RING – CHAIN TAUTOMERISM OF S-ACYLALKYL-SUBSTITUTED IMIDAZOLES AND ANNELATED IMIDAZOLE SYSTEMS

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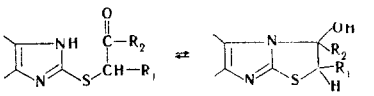
The ring–chain tautomerism of S-acylalkyl-substituted 2-mercapto-4,5-diphenylimidazoles, 2-mercaptobenzimidazoles, 2-mercaptonaphth[1,2-d]imidazoles, 8-mercaptopurines, 8-mercaptotheophyllines, and 2-mercaptoimidazolines was studied by means of PMR and IR spectra. It was established that, depending on the structure of the aldehyde or ketone residue, the character of the heteroring condensed with the imidazole ring, the aggregate state, and the solvent used, these substances exist as open heterylmercapto aldehydes (ketones), cyclic 3-hydroxy derivatives of imidazothiazoline systems, or as mixtures of the indicated tautomeric forms. When there is a substituent in the 2 position of the thiazoline ring, the cyclic compounds exist as mixtures of two diastereoisomeric forms.

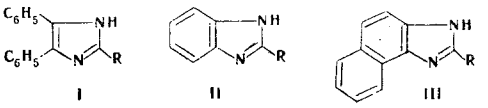
It has been demonstrated on the basis of IR spectra and several chemical reactions that S-acylalkyl-substituted imidazoles [1-8], imidazolines [5, 7, 9, 10], benzimidazoles [5, 6, 10-17], naphth[1,2-d]imidazoles [18, 19], purines [15, 20], and xanthines [5, 20] have open heterylthioaldehyde (ketone) structures (A) or the cyclic structures (B) of 3-hydroxy derivatives of imidazothiazoline systems, and both forms apparently exist in equilibrium.



A B

The existence of this sort of ring–chain tautomerism in a number of imidazole [6], imidazoline [10], and benzimidazole [6, 10, 13-17] derivatives was also confirmed by means of the PMR spectra.

In the present research, we have made a further investigation, on the basis of the PMR spectra and IR spectra, of the ring–chain tautomerism of S-acylalkyl-substituted 2-mercapto-4,5-diphenylimidazoles (I), of the corresponding 2-mercaptoimidazole derivatives, which are condensed with various aromatic and heterocyclic systems – benzene (II), naphthalene (III), pyrimidine (IV), and 1,3-dimethyluracil (V) – and of substituted 2-mercaptoimidazolines (VI).



I II III

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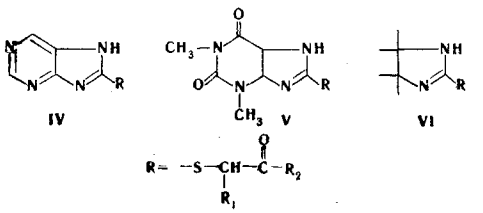
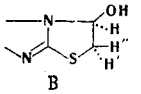


IV V VI

The following substituents were used for R_1 and R_2:

a) $R_1=R_2=H$; d) $R_1=H$; $R_2=C_6H_5$;
b) $R_1=CH_3$; $R_2=H$; e) $R_1=R_2=CH_3$.
c) $R_1=H$; $R_2=CH_3$;

A system of signals of the ABX type with $J_{AX} \neq J_{BX}$ corresponds to the protons of the saturated portion of the molecules in the PMR spectra of Ia-Va in perdeuterodimethylformamide (C_3D_7NO) or in perdeuterodimethyl sulfoxide (C_2D_6SO), which is in agreement only with a cyclic structure for molecules B.

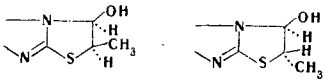


B

The AB portion of the system corresponds to the 2-H' and 2-H" protons of the thiazoline ring ($J_{2',2''}$ = 12.5 Hz, $J_{2',3}$ = 2.5 Hz, $J_{2'',3}$ = 5.2 Hz), while the X portion corresponds to the 3-H proton ($J_{2',3}$ = 2.5 Hz, $J_{2'',3}$ = 5.2 Hz). On the basis of the available data on the J_{cis} and J_{trans} values of the protons in five-membered heterocyclic systems [21, 22], we assigned the strong-field signal of the AB portion of the system (J_{gem} = 12.5 Hz, J_{trans} = 2.5 Hz) to the 2-H' proton in the cis position relative to the OH group, and the signal at weaker field (J_{gem} = 12.5 Hz, J_{cis} = 5.2 Hz) to the 2-H" proton in the trans position relative to the OH group. The chemical shifts of 2-H', 2-H", and 3-H and the spin–spin coupling constants are presented in Table 1.

The PMR spectra of Ia and Va in a mixture of perdeuteromethanol (CD_3OD) and perdeuteropyridine (C_5D_5N) contains, in addition to signals of the protons of the thiazoline ring (ABX system), signals of the A_2X type (J_{AX} = 6 Hz), which we assigned to the protons of open form A. The amount of this form present depends on the ratio of the indicated solvents and increases as the CD_3OD concentration rises. Only the signals of the protons of open form A are observed in the spectrum of hydrochloride Ia in CD_3OD, while only those of cyclic form B are observed in C_3D_7NO solution. The anomalous shift in the triplet of the proton of the CHO group of the open form to stronger field (to 5.0 ppm) as compared with the usual chemical shifts for aldehyde protons (9-10 ppm) is probably associated with hydration of the aldehyde group to $CH(OH)_2$ due to the moisture present in the deuteromethanol. This sort of assumption is in agreement with the IR spectra: the absorption band of a C=O group is not observed in the spectrum of hydrochloride Ia in CD_3OD.

According to the PMR spectra, Ib-IIIb and Vb, for which $R_1 = CH_3$ and $R_2 = H$, exist in solution in C_3D_7NO as a mixture of two cyclic isomers – the cis (B_1) and trans (B_2) forms.



B_1 B_2

Two systems of signals of the AX type with different chemical shifts of the 2-H and 3-H protons and different spin–spin coupling constants are observed in the spectra (see Table 1). The magnitudes of the spin–spin coupling constants ($J^1_{2,3}$ = 5.2 Hz and $J^2_{2,3}$ = 2.5 Hz) exclude the assignment of these signals to the protons of open form A and are in good agreement with their affiliation with cis and trans cyclic forms B_1 and B_2. The signals of the 2-H and 3-H protons of the trans cyclic isomer B_2 are observed at stronger field as compared with the same protons in cis cyclic isomer B_1.

The IR spectra of Ia, IIa, IVa, VIa, Ib, and IIb indicate the presence of only one cyclic form (B) in the crystals, since the absorption band of a carbonyl group is absent in the spectra. Similar data were obtained for Ia, IIa, IVa, and VIa in $CHCl_3$; the $\nu_{C=O}$ band is also absent, and absorption characteristic for the stretching vibrations of free and associated OH groups is observed at 3560-3605 cm^{-1}. In contrast to the spectra of Ia, IIIa, IVa, and VIa, the weak absorption bands of CO and NH groups that are characteristic

TABLE 1. Parameters of the PMR Spectra of Ia-Va and Ib-Vb

Comp.	Solvent	Form of compound	δ, ppm			J, Hz		
			2-H′	2-H″	3-H	2′,2″	2′,3	2″,3
Ia	C_3D_7NO	B	3,68	4,29	6,04	12,5	†	5,2
	C_5D_5N—	B	3,62	4,15	5,98	12,5	†	5,2
	CD_3OD, 1 : 1	A	3,49 (2H) doublet		5,00 triplet	—	6,0	
Ia · HCl	C_3D_7NO	B	3,95	4,58	6,38	12,5	†	5,2
	CD_3OD	A	3,36 (2H) doublet		4,87 triplet		6,0	
IIa *	C_3D_7NO	B	3,77	4,35	6,38	12,5	2,5	5,2
IIIa *	C_3D_7NO	B	3,83	4,41	6,55	12,5	2,5	5,2
IVa *	C_2D_6SO	B	3,88	4,44	6,60	12,5	2,5	5,2
Va	C_3D_7NO	B	3,70	4,28	6,25	12,5	†	5,2
	C_5D_5N—	B	3,80	4,30	6,46	12,5	†	5,2
	CD_3OD, 1 : 1	A	3,60 (2H) doublet		5,02 triplet	—	6,0	
			δ_{2-H}	δ_{3-H}	δ_{2-CH_3}	J_{cis}	J_{trans}	J_{2-H,CH_3}
Ib	C_3D_7NO	B_2 / B_1 5 : 4	4,15 4,66	5,60 5,76	1,55 1,55	— 5,2	†	7,5 7,5
IIb	C_3D_7NO	B_2 / B_1 4 : 3	4,30 4,75	6,01 6,17	1,54 1,54	— 5,2	2,5 —	7,5 7,5
IIIb	C_3D_7NO	B_2 / B_1 3 : 2	4,57 5,07	6,00 6,18	1,56 1,56	— 5,2	2,5 —	7,5 7,5
Vb	C_3D_7NO	B_2 / B_1 4 : 5	4,19 4,67	5,88 6,05	1,52 1,52	— 5,2	† —	7,5 7,5

*Compounds IIa-IVa could not be investigated in CD_3OD and C_5D_5N because of their low solubilities.

† The spin–spin coupling constant is close to zero.

TABLE 2. Absorption Frequencies (cm^{-1}) of the Functional Groups in the IR Spectra of the Investigated Compounds

Comp.	Crystalline state		In $CHCl_3$			
	$\nu_{C=O}$	tautomeric form	$\nu_{C=O}$	ν_{NH}	ν_{OH}	tautomeric form
Ia*	—	B	—	—	3560—3602	B
IIa*	—	B	—	—	3565—3607	B
IVa*	—	B	—	—	3600	B
VIa*	—	B	—	—	3600	B
Ib	—	B	1698 w	3140 s,b 3420 w	3560 m 3600 w	B + A †
IIb	—	B	1710 w	3448 w	3605 m	B + A †
Ic	1730 m	B + A	1717 vs	3440 s	3580 vw	A ‡
IIc	—	B	1715 m	3455 m	3569 w — 3605 w	A + B
IIIc	—	B	1712 vs	3460 s	3570 vw — 3600 vw	A ‡
IVc	1725 s	A	1718 m	3440 m	3610 m	B + A †
IId	1678— 1690 s	A	1682 vs	3460 s	3600 w	A + B ‡
IVd	1673 s	A	1683** 1698			A + B
VId	—	B	1673 m	3420 w	3560 s — 3600 m	B + A †
Ie	1715 s	A	1710 s	3320 w,b 3438 s	—	A
IIe	—	B	1706 m	3460 m	3570 m— 3603 w	A + B
IIIe	—	B	1713 s	3448 s	3560 w — 3605 w	A + B ‡

*A qualitative evaluation of the band intensities is not presented because of the low solubilities of Ia, IIa, IVa, and VIa.

† Cyclic tautomeric form B predominates.

‡ Open tautomeric form A predominates.

**The spectrum of a solution in pyridine was recorded, and the presence of the cyclic tautomeric form cannot therefore be evaluated.

TABLE 3. Parameters of the PMR Spectra of Ic-Vc, IId-IVd, and Ie-IIIe

Comp.	Solvent	Form of comp. and ratios of the forms	δ, ppm			J, Hz
			2-H′	2-H″	3-CH_3	J, Hz
Ic	C_3D_7NO	A	4,08(2H)		2,29	
IIc*	C_2D_6SO	A, B (1 : 1)	4,23(2H)	3,78 3,92	2,30 1,84	12,5
IIIc	C_3D_7NO	A, B (4 : 1)	4,44(2H)	4,00 4,16	2,40 2,06	12,5
IVc	C_2D_6SO	A	4,54(2H)		2,37	
Vc	C_2D_6SO	A	4,19(2H)		2,29	
IId	C_3D_7NO	A	5,15(2H)			
IIId	C_3D_7NO	A	5,20(2H)			
IVd	C_3D_7NO	A	5,27(2H)			
			δ_{2-H}	δ_{2-CH_3}	δ_{3-CH_3}	J_{2-H, CH_3}
Ie	C_5D_5N	A	4,46	1,57	2,43	7,5
IIe	C_5D_5N	B_2, B_1, A (3 : 2 : 1)	4,26 4,46 4,76	2,09 1,31 2,31	1,18 1,07 1,13	7,5 7,5 7,5
IIIe	C_5D_5N	B_2, B_1, A (5 : 3 : 2)	4,41 4,66 4,88	2,07 1,75 2,44	1,62 1,50 1,62	7,5 7,5 7,5

*The chemical shifts of compounds substituted with CH_3 groups in the 6 and 7 positions are presented.

for open form A are observed along with the absorption bands of the OH group of cyclic form B in the IR spectra of Ib and IIb in $CHCl_3$ (Table 2).

Turning to Ic-Vc, it may be noted that IIc and IIIc in solution in C_3D_7NO or in C_2D_6SO exist as a mixture of forms A and B. A quartet of an AB system, which corresponds to the two nonequivalent 2-H′ and 2-H″ protons of cyclic form B, and a singlet, which corresponds to the CH_2 group of open form A, are simultaneously present in their PMR spectra. Signals of the CH_3 groups of both forms are also observed in the spectra, and $\delta_{CH_3}(A) < \delta_{CH_3}(B)$. The equilibrium between forms A and B in IIc and IIIc is shifted to favor the open form. Under similar conditions, Ic, IVc, and Vc, as well as compounds in which the substituent attached to the carbonyl group is C_6H_5 (IId-IVd), display only signals of the open form – singlets of the CH_2 and CH_3 groups – in the spectra (Table 3).

An examination of the PMR spectra of Ie-IIIe (Table 3) demonstrates that these substances exist as a mixture of three forms in C_5D_5N solution – trans-cyclic (B_1),* cis-cyclic (B_2), and open (A). The PMR spectrum of IIIe is presented in Fig. 1. The three quartets observed in the weak-field portion of the spectrum correspond to the 2-H proton of each of the three indicated forms. On the basis of a comparison of the chemical shifts of the protons of the CH_2 groups in the open (A) and cyclic (B) forms (Table 3), the weakest-field signal at 4.88 ppm was assigned to the 2-H proton of the open form. The two remaining quartets are affiliated with the cyclic forms: the quartet centered at 4.66 ppm is ascribed to the 2-H proton of the cis cyclic isomer (B_1), and the quartet centered at 4.41 ppm is due to the 2-H proton of the trans cyclic isomer (B_2). The singlets at 1.75, 2.07, and 2.44 ppm were assigned to the CH_3 group in the 3 position, respectively, of the cis cyclic (B_1), trans cyclic (B_2), and open (A) forms. Signals of the protons of the CH_3 group in the 2 position of the molecule are found in the strong-field region of the spectrum.

Compound Ie in C_5D_5N solution exists only in the open form.

Absorption bands of both the open form (ν_{C-O} and ν_{NH}) and the cyclic form (ν_{OH}) are simultaneously observed in the IR spectra ($CHCl_3$) of Ic-IVc, IId-IVd, VId, and Ie-IIIe, which contain CH_3 or C_6H_5 groups in the

*In analogy with the compounds considered above (Ic-Vc), the isomer in which the 2-H proton is in the cis position relative to the OH group and the trans position relative to the CH_3 group is considered to be the trans isomer in this case.

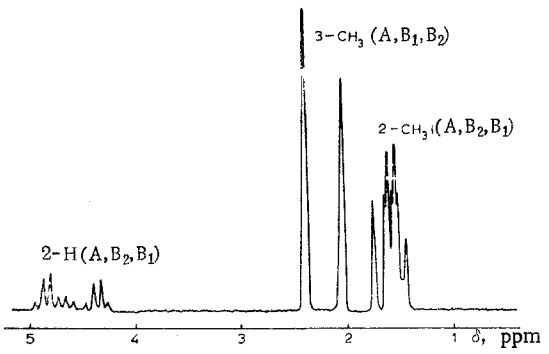


Fig. 1. PMR spectrum of IIIe in perdeuteropyridine.

3 or 2 and 3 positions of the thiazoline ring. The percentages of these forms were qualitatively estimated from the intensities of the CO, NH, and OH groups, and these results are presented in Table 2.

Thus, an examination of the PMR and IR spectra of S-acylalkyl-substituted imidazoles, benzimidazoles, naphthimidazoles, purines, and xanthines demonstrates that the ability of these compounds to exist in the heterylmercaptoaldehyde (ketone) form or in the form of 3-hydroxy derivatives of the imidazo-thiazoline systems depends on the following factors: the structure of the carbonyl portion of the molecule, the character of the aromatic and heteroaromatic rings condensed with the imidazole ring, the aggregate state, and the solvent used.

In both the solid state and in solution, all of the heterylthioaldehydes (Ia-Va, Ib-IIIb, Vb) exist as tautomeric cyclic forms (B). The presence in $CHCl_3$ of a small amount of the open aldehyde form (Table 2) could be detected only in the case of Ib and IIb by means of the IR spectra.

Heterylmercapto ketones of the aliphatic series that contain benzimidazole or naphthimidazole rings (IIc and IIIc, Table 3) exist as a mixture of cyclic and open forms with predominance of the latter, while the corresponding 4,5-diphenylimidazole, purine, and xanthine derivatives, as well as all of the heterylmercapto ketones of the aromatic series, are found only in the open form.

The effect of substituents in the carbonyl portion of the molecule is probably primarily associated with steric factors, which lower the stability of the cyclic structures as bulky substituents accumulate in the molecule and decrease the probability of closing of the thiazoline ring. The effect of the phenyl group may also be due to the energetic advantageousness of the conjugated benzoyl system (C_6H_5-CO-), which promotes the stability of the open form.

A comparison of the data obtained on the effect of the aggregate state and character of the solvent on the position of the tautomeric equilibrium shows that the crystalline state shifts the equilibrium to favor the cyclic form, while, at the same time, hydroxyl-containing solvents increase the percentage of the open form.

EXPERIMENTAL

The PMR spectra were recorded with a JNM-4H-100 spectrometer. The chemical shifts were measured on the δ scale with $Si(CH_3)_4$ as the internal standard.

The IR spectra of mineral oil pastes of the crystals or of solutions ($CHCl_3$ and, in a number of cases, pyridine) were recorded with UR-10 and Perkin Elmer 457 spectrophotometers.

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