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SYNTHESIS AND STRUCTURE OF 1,3-DIALKYL-4-(SULFONYLIMINO)IMIDAZOLIDIN-2-ONES

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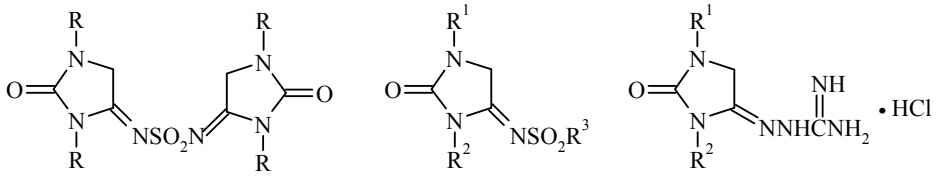
The reactions of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones with alkyl sulfamides have been studied and previously undescribed 1,3-dialkyl-4-(alkylaminosulfonylimino)imidazolidin-2-ones have been obtained. The structure of 1,3-dimethyl-4-(benzenesulfonylimino)imidazolidin-2-one was investigated by X-ray structural analysis.

Keywords: 1-alkylsulfamides, 1,3-dialkyl-4-(alkylaminosulfonylimino)imidazolidin-2-ones, 4,5-dihydroxyimidazolidin-2-ones, 1,3-dimethyl-4-(benzenesulfonylimino)imidazolidin-2-one, X-ray structural analysis.

Imidazolidin-2-one derivatives possess a broad spectrum of biological activity. In particular, hydantoins are used in medicine and agrochemistry as anticonvulsants [1, 2], anticancer preparations [3], fungicides [4], and herbicides [5]. On the other hand compounds containing a sulfamide fragment display bacteriostatic, hypoglycemic, diuretic, and herbicidal action [2, 6-8]. For several years the reactions of 4,5-dihydroxyimidazolidin-2-ones (DHI) with ureas and their hetero analogues have been among our scientific interests. Recently as a result of investigations carried out by us on the interaction of 1-alkyl and 1,3-dialkyl-DHI with sulfamide and amides of sulfonic acids, an unusual reaction has been detected [9] leading to 4,4'-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-one) **1** and 4(5)-aryl(or alkyl)-sulfonyliminoimidazolidin-2-one **2**, containing both pharmacophoric fragments. We later showed that the reaction of 1,3-dialkyl-DHI with aminoguanidine proceeds analogously with the formation of 1,3-dialkyl-4-guanidinoiminoimidazolidin-2-ones **3** [10].



1 **2** **3**

With the aim of broadening the scope of the discovery, the reaction of 1,3-dialkyl-DHI **4a,b** with 1-alkylsulfamides **5a-d** under conditions analogous to the conditions of obtaining compounds **2** and **3** (methanol, HCl) (Scheme 1) has been investigated.

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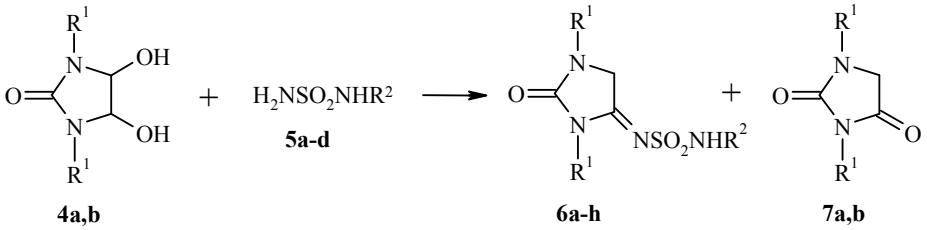
Scheme 1



4a, **6a**, **c**, **e**, **g**, **7a** R^1 = Me; **4b**, **6b**, **d**, **f**, **h**, **7b** R^1 = Et; **5a**, **6a**, **b** R^2 = Pr; **5b**, **6c**, **d** R^2 = Bu; **5c**, **6e**, **f** R^2 = *s*-Bu; **5d**, **6g**, **h** R^2 = *cyclo*-C_6H_{11}

Analysis of the reaction products was carried out by ^{1}H NMR spectroscopy of the reaction mass after evaporation to dryness. In these spectra characteristic signals were detected for the protons of the N-alkyl groups (0.83-3.49), the CH_2 group of the imidazolidine ring (4.44-4.48), and the NH group of the sulfamide fragment (7.00-7.12 ppm), from the intensities of which it may be suggested that the reaction products are the previously unknown 1,3-dialkyl-4-(alkylaminosulfonylimino)imidazolidin-2-ones **6a-h**. In the 3.9-4.0 ppm region signals were also recorded for the CH_2 group protons of hydantoins **7a,b**, which are formed as byproducts. Hydantoins **7a,b** were not isolated.

After isolation in a pure state the structures of compounds **6a-h** were confirmed by a combination of data of elemental analysis, IR, ^{1}H NMR, and mass spectra (Tables 1, 2).

TABLE 1. Characteristics of Compounds **6a-h**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	S		
6a	$C_8H_{16}N_4O_3S$	38.72 / 38.70	6.52 / 6.49	22.55 / 22.56	12.88 / 12.91	64-66	37-39
6b	$C_{10}H_{20}N_4O_3S$	43.45 / 43.46	7.31 / 7.29	20.31 / 20.27	11.55 / 11.60	71-73	50-52
6c	$C_9H_{18}N_4O_3S$	41.22 / 41.21	6.88 / 6.92	21.39 / 21.36	12.17 / 12.22	72-74	43-45
6d	$C_{11}H_{22}N_4O_3S$	45.52 / 45.50	7.67 / 7.64	19.26 / 19.29	10.99 / 11.04	65-67	51-53
6e	$C_9H_{18}N_4O_3S$	41.18 / 41.21	6.91 / 6.92	21.38 / 21.36	12.19 / 12.22	89-91	29-31
6f	$C_{11}H_{22}N_4O_3S$	45.53 / 45.50	7.64 / 7.64	19.27 / 19.29	11.01 / 11.04	86-88	36-39
6g	$C_{11}H_{20}N_4O_3S$	45.78 / 45.82	7.03 / 6.99	19.51 / 19.43	11.07 / 11.12	117-119	33-35
6h	$C_{13}H_{24}N_4O_3S$	49.38 / 49.35	7.67 / 7.65	17.69 / 17.71	10.10 / 10.13	120-124	41-44

In the IR spectra of compounds **6a-h** a broad absorption peak is observed for the sulfamide NH bond at 3244-3292 cm^{-1}, and also intense absorption for the C=O bond at 1728-1760 cm^{-1}. Stretching vibrations for the C=N bond are displayed at 1612-1624, and for the S=O bond at 1248-1344 cm^{-1} (Table 2).

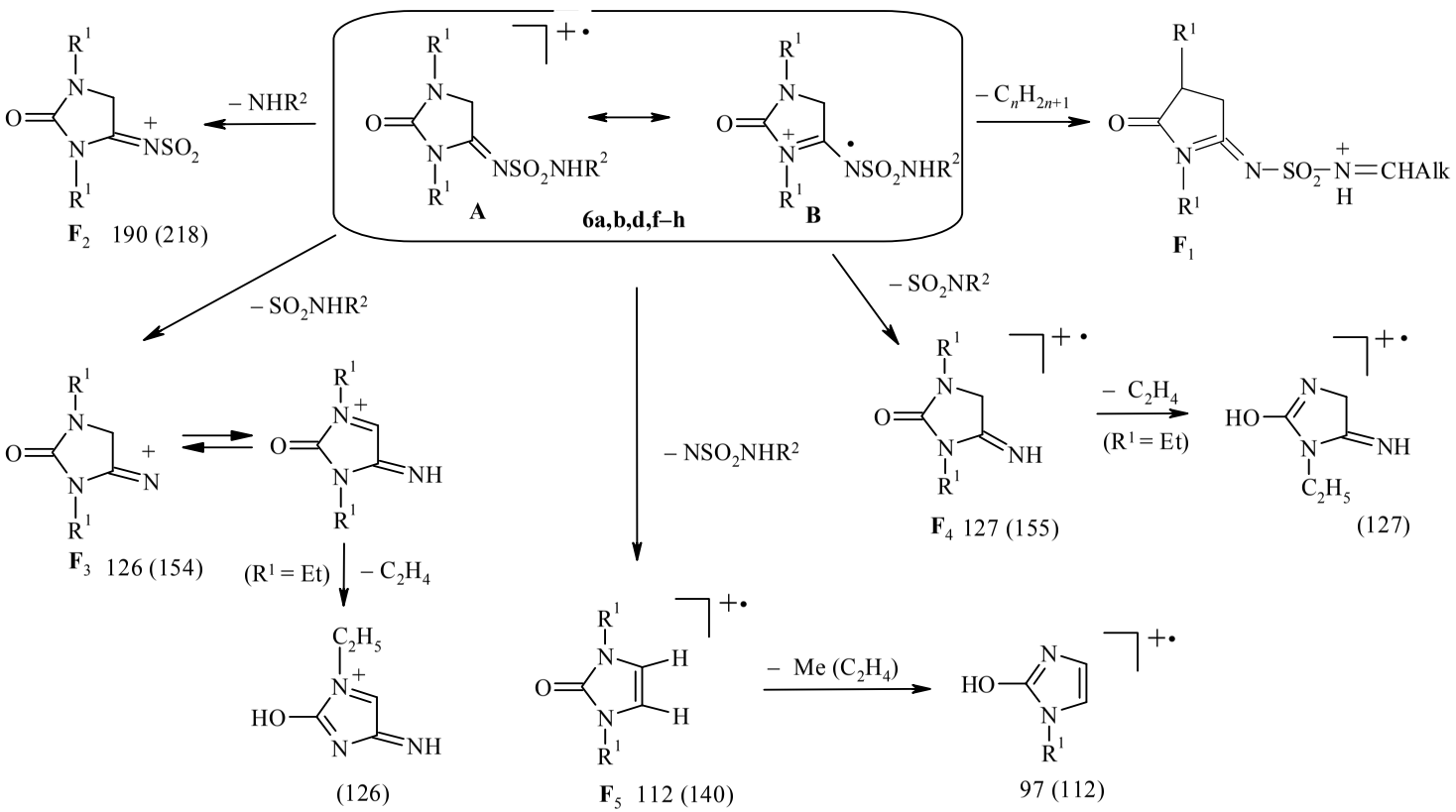
Analysis of the mass spectra of sulfonylimines **6a,b,d,f-h** showed the general character of the fragmentation. Peaks were present for molecular ions in the spectra of all the investigated compounds. The positive charge is localized predominantly on the sulfamide nitrogen atoms.

TABLE 2. Spectral Characteristics of Compounds **6a-h**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)	Mass spectrum, *m/z* (*I*, %)
6a	3284, 1736, 1618, 1320, 1260	0.85 (3H, t, *J* = 7.3, CH_3); 1.45 (2H, m, CH_2); 2.70 (3H, s, NCH_3), 2.74 (3H, s, NCH_3); 2.84 (2H, m, NCH_2), 4.48 (2H, s, CH_2); 6.97 (1H, br. s, NH)	248 (5), 219 (48), 190 (100), 140 (35), 127 (36), 126 (32), 112 (29), 98 (10), 97 (13), 83 (41)
6b	3292, 1728, 1612, 1340, 1316, 1248	0.86 (3H, t, *J* = 7.5, CH_3); 1.09 (6H, t, *J* = 7.0, $2CH_3$); 1.47 (2H, m, CH_2), 2.85 (2H, m, NCH_2); 3.33, 3.49 (both 2H, m, NCH_2); 4.48 (2H, s, CH_2), 7.12 (1H, t, *J* = 6.5, NH)	276 (12), 247 (19), 218 (100), 154 (67), 153 (84), 140 (62), 127 (25), 112 (30), 109 (47), 97 (18), 83 (79)
6c	3266, 1754, 1622, 1344, 1316, 1252	0.83 (3H, t, *J* = 6.7, CH_3); 1.27 (2H, m, CH_2); 1.39 (2H, m, CH_2); 2.84 (3H, s, NCH_3); 2.90 (3H, s, NCH_3); 4.44 (2H, s, CH_2); 7.08 (1H, br. s, NH)	
6d	3276, 1736, 1624, 1320, 1252	0.83 (3H, t, *J* = 7.3, CH_3); 1.06 (6H, t, *J* = 7.0, $2CH_3$); 1.27 (2H, m, CH_2); 1.40 (2H, m, CH_2); 2.87 (2H, m, NCH_2); 3.30 (2H, m, NCH_2); 3.47 (2H, m, NCH_2); 4.45 (2H, s, CH_2); 7.06 (1H, t, *J* = 5.8, NH)	290 (5), 247 (23), 218 (100), 155 (48), 154 (74), 140 (15), 127 (17), 112 (15), 99 (7), 83 (46)
6e	3268, 1760, 1624, 1318, 1252	0.83 (3H, t, *J* = 7.3, CH_3); 1.07 (3H, d, *J* = 6.1, CH_3); 1.40 (2H, m, CH_2); 2.85 (3H, s, NCH_3); 2.90 (3H, s, NCH_3); 3.16 (1H, m, NCH); 4.45 (2H, s, CH_2); 7.00 (1H, d, *J* = 8.0, NH)	
6f	3252, 1760, 1620, 1344, 1304, 1252	0.82 (3H, t, *J* = 7.3, CH_3); 1.06 (9H, m, $3CH_3$); 1.38 (2H, m, CH_2); 3.17 (1H, m, NCH); 3.28 (2H, m, NCH_2); 3.45 (2H, m, NCH_2); 4.45 (2H, s, CH_2); 7.01 (1H, d, *J* = 7.9, NH)	290 (2), 261 (64), 218 (100), 154 (18), 153 (52), 127 (13), 111 (16), 83 (44)
6g	3264, 1760, 1624, 1312, 1296	1.09-1.91 (10H, m, $5CH_2$); 2.88 (3H, s, NCH_3); 2.93 (3H, s, NCH_3); 3.10 (1H, m, CH); 4.47 (2H, s, CH_2); 7.04 (1H, d, *J* = 7.3, NH)	288 (30), 245 (49), 190 (100), 127 (35), 126 (39), 112 (16), 98 (53), 97 (21), 83 (45)
6h	3244, 1760, 1624, 1344, 1316, 1296, 1252	1.04-1.86 (16H, m, $2CH_3 + 5CH_2$); 3.05 (1H, m, CH); 3.31 (2H, m, NCH_2); 3.46 (2H, m, NCH_2); 4.46 (2H, s, CH_2); 7.09 (1H, d, *J* = 7.9, NH)	316 (9), 273 (43), 235 (15), 218 (100), 154 (56), 153 (74), 140 (9), 127 (25), 112 (13), 111 (13), 98 (59), 83 (56)

A characteristic of the mass spectra of all compounds **6** was the primary alkylamine splitting of radical R^2 (ions $\mathbf{F_1}$, Scheme 2), and also elimination of fragments R^2NH with the formation of ions $\mathbf{F_2}$, the peaks of which were maximal in the mass spectra of all the investigated compounds. Primary routes of breakdown of the molecular ions of compounds **6** were also characterized by splitting of the second N-S bond with elimination of the sulfamide substituent, and the process was accompanied by the partial transfer of hydrogen to the imine nitrogen atom (ions $\mathbf{F_3}$ and $\mathbf{F_4}$). One further unusual route of fragmentation of the molecular ions of imidazolidinones **6** was linked with the splitting off entirely of all the sulfodiamide fragment (possibly from the resonance form **B**) with the formation of the odd-electron ion $\mathbf{F_5}$. The initial fragment ions $\mathbf{F_2}$-$\mathbf{F_5}$ of compounds **6** with radicals $R^1 = C_2H_5$ eliminate a molecule of ethylene by a 1,5-sigmatropic transfer of hydrogen (McLafferty rearrangement).

Scheme 2


– NHR2
– CnH2n+1
– SO2NHR2
– SO2NR2
– NSO2NHR2
– C2H4
(R1 = Et)
– Me (C2H4)
A
6a,b,d,f–h
B
F2 190 (218)
F1
F3 126 (154)
F4 127 (155)
(127)
(126)
F5 112 (140)
97 (112)

During the investigation a dependence was discovered of the yields of compound **6** on the length of the carbon chain of substituents at the nitrogen atom of the DHI. Unsubstituted DHI does not react with sulfamides with the formation of a C=N bond, but on going from 1,3-dimethyl (**6a,c,e,g**) to 1,3-diethyl DHI (**6b,d,f,h**) the yields of the corresponding products **6** increased (see Table 1).

The new direction for the reaction of N-alkyl-DHI with urea heteroanalogs therefore has a fairly general character. Under acid catalysis conditions several types of imino derivatives of imidazolidin-2-one **1-3**, **6** were obtained. For unequivocal proof of structure of the obtained compounds an X-ray diffraction analysis was carried out in the present work on the example of 4-(benzenesulfonylimino)-1,3-dimethylimidazolidin-2-one **2a**, synthesized by the procedure of [9].

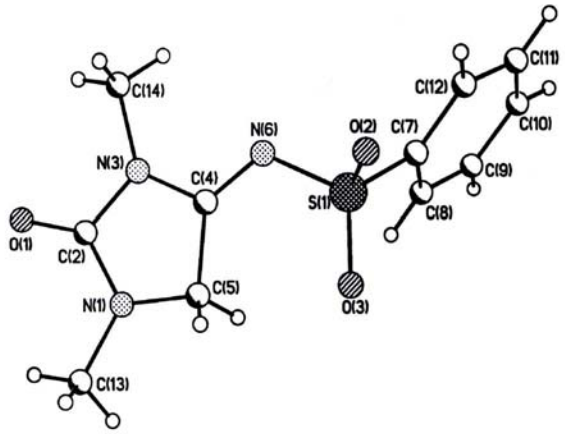


Fig. 1. General form of compound **2a**.

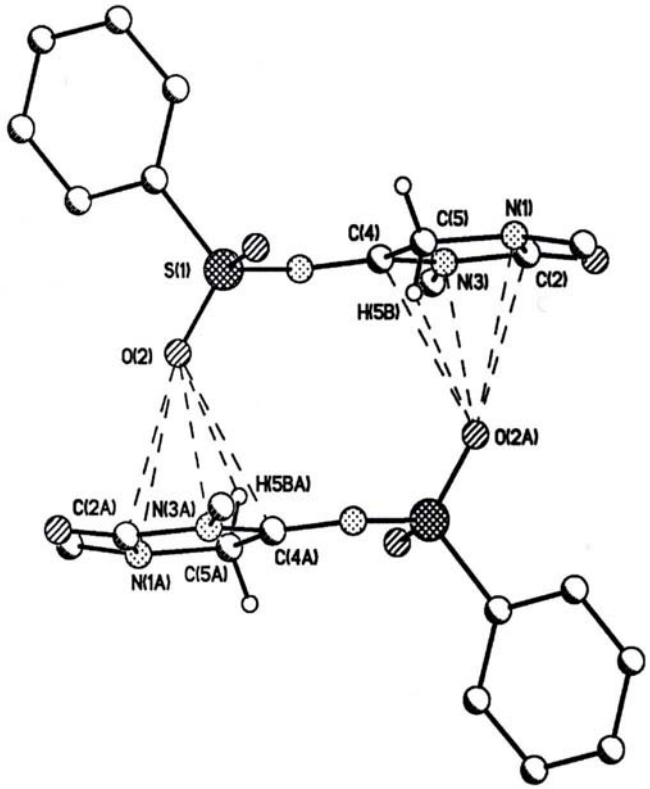


Fig.2. O…π and C-H…O bonded dimer in the **2a** crystal.

In the crystal of **2a**, according to X-ray crystallographic data, the imidazolidine ring is in fact planar with the maximum deviation by atom C(2) of 0.088(7) Å [atoms N(1), N(3), C(4), and C(5) are coplanar with a precision of 0.007 Å] (Fig. 1).

Analysis of the ring bond lengths in the **2a** crystal showed that the N(3) atom is involved in conjugation with the C(4)–N(6) double bond, while the unshared electron pair of the N(1) atom on the other hand, is coupled with the C=O bond. In reality, the C(2)–N(1) bond is appreciably shorter [1.345(2) Å] than the C(2)–N(3) bond [1.414(2) Å] and in fact is not distinguished from the N(3)–C(4) bond [1.360(2) Å] (Table 3). The observed differences also lead to variation of the configuration of the ring nitrogen atoms. Atom N(3) is characterized by a planar configuration, while atom N(1) deviates insignificantly from the plane of its substituents. The sum of the valence angles for the N(1) and N(3) nitrogen atoms are equal to 355.7(1) and 359.6(1)° respectively.

Analysis of the intermolecular interactions in the **2a** crystal showed that the O(2) atom of the sulfo group forms fairly unusual interactions with the π-system of the imidazolidine ring, and there is also C–H…O contact [O(2)…H(5BA) 2.43 Å] with the hydrogen atom on atom C(5). The indicated contacts unite the molecules in a centrosymmetric dimer (Fig. 2).

The presence of fairly short intermolecular contacts O(2)…C [3.114(3)-3.153(3) Å and O(2)…N [3.001(3)-3.252(3) Å], and also the size of the O(2)…ring centroid (2.854 Å) distance indicate with a high probability the presence of a specific O…π interaction [11]. However (see for example [12]) it is impossible to exclude that the indicated combination of intermolecular contacts is obligatory and the formation of the dimer is caused solely by the C–H…O contact.

TABLE 3. Main Bond Lengths (*d*) in the Compound **2a** Molecule

Bond	*d*, Å	Bond	*d*, Å
S(1)–O(2)	1.4363(15)	C(4)–N(3)	1.3600(19)
S(1)–O(3)	1.4404(15)	C(4)–C(5)	1.506(2)
S(1)–N(6)	1.6408(14)	N(3)–C(2)	1.414(2)
O(1)–C(2)	1.2195(19)	N(1)–C(2)	1.345(2)
C(4)–N(6)	1.299(2)	N(1)–C(5)	1.457(2)

TABLE 4. Main Valence Angles (ω) in the Compound **2a** Molecule.

Angle	ω, deg	Angle	ω, deg
O(2)–S(1)–O(3)	117.6(1)	C(4)–N(3)–C(14)	125.4(1)
O(2)–S(1)–N(6)	106.72(9)	C(2)–N(3)–C(14)	122.70(1)
O(3)–S(1)–N(6)	112.55(8)	C(2)–N(1)–C(13)	122.43(1)
O(2)–S(1)–C(7)	108.03(8)	C(2)–N(1)–C(5)	111.63(1)
O(3)–S(1)–C(7)	108.01(8)	C(13)–N(1)–C(5)	121.72(1)
N(6)–S(1)–C(7)	102.83(7)	O(1)–C(2)–N(1)	128.7(2)
N(6)–C(4)–N(3)	120.7(1)	O(1)–C(2)–N(3)	124.2(1)
N(6)–C(4)–C(5)	132.5(1)	N(1)–C(2)–N(3)	107.1(1)
N(3)–C(4)–C(5)	106.8(1)	C(4)–N(6)–S(1)	120.4(1)
C(4)–N(3)–C(2)	111.5(1)		

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AM 300 (300 MHz) spectrometer in DMSO-d_6, internal standard was TMS. Mass spectra were obtained on a MS 30 mass spectrometer, and IR spectra on a Specord M 82 spectrometer (in KBr disks).

X-Ray Structural Investigation of Compound 2a. Crystals of compound **2a**, grown in methanol, were triclinic at 110 K: a = 8.0462(10), b = 8.2895(10), c = 9.2004(11) Å, α = 88.276(2), β = 84.394(2), γ = 85.481(2)°, V = 608.67(13) Å^3, d_{calc} = 1.458 g.cm^{-3}, space group $P\bar{1}$, Z = 2. The intensities of 6003 reflections were measured on a Smart 1000 CCD automatic diffractometer at 110 K (MoKα radiation, graphite monochromator, ω-scanning, $2\theta_{max}$ = 58°) and 3358 (R_{int} = 0.0163) observed reflections were used in the subsequent calculations. The structure was interpreted by the direct method and was refined by the full matrix least squares method in an anisotropic-isotropic approach on F^2. The hydrogen atoms were located in electron density difference syntheses and were refined with a rider model. Final divergence factors: wR_2 = 0.1057, GOF = 1.037 according to the reflections (R_1 = 0.0466 calculated on 2279 reflections with $I > 2\sigma(I)$) with the SHELXTL PLUS set of programs.

1,3-Dimethyl- [13], 1,3-diethyl-DHI [9], and 1-alkylsulfamides were synthesized by reported methods.

1,3-Dialkyl-4-(alkylaminosulfonylimino)imidazolidin-2-ones 6a-h (General Method). The appropriate 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-one **4a,b** and 1-alkylsulfamide **5a-d** (about 5 mmol of each) were dissolved in methanol (5 ml). Conc. HCl (2 drops) was added and the mixture boiled for 30 min. After cooling the reaction mass the precipitated solid compound **6e-h** was filtered off and recrystallized from methanol–water, 1:4. To obtain products **6a-d** the solvent was distilled off on a rotary evaporator. Compounds **6a** (R_f = 0.74), **6b** (R_f = 0.77), **6c** (R_f = 0.84), **6d** (R_f = 0.80) were isolated by column chromatography on SiO_2 (40 x 100), using an acetone–chloroform, 1:3 mixture.

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