ACID-BASE CONVERSIONS OF NITROGEN HETEROCYCLES BY THE METHOD OF NMR SPECTROSCOPY.

2.* SUBSTITUTED PYRIDINE- AND PYRIMIDINE-1-OXIDES

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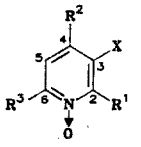
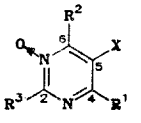
Features of the change in the chemical shifts of the protons of substituted pyridine-, pyrimidine-, 3-hydroxypyridine-, and 5-hydroxypyrimidine-1-oxides, as dependent on the basicity of the medium, were investigated. The ionization constants and the possible forms of the occurrence of the molecules were determined. The character of the influence of the substituents (alkyl, hydroxyl) on the pK_a values and the PMR spectral parameters was obtained. The comparison of the results obtained with the data on substituted pyridines and pyrimidines was carried out.

Continuing the investigations of the physicochemical properties of nitrogen heterocycles, we studied the acid-base conversions in the series of pyridine- and pyrimidine-1-oxides, and carried out a comparison with the data which we previously obtained for the substituted pyridines (I), 3-hydroxypyridines (II), pyrimidines (III), and 5-hydroxypyrimidines (IV) [1]. Pyridine-1-oxide (V), 3-hydroxypyridine-1-oxide (VI), pyrimidine-1-oxide (VII), 5-hydroxypyrimidine-1-oxide (VIII), and their methyl-substituted homologs were chosen as the compounds to be investigated.



V, VI



VII, VIII

V X=H, $R^1=R^2=R^3=H$; Va X=H, $R^1=CH_3$, $R^2=R^3=H$; Vb X=H, $R^1=R^3=CH_3$, $R^2=H$; Vc X=H, $R^1=R^2=R^3=CH_3$; VI X=OH, $R^1=R^2=R^3=H$; VIb X=OH, $R^1=R^3=CH_3$, $R^2=H$; VIc X=OH, $R^1=R^2=R^3=CH_3$; VII X=H, $R^1=R^2=R^3=H$; VIIa X=H, $R^1=CH_3$, $R^2=R^3=H$; VII'a X=H, $R^2=CH_3$, $R^1=R^3=H$; VIIc X=H, $R^1=R^2=R^3=CH_3$; VIII X=OH, $R^1=R^2=R^3=H$; VIIIa X=OH, $R^1=CH_3$, $R^2=R^3=H$; VIII'a X=OH, $R^2=CH_3$, $R^1=R^3=H$; VIIIb X=OH, $R^1=R^2=CH_3$, $R^3=H$; VIIIc X=OH, $R^1=R^2=R^3=CH_3$

The compounds (V)-(VIII) can occur in the cationic (C) and neutral (N) forms depending on the pH of the medium. The ionization of the hydroxyl group in the azines (VI) and (VIII) in the high-pH region leads to the formation of the anionic (A) form. The presence of the OH group in the ring does not exclude the formation of the bipolar (B) form. When the nitrogen atom is oxidized, it is known [2, 3] that the tautomeric equilibrium of the hydroxy-substituted azines is displaced in favor of the hydroxy form; therefore, the amount of the B form in the aqueous solutions of the investigated compounds should be significantly lower than in the case of 3-hydroxypyridine and, especially, of 5-hydroxypyrimidine [4, 5]. Consequently, the contribution of the B form to the value of the observed CS of the protons is low. In the strongly acidic media (the H_0 region), the compounds (VII) and (VIII) are present in the form of the dications (CC).

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$$CC \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} C \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} N \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} A$$
$$pK_a^{1'} \qquad pK_a^1 \qquad pK_a^2$$

There is practically no information in the literature on the acid-base equilibrium of the methyl-substituted pyridine- and pyrimidine-1-oxides, as well as their β-hydroxy derivatives.

The present work investigated the dependences of the CSs of the ring protons and the protons of the CH_3 groups on the pH value of the aqueous solutions of $D_2O/NaOD$ and D_2O/D_2SO_4 for the derivatives of pyrimidine-1-oxide; the dependence on the H_0 of the medium was also investigated. This permitted the evaluation of the values of the ionization constants ($pK_a^{1'}$, pK_a^1, pK_a^2), the CSs of the protons of the different forms (δ_{CC}, δ_C, δ_N, δ_A), and the limits of their transition (Table 1). The comparison of the character of the dependences of the CSs of the protons on the pH of the medium for the azines (V)-(VIII), as well as the analysis of the relative changes of the CS ($\Delta\delta_{CC-C}$, $\Delta\delta_{C-N}$, $\Delta\delta_{N-A}$), the SSCC of the ring protons, and the CS of the protons of the methyl groups in the transition from the N form to the form C or A, as well as from C to the form CC of the molecule, permitted an explanation of the nature of the influence of substituents (OH, CH_3) on the NMR spectral parameters and the basicity of the ring nitrogen atom and the oxygen of the N → O group. The character of the dependences of the CSs of the ring protons and the protons of the CH_3 groups on the pH of the medium for the compounds (V)-(VIII) is analogous to the dependences for the unoxidized analogs (I)-(IV) [1].

The protonation of pyridine leads to the significantly higher deshielding of the proton situated in the β- or γ-position by comparison with the α-proton [1]. In contrast to pyridine, the protonation of its N-oxide causes approximately identical changes in the CSs of the α- and β-protons. Thus, if the value of $\Delta\delta_{C-N}$ equals 0.32 and 0.67 ppm in pyridine, then the value of $\Delta\delta_{C-N}$ in the case of pyridine-1-oxide comprises 0.48 and 0.41 ppm for the α- and β-protons correspondingly. As in the case of pyridine, the distribution of the electron density at the carbon atoms of pyridine-1-oxide is such that the CSs of the protons decrease in the series 2,6; 4; 3,5. However, the electron density in the case of the pyridine-1-oxides is higher than that for the unoxidized analogs on practically all of the ring carbon atoms. The methyl substituents in the pyridine-1-oxide derivatives do not disturb the features indicated; they displace all the proton signals into the region of higher magnetic field. The mean change in the CS $\Delta\delta_{C-N}$ for the α-protons of the azines (V) equals 0.46 ppm; the change for the protons of the CH_3 groups is 0.22 ppm.

Pyridine-1-oxide is a much weaker base than pyridine itself. We observed that the contribution of the 2-CH_3 and 6-CH_3 groups to the CS of the 4-H and 5-H protons of the compound (Vb) is additive. The analysis of the data in Table 1 shows that the hydroxy group of 3-hydroxypyridine-1-oxide has virtually unchanged basicity by comparison with the basicity of the azine (V). However, the degree of the deshielding of the α-, β-, and γ-protons in the ring of 3-hydroxypyridine-1-oxide decreases somewhat on protonation. Thus, the value of $\Delta\delta_{C-N}$ for the α-protons of compound (VI) comprises the mean of 0.40 ppm. The CH_3 group in the ring of 3-hydroxypyridine-1-oxide exerts a greater influence on the value of pK_a^1 in comparison with the methyl-substituted pyridine-1-oxides. The contribution of each CH_3 group to the pK_a^1 value for the azines (V) and (VI) comprises 0.2 and 0.4 pK_a units correspondingly. In the process of the protonation of the derivatives (VI), the CSs of the protons of the CH_3 groups change, on average, by 0.21 ppm.

The signals of the ring protons in the derivatives of pyrimidine- and 5-hydroxypyrimidine-1-oxides are situated in the region of a weaker field by comparison with the corresponding signals of the derivatives of pyridine- and 3-hydroxypyridine-1-oxides owing to the strong deshielding effect both of the nitrogen atom and of the N → O group. The basicity of the azines (VII) and (VIII) decreases in comparison with the basicity of the compounds (V) and (VI). Thus, the pK_a^1 of pyrimidine-1-oxide is 1.4 pK_a units lower than that of pyridine-1-oxide, and the second protonation of the azines (VII) and (VIII) is observed in the H_0 region below 7.5.

The hydroxyl group increases the basicity of 5-hydroxypyrimidine-1-oxide in comparison with pyrimidine-1-oxide to the extent of 0.4 pK_a units; it shifts the signals of the protons to the region of higher field. In the case of the monomethyl-pyrimidine-1-oxides, the CH_3 group which is situated in the para position to the N-oxide group [(VIIa), (VIIIa)] has a greater influence on the pK_a^1 value than the CH_3 group in the ortho position [(VII'a),

TABLE 1. PMR Spectra and Ionization Constants in the Series of Pyridine- and Pyrimidine-N-oxides (solvents D_2O/D_2SO_4 and $D_2O/NaOD$; internal standard tert-butyl alcohol)

Compound	Proton	δ, ppm, form of the molecule			Relative changes of CSs, Δδ, ppm			$pK_a^{1'}$	pK_a^1	pK_a^2
		cationic	neutral	anionic	$\Delta\delta_{CC-C}$	$\Delta\delta_{C-N}$	$\Delta\delta_{N-A}$			
V	2-H, 6-H	7,56	7,08			0,48			0,9	
	3-H, 5-H	6,79	6,38			0,41				
	4-H	7,16	6,55			0,61				
Va	3-H	6,68	6,31			0,37			1,1	
	4-H	7,02	6,41			0,61				
	5-H	6,58	6,21			0,37				
	6-H	7,49	7,05			0,44				
	2-CH_3	1,52	1,27			0,25				
Vb	3-H, 5-H	6,47	6,14			0,33			1,3	
	4-H	6,86	6,21			0,65				
	2,6-CH_3	1,50	1,25			0,25				
Vc	3-H, 5-H	6,38	6,05			0,33			1,5	
	2,6-CH_3	1,45	1,23			0,22				
	4-CH_3	1,26	1,10			0,16				
VI	2-H	7,15	6,75	6,37		0,40	0,38		0,9	6,4
	4-H	6,57	6,06	5,74		0,51	0,32			
	5-H	6,57	6,23	5,99		0,34	0,24			
	6-H	7,11	6,70	6,33		0,41	0,37			
VIb	4-H	6,43	5,81	5,50		0,62	0,31		1,7	
	5-H	6,29	5,91	5,72		0,38	0,19			
	2-CH_3	1,38	1,14	1,04		0,24	0,10			
	6-CH_3	1,36	1,14	1,00		0,22	0,14			
VIc	5-H	6,20	5,90	5,70		0,30	0,20		2,2	7,9
	2-CH_3	1,38	1,19	1,11		0,19	0,08			
	4-CH_3	1,15	1,00	0,87		0,15	0,13			
	6-CH_3	1,34	1,14	1,05		0,20	0,09			
VII	2-H	8,29	7,89		0,70	0,40		−7,9	−0,5	
	4-H	7,95	7,40		0,37	0,55				
	5-H	6,88	6,50		0,64	0,38				
	6-H	7,89	7,45		0,58	0,44				
VIIa	2-H	8,14	7,75		0,54	0,39		−8,1	0,2	
	5-H	6,71	6,35		0,36	0,36				
	6-H	7,68	7,25		0,32	0,43				
	4-CH_3	1,52	1,35		0,16	0,17				
VIIá	2-H	8,17	7,82		0,64	0,35		−6,3	−0,3	
	4-H	7,69	7,17		0,34	0,52				
	5-H	6,76	6,43		0,54	0,33				
	6-CH_3	1,54	1,31		0,16	0,23				
VIIc	5-H	6,48	6,17			0,31			0,4	
	2-CH_3	1,62	1,43			0,19				
	4-CH_3	1,41	1,24			0,17				
	6-CH_3	1,47	1,26			0,21				
VIII	2-H	7,84	7,48	7,04		0,36	0,44	<−7,5	−0,1	4,8
	4-H	7,57	7,03	6,69		0,54	0,34			
	6-H	7,45	7,07	6,54		0,38	0,53			
VIIIa	2-H	7,76	7,38	6,95		0,38	0,43		0,4	4,8
	6-H	7,28	6,93	6,37		0,35	0,56			
	4-CH_3	1,37	1,22	1,10		0,15	0,12			
VIIIá	2-H	7,78	7,48	7,26	0,64	0,30	0,22	−6,7	0,3	4,5
	4-H	7,35	6,90	6,70	0,19	0,45	0,20			
	6-CH_3	1,41	1,23	1,19	0,20	0,18	0,04			
VIIIb	2-H	7,75	7,41	6,95	0,57	0,34	0,46	−6,4	0,6	5,1
	4-CH_3	1,37	1,22	1,08	0,15	0,15	0,14			
	6-CH_3	1,42	1,24	1,14	0,12	0,18	0,10			
VIIIc	2-CH_3	1,54	1,35	1,25	0,17	0,19	0,10	−4,3	0,9	5,7
	4-CH_3	1,35	1,18	1,08	0,14	0,17	0,10			
	6-CH_3	1,43	1,23	1,16	0,11	0,20	0,07			

(VIII'a)]. The change in the pK_a^1 value with the introduction of the CH_3 groups into the heteroaromatic ring is more marked for the hydroxy derivatives of compounds, (VI) and (VIII), than for the pyridine- and pyrimidine-1-oxides (V) and (VII).

The CSs of the protons of the CH_3 groups in the azines (VII) and (VIII) change to a lesser degree than those in the compounds (V) and (VI). The analysis of the experimental data showed that the first protonation of the azines (VII) and (VIII) leads to approximately the same change in the CSs of the 2-, 6-, and 5-H protons which are situated in the α-

and β-positions to the N → O group. In fact, the mean value of the shift $\Delta\delta_{C-N}$ of the signals of the protons indicated comprises 0.42 and 0.38 ppm correspondingly in pyrimidine-1-oxide. The value of $\Delta\delta_{C-N}$ decreases with the increase in the number of the methyl groups in the ring.

In the molecules of the pyrimidine- and 5-hydroxypyrimidine-1-oxides and their methyl-substituted derivatives, there are two centers of protonation – the ring nitrogen atom and the oxygen atom of the N → O group. It proved to be possible to determine the center of the first protonation on the basis of the analysis of the PMR spectral parameters of the azines (VII) and (VIII) and their unoxidized analogs (III) and (IV) [1]. As we already mentioned, the addition of a proton at the oxygen atom of the N → O group in the derivatives (V) and (VI) shifts the signals of the α- and β-protons to low field to practically the same degree.

When the pyrimidine-1-oxides are protonated, the values of the shift of these signals are close both to each other, and to the corresponding values of $\Delta\delta_{C-N}$ in the azines (V) and (VI); this provides the basis of the proposition that the first protonation is accomplished at the oxygen atom of the N → O group. The addition of the proton at the $N_{(3)}$ nitrogen atom should lead to the significantly larger shift of the 6-H signal (the γ-position relative to the $N_{(3)}$ atom) by comparison with the shift of the 2-H signal (the α-position), and the values of $\Delta\delta_{C-N}$ for the 2-H and 4-H protons should be close; this is not observed experimentally. As was shown for the pyrimidine derivatives (III), the shift $\Delta\delta_{C-N}$ for the α-proton in the case of the protonation at the nitrogen atom comprises the mean of 0.48 ppm [1], whereas this value is close to 0.38 ppm for all the investigated pyrimidine-1-oxides (VII). The molecule of 4,6-dimethyl-5-hydroxypyrimidine-1-oxide is asymmetric in the N and A forms. Consequently, the CH_3 groups are nonequivalent, and two singlets due to the protons of the 4-CH_3 and 6-CH_3 groups are present in the spectrum. The asymmetry of the molecule is preserved in the first protonation; this also testifies to the protonation at the oxygen atom of the N → O group.

The merging of the signals of the two CH_3 groups is only observed at the stage of the second protonation. As in the case of the unoxidized analog, such a spectral form is characteristic of the symmetrical molecule, i.e., the CC form, in which the addition of the proton also proceeded at the $N_{(3)}$atom. The analogous picture was observed in the investigation of the protonation of the N-methyl derivative of 4,6-dimethyl-5-hydroxypyrimidine.

The comparison of the spectral parameters of the neutral and protonated forms of the N-oxides (V)-(VIII) of the substituted pyridines and pyrimidines and their unoxidized analogs (I)-(IV) showed that the position of cationoid center can also be established from the change in the value of the SSCC of the meta-protons by the unoxidized ntrogen atom. In the spectra of the neutral molecules (VII) and (VIII), $J_{24} \approx 0$ (as also occurs in the case of the unoxidized compounds), and J_{26} = 2.0 and 1.4 Hz, correspondingly. In the spectra of the corresponding monocations, the value of J_{26} increases to 3.0 Hz for (VII) and to 1.8 Hz for (VIII), whereas the value of J_{24} is virtually unchanged for both compounds. The absence of a change in the SSCC of the meta-protons by the $N_{(3)}$ atom confirms the protonation at the oxygen atom of the N → O group in the pH region considered. In the azines (III) and (IV), an increase of J_{24} was observed in the process of the protonation at the nitrogen atom [1]. Therefore, the unoxidized $N_{(3)}$ nitrogen atom in the N-oxides of pyrimidine and 5-hydroxypyrimidine possesses lower basicity than the oxygen atom of the N → O group; this is primarily determined by the electron-acceptor properties of the N-oxide group. It should be noted that the first proton addition proceeded at the ring nitrogen atom, and the second proceeded at the oxygen atom of the N → O group, in the case of the monooxides of pyridazine and quinoxaline [6, 7] in an aqueous medium.

The N-oxidation of the pyrimidine ring significantly decreases the basicity of the second nitrogen atom. Thus, the protonation at the $N_{(3)}$ nitrogen atom in the derivatives (VII) and (VIII) proceeds in the region of higher acidities (H_0 below 4); the further displacement of the signals of the ring protons and the CH_3 groups to low field is thereby observed. All the SSCCs increase in the process of the formation of the CC form, and the value of J_{24} is now nonvanishing. The deshielding effect of the 2-H proton at the stage of the second protonation (on average 0.62 ppm) is greater than the change of the shielding in the transition to the monocation (on average 0.38 ppm) and exceeds the mean value of $\Delta\delta_{CC-C}$ for the unoxidized analogs (0.50 ppm). The methyl substituents increase the ionization constants $pK_a^{1'}$ and the shielding of all the ring protons. The basicity of the $N_{(3)}$ nitrogen

atom depends on the position of the methyl group in the heteroaromatic ring. Thus, in the case of the monomethylpyrimidine-1-oxides, the CH_3 group situated in the paraposition to the $N_{(3)}$ atom (VII'a) increases the basicity of the last compound by 1.6 pK_a units; the basicity of the $N_{(3)}$ atom decreases in the case of the ortho disposition of the methyl group. An increase of the $pK_a^{1'}$ value on the introduction of the CH_3 groups is observed for the methyl-substituted 5-hydroxypyrimidine-1-oxides.

In the high-pH region, the 3-hydroxypyridine- and 5-hydroxypyrimidine-1-oxides can occur in the form A. The ionization of the OH group is accompanied by an increase of the shielding of all the ring protons and the CH_3 groups. The mean changes of the CS $\Delta\delta_{N-A}$ during the ionization are close for the protons in the 2,4, and 6 positions of the ring of 3-hydroxypyridine-1-oxide. However, the influence of the ionization of the OH group on the CSs of the protons of the pyrimidine ring of (VIII) is more nonuniform, and it changes in the series 6 > 2 > 4. The methyl groups in the compounds (VI) and (VIII) increase the value of pK_a^2, and shift the proton signals into the high-field region.

The comparison of the values of pK_a^2 for phenol and 3-hydroxypyridine showed that the presence of the nitrogen atom in the ring markedly lowers the pK_a^2 (9.99 for phenol; 8.80 for 3-hydroxypyridine). The introduction of a second nitrogen atom into the ring of hydroxypyridine also leads to the decrease of the pK_a^2 (6.8 for 5-hydroxypyrimidine); this is associated with the significant increase in the electron-acceptor properties of the pyrimidine ring in comparison with pyridine. In changing from 3-hydroxypyridine and 5-hydroxypyrimidine to their N-oxides, the decrease in the values of pK_a^2 is primarily determined by the increase in the electron-accepting property of the N → O group in comparison with the nitrogen atom.

On the basis of the results of the investigation of acid-base conversions of the N-oxides (V)-(VIII) of azines, satisfactory correlations between the experimental values of pK_a^1 and the number of the CH_3 groups in the ring were shown. As also shown in the case of the unoxidized compounds (I)-(IV), the spectral parameter $\Sigma\Delta\delta_{C-N}$ (the total change of the CSs of the ring protons on protonation) correlates satisfactorily with the pK_a^1 values for the 1-oxides. It is possible to evaluate the values of pK_a^1 for the derivatives (V)-(VIII) from the NMR data using the following equations:

$$\begin{aligned} pK_a^1 &= -0.35\ \Sigma\Delta\delta_{C-N} + 1.74; \\ pK_a^1 &= -0.95\ \Sigma\Delta\delta_{C-N} + 2.54; \\ pK_a^1 &= -0.61\ \Sigma\Delta\delta_{C-N} + 0.57; \\ pK_a^1 &= -0.77\ \Sigma\Delta\delta_{C-N} + 0.88 \end{aligned} \qquad (r = 0.99)$$

In the case of the monomethyl-substituted pyrimidine- and 5-hydroxypyrimidine-1-oxide, only the pK_a^1 values of the azines (VII'a) and (VIII'a) satisfy the indicated dependences. The linearity of the dependences indicates that the parameter $\Sigma\Delta\delta_{C-N}$ may serve as a characteristic of the change of the electronic structure of the investigated molecules. The value of $\Sigma\Delta\delta_{C-N}$ decreases with the increase in the number of the methyl groups in the heteroaromatic ring. It should be noted that the total change in the shielding of the ring protons in the process of the protonation is less for 5-hydroxypyrimidine-1-oxide than for 3-hydroxypyridine-1-oxide. The analogous dependences were obtained in the comparison of $\Sigma\Delta\delta_{C-N}$ for pyridine- and pyrimidine-1-oxides. On the basis of the analysis of the CSs of the ring protons and the protons of the CH_3 groups in the azines (V)-(VIII), the linear correlation between the CSs of the protons of the form N and C, C and CC, and N and A was established.

In the series of azines (V)-(VIII), $\delta_N = 0.96\delta_C - 0.14$. In the series (VII)-(VIII), $\delta_C = 0.95\delta_{CC} - 0.05$. In the series (VI), (VIII), $\delta_N = 1.04\delta_A + 0.02$. In all cases, high correlation coefficients (r = 0.99) are observed; the value of the standard deviation does not exceed the error in the determination of the CS. The equations presented above are analogous to the equations derived for the unoxidized compounds (I)-(IV) [1], i.e., the values of the protonic CSs lie on one and the same line both in the case of the pyridine and pyrimidine derivatives, and in the case of their N-oxides. The presence of the linear dependences of such a type indicates the monotypic influence of the protonation at the oxygen atom of the N → O group, the protonation at the ring nitrogen atom, or the ionization of the OH group on the CSs of the protons in the investigated series of azines. We observed the linear dependences between the pK_a^2 values and the number of the CH_3 groups in the ring, and also between the pK_a^1 and pK_a^2 values for the mono-, di-, and trimethyl-5-hydroxypyrimidine-1-oxides (VIIIa-c). The correlation between the experimental values of $\Sigma\Delta\delta_{C-N}$ for the derivatives (V), (VI) and (VII), (VIII) was also established; it is described by the equation:

TABLE 2. Calculated Values of the Total Changes of the CSs of the Ring Protons in the Process of Protonation and the Ionization Constants in the Series Pyridine, 3-Hydroxypyridine, Pyrimidine, 5-Hydroxypyrimidine, and Their N-Oxides

Type of substitution	$\Sigma\Delta\delta_{C-N}$, ppm								pK_a^1							
	I	V	II	VI	III	VII	IV	VIII	I	V	II	VI	III	VII	IV	VIII
Initial azine	2,80	2,37	1,98	1,71	2,15	1,74	1,38	1,23	5,47	0,90	4,92	0,89	1,30	−0,50	1,81	−0,07
Monomethyl	2,26	1,78	1,43	1,27	1,63	1,25	0,92	0,82	6,14	1,10	5,57	1,32	2,10	−0,20	2,47	0,26
Dimethyl-	1,72	1,25	0,88	0,83	1,11	0,76	0,46	0,41	6,82	1,30	6,22	1,75	2,90	0,10	3,13	0,59
Trimethyl-	1,18	0,60	0,33	0,39	0,59	0,27	0,00	0,00	7,48	1,50	6,87	2,18	3,70	0,40	3,79	0,92

$$\Sigma\Delta\delta_{C\text{-}N}\ (V, VI) = 1.09\ \Sigma\Delta\delta_{C\text{-}N}\ (VII, VIII) + 0.40$$

It follows from the comparison of the values of the change in the CSs and the ionization constants of the pyrimidine derivatives and their N-oxides that the first protonation of the N-oxides proceeds at the oxygen atom of the N → O group, and the addition of the proton at the $N_{(3)}$ atom at the stage of the second protonation is observed in the region of higher acidities than for the unoxidized analogs. The ionization constants of the OH group (pK_a^2) of the N-oxides (VI) and (VIII) are also more than two orders of magnitude lower than the pK_a^2 of the hydroxy derivatives of pyridine and pyrimidine. The acidity of the hydroxy group increases significantly in the series 3-hydroxypyridine, 5-hydroxypyrimidine, 3-hydroxypyridine-1-oxide, and 5-hydroxypyrimidine-1-oxide (the pK_a^2 values comprise 8.8, 6.8, 6.4, and 4.7 correspondingly); this is associated with the introduction of the electron-acceptor aza and N-oxide groups. In the case of 3-hydroxypyridine, a decrease in the pK_a^1 in comparison with pyridine is observed, whereas the introduction of the hydroxy group into the ring of pyridine-1-oxide has practically no influence on the basicity of pyridine-1-oxide in the aqueous solution.

The presence of the linear dependences between the values of pK_a^1, $\Sigma\Delta\delta_{C\text{-}N}$, and the number of the CH_3 groups in the ring in each investigated series of azines and their N-oxides permitted us to evaluate the values of pK_a^1 and $\Sigma\Delta\delta_{C\text{-}N}$ in those derivatives which we did not investigate. The calculated values of $\Sigma\Delta\delta_{C\text{-}N}$ and the ionization constants pK_a^1 for pyridine, pyrimidine, and their methyl substituted derivatives and N-oxides are presented in Table 2. The analysis of the data in Table 2 showed that the value of the total change in the shielding of the ring protons of the investigated unoxidized azines is greater than the value of $\Sigma\Delta\delta_{C\text{-}N}$ of their N-oxides. The lower value of $\Sigma\Delta\delta_{C\text{-}N}$ in the hydroxy derivatives of the compounds in comparison with the pyridine and pyrimidine derivatives is evidently determined by the electron-donor properties of the OH group in conjunction with the aromatic ring. A satisfactory correlation was obtained by the comparison of the values of $\Sigma\Delta\delta_{C\text{-}N}$ in the pyridine and pyrimidine series with the corresponding values of $\Sigma\Delta\delta_{C\text{-}N}$ of their N-oxides. The analogous features are also shown in the series of 3-hydroxypyridine, 5-hydroxypyrimidine, and their oxidized analogs:

$$\Sigma\Delta\delta_{C\text{-}N}\ (I, III) = 1.02\ \Sigma\Delta\delta_{C\text{-}N}\ (V, VII) + 0.40$$
$$\Sigma\Delta\delta_{C\text{-}N}\ (II, IV) = 1.11\ \Sigma\Delta\delta_{C\text{-}N}\ (VI, VIII)$$

The following linear dependences between the pK_a^1 values in the series of the investigated azines and their N-oxides were observed:

$$pK_a^1\ (I) = 3.35\ pK_a^1\ (V) + 2.46;$$
$$pK_a^1\ (II) = 1.62\ pK_a^1\ (VI) + 3.44;$$
$$pK_a^1\ (III) = 2.57\ pK_a^1\ (VII) + 2.71;$$
$$pK_a^1\ (IV) = 1.99\ pK_a^1\ (VIII) + 1.95.$$

EXPERIMENTAL

The samples of (I)-(VIII) are prepared in the form of 0.2 M solutions in D_2O; the internal standard is tert-butyl alcohol. The acidity in the region of pH 0-10 is changed by the addition of small amounts of D_2SO_4 or NaOD to the solution of the investigated substance in D_2O. The pH value of the solution is measured with the accuracy of ±0.05 pH units on the pH-121 pH-meter with the ÉSL-63-07 glass electrode. The solutions of the compounds (VII) and (VIII), having defined H_0 values, are prepared according to [8]. The PMR spectra are registered on a Varian HA-100 spectrometer at 26°C. The accuracy of measurement of the CSs is ±0.02 ppm. The method of the calculation of the ionization constants from the dependence of the CSs of the protons on the pH of the medium, and the reliability of the application of the NMR method for the evaluation of the pK_a values, were examined in the work [4]. The accuracy of the evaluation of the ionization constants is not worse than ±0.1 pK_a units; the conformity with the literature data is not worse than ±0.2 pK_a units.

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CYCLIZATION REACTIONS OF NITRILES.

26.* SYNTHESIS, STRUCTURE, AND PROPERTIES OF 2-AMINO-4-METHYLTHIO-5-CYANO-6(1H)-PYRIMIDINETHIONE

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2-Amino-4-methylthio-5-cyano-6(1H)-pyrimidinethione has been prepared via treatment of N-cyanodimethyldithioimidate or 1,1-di(methylthio)-2-thiocarbamoyl-2-cyanoethylene with cyanothioacetamide or cyanamide. The structure of the complex formed between 2-amino-4-methylthio-5-cyano-6(1H)-pyrimidinethione and urea has been studied by x-ray structural analysis. Thieno[2,3-d]pyrimidines and thiazolo[3,2-c]pyrimidinium salts have been synthesized based on the 6(1H)-pyrimidinethione.

The preparation of 5-cyano-6(1H)-pyrimidinethiones based on active methylene nitriles has been described in the literature. Thus, for instance, 2-amino-1-acetylthiocarbamoyl-1-cyanoethylene cyclizes to give 2,4-dimethyl-5-cyano-6(1H)-pyrimidinethione [2]. Related thiones have been synthesized by treatment of ethoxymethylenemalonitriles with thioamides [3]. It was therefore of interest to examine the reactions of alkoxymethylenecyanamide [4] and alkoxymethylenecarbamic acid esters [5] with cyanothioacetamide. The structures and chemical properties of 5-cyano-6(1H)-pyrimidinethiones have received practically no attention until recently.

We have studied the reaction of N-cyanodimethyldithioimidate (I), which is easily accessible, with cyanothioacetamide (II). In ethanol solution in the presence of sodium ethoxide at 45-50°C the reaction proceeds regioselectively to give sodium 2-amino-4-methyl-5-cyano-6-pyrimidinethiolate (III) (method A). The 6-pyrimidinethiolate (III) could also be obtained from cyanamide V and 1,1-di(methylthio)-2-thiocarbamoyl-2-cyanoethylene (IV) in the presence of sodium ethoxide (method B). The formation of salt III in these reactions is accompanied by elimination of methyl mercaptan, which prevents oxidation of the pyrimidinethione to disulfide. 2-Amino-4-methylthio-5-cyano-6(1H)-pyrimidinethione (VI) was isolated after acidification of salt III in ethanol solution with hydrochloric acid.

*For Communication 25, see [1].

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