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RING—CHAIN TAUTOMERISM OF 3-ALKYLTHIO-1,5-DIHYDRO-1,2,4-TRIAZOLIUM SALTS

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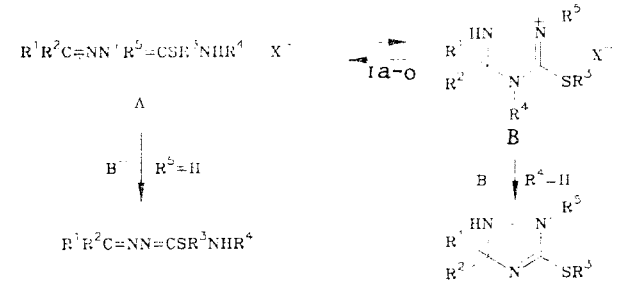
Ring—chain tautomerism in S-alkylisothiosemicarbazonium salts was detected for the first time by PMR and ^{13}C NMR spectroscopy. It was shown that substitution at the nitrogen atoms stabilizes the cyclic 1,5-dihydro-1,2,4-triazolium form. The data from the mass spectra are given.

The ability to undergo ring—chain tautomerism with the formation of 1,2,4-triazole derivatives with specific structural parameters of the same type is a characteristic feature of 1-alkylidene(arylidene)amidrazonium [1-3] and 1-alkylidene(arylidene)aminoguanidinium salts [4] and also thiosemicarbazone S,S,S-trioxides [5]. There are no data in this respect on their analogs, the isothiosemicarbazonium salts, which are easily synthesized by the alkylation of thiosemicarbazones. Only data on the stereoisomerism of their free bases, i.e., isothiosemicarbazones, have been described [6].

In the present work we examine the structure of S-alkylisothiosemicarbazonium salts (Ia-o) in DMSO-d_6 solution by PMR and ^{13}C NMR spectroscopy (Table 1). The previously obtained criteria for choosing between the linear and ring tautomers A and B were used [1-4].



IIc,e,j III h,i

Ia—e,h,j—o X=I; f,i,k X=Br; g X=Cl; a $R^1=R^4=R^5=H$, $R^2=R^3=CH_3$; b $R^1=H$, $R^2=R^3=R^4=R^5=CH_3$; c $R^1=R^4=R^5=H$, $R^2=C_6H_5$, $R^3=CH_3$; d $R^1=H$, $R^2=4\text{-}OCH_3C_6H_4$, $R^3=R^4=R^5=CH_3$; e $R^1=R^2=R^3=CH_3$, $R^4=R^5=H$; f $R^1=R^2=CH_3$, $R^3=C_2H_5$, $R^4=R^5=H$; g $R^1=R^2=CH_3$, $R^3=CH_2C_6H_5$, $R^4=R^5=H$; h $R^1=R^2=R^3=R^5=CH_3$, $R^4=H$; i $R^1=R^2=R^5=CH_3$, $R^3=C_2H_5$, $R^4=H$; j $R^1=R^2=R^3=R^4=CH_3$, $R^5=H$; k $R^1=R^2=R^4=CH_3$, $R^3=C_2H_5$, $R^5=H$; l $R^1=R^2=R^3=CH_3$, $R^4=C_2H_5$, $R^5=H$; m $R^1=R^2=R^3=CH_3$, $R^4=CH_2C_6H_5$, $R^5=H$; n $R^1=R^2=CH_3$, $R^3=R^4=CH_2C_6H_5$, $R^5=H$; o $R^1=R^2=R^3=R^4=R^5=CH_3$; IIc $R^1=R^4=H$, $R^2=C_6H_5$, $R^3=CH_3$; e, $R^1=R^2=R^3=CH_3$, $R^4=H$; j $R^1=R^2=R^3=R^4=CH_3$; IIIh $R^1=R^2=R^3=R^5=CH_3$; i $R^1=R^2=R^5=CH_3$, $R^3=C_2H_5$

It was found that even such a well known compound as S-methylacetoneisothiosemicarbazonium iodide (Ie) is represented by the ring tautomer to the extent of 3%, as follows from the data from both the PMR (Table 1) and the ^{13}C NMR (see the Experimental section) spectra. Variation in the structure of the salts not having substituents at the nitrogen atoms, i.e., change of the substituents R^3 in the acetone derivatives [the salts (If, g)] and the transition to derivatives of acetaldehyde and benzaldehyde [the salts (Ia, c)], gives rise to stabilization of the linear form. It is interesting to note that the salt (Ig) is a mixture of stereoisomers with respect to the $C{=}N_{(2)}$ bond, as observed earlier for certain isothiosemicarbazones [6]. We did not make structural assignments of these isomers, like determination of the structure of other linear salts, represented by one geometric isomer.

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TABLE 1. Characteristics of the S-Alkylisothiosemicarbazonium Salts (Ia-o)

Compound	mp, °C	Form	Content, %	PMR spectrum in DMSO-d_6, δ, ppm (SSCC, Hz)					
				R^1	R^2	R^3	R^4	R^5	NH
Ia	145...147	A	100	2,03 d (J=5,0)	7,80 q (J=5,0)	2,72 s	9,40 s	13,5 bs	9,40 s
Ib	85...87	B	100	1,32 d (J=6,0)	5,20 q (J=6,0)	2,68 s	3,13 s	3,33 s	—*
Ic	137...139 [6]	A	100	7,38...7,56 m, $H_{m-,p-}$; 7,86...8,04 m, H_{n-}	8,36 s	2,76 s	—	—	9,60 bs
Id	171...172	A	100	3,83 s 7,05 d (J=9,0); 7,98 d (J=9,0)	8,44 s	2,68 s	3,28 s	3,78 s	—
Ie	182...183 [6]	A	97	1,97 s	2,00 s	2,63 s	9,06 s	11,20 s	9,60 s
		B	3	1,46 s		2,50 s	—	—	—
If	158...159	A	100	2,05 s		1,25 s (J=7,0); 3,27 q (J=7,0)	9,30 s	—	9,30 s
Ig	193...195		60	2,04 s		4,66 s	9,38 s	—	9,80 s
		A	100			7,35...7,50 m			
			40	1,95 s	2,05 s	4,51 s	—	—	—
						7,35...7,50 m	—	3,33 s	—
Ih	178...179	A	10	1,97 s	2,10 s	2,74 s			
		B	90	1,44 s		2,74 s	6,81	3,19 s	10,20 s
Ii	85...86	B	100	1,50 s		1,35 t (J=7,0); 3,49 q (J=7,0)	5,33 ns	3,30 s	8,68 s
Ij	170...171	A	73	2,07 s		2,66 bs	3,06 bs	—	—
		B	27	1,55 s		2,52 s	2,85 s	—	—
Ik	Oil	A	60	2,17 s		1,32 t (J=7,0); 3,30...3,70 m	3,10 s	—	—
		B	40	1,57 s		1,35 t (J=7,0); 3,30...3,70 m	2,83 s	—	—
Il	152...153	A	85	2,05 s	2,09 s	2,64 s	1,16 t (J=7,0); 3,44 m	—	—
		B	15	1,52 s		2,54 s	1,12 t (J=7,0); 3,44 m	—	—
Im	119...120	A	83	2,07 s	2,20 s	2,65 s	4,63 s 7,35 s	—	—
		B	17	1,58 s		2,51 s	4,52 s 7,35 s	—	—
In	135...137	A	80	2,00 s	2,16 s	4,41 s	7,32 m	—	—
		B	20	1,54 s		4,54 s	7,32 m	—	—
Io	135...136	B	100	1,45 s		2,69 s	3,14 s	3,37 s	6,80 s

*A dash signifies that the signal was not detected.

TABLE 2. Characteristics of the Free Bases (II, III)

Compound	mp, °C	PMR spectrum in deuterochloroform, δ, ppm (SSCC, Hz)				
		R^1	R^2, c	R^3	$R^4(R^5)$, s, 3H	NH
IIc	79...80 [6]	7,20...7,32 (m 3H, H_{m-}, b); 7,48...7,70 (m 2H, H o)	8,33 (1H)	2,40 (s, 3H)		5,62 (s, 2H)
IIe	63...65 [6]	1,95 (s 3H)	1,98 (3H)	2,38 (s, 3H)	2,79	5,28 (s, 2H)
IIj	Oil	1,88 (s 3H)	1,94 (3H)	2,30 (s, 3H)		6,06 (bs, 1H)
IIIa	Oil	1,32 (s, 6H)		2,42 (s, 3H)	2,86	4,13 (s, 1H)
IIIb	Oil	1,30 (s, 6H)		1,26 (t, J=7,0, 3H); 2,98 (q, J=7,0, 2H)	2,84	3,76 (s, 1H)

TABLE 3. Mass Spectra of Compounds (I, II)

Compound	m/z (I_{rel}, %)
Ia	142 (25), 131 (52), [M−HI], 128 (46), 127 (38), 116 (28), 84 (26), 60 (39), 47 (32), 45 (26), 43 (100), 42 (90)
Ic	193 (85) [M−HI], 146 (26), 116 (37), 105 (33), 104 (100), 103 (44), 90 (26), 77 (88), 60 (34), 51 (33), 43 (23)
Id	237 (39) [M−CH_3I], 235 (67), 164 (32), 163 (31), 142 (95), 134 (35), 133 (30), 127 (100), 77 (28), 74 (65), 71 (40), 69 (33)
Ie	145 (56), [M−HI], 128 (61), 127 (35), 98 (39), 60 (32), 57 (20), 56 (100), 47 (26), 43 (42), 42 (62), 41 (20)
If	159 (23) [M−HBr], 82 (25), 80 (23), 62 (34), 60 (40), 58 (33), 57 (31), 56 (89), 47 (22), 43 (35), 42 (100), 41 (21)
Ig	221 (13) [M−HCl], 124 (16), 97 (16), 91 (100), 65 (20), 58 (19), 56 (46), 45 (25), 43 (16), 42 (43), 41 (16)
Ih	159 (3) [M−HI], 145 (11), 144 (100), 142 (17), 128 (57), 127 (37), 100 (38), 74 (10), 71 (39), 57 (15), 56 (31)
Ii	173 (7) [M−HBr], 158 (72), 98 (45), 97 (94), 82 (83), 81 (44), 80 (71), 56 (91), 46 (55), 45 (91), 43 (53), 42 (100)
Ij	159 (35) [M−HI], 128 (30), 112 (21), 88 (18), 74 (31), 57 (43), 56 (100), 47 (22), 45 (18), 42 (51), 41 (19)
Il	173 (36) [M−HI], 128 (36), 127 (22), 74 (27), 71 (21), 58 (25), 56 (100), 47 (22), 45 (26), 43 (21), 41 (22)
Im	235 (11) [M−HI], 142 (32), 131 (24), 127 (15), 106 (22), 92 (9), 91 (100), 74 (9), 65 (10), 58 (24), 56 (14)
In	187 (6), 127 (6), 92 (19), 91 (100), 90 (7), 89 (11), 65 (27), 63 (12), 51 (9), 42 (7), 41 (7)
Io	173 (41) [M−HI], 159 (46), 144 (62), 143 (79), 142 (73), 74 (92), 69 (78), 56 (55), 45 (100), 44 (66), 42 (98)
IIc	193 (54) [M], 105 (44), 104 (100), 103 (91), 77 (88), 76 (36), 60 (26), 51 (37), 48 (28), 47 (40), 42 (25)
IIe	145 (47) [M], 115 (19), 98 (31), 74 (18), 60 (25), 57 (18), 56 (100), 47 (27), 45 (22), 43 (37), 42 (65)

TABLE 4. Mass Spectra of Compounds (Ia, c-g, j, *l*-n, IIc, e)

Compound	Peak intensities of characteristic ions (%, Σ_{40})									
	[M−HHal]$^+$	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	CH_3I^+	$HHal^+$ (Hal)	$C_7H_7^+$
Ia	5.6	3,0	9,7	0,7	2,7	0,6	1,5	2,7	4,9	—
Ic	7.9	3,5	9,3	1,9	2.4	0,9	1,4	0,5	1,8	—
Id	3,2*	0,5	2,9	0,5	0,2	1,1	0,2	7,8	(8,2)	—
Ie	6.9	2,0	12,4	1,2	4,8	0,6	1,4	0,3	7,6	—
If	2,6	0,3	10,4	0,3	1,7	0,5	0,2	—	5,6	—
Ig	1.9	—	6,7	0,3	2,4**	1,1	—	—	—	14,7
Ij	5,4	2,2	15,4	1,0	3,2	0,9	2.7	0,1	4,6	—
Il	4,8	1,1	13,2	0,7	1,9	2,8	0,8	0,4	4.8	—
Im	2,6	0,5	3,3	1,0	0,7	—	—	7,2	(3,3)	22,7
In	0,04	—	0,6	—	1,6**	—	—	—	(1,8)	28,5
IIc	5,4***	2,3	10,0	1,7	1,8	0,7	1,6	—	—	—
IIe	6,7***	1,8	14,3	1,1	4,4	0,8	2,6	—	—	—

*Peak of the [M − MeI]$^+$ ion. **Peak of the [M − HHal, $-PhCH_2SH$]$^+$ ion. ***Peak of the M^+ ion.

It is seen from the data in Table 1 that the introduction of substituents R^4 and R^5 helps to increase the fraction of the cyclic tautomer B, but the presence of the substituent R^4 does not yet give rise to its predominance. Variation of the substituents R^3 and R^4 did not reveal an effect from their steric volume on the position of the tautomeric equilibrium [salts (Ij-n)].

Substitution at position 2 stabilizes the cyclic form significantly more strongly [see compounds (Ih-i)]. The simultaneous presence of substituents at positions 2 and 4 leads, accordingly, to the result that the iodide (Io) exists entirely in the form of the cyclic tautomer B. It is noteworthy that the 2,4-disubstituted derivative of acetaldehyde (Ib) also has a cyclic structure, whereas its aromatic analog (Id) retains the linear structure A. This is a general relationship [1-4], which must probably be attributed to stabilization of the linear tautomer in the 1-arylidene derivatives on account of conjugation.

TABLE 5. Mass Spectra of Compounds (Ih, i, o)

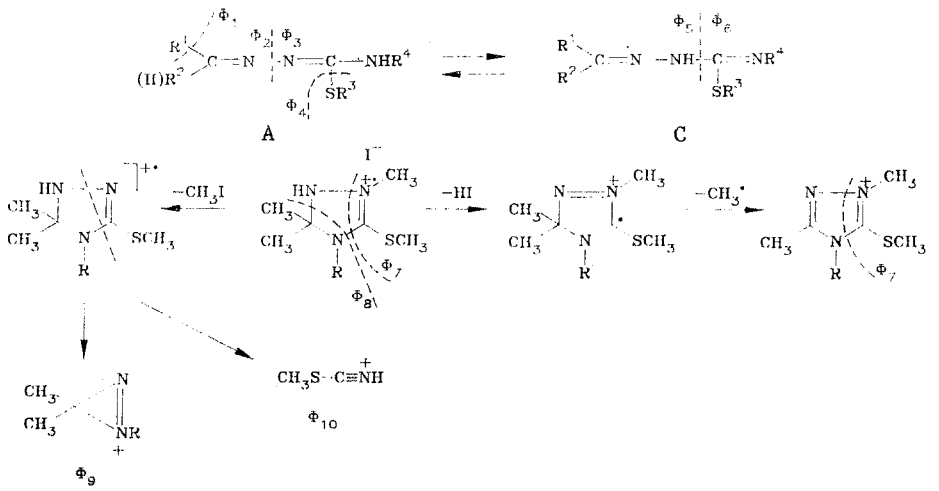
Compound	Peak intensities of characteristic ions							
	$[M-HHal]^+$	Φ_1	Φ_7	Φ_8	Φ_9	Φ_{10}	CH_3I^+	$HHal^+$ (Hal^+)
Ih	0,4	14,5	—	2,1	5,6	1,5	2,5	8,3
Ii	0,3	3,3	0,3	1,9	1,8	0,6	—	7,2
Io	0,3	0,4	0,6	1,9	0,7	5,5	4,4	(2,3)

The single or predominant tautomeric form is preserved in the transition from the salts (I) to the free bases (II, III). Thus, the S-alkylisothiosemicarbazones (IIc, e, j) were obtained from the iodides (Ic, e, j), and the structure of the bases (IIc, e) was proved not only by the PMR spectra (Table 2) but also by the carbon spectra (see the Experimental section). On the other hand, 3-alkylthio-1,2,4-triazolines (IIIh, i) were obtained from the iodides (Table 2).

In order to exclude the effect of the solvent on the conversion of the linear compounds into the cyclic form we investigated the behavior of the salts (Ia-o) and of the free bases (IIc, e) in the gas phase by electron impact (EI).

As follows from the data of the mass spectra (Table 3) and from comparison of the fractions of the characteristic fragments in the total ion current (TIC) (Table 4), the peaks with the largest mass in the mass spectra of the salts (I) correspond to the $[M - HHal]^+$ ions or, in certain cases, $[M - R^5Hal]^+$ and $[M - R^3Hal]^+$ ions. Comparison of the mass spectra of the salts (Ic, e) with the spectra of the corresponding compounds (IIc, e) shows that in the gas phase the salts probably undergo dehydrohalogenation with the formation of the initial compounds, and this leads to almost identical mass spectra.

From analysis of the fragmentation of the salts (I) it follows that most of them exist preferentially in the linear form of the isothiosemicarbazones (fragment ions Φ_1 and Φ_2 and rearrangement ions $[\Phi_2 + H]^+$, Φ_5, and Φ_6, see the scheme). The formation of the last two ions makes it possible to suppose that the isomeric form of the isothiosemicarbazone C exists in the gas phase.



For the derivatives of the aldehydes (Ia, c, d), in addition to the above-mentioned fragments of the linear form, the mass spectra also contain the ions formed as a result of the loss of two hydrogen atoms by the $[M - HHal]$ or $[M - CH_3Hal]$ ion. In our opinion this indicates the presence of small amounts of the cyclic alkylthiotriazoline form in the gas phase, since it is known [8] that such heterocycles readily undergo dehydroaromatization under thermal influences or electron impact. However, only in the case of the derivative of anisaldehyde (Id) was the intensity of the peak for the fragment $[M - CH_3I, -2H]^+$ sufficiently high (5.5% of the total ion current).

The difference in the substituents at the sulfur atom has an effect on the nature of the fragmentation of the investigated compounds at the $C_{(3)}$—S bond. Thus, whereas the S-methyl derivatives are characterized by the loss of the CH_3S radical, the peaks of the $C_7H_7SH^+$ and $[M - C_7H_7]^+$ fragments are observed in the spectra of the S-benzyl derivatives, and the peaks of the $[M - SC_2H_5]^+$ and $[M - C_2H_4]^+$ ions are found in the spectra of compounds (If, i). Loss of the ethylene molecule probably occurs with migration of a hydrogen atom to the $N_{(2)}$ atom according to the mechanism of a 1,5-sigmatropic shift (a McLafferty rearrangement).

The fraction of the ions characterizing the linear form in the case of compounds (Ih, i, o) is small, and the intensity of the Φ_7-Φ_{10} ions, characterizing the cyclic form, increases (Tables 4 and 5). This indicates that the data from the mass spectra agree in principle with the structures established from the data of the NMR spectra.

Thus, the susceptibility for the reversible cyclization in the derivatives of 1,2,4-triazoline must be considered a common feature of the protonated forms of compounds with the >=N—N=<NH fragment, and it must be taken into account both during their chemical transformations and during explanation of their biological action. This is particularly important for the isothiosemicarbazones, many of which are physiologically active.

EXPERIMENTAL

The PMR spectra (100 MHz) and ^{13}C NMR spectra (20.41 MHz) were recorded on a Tesla BS-497 instrument with HMDS as internal standard. The mass spectra were obtained on a Kratos MS 25 instrument at 70 eV with direct injection of the sample.

The composition of the compounds (Ia, b, d, f, h-o, IIj, IIIh, i) obtained for the first time was confirmed by determination of the percentage C, H, N, and S contents.

S-Alkylisothiosemicarbazonium Salts (Ia-o). The compounds were obtained by the action of alkyl halides on the respective thiosemicarbazones.

Compounds (Ia-e, h, j, *l*, m, o). The compounds were obtained by the addition of an equivalent amount of methyl iodide to 0.1 mole of thiosemicarbazone in benzene. After 24 h the crystals were filtered off and recrystallized from acetonitrile.

Compounds (If, g, i, k, n). The compounds were obtained by boiling equivalent amounts of the thiosemicarbazone and alkyl halide in benzene for 8 h. The solvent was removed, and the residue was recrystallized from acetonitrile.

Compound (Ic) [6]. ^{13}C NMR spectrum (DMSO-d_6): 14.1 (SCH_3); 128.6; 128.9; 131.6; 132.5 (C_{arom}); 151.9 (HC=N); 166.1 m.d. (C=N^+).

Compound (Ie) [6]. ^{13}C NMR spectrum (DMSO-d_6): form A 14.1 (SCH_3), 19.3 and 25.1 (CH_3C), 165.0 and 166.1 ppm (C=N and C=N^+); form B 11.1 (SCH_3), 80.7 ($C_{(3)}$), 167.3 ppm (C=N^+); the signal of the $(CH_3)_2C$ carbon atom was not detected.

Compound (I*l*). ^{13}C NMR spectrum (DMSO-d_6): form A 14.2 (SCH_3), 14.5 (CH_3CH_2), 19.5 and 24.8 (CH_3C), 39.6 (CH_2), 166.1 (C=N), 168.4 ppm (C=N^+); form B 13.7 (SCH_3), 15.3 (CH_3CH_2), 22.7 [$(CH_3)_2C$], 39.9 (CH_2), 83.9 ($C_{(3)}$), 167.0 ppm (C=N^+).

Compounds (IIc, e, j, IIIh, i). The compounds were obtained by the action of an excess of triethylamine on the respective salts (Ic, e, h-j). After the addition of benzene the precipitated triethylammonium halide was filtered off, and the solvent was removed to constant weight under vacuum (Table 2).

Benzaldehyde S-Methylisothiosemicarbazone (IIc). ^{13}C NMR spectrum (deuterochloroform): 12.4 (SCH_3), 127.4, 128.3, 129.6, 134.9 (C_{arom}), 153.9 (C=N), 162.0 ppm (C=N).

Acetone S-Methylisothiosemicarbazone (IIe). ^{13}C NMR spectrum (deuterochloroform): 12.2 (SCH_3), 17.5 and 24.7 (CH_3C), 157.5 (C=N), 161.3 ppm (C=N).

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