	$C_{23}H_{21}N_3O_2S$	10.41	7.94
VIIIf	53	190–192 (EtOH)	9.63	7.39	$C_{26}H_{25}N_3OS$	9.82	7.50
VIIIg	59	179–181 (*i*-PrOH)	8.49	6.41	$C_{28}H_{29}N_3O_3S$	8.61	6.57
VIIIh	74	161–163 (CH_3CN)	8.91	6.80	$C_{28}H_{23}N_3O_2S$	9.02	6.88
VIIIi	79	122–124 (EtOH)	9.51	7.23	$C_{24}H_{23}N_3O_3S$	9.69	7.39
VIIIj	69	143–144 (MeOH)	9.03	6.81	$C_{26}H_{25}N_3O_3S$	9.14	6.97
VIIIk	83	147–149 (EtOH)	9.09	6.93	$C_{26}H_{21}N_3O_3S$	9.22	7.03
IX	76 (81)	223–224[d] (EtOH)	14.42	16.74	$C_9H_8N_2OS$	14.57	16.68
X	71 (75)	247–248 (EtOH)	13.43	15.39	$C_{10}H_{10}N_2OS$	13.58	15.54
XIa	88	153–154[e] (C_6H_6)	13.41	15.37	$C_{10}H_{10}N_2OS$	13.58	15.54
XIb	78	150–151 (EtOH)	9.75	11.65	$C_{16}H_{14}N_2OS$	9.92	11.35
XIc	87	227–229[f] (MeOH)	10.40	11.96	$C_{15}H_{12}N_2OS$	10.44	11.94
XId	86	233–235[g] (CH_3CN)	9.83	11.19	$C_{16}H_{14}N_2OS$	9.92	11.35
XIIa	86	157–158 (C_6H_6)	12.53	14.39	$C_{11}H_{12}N_2OS$	12.71	14.55
XIIb	78	127–129 (EtOH)	9.40	10.75	$C_{17}H_{16}N_2OS$	9.45	10.81
XIIc	79	232–233 (EtOH)	9.85	11.19	$C_{16}H_{14}N_2OS$	9.92	11.35
XIId	83	203–205 (EtOH)	9.29	10.69	$C_{17}H_{16}N_2OS$	9.45	10.81

Table 1. (Contd.)

Comp. no.	Yield, %[a]	mp, °C (solvent)	Found, %		Formula	Calculated, %	
			N	S		N	S
XIIIa	(69)	202–204 (EtOH)	9.79	11.29	$C_{16}H_{14}N_2OS$	9.92	11.35
XIIIb	81	121–122 (EtOH)	8.43	9.73	$C_{18}H_{18}N_2O_2S$	8.58	9.82
XIIIc	79	140–141 (EtOH)	7.79	9.01	$C_{20}H_{20}N_2O_2S$	7.94	9.09
XIIId	82 (71)	191–192 (CH_3CN)	7.71	8.79	$C_{22}H_{18}N_2OS$	7.81	8.94
XIIIe	91 (86)	188–190 (AcOH)	7.15	8.09	$C_{23}H_{20}N_2O_2S$	7.21	8.25
XIIIf	83	149–150 (EtOH)	7.95	9.11	$C_{20}H_{16}N_2O_2S$	8.04	9.20
XIIIg	81	180–192[h] (EtOH)	7.39	8.49	$C_{23}H_{20}N_2OS$	7.52	8.60
XIIIh	83	182–184 (CH_3CN)	6.31	7.35	$C_{25}H_{24}N_2O_3S$	6.47	7.41
XIVa	75 (63)	184–186 (EtOH)	9.31	10.75	$C_{17}H_{16}N_2OS$	9.45	10.81
XIVb	81	129–131 (EtOH)	7.51	8.69	$C_{21}H_{22}N_2O_2S$	7.64	8.75
XIVc	75 (68)	201–202 (CH_3CN)	7.45	8.53	$C_{23}H_{20}N_2OS$	7.52	8.60
XIVd	(71)	185–187 (CH_3CN)	6.83	7.90	$C_{24}H_{22}N_2O_2S$	6.96	7.96
XIVe	69	169–170 (EtOH)	7.64	8.75	$C_{21}H_{18}N_2O_2S$	7.73	8.84
XIVf	79	144–146 (EtOH)	7.11	8.19	$C_{24}H_{22}N_2OS$	7.24	8.29
XIVg	76	164–166 (EtOH)	6.09	7.03	$C_{26}H_{26}N_2O_3S$	6.27	7.18

[a] The yields according to method *b* are given in parentheses. [b] **VIIb**·HCl. Found, %: Cl 8.61. Calculated, %: Cl 8.77. [c] **VIIf**·HCl. Found, %: Cl 8.21. Calculated, %: Cl 8.32. [d] Published data: mp 220°C [12], 227°C [13], 225°C [14]; samples were synthesized from phenylglycine. [e] Published data [15]: mp 159–160°C. [f] Published data: mp 232–233°C [16], 232.1–233.6°C [17]; samples were synthesized from phenylglycine. [g] Published data [16]: mp 237–238°C; sample was synthesized from the corresponding amino acid and phenyl isothiocyanate. [h] Coincided with the melting point of the condensation product of phenyl(oxo)acetaldehyde with *N*,*N*′-bis(*p*-tolyl) thiourea [18].

Table 2. IR and ^{1}H NMR spectra of compounds **III–XIV**[a]

Comp. no.	^{1}H NMR spectrum (DMSO-d_6), δ, ppm
III	1.99 s (3H, CH_3), 6.70 br.s (2H, NH_2), 7.21–7.68 m (5H$_{arom}$), 9.80 s (1H, NH)
IV	1.98 s (3H, CH_3), 2.32 s (3H, CH_3), 6.59 br.s (2H, NH_2), 7.14–7.56 m (4H, H$_{arom}$), 9.64 s (1H, NH)
Va	2.00 s (3H, CH_3), 2.83 d (3H, CH_3), 7.20 m (1H, NH), 7.23–7.72 m (5H, H$_{arom}$), 9.76 s (1H, NH)
Vb	1.99 s (3H, CH_3), 4.44 d (2H, CH_2), 7.77 t (1H, NH), 7.21–7.71 m (10H, H$_{arom}$), 9.73 s (1H, NH)
Vc	2.07 s (3H, CH_3), 6.95–7.77 m (10H, H$_{arom}$), 9.95 s (1H, NH), 10.18 s (1H, NH)
Vd	2.06 s (3H, CH_3), 2.28 s (3H, CH_3), 7.09–7.76 m (9H, H$_{arom}$), 9.91 s (1H, NH), 10.14 s (1H, NH)
VIb	1.99 s (3H, CH_3), 2.31 s (3H, CH_3), 4.44 d (2H, CH_2), 7.18–7.59 m (9H, H$_{arom}$), 7.95 t (1H, NH), 9.81 s (1H, NH)
VId	2.05 s (3H, CH_3), 2.25 s (3H, CH_3), 2.34 s (3H, CH_3), 7.10–7.67 m (8H, H$_{arom}$), 9.89 s (1H, NH), 10.06 s (1H, NH)
VIIb	1.99 s (3H, CH_3), 3.11 s (3H, CH_3), 3.49 t (2H, CH_2), 4.26 t (2H, CH_2), 7.40–7.69 m (10H, H$_{arom}$), 10.59 s (1H, NH)
VIIc	1.31 t (3H, CH_3), 1.82 s (3H, CH_3), 4.00 m (2H, CH_2), 4.25 d (2H, CH_2), 4.88–5.07 m (2H, CH_2), 5.74 m (1H, CH), 6.87–7.48 m (9H, H$_{arom}$), 9.42 s (1H, NH)
VIId	1.81 s (3H, CH_3), 4.92 s (2H, CH_2), 6.92–7.41 m (15H, H$_{arom}$), 9.39 s (1H, NH)
VIId	1.98 s (3H, CH_3), 3.72 s (3H, CH_3), 5.36 s (2H, CH_2), 6.77–7.56 m (14H, H$_{arom}$), 10.61 s (1H, NH)
VIIe[b]	2.05 s (3H, CH_3), 5.41 s (2H, CH_2), 6.31–7.56 m (13H, H$_{arom}$)
VIIg	1.85 s (3H, CH_3), 2.24 s (3H, CH_3), 2.26 s (3H, CH_3), 6.74–7.22 m (13H, H$_{arom}$), 9.50 s (1H, NH)
VIIh	1.31 m (6H, 2CH_3), 1.85 s (3H, CH_3), 3.95 m (4H, 2CH_2), 6.73–7.24 m (13H, H$_{arom}$), 9.47 s (1H, NH)
VIIi	3.14 s (3H, CH_3), 3.58 m (2H, CH_2), 3.89 m (2H, CH_2), 6.96–7.71 m (15H, H$_{arom}$), 9.75 s (1H, NH)
VIIj	1.35 t (3H, CH_3), 3.97 m (2H, CH_2), 4.33 m (2H, CH_2), 4.98–5.11 m (2H, CH_2), 5.83 m (1H, CH), 6.81–7.70 m (14H, H$_{arom}$), 9.72 s (1H, NH)

Table 2. (Contd.)

Comp. no.	^{1}H NMR spectrum (DMSO-d_6), δ, ppm
VIIk	4.98 s (2H, CH_2), 6.01–7.69 m (18H, H_{arom}), 9.91 s (1H, NH)
VIIl	3.09 s (3H, CH_3), 3.54 t (2H, CH_2), 3.88 t (2H, CH_2), 6.59–7.84 m (13H, H_{arom}), 9.76 s (1H, NH)
VIIm	1.32 t (3H, CH_3), 3.98 m (2H, CH_2), 4.32 d (2H, CH_2), 4.93–5.11 m (2H, CH_2), 5.79 m (1H, CH), 6.60–7.84 m (12H, H_{arom}), 9.76 s (1H, NH)
VIIIa	1.81 s (3H, CH_3), 2.39 s (3H, CH_3), 6.94–7.31 m (9H, H_{arom}), 9.32 s (1H, NH)
VIIIb	1.31 t (3H, CH_3), 1.82 s (3H, CH_3), 2.36 s (3H, CH_3), 3.99 m (2H, CH_2), 4.23 d (2H, CH_2), 4.89–5.08 m (2H, CH_2), 5.74 m (1H, CH), 6.82–7.29 m (8H, H_{arom}), 9.43 s (1H, NH)
VIIIc	1.81 s (3H, CH_3), 2.35 s (3H, CH_3), 4.90 s (2H, CH_2), 6.90–7.31 m (14H, H_{arom}), 9.33 s (1H, NH)
VIIIe	1.81 t (3H, CH_3), 2.39 s (3H, CH_3), 4.83 s (2H, CH_2), 6.02–7.41 m (12H, H_{arom}), 9.33 s (1H, NH)
VIIIf	1.85 s (3H, CH_3), 2.26 s (9H, $3CH_3$), 6.72–7.07 m (12H, H_{arom}), 9.43 s (1H, NH)
VIIIh	2.35 s (3H, CH_3), 4.93 s (2H, CH_2), 6.06–7.71 m (17H, H_{arom}), 9.73 s (1H, NH)
VIIIi	2.34 s (3H, CH_3), 3.11 s (3H, CH_3), 3.53 t (2H, CH_2), 3.86 t (2H, CH_2), 6.59–7.83 m (12H, H_{arom}), 9.69 s (1H, NH)
VIIIj	1.31 t (3H, CH_3), 2.33 s (3H, CH_3), 4.00 m (2H, CH_2), 4.31 d (2H, CH_2), 4.95–5.12 m (2H, CH_2), 5.79 m (1H, CH), 6.59–7.29 m (11H, H_{arom}), 9.68 s (1H, NH)
VIIIk	2.33 s (3H, CH_3), 4.93 s (2H, CH_2), 6.04–7.84 m (15H, H_{arom}), 9.74 s (1H, NH)
IX	5.28 s (1H, CH), 7.26–7.43 m (5H, H_{arom}), 10.40 s (1H, NH), 11.75 s (1H, NH)
X	2.32 s (3H, CH_3), 5.20 s (1H, CH), 7.24–7.43 m (4H, H_{arom}), 10.32 s (1H, NH), 11.68 s (1H, NH)
XIa	3.12 s (3H, CH_3), 5.32 s (1H, CH), 7.28–7.41 m (5H, H_{arom}), 10.69 s (1H, NH)
XIb	4.91 s (2H, CH_2), 5.41 s (1H, CH), 7.22–7.41 m (10H, H_{arom}), 10.77 s (1H, NH)
XIc	5.52 s (1H, CH), 7.26–7.51 m (10H, H_{arom}), 10.94 s (1H, NH)
XId	2.37 s (3H, CH_3), 5.50 s (1H, CH), 7.13–7.44 m (9H, H_{arom}), 10.92 s (1H, NH)
XIIc	2.33 s (3H, CH_3), 5.55 s (1H, CH), 7.28–7.52 m (9H, H_{arom}), 10.98 s (1H, NH)
XIIIa	3.16 s (3H, CH_3), 5.53 s (1H, CH), 7.31–7.51 m (10H, H_{arom})
XIIIb	3.25 s (3H, CH_3), 3.26–4.31 m (4H, $2CH_2$), 5.58 s (1H, CH), 7.32–7.51 m (10H, H_{arom})
XIIIc	1.38 t (3H, CH_3), 3.72 m, 4.82 m (2H, CH_2), 4.07 m (2H, CH_2), 5.14 m (2H, CH_2), 5.45 s (1H, CH), 5.76 m (1H, CH), 6.95–7.47 m (9H, H_{arom})
XIIId	4.26 d and 5.49 d (1H each, CH_2, J = 15.3 Hz), 5.36 s (1H, CH), 7.21–7.56 m (15H, H_{arom})
XIIIe	3.74 s (3H, CH_3), 4.15 d and 5.46 d (1H each, CH_2, J = 15.0 Hz), 5.32 s (1H, CH), 6.82–7.51 m (14H, H_{arom})
XIIIf	4.37 d and 5.39 d (2H, CH_2, J = 15.6 Hz), 5.40 s (1H, CH), 6.26–7.52 m (13H, H_{arom})
XIIIg	2.42 s (3H, CH_3), 2.38 s (3H, CH_3), 6.21 s (1H, CH), 7.15–7.44 m (13H, H_{arom})
XIIIh	1.32 t (3H, CH_3), 1.39 t (3H, CH_3), 3.95 m (2H, CH_2), 4.06 m (2H, CH_2), 6.05 s (1H, CH), 6.81–7.38 m (13H, H_{arom})
XIVa	2.35 s (3H, CH_3), 3.13 s (3H, CH_3), 5.47 s (1H, CH), 7.20–7.51 m (9H, H_{arom})
XIVb	1.38 t (3H, CH_3), 2.36 s (3H, CH_3), 3.68 m, 4.81 m (2H, CH_2), 4.08 m (2H, CH_2), 5.15 m (2H, CH_2), 5.39 s (1H, CH), 5.75 s (1H, CH), 6.69–7.27 m (8H, H_{arom})
XIVc	2.36 s (3H, CH_3), 4.19 d, 5.51 d (2H, CH_2, J = 15.3 Hz), 5.28 s (1H, CH), 7.16–7.51 m (14H, H_{arom})
XIVd	2.37 s (3H, CH_3), 3.75 s (3H, CH_3), 4.10 d and 5.48 d (1H each, CH_2, J = 15.0 Hz), 5.23 s (1H, CH), 6.82–7.51 m (13H, H_{arom})
XIVe	2.36 s (3H, CH_3), 4.29 d and 5.42 d (1H each, CH_2, J = 15.6 Hz), 5.33 s (1H, CH), 6.27–7.52 m (12H, H_{arom})
XIVf	2.27 s (6H, $2CH_3$), 2.40 s (3H, CH_3), 6.07 s (1H, CH), 7.11–7.39 m (12H, H_{arom})

[a] IR spectra, ν, cm^{-1}: compounds **III**–**VI**: 3100–3400 (NH_{as}), 1640–1660 (C=O); **VII**–**VIII**: 3100–3400 (NH_{as}), 1610–1660 (band with a shoulder; C=O, C=N); **IX**–**XII**: 3150–3180 (NH_{as}), 1740–1760 (C=O); **XIII**–**XIV**: 1740–1760 (C=O). [b] The ^{1}H NMR spectrum was recorded in CF_3COOD.

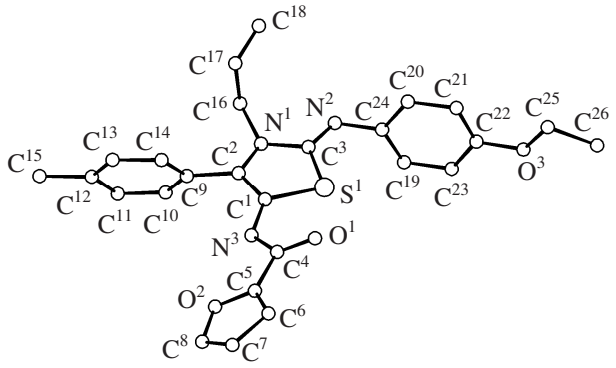
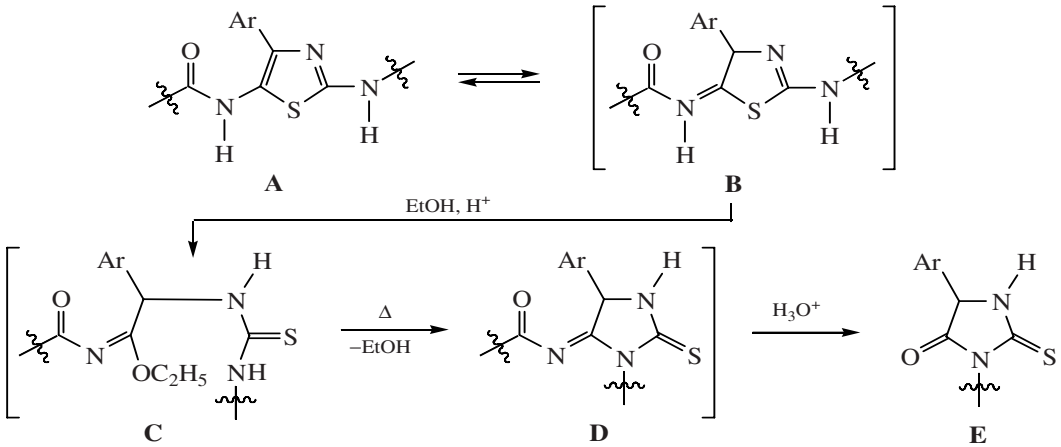


Fig. 1. Structure of the molecule of *N*-[3-methyl-4-(4-methylphenyl)-2-phenylimino-2,3-dihydro-1,3-thiazol-5-yl] acetamide (**VIIIj**) according to the X-ray diffraction data. Principal bond lengths (Å) and bond angles (deg): S^1–C^1 1.752(3), S^1–C^3 1.782(3), N^1–C^2 1.396(5), N^1–C^3 1.383(4), N^2–C^3 1.269(5), N^2–C^{24} 1.427(5), N^3–C^1 1.400(5), N^3–C^4 1.349(5), C^1–C^2 1.334(5), $C^1S^1C^3$ 90.2(2), $C^2N^1C^3$ 114.7(3), $C^3N^2C^{24}$ 118.2(3), $C^1N^3C^4$ 125.2(3), $S^1C^1C^2$ 112.8(3), $N^1C^2C^1$ 113.4(3).

according to the Hantzsch reaction scheme and lead to the formation of compounds **III–VIII**. Many simpler α-halocarbonyl compounds are known [21, 22] to react with substituted thioureas in a similar way; unlike these, reagents **I** and **II** contain a very labile chlorine atom, which allows the reaction to occur under mild conditions ensuring enhanced regioselectivity. Undoubtedly, selective introduction of an acylamino substituent into the 5 position of 2-amino-1,3-thiazole or 2-imino-2,3-dihydro-1,3-thiazole system attracts strong interest from the preparative viewpoint, for the above approach is often the only one leading to such thiazole derivatives. Among other methods, the reaction of 1-benzoylaminoacetophenone with thiourea in the presence of iodine should be noted; it gives 2-amino-5-benzoylamino-4-phenyl-1,3-thiazole [23]. However, the scope of application of this simple synthesis was poorly studied, the yields of substituted thiazoles like **III** are considerably lower than in the reactions with compounds **I** and **II**, and derivatives like **V–VIII** are quite difficult to obtain due to lower regioselectivity of the cyclization.

Interestingly, all cyclization products **III–VIII** were converted into the corresponding 2-thiohydantoin derivatives **IX–XIV** on heating with hydrochloric acid in ethanol (Scheme 1). Among these transformations, only the reaction of 2-amino-5-benzoylamino-4-phenyl-1,3-thiazole with 10% hydrochloric acid has been reported previously [24]. Thus we have demonstrated general character of the reaction of various 2-amino-5-acylamino-1,3-thiazoles **III–VI** with hydrochloric acid. Obviously, the transformation begins with recyclization which is followed by acid hydrolysis of the acylamino group. A plausible mechanism of this complex process is ahown in Scheme 2. Recyclization of **III–VI** is unlikely to directly involve the thiazole ring, for the latter is aromatic and its cleavage is difficult. However, the presence of an acylamino group in the 5 position of the thiazole ring could give rise to prototropy, and structure **A** can be converted (at least to a small extent) into nonaromatic structure **B** which can be readily cleaved with ethanol in the presence of hydrogen chloride. The subsequent recyclization **C**→**D** and hydrolysis of the acylamino group **D**→**E** seem to be quite feasible (Scheme 2). Naturally, analogous transformations could be drawn for substituted 2-imino-2,3-dihydro-1,3-thiazoles **VII** and **VIII**.

Scheme 2.



The structure of the products obtained by reactions of **III–VIII** with hydrochloric acid in ethanol is beyond doubt, for some of these were synthesized previously by independent methods (Table 1), while the others were identified as substituted 2-thiohydantoins on the basis of their spectral parameters and chemical transformations. For example, treatment of both compound **III** and 2-amino-5-benzoylamino-4-phenyl-1,3-thiazole [7] (these compounds differ only by the *N*-acyl residues) with hydrochloric acid gave the same product, 5-phenyl-2-thiohydantoin **IX**. The latter was identical in melting point to an authentic sample of **IX** prepared by reaction of *N*-phenylaminoacetic acid with ammonium thiocyanate (Table 1). The IR spectrum of the product contained a strong absorption band at 1750 cm^{-1}, corresponding to stretching vibrations of the C^5=O group in the imidazolidine ring (cf. [16]). The structure of compound **IX** was finally proved by heteronuclear ^1H–^{13}C NMR correlation experiments (through 2 and 3 bonds, HMQC and HMBC techniques). The HMQC and HMBC data allowed us to assign all ^1H and ^{13}C signals. The principal correlations are shown in Fig. 2, and their complete list is given in Table 3.

Thus the formation of 5-phenyl-2-thiohydantoin as a result of the transformation sequence **Ia**→**III**→**IX** casts no doubt. Substituted analogs of **IX**, compounds **XI–XIV**, were synthesized by treatment of **V–VIII** with hydrochloric acid. These reactions occurred in a regioselective fashion even under one-pot conditions; therefore, they provide a useful alternative to the known method for the preparation of substituted 2-thiohydantoins from *N*-arylglycines or their esters [15–17, 25, 26]. Insofar as the series of accessible reagents like **I** and **II** and their analogs like HtCOCHCl·NHCOR continuously extends, at least some of these compounds could appear to be suitable for the synthesis of 2-thiohydantoin derivatives that are difficult to obtain by the procedures developed previously [15–18, 25, 26].

It should also be noted that the preparative importance of products of selective cyclocondensation of compounds **I** and **II** with thioureas is not limited to their recyclization; these compounds can be involved in some other interesting transformations (see, e.g., [11]) which will be reported in detail in our subsequent publications.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord M-80 spectrometer. The ^1H NMR spectra were measured on a Varian VXR-300 instrument, and the ^1H–^{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.

Table 3. Principal correlations in the HMQC and HMBC spectra of compound **IX**[a]

^1H chemical shifts δ, ppm	^{13}C chemical shifts δ_C, ppm	
	HMQC	HMBC
7.38 (C^4H)	129.27 (C^4)	127.42 (C^2, C^6)
7.42 (C^3H, C^5H)	129.59 (C^3, C^5)	129.59 (C^3, C^5); 135.21 (C^1)
7.26 (C^2H, C^6H)	127.42 (C^2, C^6)	127.42 (C^2, C^6); 129.27 (C^4)
5.39 (CH)	64.63 (CH)	64.63 (CH); 127.42 (C^2, C^6); 135.21 (C^1); 175.54 (CO); 183.59 (CS)
10.50 (CS–N–H)		64.63 (CH); 183.59 (CS); 175.54 (CO)
11.87 (CO–N–H)		64.63 (CH); 183.59 (CS); 175.54 (CO)

[a] For atom numbering, see Fig. 2.

The X-ray diffraction data for compound VIIIj were obtained from a 0.19×0.25×0.48-mm single crystal at room temperature on an Enraf–Nonius CAD-4 automatic four-circle diffractometer (CuK_α radiation, λ = 1.54178 Å, scan rate ratio 2θ/ω = 1.2, θ_{max} = 68°, spherical segment $0 \le h \le 9$, $0 \le k \le 20$, $0 \le l \le 17$). A total of 3128 reflections were measured, 2250 of which were symmetry-independent (R_{int} = 0.021).

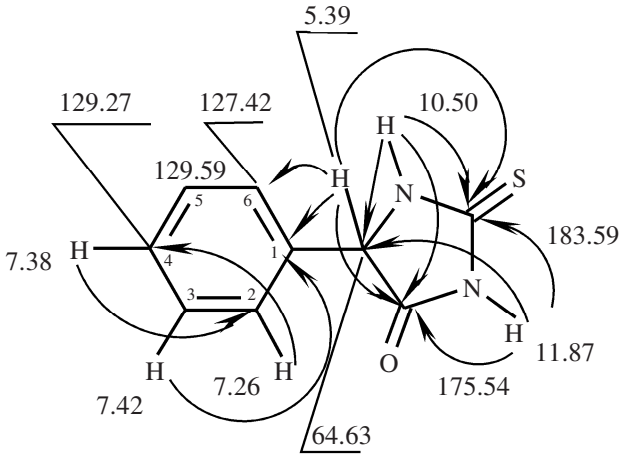


Fig. 2. Principal correlations (denoted with arrows) and signal assignment (δ, δ_C, ppm) in the ^1H and ^{13}C NMR spectra of 5-phenyl-2-thioxoimidazolidin-4-one (**IX**).

Rhombic crystals with the following unit cell parameters: a = 8.933(4), b = 17.567(7), c = 15.166(7) Å; V = 2380(2) Å^3; M 459.6; Z = 4; d_{calc} = 1.29 g/cm^3; μ = 14.30 cm^{-1}; F(000) = 975.8; space group $Pna2_1$ (no. 33). 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 [27]. The refinement procedure was performed using 1988 reflections with $I > 3\sigma(I)$ (302 refined parameters, 6.6 reflections per parameter). About 50% of hydrogen atoms were visualized by difference syntheses of electron density, and positions of the other hydrogen atoms were calculated on the basis of geometry considerations. All hydrogen atoms were included in the refinement procedure with fixed positional and thermal parameters. Chebyshev's weight scheme [28] with the following four parameters was applied: 0.72, –0.64, 0.14, and –0.43. The final divergence factors were R = 0.037 and R_w = 0.037; goodness of fit 1.139. The residual electron density from the Fourier difference series was 0.14 and –0.34 e/Å^3. Absorption by the crystal was taken into account using the azimuthal scanning technique [29]. The absolute configuration of molecule **VIIIj** was determined according to Flack [30]: the enantiopole parameter was refined to 0.02(3) by 2466 unaveraged Friedel-equivalent reflections. The complete set of crystallographic data for compound **VIIIj** was deposited to the Cambridge Crystallographic Data Center (entry no. CCDC 653733).

***N*-(2-Aryl-1-chloro-2-oxoethyl) carboxylic acid amides Ia–Ic and IIa–IIc** were synthesized by the procedure described previously [6].

***N*-(2-Amino-4-aryl-1,3-thiazol-5-yl)acetamides III and IV** (*general procedure*)**.** Compound **Ia** or **IIa**, 0.01 mol, was added to a suspension of 0.01 mol of thiourea in 25 ml of anhydrous THF, and the mixture was stirred for 24 h at 20–25°C. The solvent was removed under reduced pressure, 30 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 recrystallized from appropriate solvent.

***N*-[2-Alkyl(aryl)amino-4-aryl-1,3-thiazol-5-yl)acetamides V and VI** were synthesized in a similar way from the corresponding *N*-alkyl- and *N*-arylthioureas.

***N*-[3-Alkyl(aryl)-4-aryl-2-arylimino-2,3-dihydro-1,3-thiazol-5-yl]carboxamides VII and VIII** were synthesized in a similar way from compounds **Ia**–**Ic** and **IIa**–**IIc** and the corresponding *N*,*N*′-disubstituted thioureas. Compounds **VIIa** and **VIIId** were brought into further transformations without additional purification, while compounds **VIIb** and **VIIf** were isolated as hydrochlorides.

5-Aryl-2-thioxoimidazolidin-4-ones IX and X *(general procedure). a.* Concentrated hydrochloric acid, 15 ml, was added to a solution of 0.006 mol of compound **III** or **IV** in 40 ml of ethanol. The mixture was heated for 2 h under reflux and cooled, 100 ml of a saturated aqueous solution of sodium hydrogen carbonate was added, and the precipitate was filtered off and recrystallized from appropriate solvent.

b. Compound **Ia** or **IIa**, 0.006 mol, was added to a suspension of 0.006 mol of thiourea in 10 ml of THF, and the mixture was stirred for 24 h at 20–25°C. The solvent was removed under reduced pressure, 40 ml of ethanol was added, the mixture was heated for 1 h under reflux and cooled, 15 ml of concentrated hydrochloric acid was added, the mixture was heated for 2 h under reflux and cooled, 100 ml of a saturated aqueous solution of sodium hydrogen carbonate was added, and the precipitate was filtered off and recrystallized from appropriate solvent. Samples of compounds **IX** and **X** obtained according to methods *a* and *b* showed no depression of the melting point on mixing, and their IR and ^{1}H NMR spectra were identical.

3-Alkyl(aryl)-5-aryl-2-thioxoimidazolidin-4-ones XIa–XId and XIIa–XIId were synthesized as compounds **IX** and **X** from substituted thiazoles **Va**–**Vd** and **VIa**–**VId**, respectively, according to method *a*.

1-Alkyl(aryl)-3,5-diaryl-2-thioxoimidazolidin-4-ones XIIIa–XIIIh and XIVa–XIVg were synthesized in a similar way from substituted thiazoles **VIIa**–**VIIh** and **VIIIa**–**VIIIg**, respectively, according to method *a* or *b* (Table 1).

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