Synthesis and structures of 5(3*H*)-oxotetrahydro-1*H*-imidazo[4,5-*c*][1,2,5]thiadiazole 2,2-dioxides

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The reactions of sulfamides with 4,5-dihydroxyimidazolidin-2-ones were studied at ambient and high pressure. The previously unknown derivatives of 5(3*H*)-oxotetrahydro-1*H*-imidazo-[4,5-*c*][1,2,5]thiadiazole 2,2-dioxide, *viz.*, sulfo analogs of tetrahydroimidazo[4,5-*d*]imidazole-2,5-(1*H*,3*H*) diones (glycolurils), were synthesized. The structures of some of these compounds were established by X-ray diffraction. The high-pressure reactions performed under conditions of solvent phase transitions afforded also *N*-(1,3-diethyl-5-hydroxy-2-oxoimidazolidin-4-yl)-*N*,*N*′-dialkylsulfamides. Among these compounds, a new conglomerate was found.

Key words: α-ureidoalkylation, 5(3*H*)-oxotetrahydro-1*H*-imidazo[4,5-*c*][1,2,5]thiadiazole 2,2-dioxides, *N*-(1,3-diethyl-5-hydroxy-2-oxoimidazolidin-4-yl)-*N*,*N*′-dialkylsulfamides, X-ray diffraction study, conglomerate.

Imidazolidin-2-one derivatives exhibit antispasmodic, analgesic, neurotropic, *etc.* activities.[1—4] Substituted 1,2,5-thiadiazolidine 1,1-dioxides inhibit the enzymes human leukocyte elastase and cathepsin G and have antiulcer and antispasmodic activities.[5—7] Hence, the design of potent biologically active compounds containing the annulated imidazolidine and thiadiazolidine rings continues to be an important problem.

Earlier, we have shown for some examples that the simplest procedure for the synthesis of such compounds is based on the condensation of 4,5-dihydroxyimidazolidin-2-ones (DHIs) **1** with sulfamides.[8—11] First representatives of 1,3,4,6-tetraalkyl-5(3*H*)-oxotetrahydro-1*H*-imidazo-[4,5-*c*][1,2,5]thiadiazole 2,2-dioxides **2a,b** were synthesized in 52% and 8% yields, respectively, in water at pH 1, atmospheric pressure, and 80—90 °C.[8,9] Under these conditions, unsubstituted sulfamide gives 4,4′-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) **3a,b** in 40—45% yields.[9,10] Tetrahydroimidazothiadiazoles **2c,d** were synthesized in 45—63% yields by condensation of **1a,b** with unsubstituted sulfamide at pH 5—6 and 60 °C.[8] More recently,[12] we have found that the acid-catalyzed reactions of 1-alkylsulfamides with DHIs in methanol afford compounds containing the imine bond, *viz.*, 1,3-dialkyl-4-(alkylaminosulfonylimino)imidazolidin-2-ones **4a—h**.

In continuation of our studies aimed at extending the range of potent biologically active monosulfo analogs of glycolurils **2** containing different numbers of alkyl substituents at the nitrogen atoms, here we report a comprehensive study of the condensation of **1a—d** with sulfamides **5a—f** at ambient and high pressure and the structural investigations of the resulting compounds by different physicochemical methods, including X-ray diffraction.

Under atmospheric pressure, the reactions of **1a—d** with sulfamides **5a—f** were carried out at 80—90 °C and pH 1 in water for 0.5—1 h (conditions ***A***), at 60—70 °C in H_2O at pH 6 (conditions ***B***), or in MeOH both in the presence of acids (conditions ***C***) and in their absence (conditions ***D***) (Scheme 1). In addition, analogous reactions were studied at high pressure using different modes.

Di-*N*-substituted tetrahydroimidazothiadiazoles were synthesized using the following two approaches: by the reactions of DHI **1a** containing unsubstituted nitrogen atoms with 1,3-dialkylsulfamides **5e,f** or by the reactions of 1,3-dialkyl-substituted compounds **1b—d** with sulfamide **5a**. To synthesize tri-*N*-alkylimidazothiadiazoles, we studied the reaction of 1,3-dialkyl-substituted DHIs **1b—d** with 1-alkylsulfamides **5b—d**. Tetra-*N*-alkyl derivatives were prepared by condensation of **1b—d** with 1,3-dialkylsulfamides **5e,f**. The compositions of the reaction products were determined based on the ^{1}H NMR spectra measured for the reaction mixtures evaporated to dryness. The results of investigations performed under atmospheric pressure are presented in Scheme 1 and Table 1.

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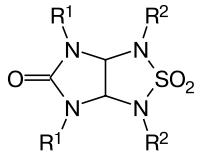
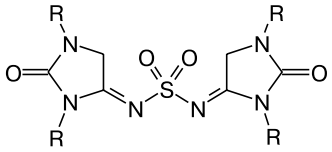
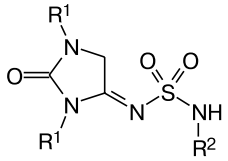


2a—d



3a,b

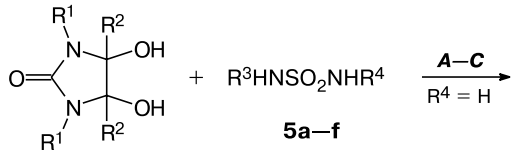


4a—h

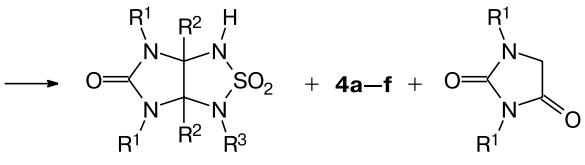
Compound	R	R^1	R^2
2a	—	Me	Me
2b	—	Et	Me
2c	—	Me	Et
2d	—	Et	H
3a	Me	—	—
3b	Et	—	—

Compound	R^1	R^2
4a	Me	Pr
4b	Et	Pr
4c	Me	Bu
4d	Et	Bu
4e	Me	C_6H_{11}-*cyclo*
4f	Et	C_6H_{11}-*cyclo*
4g	Me	Bu-*sec*
4h	Et	Bu-*sec*

Scheme 1



1a—d **5a—f**



2e—h **6a—c**

1,6: R^2 = H, R^1 = H (**a**), Me (**b**), Et (**c**), R^2 = Ph, R^1 = Me (**d**);
2: $R^1 = R^2 = R^3$ = H (**e**), R^1 = Me, R^2 = H, R^3 = Pr (**f**), R^1 = Et, R^2 = H, R^3 = Pr (**g**), R^1 = Me, R^2 = Ph, R^3 = H (**h**);
5: R^4 =H, R^3 = H (**a**), Pr (**b**), Bu (**c**), *cyclo*-C_6H_{11} (**d**), $R^3 = R^4$ = Me (**e**), R^3 = Me, R^4 = Et (**f**).

Table 1. Influence of the reaction conditions on the yield of the products prepared by the reaction of 4,5-dihydroxyimidazolidin-2-ones **1a—d** with sulfamides **5a—f** at ambient pressure

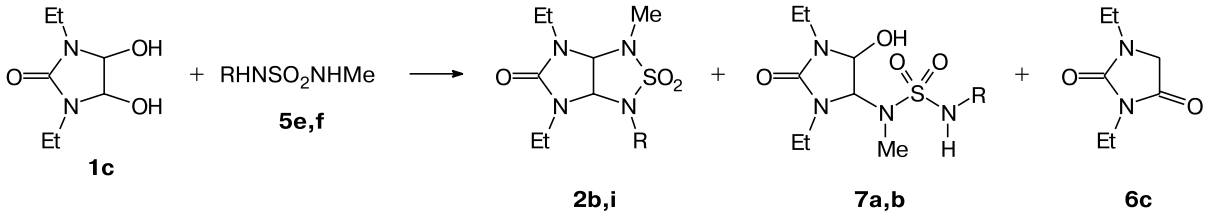
Method	Conditions	DHI	Sulfamide	Products	Yield (%)
A	80—90 °C, H_2O, pH 1	**1a**	**5b—d,f**	**6a** (+**5b—d,f**)	—*
		1b	**5b—d,f**	**6b** (+**5b—d,f**)	—*
		1c	**5b—d,f**	**6c** (+**5b—d,f**)	—*
B	60—70 °C, H_2O, pH 6	**1a**	**5a**	**2e**	55
		1a	**5b—f**	—	—
		1b	**5b**	**2f**	35
		1b	**5c,d**	—	—
		1c	**5b**	**2g** (+**4b**)	13 (29)
		1c	**5c—f**	—	—
C	Refluxing in MeOH, HCl	**1a**	**5a,b**	**6a**	5—10
		1b	**5b—d**	**4a,c,e** (+**6b**)	37—45[12]
		1c	**5b—d**	**4b,d,f** (+**6c**)	41—53[12]
		1d	**5a**	**2h**	27
		1d	**5b—e**	—	—
D	Refluxing in MeOH in the absence of acids	**1a**	**5b—f**	—	—
		1b	**5b**	**2f** (+**4a**)	19 (8)
		1c	**5b**	**2g** (+**4b**)	7 (32)
		1d	**5a—d**	—	—

* The yields of hydantoins **6a—c** were not determined, but the ^{1}H NMR spectra of the reaction mixtures evaporated to dryness show proton signals of hydantoins.[14]

As can be seen from Table 1, sulfamides **5b—d,f** do not react with compounds **1a—c** under the conditions ***A*** and remain unconsumed, compounds **1a—c** being transformed into the corresponding hydantoins **6a—c**.

Under the conditions ***B***, unsubstituted DHI **1a** reacts only with unsubstituted sulfamide **5a** to form the parent compound of the homologous series of tetrahydroimidazo-[4,5-*c*][1,2,5]thiadiazoles containing the sulfamide and urea fragments (compound **2e**) in 55% yield. The reactions of 1,3-dialkyl-substituted DHIs **1b,c** with sulfamide **5b** gave rise to the first representatives of tri-*N*-alkyl-substituted bicyclic products **2f,g** in 35 and 13% yields, respectively. The reaction of **1c** afforded compound **2g** along with 1,3-diethyl-4-(propylaminosulfonylimino)-imidazolidin-2-one (**4b**), which have been described in our earlier study.[12] The ^{1}H NMR analysis of the reaction mixtures evaporated to dryness showed that the ratio of the bi- (**2g**) to monocyclic (**4b**) products is 2 : 5. The ratio was estimated based on the integrated intensity ratio for the proton signals of the CH—CH groups of compound **2g** at δ 5.32 and the signals of the cyclic CH_2 group of compound **4b** at δ 4.48. Compounds **2g** and **4b** were isolated in the individual state by preparative silica gel column chromatography. Under these conditions,

Scheme 2



R = Me (**2b**, **5e**, **7a**), Et (**2i**, **5f**, **7b**)

1,3-dialkyl-substituted compounds **1b,c** do not react with sulfamides **5c—f**, and 1,3-dimethyl-4,5-diphenyl-substituted compound **1d** does not react with sulfamides **5a—d**.

The formation of imino derivative **4b** can be attributed to the intramolecular disproportionation of compound **2g**, because the latter compound is partially or completely transformed into product **4b** after heating of **2g** in solution, in particular, during its recrystallization. Earlier, we have observed[13] an analogous situation when studying the chemical properties of 4,6-dialkyl-5(3*H*)-oxotetrahydro-1*H*-imidazo[4,5-*c*][1,2,5]thiadiazole 2,2-dioxides **2c,d**. The latter compounds readily undergo disproportionation in the presence of acids or acetyl chloride to give 4,4′-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) **3a,b** and sulfamide (the activation energy of the transformation of 6,8-diethyl derivative **2d** is 54±12 kJ mol^{-1}).

The study of the condensation of compounds **1a—d** with sulfamides **5a—d** under the conditions ***C*** showed that **1a** does not react with sulfamides **5a—d** and is partially (by no more than 10%) transformed into hydantoin **6a** within 1 h. In these experiments, unconsumed DHI and sulfamides remained intact.

Under both the conditions ***C*** and ***D***, the reactions of **1b,c** with 1-alkylsulfamides **5b—d** either afford bicyclic products **2f,g** in yields two times lower (conditions ***D***) compared to the analogous reactions under the conditions ***B*** or do not give these products at all (conditions ***C***). In these reactions, monocyclic derivatives **4a—f**, which have been described in our earlier study,[12] either appear or are produced in higher yields.

Compound **1d** undergoes condensation with sulfamide **5a** only under the conditions ***C*** to give compound **2h** in 27% yield and does not react with sulfamides **5b—f**.

The studies of α-ureidoalkylation of sulfamides with DHI at atmospheric pressure allowed us to find conditions for the synthesis of the previously unknown monosulfo analogs of glycolurils, *viz.*, tetrahydroimidazothiadiazoles **2e—h** containing different substituents at the nitrogen atoms. Bicyclic compound **2e** containing unsubstituted nitrogen atoms was synthesized at pH 6 in H_2O at 60—70 °C (conditions ***B***). The conditions ***B*** are optimal for the synthesis of trialkyl-substituted imidazothiadiazoles **2f,g**. Dialkyl-substituted product **2h** was synthesized by refluxing in MeOH in the presence of HCl (conditions ***C***).

With the aim of increasing the yield of tetra-*N*-alkylimidazothiadiazole **2b**, which has been synthesized earlier at atmospheric pressure in substantially lower yield (8%)[8] than derivatives **2a,c,d** (45—63%), we studied the influence of high pressure[11] on the yields of bicyclic compounds **2b** and **2i**. The study of the condensation of **1c** with 1,3-dialkylsulfamides **5e,f** showed that this reaction performed in the high-pressure mode affords different products, such as the target bicyclic compounds **2b,i**, *N*-(1,3-diethyl-5-hydroxy-2-oxoimidazolidin-4-yl)-*N,N*′-dialkylsulfamides **7a,b**, and hydantoin **6c** characterized earlier[9,14] (Scheme 2). It was also found that the formation and the yields of these products depend on the following reaction conditions: the amount of the acid (HCl or MeCOOH) in the reaction mixture, the reaction temperature (11—100 °C), the produced pressure (700 or 1000 MPa), the reaction time (4.5, 5, or 16 h), the number of load cycles (1, 9, or 12), and the nature of the solvents (water, MeCOOH, acetone, or dioxane). The results of these studies are presented in Table 2.

The reaction conditions presented in Table 2 (except for runs *1*, *5*, and *9*) correspond to the liquid—solid phase transition of the solvent,[15] resulting in a substantial increase in the rate of some organic reactions.[16,17] As can be seen from Table 2, the highest yield of bicyclic products **2b,i** was achieved in acetone and acetic acid in the solidified solvent at 1000 MPa (runs *3*, *4*, and *12*). A comparison of the results of runs *5* and *6* shows that in the case of repeated phase transitions, the yield of new product **7a** that is formed along with compound **2b** increases by a factor of more than 8 in spite of a fourfold decrease in the temperature. Under these conditions, compound **7b** is formed in comparable yield (run *11*). The use of more than nine cycles producing the phase transition has no substantial effect on the yields of products **2b** and **7a** (run *7*). Since the phase transition of dioxane at 1000 MPa occurs at lower temperature than the phase transition of acetone, the yield of compound **7a** increases as the temperature increases to 80 °C in the solidified solvent (see runs *8* and *10*). An increase in the temperature to 80 °C in acetone and to 100 °C in dioxane does not lead to solidification of the solvent, resulting in a substantial decrease in the yield of compounds **2b** and **7a** (see runs *5* and *9*).

Table 2. Influence of the reaction conditions on the yield of the products prepared by the reaction of 1,3-diethyl-4,5-dihydroxyimidazolidin-2-one **1c** with 1,3-dialkylsulfamides **5c,d** at high pressure

Run	*t*/h	Acid	*T*/°C	*p*/MPa	Solvent	Yield (%)	
						2b (2i)	**7a (7b)**
1	16	HCl (pH 1—2)	12	1000	H_2O	2	—
2	16		12	1000	MeCOOH	5	Traces
3	5		80	1000	MeCOOH	8	Traces
4	16	concentrated HCl (1 drop)	12	1000	$(Me)_2CO$	12	2
5	4.5	MeCOOH (2 drops)	80	1000	$(Me)_2CO$	—	4
6	4.5[a]	MeCOOH (2 drops)	19	1000	$(Me)_2CO$	4	33
7	5[b]	MeCOOH (2 drops)	19	1000	$(Me)_2CO$	4	31
8	5	MeCOOH (2 drops)	80	1000	Dioxane	Traces	11
9	4.5	MeCOOH (2 drops)	100	1000	Dioxane	—	Traces
10	4.5[a]	MeCOOH (2 drops)	40	700	Dioxane	—	7.5
11	4.5[a]	MeCOOH (2 drops)	11	1000	$(Me)_2CO$	(5)	(32)
12	16	конц.HCl (1 drop)	12	1000	$(Me)_2CO$	(8)	(Traces)

[a] Nine load cycles. The pressure was produced and relieved in 5 min intervals; nine cycles were carried out during 10 min each, and then the reaction mixture was kept under this pressure for 3 h.
[b] Twelve load cycles.

Therefore, the high-pressure experiments showed that under the conditions giving rise to phase transitions of the solvents (acetic acid, acetone, and dioxane), the yield of tetrahydroimidazothiadiazole **2b** increases from 8% (see Ref. 8) to 12% and product **2i** is formed in 8% yield. The latter compound is not produced under other conditions. In addition, these reactions afford large amounts of the previously unknown compounds **7a,b** containing both the imidazolidin-2-one and sulfamide fragments, as well as the hydroxy group, at which the product can further be modified. Compounds **7a,b** are analogous to the intermediates, whose formation has been suggested earlier[18,19] when discussing the mechanisms of α-ureidoalkylation of ureas and their analogs with DHIs.

The structures of tetrahydroimidazothiadiazoles **2e—i** and *N*-(1,3-diethyl-5-hydroxy-2-oxo-4-imidazolidinyl)-*N,N′*-dialkylsulfamides **7a,b** were confirmed by elemental analysis, ^{1}H NMR spectroscopy, and, in some cases, by mass spectrometry (Tables 3 and 4).

To more reliably establish the structures of compounds **2a—h** (including products **2a—d** synthesized earlier[8]) and **7a,b**, on the one hand, and to found new conglomerates among chiral compounds **2f,g,i** and **7a,b**, on the other hand, we studied their crystallization from water, methanol, acetone, and dioxane and obtained crystals suitable for X-ray diffraction. The X-ray diffraction study of a single crystal of **7a**, which was grown by crystallization from acetone, showed[11] that compound **7a** crystallizes in

Table 3. Characteristics of compounds **2e—i** and **7a,b**

Compound	Yield (%)	M.p./°C	Found / Calculated (%)				Molecular formula
			C	H	N	S	
2e	53—55	237—239 (decomp.)	20.24 20.22	3.42 3.39	31.44 31.45	17.93 17.99	$C_3H_6N_4O_3S$
2f	34—36	185—187	38.73 38.70	6.46 6.49	22.59 22.56	12.87 12.91	$C_8H_{16}N_4O_3S$
2g	11—13	139—141	43.44 43.46	7.33 7.29	20.25 20.27	11.56 11.60	$C_{10}H_{20}N_4O_3S$
2h	26—28	>300	57.01 56.97	5.08 5.06	15.62 15.63	8.90 8.94	$C_{17}H_{18}N_4O_3S$
2i	8	74—76	43.49 43.46	7.32 7.29	20.23 20.27	11.54 11.60	$C_{10}H_{20}N_4O_3S$
7a	30—33	149—151	38.58 38.56	6.21 7.19	20.02 19.99	11.39 11.44	$C_9H_{20}N_4O_4S$
7b	32	141—143	40.78 40.80	7.54 7.53	19.01 19.03	10.87 10.89	$C_{10}H_{22}N_4O_4S$

Table 4. ^{1}H and ^{13}C NMR spectra ([$^{2}H_6$]DMSO) of compounds **2e—i** and **7a,b**

Compound	^{1}H NMR, δ (*J*/Hz)	MS, *m/z*, *I* (%)
2e	5.34 (s, 2 H, CHCH); 7.24 (s, 2 H, 2 NH); 7.55 (s, 2 H, 2 NH)	96 (3), 79 (73), 64 (100)
2f	0.89 (t, 3 H, CH_3 (Pr), *J* = 7.3); 1.61 (m, 2 H, CH_2 (Pr)); 2.65 (s, 3 H, NCH_3); 2.72 (s, 3 H, NCH_3); 2.88 (m, 1 H, NCH_2 (Pr)); 3.12 (m, 1 H, NCH_2 (Pr)); 5.22 (m, 2 H, CHCH); 7.93 (br.s, 1 H, NH)	219 (50), 190 (100),148 (37), 140 (55), 133 (46), 126 (58), 112 (37)
2g	0.91 (t, 3 H, CH_3 (Pr), *J* = 7.3); 1.04 (t, 6 H, 2 CH_3 (Et), *J* = 7.0); 1.62 (m, 2 H, CH_2 (Pr)); 2.82—3.31 (m, 6 H, 3 NCH_2 (2 Et, Pr)); 5.34 (m, 2 H, CHCH); 7.90 (d, 1 H, NH, *J* = 4.9)	
2h*	2.62 (s, 6 H, 2 NCH_3); 6.98 (m, 4 H, Ph); 7.08 (m, 6 H, Ph); 8.99 (br.s, 2 H, 2 NH)	294 (10) [$M^+ - 64$ (SO_2)], 293 (23), 278 (12), 217 (39), 190 (91), 133 (95), 118 (64), 104 (100)
2i	1.08—1.13 (m, 9 H, 3 CH_3); 2.76 (s, 3 H, NCH_3); 2.96—3.12 (m, 2 H, NCH_2); 3.15—3.40 (m, 4 H, 2 NCH_2); 5.26, 5.41 (both d, 1 H each, CH, *J* = 8.6)	
7a	1.02 (t, 3 H, CH_3, *J* = 7.2); 1.05 (t, 3 H, CH_3, *J* = 7.2); 2.41 (s, 3 H, NCH_3); 2.48 (s, 3 H, NCH_3); 2.81—2.95 (m, 1 H, NCH_2); 2.98—3.12 (m, 1 H, NCH_2); 3.21—3.33 (m, 1 H, NCH_2); 3.33—3.45 (m, 1 H, NCH_2); 4.87 (d, 1H, CH, *J* = 6.6); 4.99 (s, 1 H, CH); 6.44 (d, 1 H, OH, *J* = 7.2); 7.31 (d, 1 H, NH, *J* = 4.9)	
7b	0.98 (t, 3 H, CH_3, *J* = 7.3); 1.02 (t, 3 H, CH_3); 1.17 (t, 3 H, CH_3, *J* = 7.0); 2.76 (s, 3 H, NCH_3, *J* = 7.3); 2.77—2.91 (m, 2 H, NCH_2); 2.96—3.12 (m, 2 H, NCH_2); 3.18—3.39 (m, 2 H, NCH_2); 4.82 (d, 1 H, CH, *J* = 6.7); 4.97 (s, 1 H, CH); 6.42 (d, 1 H, OH, *J* = 7.3); 7.37 (d, 1 H, NH, *J* = 4.3)	

* The ^{13}C NMR spectrum of compound **2h**, δ: 26.61 (CH_3), 85.49 (CH),127.45, 127.91, 128.52, 134.39 (Ph), 158.54 (C=O).

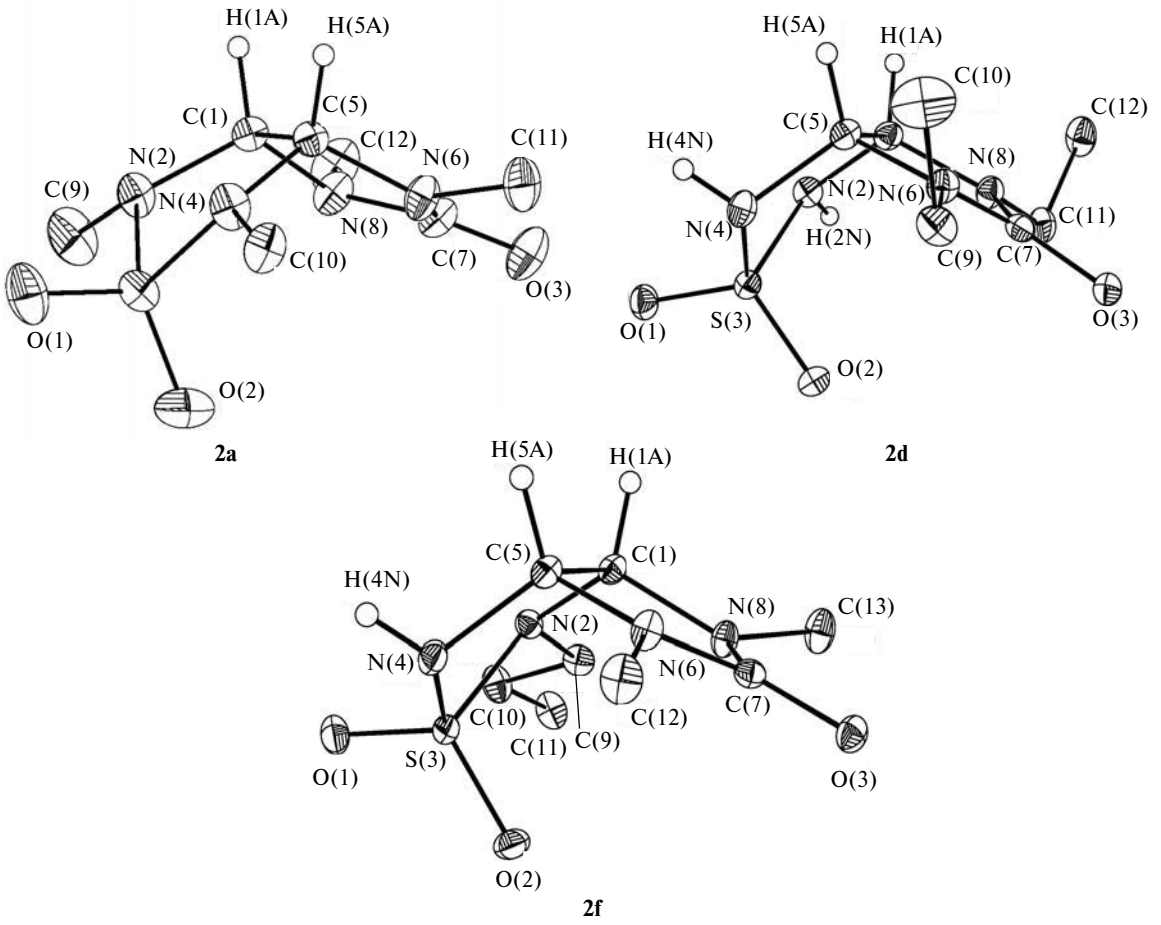


Fig. 1. General views of molecules **2a** and **2d** and one of the independent molecules of **2f** with displacement ellipsoids drawn at *p* = 50%.

Table 5. Principal crystallographic characteristics and the refinement statistics for compounds **2a,d,f**

Parameter	**2a**	**2d**	**2f**
Molecular formula	$C_7H_{14}N_4O_3S$	$C_7H_{14}N_4O_3S$	$C_8H_{16}N_4O_3SM$
M	234.28	234.28	248.31
T/K	173	120	100
Diffractometer	Syntex $P2_1$	SMART APEX II	SMART APEX II
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_1/n$	$P2_12_12_1$	*Pc*
Z(Z´)	4(1)	4(1)	8(4)
a/Å	6.279(1)	9.0857(4)	10.0639(6)
b/Å	9.939(2)	10.3462(5)	19.690(1)
c/Å	16.596(3)	11.2241(6)	12.5829(8)
β/deg	95.95(3)	90	112.742(1)
V/Å^3	1030.0(4)	1055.09(9)	2299.6(3)
d_{calc}/g cm^{-3}	1.511	1.475	1.434
μ/cm^{-1}	3.10	3.02	2.82
F(000)	496	496	1056
$2\theta_{max}$/deg	55	57	58
Scanning mode	θ/2θ	ω	ω
Number of measured reflections (R_{int})	2515(0.0343)	5776 (0.0160)	12181 (0.0247)
Number of independent reflections	2312	2579	12181
Number of reflections with $I > 2\sigma(I)$	1771	2471	10953
Number of refined parameters	140	193	619
R_1 ($I > 2\sigma(I)$)	0.0710	0.0349	0.0398
wR_2 (based on all reflections)	0.1805	0.0777	0.0871
GOOF	1.084	1.031	1.058
Residual electron density (e_{max}/e_{min})/e Å^{-3}	0.584/−0.454	0.224/−0.327	0.770/−0.863

the chiral space group $P2_12_12_1$ as the conglomerate. The absolute configuration of the asymmetric atoms in **7a** is 4*S*, 5*S*.

The X-ray diffraction study of compounds **2a,d,f** showed that **2a** crystallizes in the racemic space group, whereas achiral compound **2d** crystallizes in the chiral space group $P2_12_12_1$. Racemic compound **2f** crystallizes in the noncentrosymmetric space group *Pc* (Table 5). As we have mentioned earlier,[20] the replacement of the carbonyl group with the sulfo group leads to a substantial change in the conformation of the five-membered rings and the character of the bond length distribution in the bicyclic system. Actually, the nitrogen atoms in glycolurils are involved in the conjugation with the carbonyl group, resulting in the flattening of the valence configuration of the nitrogen atoms and, consequently, of the five-membered ring as a whole. In the presence of the SO_2 group, the conjugation in the system is absent and, as a result, the nitrogen atoms have a pyramidal configuration.[20] In turn, the pyramidalization of the nitrogen atoms results in the fact that their lone electron pairs can be involved in stereoelectronic interactions, to be more precise, in the charge transfer from the lone electron pair of the nitrogen atom to different antibonding orbitals of the bonds (the N—S and C—N bonds of the adjacent ring and the S—O bond).

With the aim of investigating the structural features of the bicyclic compounds containing both the $N_2C{=}O$ and N_2SO_2 fragments, we studied systems **2a**, **2d**, and **2f** (Fig. 1). It should be noted that the crystals of compound **2f** contain four independent molecules, which have substantially different geometric parameters. Hence, we considered the individual (rather than average) parameters for all six independent molecules in three compounds (see Table 5).

In all the molecules under consideration, the imidazolidinone rings adopt a flattened envelope conformation; however, different atoms deviate from the mean plane. Thus, the carbonyl carbon atom deviates from the plane passing through the other four atoms of the ring in compound **2a**, the N(6) atom deviates from the corresponding plane in **2d**, and one of the bridgehead carbon atoms deviates from this plane in four independent molecules **2f**. In imidazolidin-2-one, the deviations of the atoms from the plane varies in the narrow range of 0.095—0.160 Å. In all compounds, the lengths of the formally equivalent C—N bonds in the urea fragment are somewhat different and vary in the range of 1.353(2)—1.383(5) Å. The change in the C—N bond length correlates with the sum of the bond angles (ΣN) at the nitrogen atoms N(6) and N(8). Actually, the maximum length is observed for the N(8) atom in **2a**, for which ΣN is 351.4(3)°, whereas

ΣN for the shortest distance is 359.1(2)°. A change in the degree of conjugation in the ring is, apparently, determined primarily by the packing effects. The N—C(Alk) bond lengths involving the substituted carbon atom remain virtually unchanged (1.455(2)—1.466(2) Å) and are independent of the degree of pyramidalization of the nitrogen atoms. The C=O bond lengths in the compounds under study are also determined by the packing effects, such as the strength and the number of hydrogen bonds. In all three structures, the hydrogen bonds are formed only with the involvement of the carbonyl group. Actually, the C=O bond in the structures of **2d** and **2f**, in which the carbonyl group is involved in hydrogen bonding with the hydrogen atoms of the amino groups (N...O, 2.788(2)—2.821(2) Å), is substantially elongated (to 1.232(2)—1.242(2) Å), whereas the C=O bond in **2a**, where these bonds are absent, is substantially shorter (1.217(5) Å). In the crystal structure of **2d**, the molecules are linked by hydrogen bonds to form a three-dimensional framework. The crystal structure of **2f** consists of hydrogen-bonded chains.

In the crystal structure of **2f**, there are two types of hydrogen-bonded chains. Each chain is formed by two types of independent molecules. The hydrogen bonds in the chains somewhat differ in strength. In one type of the chains, the O...N distances are slightly shorter (2.788(2)—2.796(2) Å) than those in another type of the chains (2.804(2)—2.813(2) Å), resulting in a slight shift of the chains with respect to each other. The crystal structure of **2f** consists of alternating layers of doubled chains of one type. Therefore, there are two hydrogen-bonded sublattices in the crystal structure of **2f** (Fig. 2).

The deviations of the atoms from the mean planes of the thiadiazolidine rings are substantially larger than those in the imidazolidine rings. In the compounds under study, the rings adopt different conformations. Thus, the ring in **2a** adopts an envelope conformation with the S(3) atom deviating from the plane through the remaining four atoms by 0.58 Å; the other rings have a twist conformation with the S(3) and N(2) atoms deviating from the plane passing through the C(1), C(5), and N(4) atoms by 0.31—0.47 and 0.17—0.28 Å, respectively. In all three structures, the N(2) and N(4) atoms are pyramidal ($\Sigma N_{2,4}$ are 328—352°). Unlike the imidazolidine rings, the differences in the S—N bond lengths are substantially larger (up to 0.03 Å in **2f**). Since the observed differences cannot be attributed to the nature of the substituent at the nitrogen atom (see Table 6), it is reasonable to suggest that these differences are associated primarily with the stereoelectronic interactions. Moreover, unlike the imidazolidin-2-one ring, the S—N bond length does not correlate with the degree of pyramidalization of the nitrogen atoms (see Table 6). It is rather difficult to unambiguously reveal the factors responsible for variations in the N—S and C—N bond lengths in the structures under consideration based only on the geometric data. In fact, the lone electron pairs (LEP) of the nitrogen atoms in all structures can be involved in different interactions with

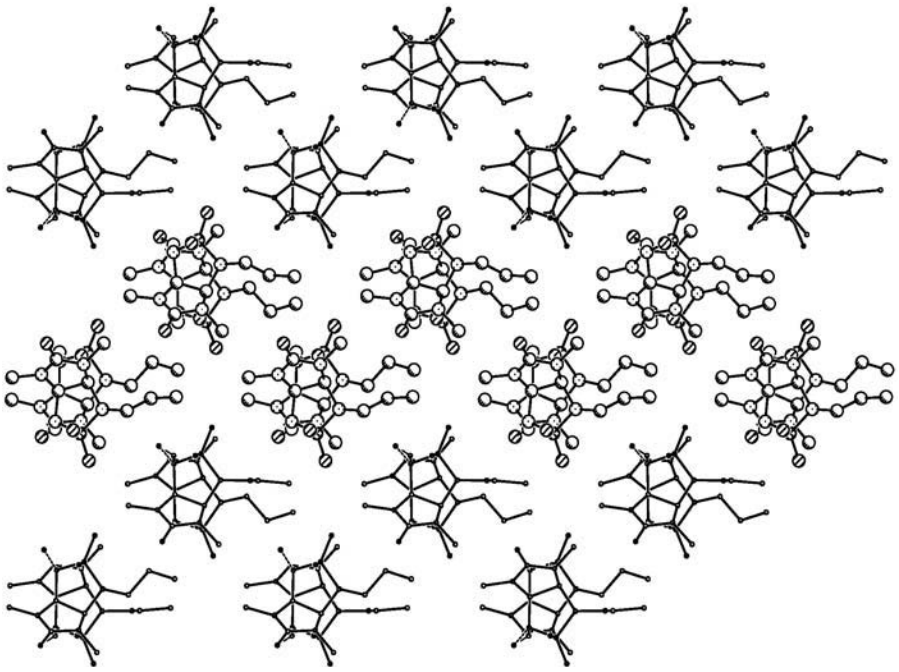


Fig. 2. Fragment of the molecular packing in the crystal structure of **2f** (the chains are perpendicular to the plane of the figure). Two types of chains are represented by spheres of different size.

equal probability. For example, in the structure of **2d**, the N(2) atom is involved in the $LEP_{N(2)}\rightarrow\sigma^*(S(3)—O(2))$ ($LEP_{N(2)}S(3)O(2)$, 172°) and $LEP_{N(2)}\rightarrow\sigma^*(C(1)—N(8))$ ($LEP_{N(2)}C(1)N(8)$, 165°) interactions, and the N(4) atom is involved only in the $LEP_{N(4)}\rightarrow\sigma^*(S(3)—N(2))$ interaction ($LEP_{N(4)}S(3)N(2)$ 152°), as evidenced by the pseudotorsion angles. Evidently, if there are simultaneously two interactions, such as $LEP_{N(2)}\rightarrow\sigma^*(S(3)—O(2))$ and $LEP_{N(4)}\rightarrow\sigma^*(S(3)—N(2))$, one of these interactions would cause a shortening of the S(3)—N(2) bond, whereas another interaction, on the contrary, would lead to its elongation. As a result, in spite of the difference in the character of interactions, the S—N bonds can be equal in length. This situation is observed in the structure of **2d**.

The dependence of the bond length distribution in the thiadiazolidine rings on the anomeric effect can be exemplified by the structure of **2f**. In this structure, the bond length distributions in four independent molecules are substantially different. In three molecules, the S—N bond lengths differ by 0.02—0.03 Å, whereas the S—N bond lengths in the fourth molecule (molecule **D** in Table 6) are equal. The N(2)—C(1) (1.447(3) Å) and N(4)—C(5) (1.473(3) Å) bond lengths in molecule **D** are, on the contrary, strongly different, whereas these bonds in the other three independent molecules are equal in length (see Table 6). Consequently, it is reasonable to suggest that the N(2) atom in molecule **D** is involved in the interaction with the C(1)—N(8) bond, resulting in a substantial shortening of the C(1)—N(2) bond compared to this bond in the other three molecules in the crystal structure of **2f**. Since the pseudotorsion angles with the involvement of the lone electron pairs of the nitrogen atoms in the independent molecules in the crystal structure of **2f** vary only slightly, the S—N bond is, apparently, most sensitive to minimal changes in the strength and the character of charge transfer in the system and, consequently, this bond is unsuitable for investigations of stereoelectronic interactions. Taking into account all the aforesaid, we plan to perform a comprehensive quantum chemical conformational analysis based on experimental data for this series of compounds.

Hence, we performed systematic studies of the condensation of 4,5-dihydroxyimidazolidin-2-ones with sulfamides at atmospheric and high pressure and developed procedures for the synthesis of the previously unknown unsubstituted and various alkyl-substituted tetrahydroimidazothiadiazoles and *N*-(1,3-diethyl-5-hydroxy-2-oxoimidazolidin-4-yl)-*N,N′*-dialkylsulfamides. The structures of selected di-, tri-, and tetraalkyl-substituted derivatives were established by X-ray diffraction.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (300.13 MHz for ^1H NMR and 75.5 MHz for ^{13}C NMR) in DMSO-d_6; the chemical shifts are measured on the δ scale using Me_4Si as the internal standard. The melting points were measured on a GALLENKAMP instrument (Sanyo). The EI mass spectra were obtained on a Kratos MS-30 mass spectrometer (70 eV). 4,5-Dihydroxyimidazolidin-2-ones were

Table 6. Selected geometric parameters for the bond lengths (*d*) and the sums of the bond angles in compounds **2a**,**d**,**f**

Parameter	**2a**	**2d**	**2f**			
			A	**B**	**C**	**D**
Bond			*d*/Å			
S(3)—O(1)	1.432(3)	1.4335(14)	1.431(2)	1.432(2)	1.429(2)	1.434(2)
S(3)—O(2)	1.432(3)	1.4317(12)	1.438(2)	1.438(2)	1.439(2)	1.435(2)
S(3)—N(2)	1.639(3)	1.6380(16)	1.660(2)	1.645(2)	1.666(2)	1.641(2)
S(3)—N(4)	1.618(3)	1.6404(17)	1.632(2)	1.628(2)	1.633(2)	1.641(2)
O(3)—C(7)	1.217(5)	1.242(2)	1.232(2)	1.233(2)	1.234(2)	1.235(2)
C(1)—N(2)	1.467(4)	1.464(2)	1.469(2)	1.470(3)	1.470(2)	1.447(3)
N(4)—C(5)	1.454(5)	1.473(2)	1.469(2)	1.467(3)	1.470(3)	1.473(3)
C(1)—C(5)	1.550(4)	1.570(3)	1.568(3)	1.568(3)	1.565(3)	1.574(3)
C(5)—N(6)	1.444(4)	1.449(2)	1.444(2)	1.442(3)	1.441(2)	1.440(2)
C(1)—N(8)	1.446(4)	1.451(2)	1.455(2)	1.454(3)	1.461(2)	1.455(3)
N(6)—C(7)	1.364(5)	1.361(2)	1.362(2)	1.354(2)	1.356(2)	1.356(2)
C(7)—N(8)	1.383(5)	1.353(2)	1.370(2)	1.378(3)	1.370(2)	1.371(2)
Angle			ω/deg			
$\Sigma_{N(2)}$*	346.2(2)	339	345.0(1)		339.6(1)	354.7(1)
$\Sigma_{N(4)}$*	352.3(3)	327	330	329	331	328
$\Sigma_{N(6)}$	354.3(3)	357.2(2)	357.7(1)	359.3(1)	358.2(1)	359.6(1)
$\Sigma_{N(8)}$	351.4(3)	359.1(2)	355.3(1)	353.6(1)	354.7(1)	353.8(1)

* For the N(2) atom in the independent molecule **B**, the value is not given because of the disorder of the propyl substituent. For the nitrogen atom bound to the hydrogen atom, the estimated standard deviations are not given.

synthesized by the reaction of the corresponding ureas with glyoxal.[9,21—23] Sulfamides were synthesized according to known procedures.[24—26]

High-pressure experiments were carried out on a piston—cylinder-type apparatus in 1.6-mL Teflon tubes.

5(3*H*)-Oxotetrahydro-1*H*-imidazo[4,5-*c*][1,2,5]thiadiazole 2,2-dioxides (2e—g) and 4-(propylaminosulfonylimino)-1,3-diethylimidazolidin-2-one (4b) (general procedure). Compound **1a** (or **1b,c**) (0.01 mol) and sulfamide **5a** (or **5b**) (0.01 mol) were dissolved in water (5 mL) at pH 6. The reaction mixture was heated at 60 °C for 1 h. After cooling to room temperature, compound **2e** (or **2f**) precipitated within a few days. In the synthesis of compounds **2g** and **4b**, water was distilled off *in vacuo* at temperature no higher than 40 °C until an oily precipitate of compounds **2g** (R_f = 0.34) and **4b** (R_f = 0.75) was obtained. The compounds were separated by silica gel column chromatography (40×100) using a 1 : 3 acetone—chloroform mixture. The yields and physicochemical characteristics of compounds **2e—g** are given in Tables 3 and 4. The characteristics of compound **4b** are consistent with those reported earlier.[12]

4,6-Diethyl-1,3-dimethyl-5(3*H*)-oxo- and 3,4,6-triethyl-1-methyl-5(3*H*)-oxotetrahydro-1*H*-imidazo[4,5-*c*][1,2,5]thiadiazole 2,2-dioxides (2b,i). 4,5-Dihydroxy-1,3-diethylimidazolidin-2-one (**1c**) (0.17 g, 1 mmol) and 1,3-dialkylsulfamide **5e** or **5f** (1 mmol) were dissolved in acetone (1.0 mL) in a Teflon tube. Then one drop of concentrated HCl was added, and acetone was added until the tube was filled. The tube was placed in a high-pressure apparatus and kept at 1000 MPa and 12 °C for 16 h. Then the pressure was relieved, the solvent was distilled off, and the oily residue was triturated with ethyl acetate until a white precipitate formed. The physicochemical characteristics of compound **2i** are given in Tables 3 and 4. The characteristics of compound **2b** have been reported earlier.[8]

***N*-(1,3-Diethyl-5-hydroxy-2-oxoimidazolidin-4-yl)-*N*,*N*′-dialkylsulfamides 7a,b.** A solution of 1,3-diethyl-4,5-dihydroxyimidazolidin-2-one **1c** (0.17 g, 1 mmol), 1,3-dialkylsulfamide **5e** or **5f** (1 mmol), and AcOH (2 drops) in acetone (1.6 mL) was placed in a Teflon tube. The tube was placed in a high-pressure apparatus and kept at 1000 MPa and room temperature for 5 min. Then the pressure was relieved and again produced after 5 min. This cycle was repeated nine times (10 min per cycle). Then the reaction mixture was kept at 1000 MPa for 3 h, the solvent was distilled off, and the oily residue was triturated with ethyl acetate until a white precipitate formed. The precipitate was recrystallized from acetone. The yields and physicochemical characteristics of compounds **7a,b** are given in Tables 3 and 4.

X-ray diffraction study. Principal crystallographic parameters and the X-ray data collection and refinement statistics for compounds **2a,d,f** are given in Table 5. The structures were solved by direct methods. The hydrogen atoms of the NH groups were located in difference electron density maps. All other hydrogen atoms were positioned geometrically. An analysis of difference Fourier maps showed that the propyl substituent in one of the independent molecules in the structure of **2f** is disordered over two positions with occupancies of 0.75 and 0.25. The structures were refined based on F^2_{hkl} with anisotropic displacement parameters for nonhydrogen atoms. The positions of the hydrogen atoms were refined isotropically using a riding model. All calculations were carried out with the use of the SHELXTL PLUS 5 program package.[27]

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References

1. E. Jagiello-Wojtowicz, I. Zebrowska-Lupina, M. Wielosz, M. Stelmasiak, G. Szurska, A. Porowska, Z. Kleinrok, *Acta Polon. Pharm.*, 1984, **41**, 495.
2. W. J. Brouillette, V. P. Jestkov, M. L. Brown, M. S. Akhar, *J. Med. Chem.*, 1994, **37**, 3289.
3. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Medicines*], Novaya Volna, Moscow, 2000, **1**, 86 (in Russian).
4. A. A. Bakibaev, R. R. Akhmedzhanov, A. Yu. Yagovkin, T. P. Novozheeva, V. D. Filimonov, A. S. Saratikov, *Khim.-farm. Zh.*, 1993, **27**, No. 6, 29 [*Pharm. Chem. J.*, 1993, **27**, No. 6, 401 (Engl. Transl.)].
5. W. C. Groutas, R. Kuang, R. Venkataraman, *Biochem. Biophys. Res. Commun.*, 1994, **198**, 341.
6. Span ES Pat. 547443; *Chem. Abstr.,* 1988, **108**, 6031.
7. C.-H. Lee, H. Kohn, *J. Pharm. Sci.,* 1990, **79**, 716.
8. G. A. Gazieva, A. N. Kravchenko, O. V. Lebedev, V. I. Abelentsev, *Khim.-farm. Zh.*, 2001, **35**, № 2, 14 [*Pharm. Chem. J.*, 2001, **35**, No. 2, 72 (Engl. Transl.)].
9. G. A. Gazieva, A. N. Kravchenko, K. Yu. Chegaev, Yu. A. Strelenko, O. V. Lebedev, *Mendeleev Commun.*, 2000, 28.
10. G. A. Gazieva, A. N. Kravchenko, O. V. Lebedev, Yu. A. Strelenko, K. Yu. Chegaev, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 1604 [*Russ. Chem. Bull.*, 1998, **47**, 1561 (Engl. Transl.)].
11. G. A. Gazieva, K. A. Lyssenko, R. G. Gaziev, A. N. Kravchenko, O. V. Lebedev, V. M. Zhulin, *Mendeleev Commun.*, 2001, 107.
12. G. A. Gazieva, P. V. Lozhkin, A. N. Kravchenko, K. A. Lyssenko, N. G. Kolotyrkina, N. N. Makhova, *Khim. Geterotsikl. Soedin.*, 2007, 1159 [*Chem. Heterocycl. Compd.*, 2007, **43**, 981 (Engl. Transl.)].
13. G. A. Gazieva, A. N. Kravchenko, Yu. A. Strelenko, O. V. Lebedev, R. G. Gaziev, V. M. Zhulin, *Khim. Geterotsikl. Soedin.*, , 2003, 912 [*Chem. Heterocycl. Compd.*, 2003, **39**, 784 (Engl. Transl.)].
14. A. S. Sigachev, A. N. Kravchenko, G. A. Gazieva, P. A. Belyakov, N. G. Kolotyrkina, O. V. Lebedev, N. N. Makhova, *J. Heterocycl. Chem.,* 2006, **43**, 1295.
15. N. Isaacs, *Liquid Phase High-Pressure Chemistry*, Wiley-Intersci. Publ., Chichester, 1981, 414.
16. V. M. Zhulin, Z. G. Makarova, E. M. Klimov, N. N. Malysheva, N. K. Kochetkov, *Dokl. Akad. Nauk SSSR*, 1989, **309**, 641 [*Dokl. Phys. Chem.*,1989, 928 (Engl. Transl.)].
17. I. P. Sedishev, G. A. Gazieva, A. N. Shumskii, E. S. Putilova, V. M. Zhulin, *Kondensirovannye sredy i mezhfaznye granitsy* [*Condensed Media and Interface Boundaries*], 2002, **4**, No. 3, 225 (in Russian).
18. A. N. Kravchenko, A. S. Sigachev, E. Yu. Maksareva, G. A. Gazieva, N. S. Trunova, B. V. Lozhkin, T. S. Pivina, M. M. Il´in, K. A. Lysenko, Yu. V. Nelyubina, V. A. Davankov, O. V. Lebedev, N. N. Makhova, V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2005**,** 680 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 691].
19. A. S. Sigachev, A. N. Kravchenko, K. A. Lyssenko, P. A. Belyakov, O. V. Lebedev, N. N. Makhova, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 836 [*Russ. Chem. Bull., Int. Ed.,* 2006, **55,** 865 (Engl. Transl.)].

20. G. A. Gazieva, K. A. Lyssenko, A. N. Kravchenko, O. V. Lebedev, *Zh. Org. Khim.*, 2007, **43**, 1714 [*Russ. J. Org. Chem.*, 2007, **43**, 1715 (Engl. Transl.)].
21. E. Grillon, R. Gallo, M. Pierrot, J. Boileau, E. Wimmer, *Tetrahedron Lett.*, 1988, **29**, 1015.
22. S. L. Vail, R. H. Barker, P. G. Mennitt, *J. Org. Chem.*, 1965, **30**, 2179.
23. R. Neville, *J. Org. Chem.*, 1958, **23**, 1588.
24. A. M. Paquin, *Angew. Chem.*, 1948, **60A**, 316.
25. M. Bermann, J. R. Van Wazer, *Synthesis*, 1972, 10, 576.
26. S. A. Gaer, G. A. Gareev, N. V. Stepanova, G. V. Sakovich, R. L. Bol´shedvorskaya, T. M. Filippova, L. I. Vereshchagin, *Zh. Obshch. Khim.*, 1990, **60**, 1490 [*J. Gen. Chem. USSR*, 1990, **60**, 1332].
27. *SHELXTL v. 5.10, Structure Determination Software Suite,* Bruker AXS, Madison, Wisconsin, USA, 1998.

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