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TAUTOMERIC AND CONFORMATIONAL ISOMERISM OF MERCAPTOACETYL-HYDRAZONES OF METHYL ALKYL KETONES

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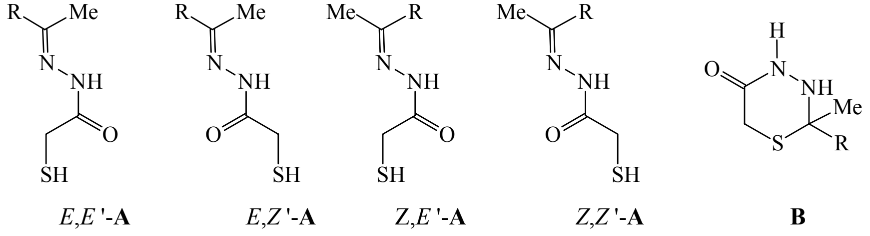
Mercaptoacetylhydrazones of methyl alkyl ketones (Alk = Me, Et, Pr, i-Pr, i-Bu, s-Bu, t-Bu) exist in solutions as a tautomeric mixture of linear and cyclic 1,3,4-thiadiazine forms.The linear hydrazone form exists as a set of conformers caused by restricted rotation of the amide group relative to the C–N bond. It is shown that tautomeric equilibrium constants correlate with the steric constants of the alkyl substituents, E_S.

Keywords: mercaptoacetylhydrazones, 1,3,4-thiadiazin-5(4H)-ones, ring-chain tautomerism, the Taft equation.

The results of studies of frequently encountered ring-chain tautomeric conversions, linked with intramolecular reversible addition of the nucleophilic groups OH, NH, and SH to the C=N group are reflected in the monographs [1, 2]. It is known that the hydrazones of lactic and α-aminopropionic acids have linear structures [3, 4], whereas the mercaptoacetylhydrazone of acetone, which we prepared recently, is inclined to ring-chain tautomerism in solutions with participation of the 1,3,4-thiadiazin-5-one ring [5].

The objective of the present work was to study the tendency to tautomeric conversion of the mercaptoacetylhydrazones **1a-g** derived from methyl alkyl ketones, and also the effect of steric parameters of alkyl substituents on the position of tautomeric equilibrium.



1a–g

1 **a** R = Me, **b** R = Et, **c** R = Pr, **d** R = *i*-Pr, **e** R = *i*-Bu, **f** R = *s*-Bu, **g** R = *t*-Bu

Compounds **1a-g** were obtained in 50-75% yield by the brief expsure of equimolar quantities of the hydrazide of thioglycolic acid and the corresponding methyl alkyl ketone in water or aqueous alcoholic solution at room temperature (see Table 1 and Experimental).

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TABLE 1. Physicochemical Characteristics of Compounds **1b-g**

Compound	Empirical formula	Found, % Calculated, %			mp, °C	Yield, %
		C	H	N		
1b	$C_6H_{12}N_2OS$	45.04 44.97	7.49 7.55	17.53 17.48	Oil	65
1c	$C_7H_{14}N_2OS$	48.31 48.25	8.06 8.10	16.14 16.08	Oil	60
1d	$C_7H_{14}N_2OS$	48.20 48.25	8.14 8.10	16.11 16.08	108-110	75
1e	$C_8H_{16}N_2OS$	50.97 51.03	8.50 8.56	14.94 14.88	92-95	70
1f	$C_8H_{16}N_2OS$	51.08 51.03	8.61 8.56	14.95 14.88	83-85	75
1g	$C_8H_{16}N_2OS$	50.96 51.03	8.63 8.56	14.82 14.88	94-96	50

It was shown previously [5] that in solution in pyridine-d_5 compound **1a** , along with ring-chain tautomerism of the type **A** $\rightleftarrows$ **B**, shows a doubling of signals for the hydrazone form **A** in its ^1H NMR spectrum, caused by restricted amide rotation of the mercaptoacetyl group relative to the C–N bond and the existence of the forms *E,E'*-**A** and *E,Z'*-**A**. In the case of compounds **1b-g** it is to be expected that there is the possibility of spatial *Z,E*-isomers of the mercaptoacetylhydrazone unit relative to the C=N bond and consequently the appearance of four possible linear forms in solution: *E,E'*-**A**, *E,Z'*-**A**, *Z,E'*-**A**, and *Z,Z'*-**A.**

Assignment of the signals to the geometric isomers *Z,E'*-**A** and *Z,Z'*-**A** can be carried out on the basis of the appearance for the hydrazones of the deshielding effect of the hydrazone unit on the methylene or methyl protons in the *cis*-positions in the ^1H NMR spectrum [6]. As a result these signals should appear at weaker field than the analogous signals for the isomeric forms *E,E'*-**A** and *E,Z'*-**A**. It should be noted that we did not observe any signals in the ^1H NMR spectra of compounds **1b-g** which could be assigned to the configurational isomers *Z,E'*-**A**, and *Z,Z'*-**A**, arising from spatial isomerization.

Compounds **1a-g** have a considerable tendency to chain-ring tautomerism in solution and the introduction of alkyl substituents favors the linear form **A**. The logarithms of the tautomeric equilibrium constants for **1a-g** show a linear correlation with the steric constants E_S according to the equation:

$$\lg K_T = -0.16 + 0.67 \cdot E_S ,$$

where the correlation coefficient $r = 0.993$.

A similar dependence is characteristic for chain-ring equilbria where the cyclic isomer arises as a result of reversible addition to the double bond carrying the bulky alkyl substituent [7, 8] (see Fig. 1). Conformational equilibria are less sensitive to a change in volume of the substituent at the C=N bond and are strongly shifted to the form *E,E'*-**A** in which steric interactions are considerably less than for the alternative form *E,Z'*-**A**.

Assignments of signals in the ^1H NMR spectrum to a particular conformational isomer of the linear forms **A** does not present a difficulty if established criteria and rules presented earlier in monographs [9, 10] are followed, together with recent work [11] on the steric structure of cyanacetylhydrazones of carbonyl compounds which are close structural analogs of the **A** forms of compounds **1a-g**. We note that one of the typical signs of forms *E,E'*-**A** in the ^1H NMR spectrum is the presence of spin-spin interaction of the protons of the methylene groups of the mercaptoacetyl group and the proton of the SH group ($J = 7.0$ Hz, Table 2) as a result of which the signals of these groups appear as a doublet and a triplet respectively. Indications of the cyclic form **B** in solution are the strong field shift of the signals of the protons of the methyl group, diasterotopy of the protons at position 6 (which in separate cases form a typical AB system with $J = 14$ Hz), and also the signal of the sp^3-hybridized $C_{(2)}$ at 70.0 ppm in the ^{13}C NMR spectra (Table 3).

TABLE 2. Tautomeric Composition, ^{1}H NMR Spectra, and Tautomeric Equilibrium Constants for Compounds **1a-g** in Pyridine-d_5

Compound	Tautomeric composition (%)	^{1}H NMR spectra, δ, ppm (*J*, Hz)*^{2}				$K_T = \frac{[\mathbf{B}]}{[\mathbf{A}]^{*2}}$
		=CMe (**A**) or $C_{(2)}$Me (**B**), s or two s	SSH_2 (**A**) or $C_{(6)}H_2$ (**B**)	SH	H, br. s or two br. s	
1a	*E,E'*-**A** (44)	1.90; 1.92	3.84, s	2.92, s	10.83	0.69
	E,Z'-**A** (15)	1.92; 1.97	3.61, s	2.50, s	10.95	
	B (41)	1.68	3.70, s	—	6.55; 10.36	
1b	*E,E'*-**A** (54)	1.90	3.85, s	2.92, s	10.85	0.56
	E,Z'-**A** (10)	1.96	3.57, s	2.49, s	10.95	
	B *(36)*	1.61	3.60; 3.69 (dd, *J* = 14.0)	—	6.42; 10.29	
1c	*E,E'*-**A** (57)	1.93	3.84, s	2.88, s	10.80	0.49
	E,Z'-**A** (10)	1.94	3.56, s	2.48, s	10.87	
	B *(33)*	1.64	3.59; 3.70 (dd, *J* = 14.0)	—	6.34; 10.20	
1d	*E,E'*-**A** (68)	1.90	3.84 (d, *J* = 7.0)	2.95 (t, *J* = 7.0)	10.93	0.33
	E,Z'-**A** (7)	1.92	3.58, s	2.58, s	10.97	
	B *(25)*	1.55	3.54; 3.71 (dd, *J* = 14.0)	—	6.42; 10.37	
1e	*E,E'*-**A** (77)	1.93	3.86 (d, *J* = 7.0)	2.93 (t, *J* = 7.0)	10.91	0.19
	E,Z'-**A** (7)	1.96	3.58, s	2.49, s	10.95	
	B *(16)*	1.69	3.48; 3.67 (dd, *J* = 14.0)	—	6.35; 10.32	
1f	*E,E'*-**A** (83)	1.90	3.85 (d, *J* = 7.0)	2.89 (t, *J* = 7.0)	10.86	0.12
	E,Z'-**A** (6)	1.92	3.57, s	2.47, s	10.94	
	B *(11)*	1.58	3.46; 3.75 (dd, *J* = 14.0)	—	6.32; 10.25	
1g	*E,E'*-**A** (88)	1.91	3.83 (d, *J* = 7.0)	2.87 (t, *J* = 7.0)	10.80	0.06
	E,Z'-**A** (6)	1.97	3.58, s	2.48, s	10.88	
	B *(6)*	1.66	3.41; 3.73 (dd, *J* = 14.0)	—	6.13; 10.15	

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* ^{1}H NMR spectra were recorded 72 h after dissolution of compound **1**; signals of the protons of the substituents R are not cited.

*^{2} [**A**] is the sum of the content of forms *E,E'*-**A** and *E,Z'*-**A**.

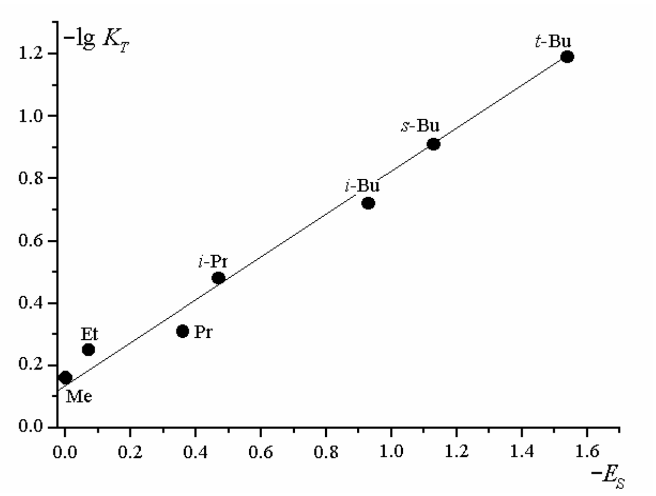

Fig. 1. Correlation of the logarithm of the tautomeric equilibrium constant with the steric constants E_S of the alkyl substituents.

TABLE 3. ^{13}C NMR Spectra of Compounds **1a** and **1e**

Compound	Solvent	Form	Chemical shifts, δ, ppm			
			MeC= / MeC$_{(2)}$	C=N / C$_{(2)}$	C=O / C$_{(5)}$	CH$_2$ / C$_{(6)}$
1a	DMSO-d$_6$	*E*,*E*'-**A**	18.2	152.2	167.2	25.5
		E,*Z*'-**A**	17.8	157.2	172.4	26.8
		B	30.5	69.1	173.9	29.4
1e	DMF-d$_7$	*E*,*E*'-**A**	16.1	153.5	166.8	26.4
		E,*Z*'-**A**	16.2	158.3	172.2	26.9
		B	29.4	73.2	173.5	27.5

Determination of the conformational state of the six-membered thiadiazine forms requires further work.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded with Bruker AC 200 and Bruker AM 500 instruments (200 and 125 MHz respectively). The quantitaive ratios of the tautomeric forms were determined from the intensities of the signals of the methyl groups in the ^{1}H NMR spectra. The measurement error was ±1%. The course of reactions and the purity of the compounds synthesized were monitore by TLC on Silufol UV-254 strips with 2:1 benzene–acetone as eluent. Compound **1a** was described previously [5].

2-Alkyl-2-methyl-2,3,56-tetrahydro-1,3,4-thiadiazin-5(4H)-ones (1b-g) (general method). A mixture of a carbonyl compound (0.015 mol) and the hydrazide of thioglycolic acid (1.06 g, 0.01 mol) in water (25 ml) (for compounds **1d-g** in 4:1 water ethanol (30 ml) was kept at 25°C for 2 h. The crystals of product **1** which formed were filtered off , dried, and recrystallized from hexane.

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