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RING-CHAIN TAUTOMERISM OF 2-MERCAPTOBENZOYLHYDRAZONES OF AROMATIC ALDEHYDES

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It has been shown by ^{1}H NMR spectroscopy that 2-mercaptobenzoylhydrazones of aromatic aldehydes 2-$HSC_6H_4CONHN{=}CHC_6H_4X$ (X = 4-NO_2, 3-NO_2, 4-Br, H, 4-Me, 4-MeO, 4-Me_2N) exist in DMSO-d_6 solution as tautomeric mixtures of linear and cyclic benzo-1,3,4-thiadiazepine forms. The linear hydrazone form is represented by (E,Z')-conformational isomers, differing in the disposition relative to the amide C–N bond. It was shown that the logarithm of the tautomeric equilibrium constant K_T correlates with the σ-constants of the substituents in the aromatic nucleus.

Keywords: benzo-1,3,4-thiadiazepines, 2-mercaptobenzoylhydrazones, ring-chain tautomerism, Hammett equation.

It was shown previously that 2-mercaptobenzoylhydrazones of aliphatic aldehydes exist in solution as tautomeric mixtures of linear and cyclic benzo-1,3,4-thiadiazepine forms. The position of the equilibrium was determined by the effective volume of the terminal alkyl substituent [1].

The aim of the present work, being a continuation of the previous investigations, was to study the structure of the products of condensation of 2-mercaptobenzoic acid hydrazide with a series of aromatic aldehydes, and also the effect of the electronic properties of a substituent in the aromatic ring of the aldehyde component on the position of the tautomeric equilibrium.

Compounds **2a-g** were obtained in 65-90% yield after briefly maintaining equimolar quantities of 2-mercaptobenzoic acid hydrazide **1** and the appropriate aromatic aldehyde in methanol solution at 25°C (Table 1 and EXPERIMENTAL).

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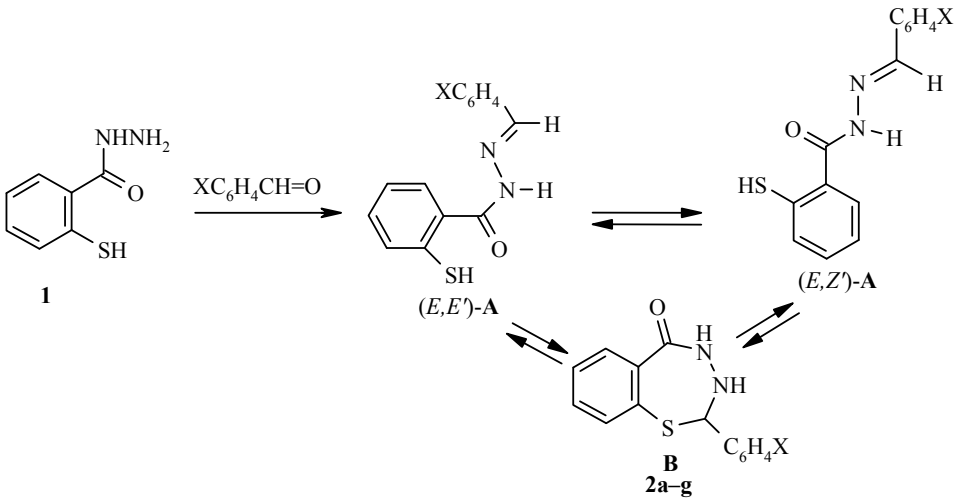


2 a X = 4-NO_2, **b** X = 3-NO_2, **c** X = 4-Br, **d** X = H, **e** X = 4-Me, **f** X = 4-MeO, **g** X = 4-Me_2N

TABLE 1. Physicochemical Characteristics of Compounds **2a-g** and **3a-g**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{14}H_{11}N_3O_3S$	55.87 / 55.80	3.60 / 3.68	13.89 / 13.95	207-209	80
2b	$C_{14}H_{11}N_3O_3S$	55.76 / 55.80	3.73 / 3.68	14.04 / 13.95	206-208	85
2c	$C_{14}H_{11}BrN_2OS$	50.21 / 50.16	3.27 / 3.31	8.41 / 8.36	189-191	70
2d	$C_{14}H_{12}N_2OS$	65.67 / 65.60	4.67 / 4.72	11.02 / 10.93	161-163	75
2e	$C_{15}H_{14}N_2OS$	66.58 / 66.64	5.28 / 5.22	10.30 / 10.36	174-176	85
2f	$C_{15}H_{14}N_2O_2S$	63.01 / 62.92	4.86 / 4.93	9.82 / 9.78	166-168	80
2g	$C_{16}H_{17}N_3OS$	64.24 / 64.19	5.67 / 5.72	13.98 / 14.04	170-172	65
3a	$C_{28}H_{20}N_6O_6S_2$	55.93 / 55.99	3.41 / 3.36	13.92 / 13.99	258-260 / 257-258 [2]	90
3b	$C_{28}H_{20}N_6O_6S_2$	56.04 / 55.99	3.30 / 3.36	14.04 / 13.99	261-263 / 263-264 [2]	90
3c	$C_{28}H_{20}Br_2N_4O_2S_2$	50.28 / 50.31	2.96 / 3.02	8.43 / 8.38	234-236	80
3d	$C_{28}H_{22}N_4O_2S_2$	65.91 / 65.86	4.29 / 4.34	11.05 / 10.97	220-222	85
3e	$C_{30}H_{26}N_4O_2S_2$	66.94 / 66.89	4.91 / 4.86	10.38 / 10.40	237-240	90
3f	$C_{30}H_{26}N_4O_4S_2$	63.07 / 63.14	4.64 / 4.59	9.77 / 9.82	254-256 / 252-253 [2]	80
3g	$C_{32}H_{32}N_6O_2S_2$	64.35 / 64.40	5.36 / 5.40	14.12 / 14.08	239-240 / 241-243 [2]	75

In the ^{1}H NMR spectra of solutions in DMSO-d_6 of all the synthesized compounds there were signals corresponding both to the linear **A** and to the cyclic benzo-1,3,4-thiadiazepine **B** tautomeric forms. The signals of the linear tautomer were doubled in the spectra.

The observed doubling of the signals of the linear form **A** in the ^{1}H NMR spectra of compounds **2a-g** must be linked with the presence of conformational (*E',Z'*)-isomers, differing in the disposition of substituents relative to the amide C–N bond. An (*E,Z'*)-structure must therefore be attributed to the main isomer and an

(*E,E′*)-structural disposition to the minor isomer. The existence of an (*E,Z*)-configuration of isomer relative to the C=N bond was not considered by us since aldoacylhydrazones exist exist primarily or completely in the (*E*)-configuration relative to this bond [3-5].

Assignment of the signals of the (*E,E′*)- and (*E,Z′*)-isomers of the linear form **A** was based on the known difference in position of the signals of the azomethine protons of the conformational (*E′,Z′*)-isomers in the ^{1}H NMR spectra. The signals of the (*E′*)-isomer of this group are disposed at lower field than the analogous signals of the (*Z′*)-isomer (Table 2). An opposite value of both signals in the ^{1}H NMR spectra is observed for the protons of the NHCO groups of the (*E′,Z′*)-conformers [6]. Taking into consideration the above-indicated it may be confirmed that the main isomer has the (*E,Z′*)-structure, and the minor isomer the (*E,E′*)-spatial disposition.

The existence of the cyclic form **B** in DMSO-d_6 solution may be judged by the doublet signals of the H-2 and NHCO protons at 5.8 and 9.6 ppm respectively and also by the doublet-doublet signals of the NH group proton at 6.2 ppm, which is caused by a spin-spin interaction with the protons in positions 2 and 4 of the seven-membered benzo-1,3,4-thiadiazepine heterocycle.

The introduction of an electron-withdrawing substituent into the aromatic ring of the aldehyde component leads to a displacement of the ring-chain equilibrium **A↔B** to the side of the cyclic benzo-1,3,4-thiadiazepine form (Table 2), and a linear correlation is then observed between the logarithms of the tautomeric equilibrium constants K_T and the Hammett σ-constant [7, 8]. The use of the σ^+-constant of Brown [8] improves the correlation (Table 3).

TABLE 2. ^{1}H NMR Spectra of Compounds **2a-g**

Compound	Tautomeric composition, %	Chemical shifts, δ, ppm (*J*, Hz)		K_T = [**B**]/[**A**]*
		HC=N, s or H-2, d	NH	
2a	(*E,E'*)-**A** (6)	8.38	12.30 (br. s)	0.754
	(*E,Z'*)-**A** (51)	8.45	12.18 (br. s)	
	B (43)	5.92 (*J* = 6.2)	6.41 (dd, *J* = 6.2, *J* = 2.5), 9.70 (d, *J* = 2.5)	
2b	(*E,E'*)-**A** (6)	8.31	12.27 (br. s)	0.695
	(*E,Z'*)-**A** (53)	8.48	12.17 (br. s)	
	B (41)	5.95 (*J* = 6.6)	6.43 (dd, *J* = 6.6, *J* = 2.7), 9.71 (d, *J* = 2.7)	
2c	(*E,E'*)-**A** (9)	8.10	12.08 (br. s)	0.587
	(*E,Z'*)-**A** (54)	8.33	11.95 (br. s)	
	B (37)	5.74 (*J* = 6.8)	6.26 (dd, *J* = 6.8, *J* = 3.0), 9.62 (d, *J* = 3.0)	
2d	(*E,E'*)-**A** (10)	8.13	12.02 (br. s)	0.408
	(*E,Z'*)-**A** (61)	8.36	11.88 (br. s)	
	B (29)	5.73 (*J* = 6.6)	6.21 (dd, *J* = 6.6, *J* = 2.7), 9.61 (d, *J* = 2.7)	
2e	(*E,E'*)-**A** (10)	8.09	11.95 (br. s)	0.370
	(*E,Z'*)-**A** (63)	8.10	11.81 (br. s)	
	B (27)	5.68 (*J* = 6.8)	6.16 (dd, *J* = 6.8, *J* = 2.9), 9.59 (d, *J* = 2.9)	
2f	(*E,E'*)-**A** (11)	8.06	11.88 (br. s)	0.205
	(*E,Z'*)-**A** (72)	8.29	11.75 (br. s)	
	B (17)	5.67 (*J* = 7.0)	6.14 (dd, *J* = 7.0, *J* = 2.7), 9.57 (d, *J* = 2.7)	
2g	(*E,E'*)-**A** (13)	7.98	11.58 (br. s)	0.075
	(*E,Z'*)-**A** (80)	8.20	11.71 (br. s)	
	B (7)	5.61 (*J* = 7.0)	6.05 (dd, *J* = 7.0, *J* = 3.9), 9.55 (d, *J* = 3.9)	

* [**A**] is the total content of forms (*E,E′*)-**A** and (*E,Z′*)-**A**.

TABLE 3. Correlation of the Logarithms of the Tautomeric Equilibrium Constants K_T with Constants of Hammett σ and Brown σ^+ According to the Equation: $\log K_T = A + B \cdot X$

X	*A*	*B*	*r*	s_D	*n*
σ	-0.520 ± 0.043	0.614 ± 0.081	0.959	0.112	7
σ^+	-0.406 ± 0.028	0.423 ± 0.034	0.987	0.064	6

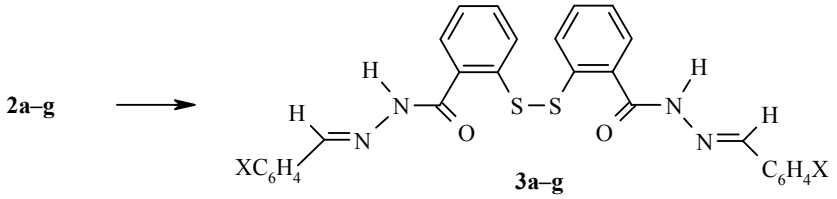
TABLE 4. ^{1}H NMR Spectra of Compounds **3a-g**

Com-pound	Chemical shifts, δ, ppm		
	HC=N (s)	NH (2H, br. s)	Ar (m)
3a	8.50	12.37	7.26-8.50 (16H)
3b	8.52	12.34	7.26-8.28 (16H)
3c	8.38	12.14	7.24-7.76 (16H)
3d	8.41	12.07	7.32-.75 (18H)
3e	8.36	12.00	2.28 (6H, s, $2CH_3$); 7.13-7.74 (16H)
3f	8.34	11.93	3.81 (6H, s, $2CH_3O$); 7.02-7.71 (16H)
3g	8.25	11.77	3.04 (6H, s, $2CH_3N$); 6.75-7.72 (16H)

The same regularity is explained by the fact that the electron-withdrawing substituents strengthen the electrophilicity of the oxygen atom towards the C=N bond, addition of the SH function to which leads to the formation of benzo-1,3,4-thiadiazepine tautomer **B**. The conformational equilibria within the linear tautomer are sensitive to a lesser extent to the nature of the substituent in the aromatic ring. Probably in both linear forms (*E,E'*)-**A** and (*E,Z'*)-**A** identical systems of conjugation occur, reacting in the same way to the change of electronic parameters of the substituent.

Compounds **2a-g** are inclined to oxidize with the formation of dimeric products **3a-g** having linear bis-hydrazone structures. This process, judging by a survey of the ^{1}H NMR spectra with time, begins 3-5 h after dissolving compounds **2a-g** in DMSO-d_6 and is complete after several days with the quantitative formation of dimers **3a-g**.

Compounds **3a-g** may also be obtained in high yield on treating methanolic solutions of 2-mercapto-benzoylhydrazones **2a-g** with 5% H_2O_2 solution (EXPERIMENTAL). One set of resonance signals was observed in the ^{1}H NMR spectra of compounds **3a-g** belonging to the conformational (*E,Z'*)-isomer relative to the amide C–N bond (Table 4).



3a–g

3 a X = 4-NO_2, **b** X = 3-NO_2, **c** X = 4-Br, **d** X = H, **e** X = 4-Me, **f** X = 4-MeO, **g** X = 4-Me_2N

Unlike the condensation products of aromatic aldehydes with hydrazides of 2-hydroxy- and 2-amino-benzoic acid known in the literature [9, 10], 2-mercaptobenzoylhydrazones display an inclination towards cyclization with the formation of a seven-membered benzo-1,3,4-thiadiazepine ring. This is a natural reflection

of the significantly larger nucleophilicity of the sulfur atom in comparison with oxygen and nitrogen atoms of OH and NH functions in hydrazones obtained on using hydrazides of 2-hydroxy- and 2-aminobenzoic acids. In this respect 2-mercaptobenzoylhydrazones **2a-g** are close to the condensation products of aromatic aldehydes with hydrazides of thiobenzoic and thioglycolic acids investigated by us previously, for which intramolecular attack by the sulfur atom at the C=N bond of the hydrazone fragment leads to the formation of 1,3,4-thiadiazoline [11] and 1,3,4-thiadiazine [12] rings respectively.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker AV 400 (400 MHz) spectrometer in DMSO-d_6, internal standard was HMDS. The quantitative content of the tautomeric forms was determined by integrating the appropriate signals in the ^{1}H NMR spectra, error of measurement was ± 1%. A check on the progress of reactions and the purity of the obtained compounds was effected by TLC on Silufol UV-254 plates in the system benzene–acetone, 4:1.

The hydrazide of 2-mercaptobenzoic acid **1** was obtained by the known procedure of [2].

2-Mercaptobenzoylhydrazones of Aromatic Aldehydes 2a-g. A mixture of carbonyl compound (10 mmol) and 2-mercaptobenzoic acid hydrazide **1** (1.68 g, 10 mmol) in methanol (50 ml) was maintained at 25°C for 2 h. The precipitated crystals were filtered off, washed with ether, and dried.

2,2'-Dithiobenzoylhydrazones of Aromatic Aldehydes 3a-g. A 5% solution of H_2O_2 (0.5 ml) was added to a solution of compound **2a-g** (5 mmol) in methanol (5 ml) and the mixture maintained at 25°C for 2 h. The precipitated crystals were filtered off, washed with ether, and dried.

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