The ^1H NMR spectra of the compounds obtained by methods A and B were identical.

2,4-Dimethyl-9-acetyl-3a,4,9,9a-tetrahydrothiazolo[4,5-b]quinoxaline (IIIc). A 1.68-g (13.7 mmole) sample of acetyl bromide was added with stirring to a solution of 3 g (13.7 mmole) of IIIa in dry benzene. The resulting precipitate was removed by filtration, washed with dry benzene, and dried in a vacuum desiccator over paraffin. The dried precipitate was dissolved in 20 ml of water, and a solution of 1 g of sodium acetate in 20 ml of water was added with stirring. The precipitated IIIc (217 g) was removed by filtration, dried in a vacuum desiccator over P_2O_5, and recrystallized from ethanol (Tables 1-3).

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MASS-SPECTROMETRIC BEHAVIOR AND PMR SPECTRA OF 9-(2-R-1,3-DIOXAN-5-YL)PURINES

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UDC 543.51

A trans configuration with an axial orientation of both the purine ring and the furyl ring or the ethoxy group in the 2 position of the dioxane residue was established by PMR spectroscopy for 9-(2-furyl-1,3-dioxan-5-yl)- and 9-(2-ethoxy-2-methyl-1,3-dioxan-5-yl)purine. A comparative analysis of the mass spectra of these compounds makes it possible to confirm conclusions regarding their stereochemistry drawn on the basis of the PMR spectra.

The configurations of 9(1)-(2-substituted-1,3-dioxan-5-yl)purines and -pyrimidines and the conformation of the dioxane ring in these compounds have been previously investigated [1, 2] by NMR spectroscopy with the aid of shift reagents and by X-ray diffraction analysis. Considering the fact that the geometrical configurations of organic compounds have an appreciable effect on the character of dissociative-ionization processes [3, 4], in the present research we investigated the mass-spectrometric behavior of configurational isomers of 6-chloro-9-(2-furyl-1,3-dioxan-5-yl)purine (I) and 6-hydroxy-9-(2-substituted-1,3-dioxan-5-yl)purines (IIa,b and III) and studied their PMR spectra. Compound I was obtained by the reaction of 6-chloro-9-(1,3-dihydroxy-2-propyl)purine with furfural in the presence of

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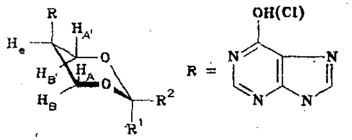
TABLE 1. Parameters of the ^{1}H NMR Spectra of 9-(2-Substituted-1,3-dioxan-5-yl)purines



Compound	Configuration	R¹	R²	Solvent (concn., %); shift reagent (in mole/liter); temp., °C	δ_H, ppm								J, Hz	
					2-H	8-H	5'-H_e[a]	H_A	H_B	2'-H	2'-OCH_2—	β-CH_3	$^2J_{AB}$	$^3J_{CH_2CH_3}$
I	trans	2-Furyl	H	$CDCl_3$ (2); 28°	9,02	8,50	4,86 (6)	4,52	4,36	5,84 (e)	—	—	−13,0	—
IIa	trans	OC_2H_5	H	$CDCl_3$ (3); 20°;	8,45	7,98	4,74 (7)	—b	3,91	5,60 (e)	3,68	1,30	−13,0	7,04
				$CD_3OD+CDCl_3+Eu(fod)_3$, (0,02); 20°	9,03	7,89	—b	4,78	4,00	5,73 (e)	3,73	1,33	−13,0	7,04
IIb	cis	H	OC_2H_5	$CD_3OD+CDCl_3$ (2); 20°;	8,44	7,98	—b	4,36		5,47 (a)	3,81	1,26	—	7,04
				$CD_3OD+CDCl_3$ (2)+ +$Eu(fod)_3$, (0,02); 20°	9,10	7,84	4,76 (8)	4,47		5,57 (a)	3,97	1,40	—	7,04
III	trans	OC_2H_5	CH_3	$CD_3OD+CDCl_3$ (3); 20°;	8,40	7,99	—b	—b	3,89	—c	3,61	1,30	−12,0	7,2
				$CD_3OD+CDCl_3$ (3)+ +$Eu(fod)_3$, (0,02); 20°	9,03	7,89	4,72	4,73	4,02	—c	3,69	1,34	−12,5	7,04

[a] The half width of the line of the 5'-H_e proton ($\Delta\nu_{1/2}$ Hz) is indicated in parentheses.

[b] These lines are overlapped by the overall broad line of the hydroxy protons of the incompletely deuterated methanol and the investigated compound.

[c] The chemical shift of the 2'-CH_3 protons is 1.53 ppm, as compared with 1.72 ppm when 0.02 M $Eu(fod)_3$ is added.

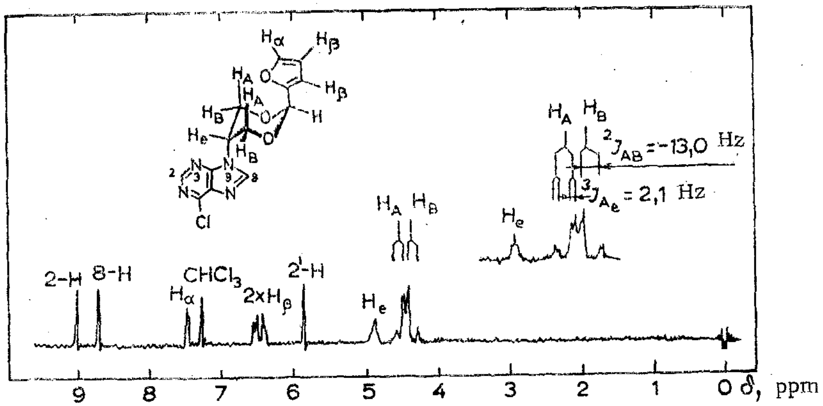


Fig. 1. PMR spectrum of 6-chloro-9-(2-furyl-1,3-dioxan-5-yl)purine (I) for ν_0 = 100 MHz and T = 28°C.

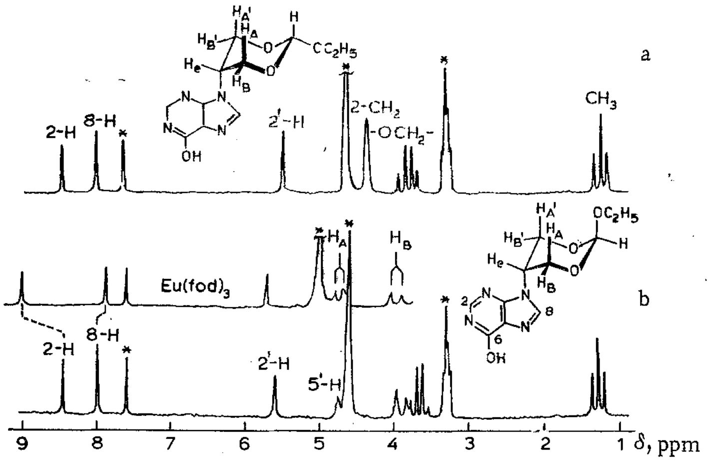
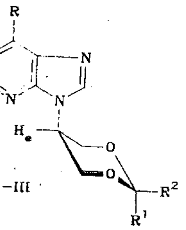


Fig. 2. PMR spectra: a) cis-6-hydroxy-9-(2-ethoxy-1,3-dioxan-5-yl)purine (IIa); b) trans-6-hydroxy-6-hydroxy-9-(2-ethoxy-1,3-dioxan-5-yl)purine (IIb) (ν_0 = 90 MHz). The lines of the incompletely deuterated solvent, including the hydroxy proton of the investigated compound, are indicated by asterisks.

Dowex-50 in the H^+ form. 6-Hydroxy-9-(2-H-2-ethoxy-1,3-dioxan-5-yl)purine was synthesized in the form of two configurational isomers (IIa,b) by the reaction of 6-hydroxy-9-(1,3-dihydroxy-2-propyl)purine with ethyl orthoformate; only one isomer, viz., 6-hydroxy-9-(2-ethoxy-2-methyl-1,3-dioxan-5-yl)purine (III), was obtained in the reaction of 6-hydroxy-9-(1,3-dihydroxy-2-propyl)purine with ethyl orthoformate.



I–III

I R=Cl,R^1=2-furyl,R^2=H;

II b R=OH,R^1=H,R^2=OC$_2$H$_5$;

IIa R=OH,R^1=OC$_2$H$_5$,R^2=H;

III R=OH,R^1=OC$_2$H$_5$,R^2=CH$_3$

Configurational isomers IIa,b were separated by means of preparative thin-layer chromatography (TLC) with monitoring of the degree of purity of the isomers on analytical plates.

The configurations of I-III and the conformation of the dioxane ring in the purines were established by analysis of the PMR spectra. The proton chemical shifts and the spin–spin coupling constants (SSCC) of the investigated compounds for solutions in $CDCl_3$ or $CDCl_3$ + CD_3OD, as well as with the addition of the Eu(fod)$_3$ shift reagent, are summarized in Table 1). The solubilities of the purines in $CDCl_3$ are extremely low, and deuterated methanol was therefore added to improve the solubilities. Additional experiments with the shift reagent were carried out for II and III in order to shift some of the lines of the 4',6'-CH_2 groups, which were superimposed on the lines of the solvents.

The PMR spectra of samples of purines I-III with the addition of Eu(fod)$_3$ display a substantial shift to weak field of the low-field line and a small shift to higher field of the signal of the 2-H proton of the purine ring. Since the 2-H proton is in the β position relative to the hydroxy oxygen atom and the 8-H proton is in the γ position, the low-field line can be assigned precisely to the 2-H proton, considering the inverse cubic dependence on the distance of Eu^{3+} to the examined proton for a pseudocontact shift [5]. Angular factor ($1 - \cos^2\theta$) is approximately identical for the two protons. In this connection, as one can see from the data in Table 1 and Figs. 1 and 2, we assign the low-field line of the purine ring to the 2-H proton and the high-field line to the 8-H proton.

In the PMR spectrum of purine I with a furyl substituent attached to the $C_{(2')}$ atom of the 1,3-dioxane ring the methylidyne 2'-H proton displays a singlet line with a chemical shift of 5.84 ppm (Fig. 1), which indicates the equatorial orientation of the 2'-H proton and, consequently, the axial orientation of the furyl substituent. The fact is that the PMR spectra of various cis-2-furyl-4-methyl-1,3-dioxanes, the dioxane ring in which has a chair conformation with a preferred diequatorial configuration of the substituents attached to the dioxane ring, whereas the axial 2-H proton resonates at 4.77-5.60 ppm, i.e., at substantially higher field than the proton in I, are presented in [6]. Taking into account the absence of the phenomenon of inversion of the proton chemical shifts in the 2' position of the 1,3-dioxane ring in the chair conformation, on the basis of the shift of the 2'-H proton (5.84 ppm) one can conclude that the furyl residue has an axial orientation.

One can draw conclusions regarding the preferred conformation of the 1,3-dioxane ring and the spatial orientation of the purine ring from the form of the resonance bands of the 4',6'-CH_2 protons, as well as the methylidyne 5'-H proton. It is apparent from Fig. 1 that in the PMR spectrum of I the signals of the protons of both methylene groups show up in the form of a typical symmetrical AB quartet with geminal constant $^2J_{AB}$ = −13.0 Hz and inversion of the axial and equatorial proton chemical shifts; this is typical for a chair conformation with an axial substituent [2] attached to the $C_{(2)}$ atom. As demonstrated in [6], the spatial orientation of the purine ring at the prochiral $C_{(5')}$ atom is proved by the magnitude of the half width ($\Delta\nu_{1/2}$) of the line of the methylidyne proton in the 5 position. This half width in the case of an axial conformation of the purine ring and a Lorentzian form of the NMR lines should be equal to $\Delta\nu_{1/2} \sim 2(^3J_{4ase} + {}^3J_{4ese}) \sim 8$ Hz. In all of the investigated compounds $\Delta\nu_{1/2}$ = 5-7 Hz. In the case of I, $\Delta\nu_{1/2}$ = 5 Hz, and this compound is consequently diaxial, i.e., it has a trans configuration.

In the PMR spectra of cis- and trans-9-(2-H-2-ethoxy-1,3-dioxan-5-yl)hypoxanthines (Fig. 2) the characteristic features of the resonance of the protons of the 1,3-dioxane ring are identical to the features of the corresponding protons of cis- and trans-1-(2-ethoxy-1,3-dioxan-5-yl)uracils, the detailed analysis of which was previously described in [2]. It may therefore be asserted that high-melting isomer IIa has a trans configuration and a diaxial orientation of the substituents, i.e., the ethoxy group attached to the $C_{(2')}$ atom replaces the axial valence. In this case the line of the equatorial methylidyne 2'-H_e proton is shifted to lower field (5.60 ppm) than in the case of the cis isomer (5.47 ppm). The low-melting isomer has a cis configuration in which the ethoxy group is equatorial, and the purine ring, as shown above, is axial in all cases. The protons of the 4',6'-CH_2 groups resonate in the form of a doublet [the doublet character is revealed when $Eu(fod)_3$ is added], whereas the 5'-H proton resonates in the form of a quintet with $^3J_{HH}$ = 2.3 Hz. However, when the $Eu(fod)_3$ shift reagent in a concentration of 0.02 mole is added, the A_4C spin system of these protons is not transformed into an AA^1BB^1X system, as in the case of cis- and trans-1-(2-ethoxy-1,3-dioxan-5-yl)uracils [2]. This is evidently due to competition in additional coordination of $Eu(fod)_3$ between the solvent molecules (CD_3OD + $CDCl_3$) and the investigated II to the detriment of the latter.

The chemical shift of the methyl protons in the spectrum of III is 1.53 ppm and is typical for its equatorial orientation [2] in the case of the chair conformation of the 1,3-dioxane ring (the methylene protons of the 4',6'-CH_2 groups display a symmetrical AB quartet with geminal constant $^2J_{AB}$ = −12.5 Hz), and, consequently, the ethoxy group is axial, and III has a trans configuration.

Rather intense peaks of molecular ions are observed in the mass spectra of all of the compounds; however, the character of their subsequent fragmentation differs, probably in connection with the difference in the site of charge localization. The positive charge in the molecular ion of I is localized primarily in the electron-saturated furan ring, which, in turn, leads to the appearance of intense peaks of "furan" ions in the mass spectrum.

In this connection, the mass spectrum of I does not contain peaks of fragments, in the formation of which from the molecular ion the asymmetric hydrogen atoms would be involved, and this does not make it possible to form a judgment regarding the geometrical configuration of the investigated compound. The overall intensity of the peaks of the ions presented in

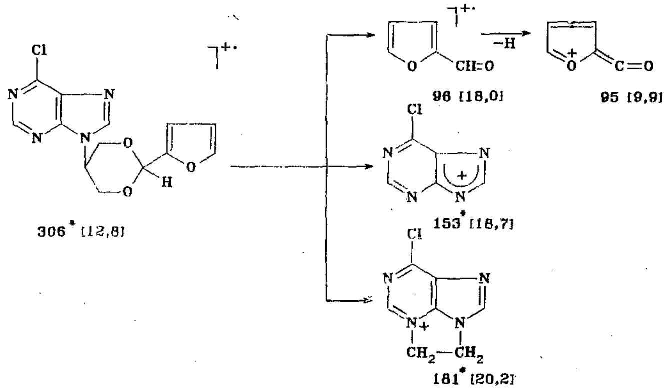
TABLE 2. Mass Spectra of I-III[a]

Compound	Configuration	m/z values (relative intensities, %)
I		306 (53), 213 (58), 193 (16), 181 (85), 154 (29), 153 (79), 124 (14), 123 (10), 96 (100), 95 (55)
IIa	trans	266 (22), 221 (65), 220 (29), 163 (66), 162 (100), 161 (59), 136 (70), 135 (52), 107 (42), 57 (30), 54 (28)
IIb	cis	266 (36), 237 (67), 236 (32), 221 (73), 220 (34), 163 (50), 162 (100), 161 (50), 136 (49), 135 (61), 107 (49)
III		280 (21), 235 (34), 234 (23), 193 (9), 192 (19), 175 (9), 163 (23), 162 (100), 136 (12), 135 (28), 107 (21)

[a]The molecular-ion peak and the 10 most intense peaks are presented.

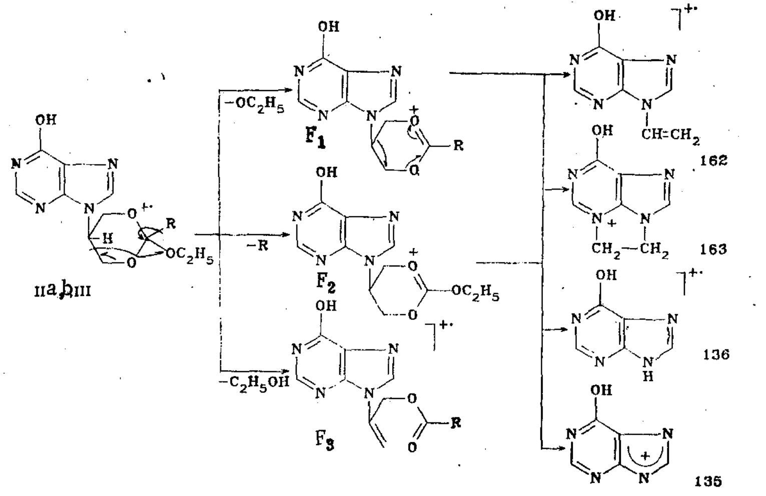
Scheme 1 (including the molecular ion) reaches 80% of the total ion current, which indicates the high selectivity of the fragmentation of this compound under electron impact. In Scheme 1 the m/z values marked by asterisks are of the ions that include the ^{35}Cl isotope; the intensities of the peaks in % Σ_{50} are given in brackets.

Scheme 1



On the other hand, the positive charge in the molecular ions of II and III is localized primarily on one of the oxygen atoms of the 1,3-dioxane ring. A consequence of this is the appearance in the spectrum of peaks of F_1-F_3 ions, in the formation of which an asymmetric carbon atom is directly involved.

Scheme 2



In addition, intense peaks of secondary ions with m/z 163, 162, 136, and 135, which are common to all II and III, are observed in the mass spectra. An analysis of the relative intensities of the peaks of the F_1-F_3 ions in the mass spectra of these compounds with respect to the intensity of the molecular-ion peak (Table 3) makes it possible to confirm the trans

TABLE 3. Relative Intensities of the Peaks of F_1–F_3 Ions

Compound	Configuration	I_{F_1}/I_M	I_{F_2}/I_M	I_{F_3}/I_M
IIa	trans	2,90	0,23	1,3
IIb	cis	2,00	0,47	0,94
III		1,60	0,06	1,1

configuration of IIa and the cis conformation of IIb. In fact, in the fragmentation of the molecular ion of the former, which has an axially oriented ethoxy group in the chair conformation, the ethoxy group is eliminated with a higher probability than in the case of cis isomer IIb. On the other hand, the loss of the equatorial hydrogen atom attached to the $C_{(2)}$ atom is a less intensive process. Drawing together of the oxygen atom of the ethoxy group and the 5-H proton, which promotes splitting out of ethanol from the molecular ion and the formation of an F_3 ion, is possible for the dioxane ring in the boat conformation in the case of the trans isomer. In this case, as in [7, 8], additional conformational isomers of purines II and III, which are absent in solution, can be detected by mass spectrometry in the gas phase.

In the case of III we have values of the indicated ratios that are close to those for IIa, and this also enables us to acknowledge a trans configuration for this compound.

Thus an analysis of the mass-spectrometric behavior of I–III makes it possible to a significant degree to confirm the conclusions regarding their stereochemistry drawn on the basis of the PMR spectra and also makes it possible to detect in the gas phase of purines II and III conformational isomers that are not identified by spectral methods in solutions.

EXPERIMENTAL

Thin-layer chromatography (TLC) was carried out on DC-Fertigplatten Kieselgel 60F-254 analytical plates with a thickness of 0.25 mm. Preparative TLC was accomplished on PSC-Fertigplatten Kieselgel 60F-254 plates with a thickness of 2 mm in a chloroform–ethanol system (9:1) with development in UV light with a UPM apparatus. The PMR spectra of solutions of the compounds in $CDCl_3$ or $CDCl_3$ + CD_3OD were recorded with a Brucker WH-90 pulse spectrometer with Fourier transformation and with a Varian HA-100 stationary spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with a Varian MAT-212 mass spectrometer at an ionization energy of 70 eV with direct introduction of the substances into the ionization region.

6-Chloro-9-(2-furyl-1,3-dioxan-5-yl)purine (I). A mixture of 0.3 g (1.3 mmole) of 6-chloro-9-(1,3-dihydroxy-2-propyl)purine, 0.13 g (1.3 mmole) of furfural, 10 ml of dry benzene, and Dowex-50 in the H^+ form (10% of the starting aldehyde) was refluxed in a flask equipped with a Dean–Stark trap until the liberation of water ceased. The reaction mixture was filtered, the filtrate was evaporated, and the residue was crystallized successively from heptane and absolute ethanol to give 0.06 g (15%) of purine I with mp 190-192°C. Found: C 50.3; H 3.7; N 17.9%. $C_{13}H_{11}ClN_4O_3$. Calculated: C 50.9; H 3.6; N 18.3%.

6-Hydroxy-9-(2-ethoxy-1,3-dioxan-5-yl)purine (IIa,b). A solution of 0.27 g (1.3 mmole) of 6-hydroxy-9-(1,3-dihydroxy-2-propyl)purine in a mixture of 5 ml of acetic anhydride and 5 ml of ethyl orthoformate was refluxed for 15 min, after which the solvent was removed by distillation, and the residue was crystallized from absolute ethanol to give 0.32 g (92%) of a mixture of IIa,b. Separation by TLC on preparative plates in a chloroform–ethanol system (9:1) gave trans isomer IIa and cis isomer IIb in a ratio of 3:2. This procedure gave 0.19 g (55%) of trans isomer IIa with mp 215-217°C. Found: C 49.4; H 4.9; N 20.7%. $C_{11}H_{14}N_4O_4$. Calculated: C 49.6; H 5.3; N 21.0%. Also isolated was 0.12 g (36%) of cis isomer IIb with mp 187-189°C. Found: C 49.9; H 5.2; N 21.0%.

6-Hydroxy-9-(2-ethoxy-2-methyl-1,3-dioxan-5-yl)purine (III). A solution of 0.27 g (1.3 mmole) of 6-hydroxy-9-(1,3-dihydroxy-2-propyl)purine in a mixture of 5 ml of acetic anhydride and 5 ml of ethyl orthoformate was refluxed for 15 min, after which the solvent was removed by distillation, and the residue was crystallized from absolute ethanol to give 0.28 g (80%) of III with mp 222-225°C. Found: C 51.4; H 5.6; N 19.7%. $C_{12}H_{16}N_4O_4$. Calculated: C 51.4; H 5.8; N 20.0%.

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NH ACIDITIES OF 7-OXO-4,7-DIHYDROPYRAZOLO- AND 1,2,4-TRIAZOLO[5,1-c][1,2,4]TRIAZINES

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and V. L. Rusinov

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The pK_a values of a number of 7-oxo-4,7-dihydropyrazolo- and 1,2,4-triazolo[5,1-c]-[1,2,4]triazines, which range from 0.33 to 6.50 and correlate with the σ meta constants of substituents in the 6 position, were determined by spectrophotometric and potentiometric methods.

Methods have been developed for the preparation of derivatives of azolo-1,2,4-triazines [1-5]; however, the literature contains no information regarding their acidic-basic properties. In this connection we have determined the ionization constants of a series of 6-R^1-7-oxo-4,7-dihydroazolo[5,1-c][1,2,4]triazines (I-XVII), for which we used spectrophotometric and potentiometric methods.

The electronic spectra of aqueous solutions of triazines I-XVII are characterized by two absorption maxima, the positions of which depend on the pH. The spectral characteristics of the compounds in the acidic (TH) and ionic (T^-) forms, as well as their ionization constants, which correspond to ionization of the NH bond of the triazine ring, are presented in Table 1. Products I, II, IV-XIII, and XV-XVII are monobasic acids, whereas carboxy derivatives III and XIV are dibasic acids. 6-Amino-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c][1,2,4]triazine (I) displays amphoteric properties and can add a proton to the amino group. A band of vibrations of a C=O group at 1690-1720 cm^{-1} is present in the IR spectra of these compounds in the TH and T^- forms. The formation of the NH form is accompanied by a hypsochromic shift of approximately the same magnitude (Table 1). An analysis of the spectra of acid III showed that the character of the spectrum and the magnitude of the hypsochromic shift of the absorption maxima change in the same way as for the remaining compounds as the pH of the solution is changed from 7 to 4, and, consequently, pK_a 5.28 corresponds to the addition of a proton to the nitrogen atom of the triazine ring. A decrease in the pH from 3.5 to 0.5 gives rise only to a shift of the isobestic point, a certain decrease in the intensity of the absorption at 270 nm, and an increase in the intensity of the absorption at 306 nm; this makes it possible to ascribe pK_a 2.00 to dissociation of the carboxy group. In the case of 6-amino derivative I, in addition to the typical spectral changes associated with dissociation of the NH bond (pK_a 6.50), an increase in the absorption at λ_{max} of the TH form and a small bathochromic shift as a consequence of the addition of a proton to the exocyclic amino group are observed upon pronounced acidification (pH 2).

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