Reactions of sulfonamides with 4,5-dihydroxyimidazolidin-2-ones

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The interaction of sulfonamides with 4,5-dihydroxyimidazolidin-2-ones was studied for the first time. The earlier unknown 4,4'-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) and 4(5)-aryl(alkyl)-sulfonyliminoimidazolidin-2-ones were synthesized. A probable pathway of the reaction was proposed. 1,3-Diethyl-4,5-dihydroxyimidazolidin-2-one was isolated and described.

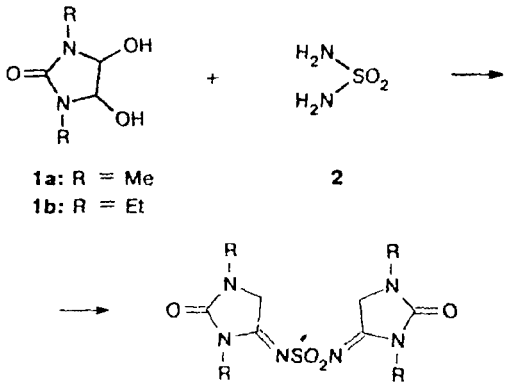
Key words: sulfonamides, 4,5-dihydroxyimidazolidin-2-ones, 4,4'-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones), 4(5)-aryl(alkyl)sulfonyliminoimidazolidin-2-ones.

Interest in compounds containing the sulfonamide fragment is due to the broad spectrum of their biological activity, including antispasmodic,[1] antiphlogistic, diuretic,[2] antiulcer,[3] herbicidal,[4] *etc.*

With the goal of discovering new pharmacologically active compounds, we studied the interaction of sulfonamides with 4,5-dihydroxyimidazolidin-2-ones and obtained, as reported earlier,[5] the unknown 4,4'-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) and 4(5)-aryl(alkyl)sulfonyliminoimidazolidin-2-ones.

Similar compounds were obtained by the reaction of sulfonamides or ureas with lactam acetals.[2] It is known that 4,5-dihydroxyimidazolidin-2-ones react with ureas to give 2,4,6,8-tetraazabicyclo[3.3.0]-octane-3,7-diones.[6] We established that the interaction of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones (**1a,b**) with sulfamide (**2**) leads to the formation of 4,4'-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) (**3a,b**) (Scheme 1).

Scheme 1



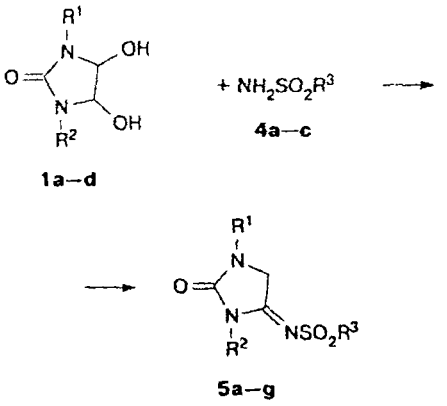
1a: R = Me
1b: R = Et

2

3a: R = Me
3b: R = Et

Compounds **1a** and **1b** react with sulfonamides such as benzene-, toluene-, and methanesulfonamides **4** to yield 4(5)-aryl(alkyl)sulfonyliminoimidazolidin-2-ones **5a—e** (Scheme 2).

Scheme 2



1a—d

4a—c

5a—g

1a: $R^1 = R^2$ = Me; **1b**: $R^1 = R^2$ = Et; **1c**: R^1 = Me, R^2 = H; **1d**: R^1 = Et, R^2 = H; **4a**: R^3 = Ph; **4b**: R^3 = *p*-MeC_6H_4; **4c**: R^3 = Me; **5a**: $R^1 = R^2$ = Me, R^3 = Ph; **5b**: $R^1 = R^2$ = Me, R^3 = *p*-MeC_6H_4; **5c**: $R^1 = R^2 = R^3$ = Me; **5d**: $R^1 = R^2$ = Et, R^3 = Ph; **5e**: $R^1 = R^2$ = Et, R^3 = *p*-MeC_6H_4; **5f**: R^1 = H, R^2 = Me, R^3 = *p*-MeC_6H_4; **5g**: R^1 = H, R^2 = Et, R^3 = *p*-MeC_6H_4

When monosubstituted **1c,d** were involved in the reaction with **4b**, from the possible isomers there were obtained only compounds **5f,g**, in which the C=N bond is formed by the C atom adjacent to the substituted N atom. This is probably explained by the fact that the amino group of sulfonamide reacts with more stable (owing to the influence of the alkyl group of the neighboring N atom) cation **6b** rather than carbocation **6a**, which is another intermediate of the reaction.

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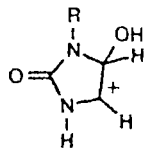
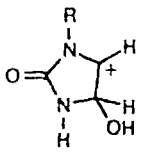


6a



6b

Since the synthesis of imines by reactions with 4,5-dihydroxyimidazolidin-2-ones is not described in the literature, there is no ready analogy for the chemism of this process. We did not exclude the probability of the reaction proceeding *via* the formation of 2,4-dioxoimidazolidines (hydantoins) because 4,5-dihydroxyimidazolidin-2-ones are known to be transformed into hydantoins in acidic media.[6,7]

Indeed, compound **1a** is transformed into hydantoin **7** in the absence of sulfonamide (Scheme 3). Nevertheless, we failed to obtain **5a** from compound **7** (both resulted from the reaction and were previously synthesized according to the known procedure)[6] even in trace amounts, which was confirmed by TLC.

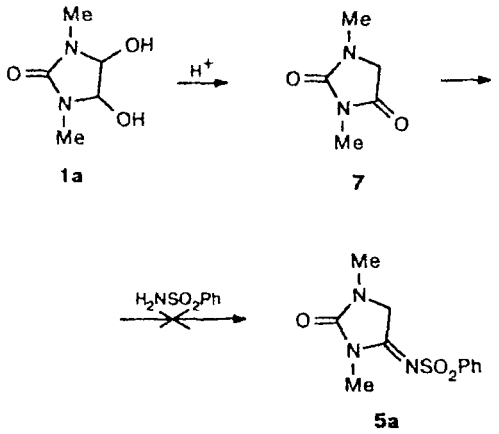
Based on these results, one can affirm that hydantoin is not an intermediate of this reaction.

Summarizing the results obtained and published data concerning the mechanisms of formation of hydantoin[7] and bicyclooctanediones[6] from 4,5-dihydroxyimidazolidin-2-ones, we postulate two probable pathways in which the reaction can proceed under acidic catalysis (Scheme 4).

Carbocation **6** resulting from the dehydration of **1** is condensed with the molecule of sulfonamide, and the intermediate **8** that forms is dehydrated anew into carbocation **9**. Further, either the proton transfer precedes deprotonation, as in the case of the formation of hydantoin,[7] or deprotonation that results in aminoimidazolone **11** precedes the proton transfer, which in any case leads to compound **5** (or **3** when sulfonamide **2** is used).

Imines **3** and **5** are white crystalline substances that are virtually insoluble in water but soluble in chloroform and acetone. Their IR spectra exhibit intense bands at 1740—1770 cm^{-1} (ν(C=O)); 1595—1640 cm^{-1} (ν(C=N)); and 1250—1370 and 1120—1173 cm^{-1} (ν(SO_2)). The following signals are observed in their ^1H NMR spectra, δ: 2.88—3.08 (s, N—Me); 3.45—3.69 (q, N—Et); 7.40 (s, N—H); 4.50—4.67 (s, CH_2 ring); 3.00 (s, S—Me); and 7.37—7.95 (m, H arom.). The characteristics of all compounds obtained are given in Tables 1 and 2.

Scheme 3



Experimental

IR spectra were obtained on a UR-20 instrument in the ranges 700—1800 and 2600—3600 cm^{-1}. NMR spectra were recorded on a Bruker AM-300 instrument (^1H, 300.13 and

Scheme 4

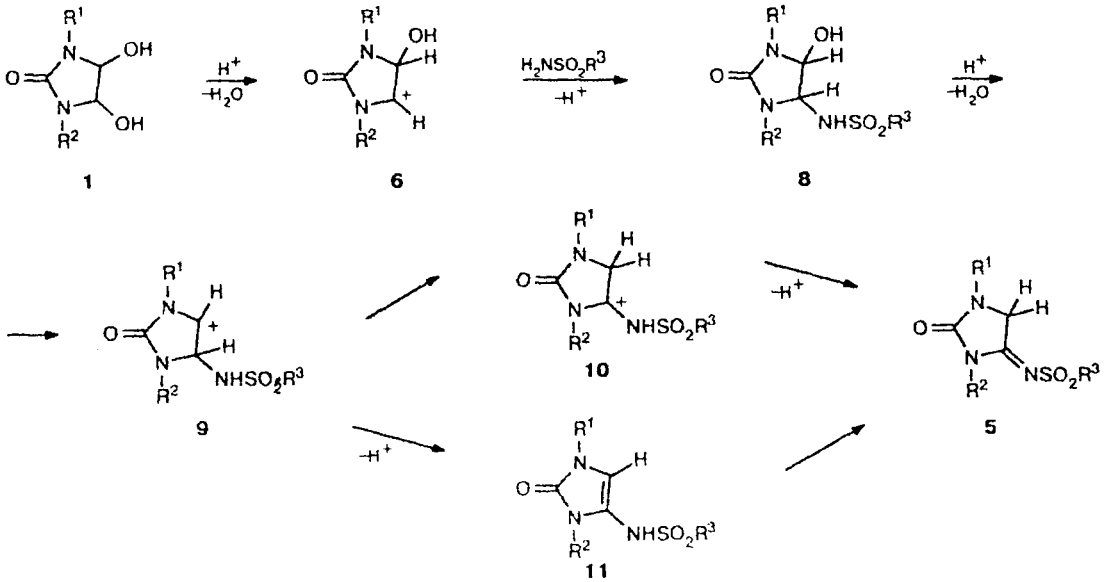


Table 1. The spectral characteristics of compounds **1b**, **3a,b**, and **5a—g**

Compound	MS, m/z $[M]^+$	IR (KBr), ν/cm^{-1}	NMR (δ)	
			^1H	^{13}C
1b	—	3350 (OH); 1675 (C=O)	1.08 (t, 6 H, Me); 3.15 (m, 2 H, NCH_2); 3.30 (m, 2 H, NCH_2); 4.70 (s, 2 H, CH)	
3a	316	1742 (C=O); 1624 (C=N); 1308, 1286, 1136, 1120 (SO_2)	2.88 (s, 6 H, NMe); 2.95 (s, 6 H, NMe); 4.50 (s, 4 H, CH_2)	
3b	372	1750 (C=O); 1595 (C=N); 1320, 1258, 1173 (SO_2)	1.21 (m, 12 H, Me); 3.48 (q, 4 H, NCH_2); 3.69 (q, 4 H, NCH_2); 4.60 (s, 4 H, CH_2)	
5a	267	1760 (C=O); 1640 (C=N); 1310, 1290, 1145 (SO_2)	3.00 (s, 6 H, NMe); 4.65 (s, 2 H, CH_2); 7.60 (m, 3 H, *m*-Ph+*p*-Ph); 7.95 (d, 2 H, *o*-Ph)	27.3 (NMe); 30.1 (NMe); 52.3 (CH_2); 127.7 (*o*-Ph); 129.9 (*m*-Ph); 133.4 (*p*-Ph); 143.5 (Ph); 167.2 (C=O)
5b	281	1765 (C=O); 1640 (C=N); 1290, 1270, 1145 (SO_2)	2.40 (s, 3 H, MePh); 2.96 (s, 3 H, NMe); 2.97 (s, 3 H, NMe); 4.62 (s, 2 H, CH_2); 7.87 (m, 2 H; *m*-Ph); 7.80 (m, 2 H, *o*-Ph)	21.6 (MePh); 27.2 (NMe); 30.0 (NMe); 52.3 (CH_2); 127.7 (*o*-Ph); 130.4 (*m*-Ph); 142.2 (Ph)
5c	205	1770 (C=O); 1605 (C=N); 1340, 1290, 1140 (SO_2)	3.00 (s, 3 H; SMe); 3.07 (s, 3 H, NMe); 3.08 (s, 3 H, NMe); 4.53 (s, 2 H, CH_2)	
5d	295	1750 (C=O); 1615 (C=N); 1310, 1250; 1160 (SO_2)	1.06 (t, 3 H, Me); 1.20 (t, 3 H, Me); 3.45 (q, 2 H, NCH_2); 3.57 (q, 2 H, NCH_2); 4.67 (s, 2 H, CH_2); 7.60 (m, 3 H, *m*-Ph+*p*-Ph); 7.95 (m, 2 H, *o*-Ph)	12.9 (Me), 13.3 (Me); 36.3 (NCH_2); 38.4 (NCH_2); 49.9 (CH_2); 127.4 (*o*-Ph); 129.9 (*m*-Ph); 133.4 (*p*-Ph); 143.4 (Ph); 155.2 (C=N); 166.7 (C=O)
5e	309	1760 (C=O); 1615 (C=N); 1350, 1290, 1150 (SO_2)	1.07 (t, 3 H, Me); 1.21 (t, 3 H, Me); 2.41 (s, 3 H, MePh); 3.45 (q, 2 H, NCH_2); 3.57 (q, 2 H, NCH_2); 4.65 (s, 2 H, CH_2); 7.38 (d, 2 H, *m*-Ph); 7.82 (d, 2 H, *o*-Ph)	12.9 (Me); 13.3 (Me); 21.6 (MePh); 36.2 (NCH_2); 38.4 (NCH_2); 49.9 (CH_2); 127.5 (*o*-Ph); 130.4 (*m*-Ph); 140.7 (*p*-Ph); 144.1 (Ph); 155.2 (C=N); 166.4 (C=O)
5f	267	3290 (NH); 1760 (C=O); 1615 (C=N); 1355, 1290, 1155 (SO_2)	2.40 (s, 3 H, MePh); 2.97 (s, 3 H, NMe); 4.63 (d, 2 H, CH_2); 7.38 (d, 2 H, *m*-Ph); 7.40 (s, 1 H, NH); 7.82 (m, 2 H, *o*-Ph)	21.6 (MePh); 26.8 (MeN); 46.9 (CH_2); 127.6 (*o*-Ph); 130.4 (*m*-Ph); 140.7 (*p*-Ph); 144.2 (Ph); 157.2 (C=N); 168.7 (C=O)
5g	281	3260 (NH); 1760 (C=O); 1610 (C=N); 1370, 1290, 1155 (SO_2)	1.10 (t, 3 H, Me); 2.40 (s, 3 H, MePh); 3.57 (q, 2 H, NCH_2); 4.63 (d, 2 H, CH_2); 7.38 (d, 2 H, *m*-Ph); 7.40 (s, 1 H, NH); 7.82 (d, 2 H, *o*-Ph)	12.9 (Me); 21.5 (MePh); 35.9 (CH_2N); 46.8 (CH_2); 127.5 (*o*-Ph); 130.4 (*m*-Ph)

^{13}C, 75.47 MHz), and chemical shifts (δ) were measured with respect to acetone (^1H, 2.05 and ^{13}C, 30.0), chloroform (^1H, 7.27 and ^{13}C, 77.0), and DMSO (^1H, 2.05). Preparative TLC was carried out in an acetone–chloroform (1 : 3) system. Plates were developed in an iodine chamber or with an alkaline solution of sodium nitroprusside (for hydantoin).

Sulfamide (2) was prepared according to a described procedure.[8] **1,3-Dimethylhydantoin (7)** was obtained according to a published procedure.[6]

4,5-Dihydroxy-1,3-dimethylimidazolidin-2-one (1a) was obtained according to a known procedure[9] and recrystallized from dioxane. **4,5-Dihydroxy-1-methyl and 1-ethyl-4,5-dihydroxyimidazolidinones (1c,d)** were obtained by analogy with **1a** and used without isolation.

1,3-Diethyl-4,5-dihydroxyimidazolidin-2-one (1b). A 10% NaOH solution was added to 16 mL of a 37.5% solution of glyoxal (0.1 mol) until pH 5 was attained. Diethylurea (11.6 g, 0.1 mol) was then added, and the reaction mixture was heated to 50 °C for 7 h and concentrated *in vacuo*. The oily residue obtained was recrystallized, and the precipitate of **1b** was filtered off.

4,4′-Sulfonyldiiminobis(1,3-dimethylimidazolidin-2-one) (3a). A solution of **1a** (1.46 g, 0.01 mol) and **2** (0.48 g, 0.005 mol) was dissolved in 2 mL of water, and two drops of a

Table 2. The characteristics of compounds **1b**, **3a,b**, and **5a—g**

Compound	Molecular mass	R_f	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)				Molecular formula
					C	H	N	S	
1b	174	—	60	109—111 (dioxane)	48.71 48.28	8.10 8.05	16.31 16.09	—	$C_7H_{14}N_2O_3$
3a	316	—	45	269—271 (water)	37.96 37.97	5.36 5.10	26.50 26.57	10.13 10.14	$C_{10}H_{16}N_6O_4S$
3b	372	—	5	232—234 (methanol)	44.08 44.15	6.53 6.49	22.54 22.56	8.52 8.61	$C_{14}H_{24}N_6O_4S$
5a	267	0.70	82	125—127 (methanol—dioxane)	49.47 49.43	5.10 4.90	15.61 15.72	12.01 11.99	$C_{11}H_{13}N_3O_3S$
5b	281	0.75	83	196—198 (methanol—dioxane)	51.35 51.23	5.64 5.37	15.04 14.94	11.29 11.40	$C_{12}H_{15}N_3O_3S$
5c	205	0.55	50	139—141 (methanol)	34.61 35.10	5.33 5.43	20.21 20.47	15.60 15.62	$C_6H_{11}N_3O_3S$
5d	295	0.80	81	61—63 (methanol)	52.94 52.87	6.05 5.80	14.25 14.23	10.48 10.86	$C_{13}H_{17}N_3O_3S$
5e	309	0.84	93	98—99 (methanol)	54.36 54.35	6.26 6.19	13.26 13.58	10.36 10.36	$C_{14}H_{19}N_3O_3S$
5f	267	0.46	16	179—181 (methanol)	49.19 49.43	4.92 4.90	15.64 15.72	12.09 11.99	$C_{11}H_{13}N_3O_3S$
5g	281	0.57	15	193—195 (methanol)	50.85 51.23	5.76 5.37	15.08 14.94	10.98 11.40	$C_{12}H_{15}N_3O_3S$

conc. HCl solution were added. The reaction mixture was heated on a water bath at 80—90 °C for 1 h, cooled, and neutralized with a 20% NaOH solution. The white precipitate of **3a** that formed was filtered off and recrystallized (yield 0.71 g).

4,4′-Sulfonyldiiminobis(1,3-diethylimidazolidin-2-one) (3b). A solution of **1a** (1.74 g, 0.01 mol) and **2** (0.48 g, 0.005 mol) in 2.5 mL of water with two drops of a conc. HCl solution was heated on a water bath at 80—90 °C. A white precipitate formed after a few minutes. The reaction mixture was cooled and neutralized with a 20% NaOH solution, and the precipitate was filtered off, washed with water, and recrystallized.

1,3-Dialkyl-4-aryl(alkyl)sulfonyliminoimidazolidin-2-ones (5a—e). A solution of the corresponding dihydroxyimidazolidinones **1** (0.01 mol) and sulfonamides **4** (0.01 mol) in 3 mL of MeOH with two drops of conc. HCl was heated on a water bath at 60—70 °C for 30 min. The reaction mixture was cooled and neutralized with a 20% NaOH solution. After rubbing with a glass rod a white precipitate of **5** formed. The precipitate was filtered off and recrystallized.

1-Alkyl-5-*p*-toluenesulfonyliminoimidazolidin-2-ones (5f—g). A solution of alkylurea (0.01 mol) in 1.6 mL of a 37.5% solution of glyoxal (0.01 mol) was adjusted with a 10% NaOH solution to pH 5 and heated on a water bath at 50 °C for 2 h. MeOH (1.5 mL), **5b** (0.005 mol), and two drops of conc. HCl were added, and the resulting solution was heated on a water bath at 80 °C for an extra 1 h. The reaction mixture was then cooled and neutralized with a 20% NaOH solution. A white precipitate of product **5** formed on standing for a while. The precipitate was filtered off and recrystallized.

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