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THIOSALICYLOYLHYDRAZONES OF ALIPHATIC ALDEHYDES AND THEIR CYCLIZATION TO GIVE 1,3,4-BENZO-THIADIAZEPINE DERIVATIVES

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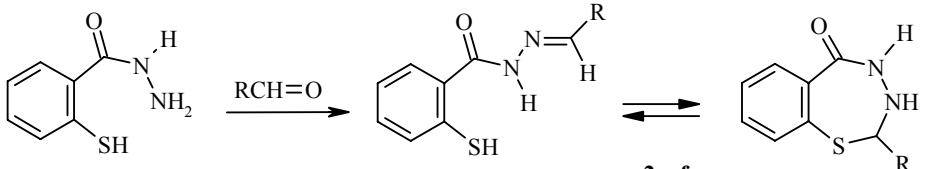
^{1}H and ^{13}C NMR spectroscopy showed that the previously unknown thiosalicyloylhydrazones of aliphatic aldehydes, 2-$HSC_6H_4CONHN=CHAlk$ (Alk = Me, Et, Pr, Bu, i-Pr, i-Bu) exist in solution as a tautomeric mixture of the linear and cyclic 1,3,4-benzothiadiazepine forms.

Keywords: 1,3,4-benzothiadiazepines, thiosalicyloylhydrazones, ring-chain tautomerism.

The tendency of functionally-substituted hydrazones to undergo intramolecular cyclization at the polar C=N bond of the hydrazone fragment is commonly used in the synthesis of five- and six-membered heterocycles [1, 2]. This reaction is sometimes reversible, which leads to the coexistence of the hydrazone and cyclic forms as their tautomeric mixture in solution [3, 4]. Thus, the thiosalicyloylhydrazone of acetone obtained in our laboratory transforms in solution to the alternative 1,3,4-benzothiadiazepine form [5]. We note that the hydrazones obtained using the hydrazides of salicylic and anthranilic acids have linear structure. The possible cyclization at the C=N bond by attack of the available OH or NH functions does not occur [6, 7].



1 *E,Z*-**A** **B**

2 a R = Me, **b** R = Et, **c** R = Pr, **d** R = Bu, **e** R = *i*-Pr, **f** R = *i*-Bu

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Table 1. Physicochemical Characteristics of **2a-f**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_9H_{10}N_2OS$	55.59 / 55.65	5.24 / 5.19	14.48 / 14.42	148-149	45
2b	$C_{10}H_{12}N_2OS$	57.71 / 57.67	5.76 / 5.81	13.39 / 13.45	113-115	70
2c	$C_{11}H_{14}N_2OS$	59.47 / 59.43	6.40 / 6.35	12.65 / 12.60	73-75	65
2d	$C_{12}H_{16}N_2OS$	60.92 / 60.99	6.88 / 6.82	11.78 / 11.85	89-92	70
2e	$C_{11}H_{14}N_2OS$	59.36 / 59.43	6.31 / 6.35	12.57 / 12.60	83-85	55
2f	$C_{12}H_{16}N_2OS$	61.03 / 60.99	6.77 / 6.82	11.90 / 11.85	136-138	65

In the present work, we studied the structure of the thiosalicyloylhydrazones of a series of aliphatic aldehydes **2a-f** and their tendency to undergo reversible intramolecular cyclization, leading to the formation of a seven-membered 1,3,4-thiadiazepine ring.

Hydrazones **2a-f** were obtained in 45-70% yield after brief maintenance of equimolar amounts of the hydrazide of thiosalicylic acid **1** and the corresponding aldehyde in aqueous ethanol at 25°C (see Table 1 and Experimental).

TABLE 2. Tautomeric Composition and ^{1}H NMR Spectra of Compounds **2a-f**

Compound	Form	Composition, %	^{1}H NMR spectrum, δ, ppm (*J*, Hz)*
2a	*E*,*Z*'-**A**	2	1.95 (d, *J* = 4.4, CH_3); 11.62 (br. s, NH)
	B	98	1.12 (d, *J* = 6.2, CH_3); 4.70 (q, *J* = 6.4, H-2); 5.79 (br. s, NH); 7.44-7.61 (m, Ar); 9.48 (d, *J* = 4.2, NH)
2b	*E*,*Z*'-**A**	4	1.37 (t, *J* = 7.6, CH_3); 2.17 (m, CH_2); 7.47 (t, *J* = 2.8, HC=N); 11.60 (br. s, NH)
	B	96	0.87 (t, *J* = 7.4, CH_3); 1.66 (m, CH_2); 4.45 (t, *J* = 6.2, H-2); 5.75 (br. s, NH); 7.43–7.61 (m, Ar); 9.44 (br. s, NH)
2c	*E*,*Z*'-**A**	5	0.97 (t, *J* = 7.5, CH_3); 1.72 (m, $2CH_2$); 7.45 (t, *J* = 3.0, HC=N); 11.59 (br. s, NH)
	B	95	0.90 (t, *J* = 7.2, CH_3); 1.37 (m, CH_2); 1.72 (m, CH_2); 4.54 (t, *J* = 6.4, H-2); 5.73 (br. s, NH); 7.43–7.61 (m, Ar); 9.41 (br. s, NH)
2d	*E*,*Z*'-**A**	7	0.94 (t, *J* = 7.4, CH_3); 1.53 (m, $2CH_2$); 7.48 (t, *J* = 3.0, HC=N); 11.63 (br. s, NH)
	B	93	0.89 (t, *J* = 7.1, CH_3); 1.44 (m, $2CH_2$); 1.73 (m, CH_2); 4.52 (t, *J* = 6.3, H-2); 5.75 (br. s, NH); 7.39-7.64 (m, Ar); 9.41 (br. s, NH)
2e	*E*,*Z*'-**A**	10	1.13 (d, *J* = 6.8, $2CH_3$); 2.56 (m, CH); 7.53 (d, *J* = 3.0, HC=N); 11.56 (br. s, NH)
	B	90	0.96 (d, *J* = 6.4, CH_3); 1.01 (d, *J* = 6.6, CH_3); 1.96 (m, CH); 4.32 (d, *J* = 7.4, H-2); 5.70 (br. s, NH); 7.40–7.65 (m, Ar); 9.42 (br. s, NH)
2f	*E*,*Z*'-**A**	11	0.94 (d, *J* = 6.7, $2CH_3$); 2.18 (m, CH); 7.62 (t, *J* = 2.8, HC=N); 11.61 (br. s, NH)
	B	89	0.87 (d, *J* = 6.5, CH_3); 0.89 (d, *J* = 6.7, CH_3); 1.37 (m, CH_2); 1.79 (m, CH); 4.62 (d, *J* = 6.4, H-2); 5.73 (br. s, NH); 7.43-7.62 (m, Ar); 9.43 (br. s, NH)

The spectra were recorded 48 h after dissolution.

Examination of the ^{1}H NMR spectra over time showed that **2a-f** exist in the cyclic thiadiazepine form in the crystalline state. The ^{1}H NMR spectra of **2a-f** taken immediately after dissolution in DMSO-d_6 show a single set of resonance signals corresponding to this form. This conclusion is indicated by finding two NH proton signals at 5.70 and 9.45 ppm and a signal with corresponding multiplicity at 4.50 ppm (H-2) (Table 2). In the ^{13}C NMR spectra yhe signal for the sp^3-hybridized carbon atom at 75 ppm (C-2) and the signal at 173 ppm (C-5) correspond to thiadiazepine to form **B** (Table 3).

Signals corresponding to the linear thiosalicyloylhydrazone form **A** appear in the ^{1}H NMR spectra 48 h after dissolution of **2a-f** in DMSO-d_6. The downfield signals of the azomethine and NH group protons at 7.50 and 11.60 ppm, respectively, are typical indications of this form, whose content for the compounds studied does not exceed 10% (Table 2). The spectra of **2a-f** do not undergo any subsequent change, which indicates establishment of a ring-chain equilibrium in solution.

The position of the equilibrium depends on the length and branching of the alkyl substituent. The fraction of linear form **A** is higher for **2e** and **2f**, which contain bulky isopropyl and isobutyl groups. On the other hand, no clear correlation was found between the position of the tautomeric equilibrium and the steric constants of the alkyl substituents. Going from polar, strongly basic, aprotic solvents such as DMSO-d_6 and DMF-d_7 to weakly polar $CDCl_3$ significantly stabilizes the cyclic thiadiazepine form **B**, which becomes the only form in this solvent for all compounds **2a-f**.

Four structures differing in the position of the substituents relative to the C=N bond (geometrical *Z,E*-isomerism) and amide C–N bond (conformational *Z*',*E*'-isomerism) are possible for acylhydrazones of carbonyl compounds [8, 9]. Aldehyde derivatives exist predominantly or entirely in the *E*-configuration relative to the C=N bond. Thus, the signals found for linear form **A** in the ^{1}H NMR spectra of the aldo derivatives of thiosalicylic acid hydrazide **2a-f** should be assigned to one of the *E*' or *Z*' conformers of this geometric isomer.

Our determination of the actual structure of linear form **A** (the *E,E*'- or *E,Z*'-isomer) was based on the reported difference in the position of the chemical shifts of the C=N and C=O bond carbon atoms in the ^{13}C NMR spectra. The signals of the *E*'-isomer of these groups are found at 145 and 170 ppm, while these signals are at 150 and 160 ppm for the *Z*'-isomer [10, 11]. Thus, the chemical shifts given in Table 3 for the C=N and C=O bond carbon atoms of form **A** in **2e** and **2f** correspond to the *E,Z*'-arrangement of the thiosalicyloylhydrazone fragment.

Therefore, in contrast to the products of the condensation of aldehydes with the hydrazides of salicylic and anthranilic acids reported in the literature [6, 7], thiosalicyloylhydrazones of aliphatic aldehydes display a tendency to cyclize to give the seven-membered 1,3,4-benzothiadiazepine ring. This naturally reflects the greater nucleophilicity of the sulfur atom of the SH function, which participates in intramolecular cyclization, in comparison with the nucleophilicity of the oxygen and nitrogen atoms in the OH and NH functions in the hydrazones obtained using salicylic and anthranilic acid hydrazides. In this regard, thiosalicyloylhydrazones are

TABLE 3. ^{13}C NMR Spectra of Compounds **2a-f**

Com-pound	Form	Chemical shifts, δ, ppm*		
		C-2 or C=N	C-5 or C=O	R
2a	**B**	68.1	173.2	20.4 (CH_3)
2b	**B**	74.6	173.2	11.1 (CH_3); 27.0 (CH_2)
2c	**B**	72.6	173.2	13.7 (CH_3); 19.3 (CH_2); 35.9 (CH_2)
2d	**B**	72.9	173.2	13.9 (CH_3); 21.9 (CH_2); 28.3 (CH_2); 33.5 (CH_2)
2e	*E,Z*'-**A**	150.1	159.2	19.6 ($2CH_3$); 33.9 (CH)
	B	79.9	173.0	19.1 (CH_3); 20.3 (CH_3); 32.5 (CH)
2f	*E,Z*'-**A**	152.3	161.8	22.1 ($2CH_3$); 31.8 (CH); 48.1 (CH_2)
	B	71.1	173.2	22.1 (CH_3); 22.6 (CH_3); 24.9 (CH); 42.3 (CH_2)

* Signals for at C_{arom} are found at 128.0-149.5 ppm.

similar to the products of the condensation of carbonyl compounds with thiobenzoic and thioglycolic acid hydrazides, for which intramolecular attack by the sulfur atom at the C=N bond of the hydrazone fragment leads to formation of 1,3,4-thiadiazoline [12] and 1,3,4-thiadiazine rings [11, 13], respectively.

The determination of the conformational state of the seven-membered 1,3,4-benzothiadiazepine ring requires further study.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were taken on a Bruker AV-400 spectrometer at 400 and 100 MHz, respectively, in DMSO-d_6 with HMDS as the internal standard (δ 0.05 ppm). The quantitative composition of the tautomeric forms was determined by integration of the corresponding signals in the ^{1}H NMR spectra. The error in this determination was ±1%. The reaction course and product purity were monitored by thin-layer chromatography on Silufol UV-254 plates with 4:1 benzene-acetone as the eluent. Thiosalicylic acid hydrazide was obtained according to Katz [14].

2-Alkyl-1,2,3,4-tetrahydro-5H-1,3,4-benzothiadiazepine-5-ones 2a-f. A mixture of thiosalicylic acid hydrazide (1.68 g, 10 mmol) and aldehyde (15 mmol) in methanol (30 ml) and water (15 ml) was maintained at 25°C for 2 h. The crystalline precipitate was filtered off, washed with ether, and dried.

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