PROTONATION OF IMIDAZO[2,1-b]THIAZOLE AND THIAZOLO[2,3-f]PURINE

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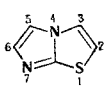
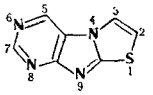
The protonation of imidazo[2,1-b]thiazole and thiazolo[2,3-f]purine was investigated by PMR spectroscopy. In CF_3COOH and D_2SO_4 the imidazothiazole forms a monocation, the structure of which corresponds to the addition of a proton to the nitrogen atom of the imidazole ring. In aqueous D_2SO_4 solutions, the thiazolopurine forms mono- and dications. The first protonation occurs at the nitrogen atom of the pyrimidine ring, while the second protonation occurs at the nitrogen atom of the imidazole ring. The effect of delocalization of the positive charge in the cations of the investigated compounds was examined.

It has been shown that the structure of the thiazolo[3,2-a]benzimidazole cation corresponds to protonation of this three-ring system at the nitrogen atom of the imidazole fragment and considerable delocalization of the positive charge on the heteroatom of the thiazole ring [1]. In order to ascertain the effect of annelation and aza substitution on the structure of the protonated forms of the heterocyclic systems of this type we studied the protonation of imidazo[2,1-b]thiazole (I) and thiazolo[2,3-f]purine (II) in the present research.



I



II

The assignment of the signals in the PMR spectrum of the neutral I molecule (Table 1) was based on a comparison with the spectra of 6-phenylimidazothiazole (Ia) and thiazolo[3,2-a]benzimidazole. The quartet at 6.86 ppm ($J_{2,3}$ = 4.5 Hz, $J_{2,6}$ = 1.05 Hz) and the doublet at 7.49 ppm were assigned to the 2-H and 3-H protons of the thiazole ring. The triplet at 7.28 ppm and the doublet at 7.47 ppm were assigned to the protons of the imidazole ring ($J_{5,6} = J_{2,6}$ = 1.05 Hz). Additional splitting of the 2-H doublet (6.86 ppm) is absent in the spectrum of Ia, and the 5-H signal is a singlet (7.76 ppm).

The protonation of the imidazothiazole was studied in mixtures of methylene chloride with trifluoroacetic acid with different CF_3COOH concentrations and in concentrated sulfuric acid. Measurement of the dependences of the chemical shifts of the protons of the two-ring system on the CF_3COOH concentration (Fig. 1) showed that the investigated compound forms a monocation, and the equilibrium is shifted completely to favor the protonated form at concentrations from 100 mole % to 6 mole %. The signals of all of the protons of the two-ring system in the spectrum of the monocation are shifted to weak field relative to the spectrum of the neutral molecule, and a considerable increase in the spin–spin coupling constant ($J_{5,6}$) of the ortho proton of the imidazole ring (from 1.1 to 2.4 Hz) is observed, while the $J_{2,3}$ and $J_{2,6}$ constants do not change. An increase in the acidity of the medium on passing from CF_3COOH to 36 N D_2SO_4 does not affect the spin–spin coupling constants. The shift in the signals of all of the protons of the two-ring system to strong field by 0.03-0.15 ppm observed in this case is apparently due to a change in the effects of

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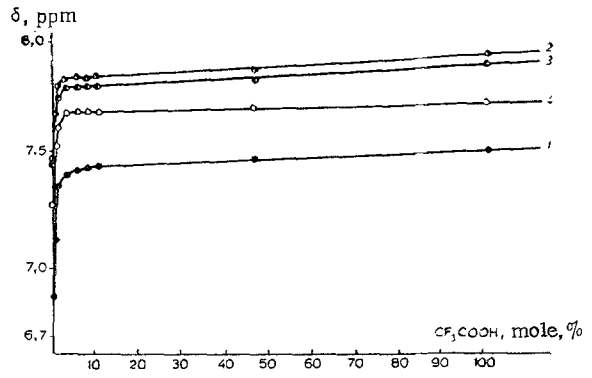


Fig. 1

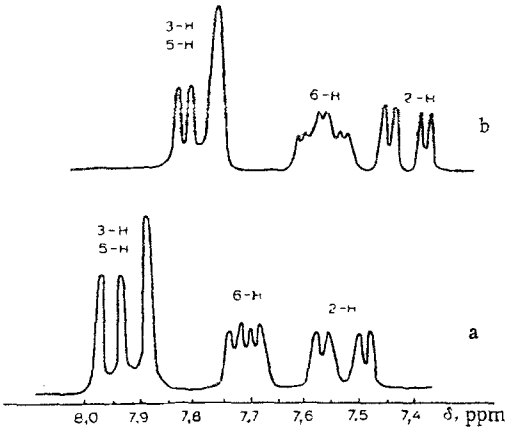


Fig. 2

Fig. 1. Dependence of the chemical shifts of the protons on the acid concentration for imidazo[2,1-b]thiazole: 1) 2-H; 2) 3-H; 3) 5-H; 4) 6-H.

Fig. 2. PMR spectrum of imidazo[2,1-b]thiazole: a) in CF_3COOH; b) in 36 N H_2SO_4.

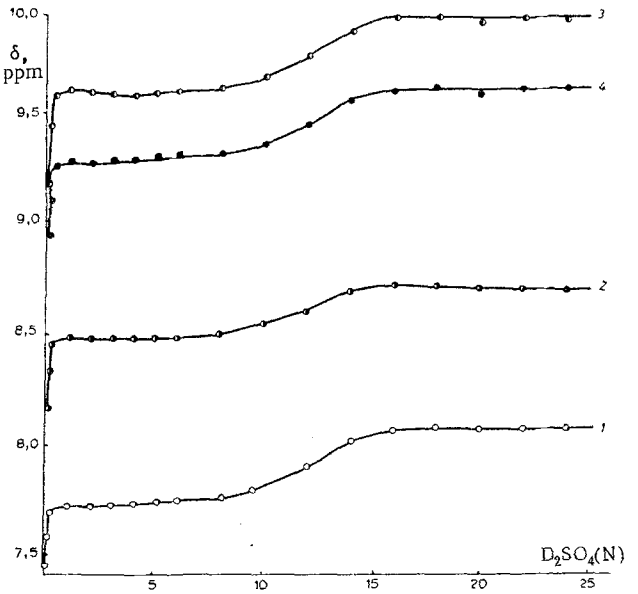


Fig. 3. Dependence of the chemical shifts of the protons of thiazolo[1,2-f]purine on the acid concentration: 1) 2-H; 2) 3-H; 3) 5-H; 4) 7-H.

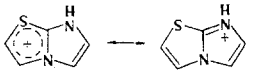
the medium. These data make it possible to exclude the possibility of the formation of an imidazothiazole dication in concentrated sulfuric acid. The position of the protonation center of the I molecule was established from the PMR spectrum of the monocation measured in 36 N H_2SO_4 (Fig. 2). The signal of the proton in the 6-position observed in CF_3COOH and D_2SO_4 as a quartet is converted to a triplet (J = 2.4 Hz) in 36 N H_2SO_4; each of the components of the triplet is additionally split with a constant of 1.1 Hz. The change in the multiplicity of the 6-H signals is due to spin–spin coupling with the proton attached to $N_{(7)}$, which arises as a consequence of a decrease in the rate of exchange of the $N_{(7)}$–H proton in concentrated sulfuric acid. The same value of the ortho spin–spin coupling constants with the proton attached to the nitrogen atom ($J_{N-H, C-H}$ = 2.4 Hz) is found in the spectrum of the imidazole cation measured under similar conditions [2]. The spectrum of the imidazole methiodide (Ib) recorded in CF_3COOH (Table 1) is extremely similar to the spectrum of the cation both with respect to the position of the signals of the protons of the two-ring system and with respect to the spin–spin coupling constants. Thus, protonation and quaternization of the imidazothiazole occur exclusively at the nitrogen atom in the 7-position.

TABLE 1. PMR Spectra of the Neutral Molecules and Cations of Imidazo[2,1-b]thiazole (I) and Thiazolo[2,3-f]purine (II)

Compound	Medium	Chemical shifts, δ, ppm					J, Hz				
		2	3	5	6	7	2,3	2,6	5,6	5,7	6,7
I	CH_2Cl_2	6,86	7,49	7,47	7,28	—	4,5	1,1	1,1	—	—
	CH_2Cl_2/6 mole% CF_3COOH	7,46	7,85	7,81	7,69	—	4,5	1,1	2,4	—	—
	CF_3COOH	7,52	7,94	7,91	7,71	—	4,5	1,1	2,4	—	
	$(CH_2Cl_2/CF_3COOH)_\infty$*	7,45	7,84	7,79	7,70	—	4,5	1,1	2,4	—	
	36 *N* H_2SO_4	7,41	7,80	7,78	7,56	—	4,5	1,1	2,4	—	2,4
Ia	CH_2Cl_2	6,86	7,48	7,77	7,2--7,8†	—	4,5	—	—	—	—
Ib	CF_3COOH	7,56	8,00	7,97	7,62		4,5	1,1	2,4	—	
II	D_2O	7,44	8,20	9,21	—	8,97	4,5	—	—	0,3	—
	1 *N* D_2SO_4	7,72	8,50	9,64	—	9,31	4,5	—	—	1,0	—
	20 *N* D_2SO_4	8,10	8,74	9,98	—	9,66	4,5	—	—	1,0	—
	36 *N* D_2SO_4	8,00	8,68	9,85	—	9,58	4,5	—	—	1,0	—

* These are the chemical shifts of the protons in the I cation extrapolated to zero CF_3COOH concentration in CH_2Cl_2.
† These are the chemical shifts of the protons of the phenyl ring in the 6-position.

In order to examine the effect of protonation at $N_{(7)}$ on the relative changes in the shielding of the protons of the two-ring system (Δδ) the chemical shifts in the spectrum of the monocation measured in mixtures of methylene chloride with trifluoroacetic acid were extrapolated to zero acid concentration. This makes it possible to exclude the contributions of the effects of the media to the Δδ values. It follows from a comparison of these values that the proton in the 2-position of the thiazole ring experiences appreciably greater deshielding than the proton attached to $C_{(6)}$, which is in the α position relative to the cationoid center ($\Delta\delta_2$ = 0.59 ppm, $\Delta\delta_6$ = 0.42 ppm). The changes in the chemical shifts of the protons in the 3- and 5-positions adjacent to the common nitrogen atom proved to be extremely close (0.35 and 0.32 ppm). These results make it possible to conclude that protonation of the imidazothiazole leads to redistribution of the electron density over the entire two-ring system, during which a considerable portion of the effective positive charge in the cation is localized on the heteroatoms of the thiazole ring.



These peculiarities of the structure of the protonated form may have a substantial effect on the relative reactivities of the various positions of the two-ring system in electrophilic substitution reactions occurring under acid-catalysis conditions. Some reactions of this type were studied in the case of a number of 6-arylimidazo[2,1-b]thiazoles (for example, see [3-7]). It follows from the data from these studies that the reactivity of the system in the 5-position is substantially higher than in the 2- and 3-positions.

The deshielding of the protons of the thiazole ring increases ($\Delta\delta_2$ = 0.69 ppm, $\Delta\delta_3$ = 0.47 ppm) during the protonation of thiazolo[3,2-a]benzimidazole[1] under the same conditions, while the changes in the chemical shifts of the protons of the benzene ring do not exceed 0.25 ppm. Consequently, the effect of transfer of positive charge from the cationoid center to the heteroatoms of the thiazole ring increases with annelation of the imidazothiazole system.

Aza substitution of the thiazolobenzimidazole can change the position of the protonation center of the system. Thus, the thiazolo[2,3-f]purine molecule (II) contains three possible cationoic centers: the nitrogen atoms in the 6-, 8-, and 9-positions. The protonation of purine was investigated in detail by PMR spectroscopy in aqueous solutions of mineral acids at various pH values [8-10] and also in strongly acidic nonaqueous media [11]. On the basis of these data, it was unambiguously established that the first protonation of purine occurs at the pyrimidine nitrogen [$N_{(1)}$], while the second protonation occurs at the nitrogen atom of the imidazole ring ($N_{(9)}$]. However, the presence of a π-surplus thiazole fragment does not make it possible to deliberately draw an analogy between the relative basicities of the nitrogen atoms of the pyrimidine and imidazole rings in the investigated system (II) and in purine.

The protonation of the thiazolopurine was studied from the PMR spectra of aqueous solutions with various concentrations of deuterosulfuric acid. Two doublets of the protons of the thiazole ring ($J_{2,3}$ = 4.5 Hz) are observed in the spectrum of the neutral II molecule. In analogy with the spectrum of I, the doublet at stronger field was assigned to the proton in the 2-position. The assignment of the signals to the protons

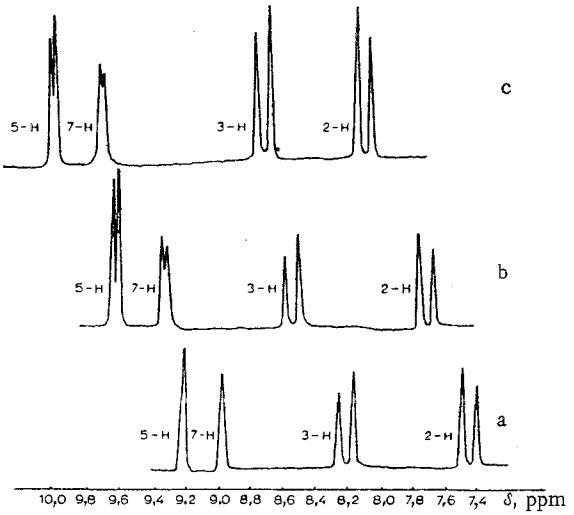
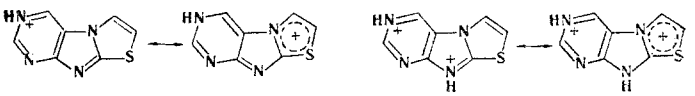


Fig. 4. PMR spectrum of thiazolo[1,2-f]purine: a) in D_2O; b) in 3 N D_2SO_4; c) in 22 N D_2SO_4.

of the pyrimidine ring was based on a comparison with the spectrum of purine [12]. The greater deshielding of 5-H as compared with 7-H is apparently due to the effect of the ring currents of the imidazothiazole fragment. The relative intensity of the observed signals corresponds to this assignment. The considerably greater broadening of the 7-H signal is associated with the effect of the quadrupole relaxation of the two adjacent nitrogen atoms. Measurement of the dependence of the chemical shifts of the protons of the three-ring system on the D_2SO_4 concentration (Fig. 3) made it possible to determine the degree of protonation of the II molecule at various acidities of the medium. The compound exists exclusively in the monocation form at D_2SO_4 concentrations from 1 to 8 N and in the dication form at D_2SO_4 concentrations from 18 to 36 N. The parameters of the spectra of the neutral molecule, the monocation, and the dication of the thiazolopurine are presented in Table 1. The position of the center of the first protonation was established from the change in the multiplicity of the signals of the protons of the pyrimidine ring that was observed as the D_2SO_4 concentration was increased from 0 to 1 N. The equilibrium between the neutral and monoprotonated forms of the compound corresponds to this acidity interval. The $J_{5,7}$ constant in the spectrum of the neutral molecule is close in absolute value to zero and is not observed because of broadening of the signals caused by the quadrupole relaxation effect. The $J_{5,7}$ constant increases to 1 Hz as the acid concentration is increased to 1 N, and the 5-H and 7-H signals are observed as doublets in the spectrum of the monocation. A further increase in the acidity of the medium does not affect the magnitude of the $J_{5,7}$ constant. A completely similar increase in the spin–spin coupling constant of the protons of the pyrimidine ring up to 1.04 Hz is observed on passing from the neutral molecule to the purine monocation [10]. It follows from these data that the first protonation of the thiazolopurine occurs at the nitrogen atom of the pyrimidine ring in the 6-position. Moreover, the signals of all of the protons of the three-ring system are shifted to the weak field. Large deshielding is observed for the protons of the pyrimidine ring ($\Delta\delta_5$ = 0.43 ppm, $\Delta\delta_7$ = 0.34 ppm). However, the changes in the chemical shifts of these protons are considerably less than the changes observed during protonation of purine under similar conditions (0.68 and 0.65 ppm, respectively) [10]. In addition, the deshielding of the thiazole ring protons that are remote from the cationoid center is quite high ($\Delta\delta_2$ = 0.28 ppm, $\Delta\delta_3$ = 0.30 ppm). These results and the observed $\Delta\delta_5 > \Delta\delta_7$ ratio attest to the fact that the effect of transfer of positive charge to the thiazole ring plays an important role in the thiazolopurine cation.



The established structure of the monocation gives every reason to assume that the second protonation of the thiazolopurine, in analogy with purine, should occur at the nitrogen atom of the imidazole ring in the 9-position. This is in agreement with the spectrum of the dication of II. The 7-H doublet in the spectrum of the monocation is broadened as a consequence of the effect of quadrupole relaxation of the $N_{(8)}$ atom. Although the constants due to spin–spin coupling with the N–H proton cannot be fixed in the spectrum of the dication in concentrated sulfuric acid because of rapid proton exchange, the absence of any changes whatso-

ever in the width of the 7-H signal as compared with the spectrum of the monocation (Fig. 4) does not correspond to the addition of a second proton to $N_{(8)}$. In addition, the proton in the 2-position of the thiazole ring experiences the greatest deshielding on passing from the monocation to the dication of II, as is also observed in the protonation of the thiazolobenzimidazole at the $N_{(9)}$ atom of the imidazole ring.

EXPERIMENTAL

The investigated compounds were synthesized by methods described in [13, 14]. The PMR spectra of 0.17 M solutions of the compounds were recorded with a C-60HL spectrometer. The chemical shifts were measured on the δ scale. Sodium 4,4-dimethyl-4-silapentane-1-sulfonate was used as the internal standard for solution in D_2O/D_2SO_4 and H_2O/H_2SO_4, while tetramethylsilane, the signals of which were taken as zero on the indicated scale, was used as the internal standard for solutions in CH_2Cl_2/CF_3COOH.

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