B. A solution of nitrosopyrimidine VIIa-c in 300 ml chloroform prepared as described above was also sparged with ozone (flow rate 2-3 mmole/h) until the nitrosopyrimidine had disappeared (based on TLC analysis with chloroform eluent). The reaction mixture was worked up as described above in Part A, to give compounds XIa-c.

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UV SPECTROSCOPIC STUDY OF THE ACID-BASE REACTIONS OF 3-HYDROXYPYRIDINES AND 5-HYDROXYPYRIMIDINES

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The acid-base equilibrium behavior of alkyl(phenyl)-substituted 3-hydroxypyridines and 5-hydroxypyrimidines, and their dependence on pH values in aqueous solution, on the solvent, and on the phase composition, have been studied using UV spectroscopy. It has been found that in neutral aqueous solution all of the substituted 3-hydroxypyridines examined contain, in addition to the neutral form, a bipolar form, whose concentration depends on the nature and position of the substituent. In contrast, methyl substituted 5-hydroxypyrimidines form significant amounts of the bipolar form only in more acidic media.

It is known that substituted 3-hydroxypyridines I and 5-hydroxypyrimidines II act as inhibitors of radical reaction processes, and that they are also useful starting materials for the synthesis of biologically active compounds [1, 2]. It is possible that the biological activity of 3-hydroxypyridines depends on the equilibrium conversions or reactions of these compounds [3].

The acid-base reactions of 3-hydroxypyridine Ia and a variety of substituted 3-hydroxypyridines, such as pyridoxine, pyridoxal, and pyridoxamine, have been studied previously

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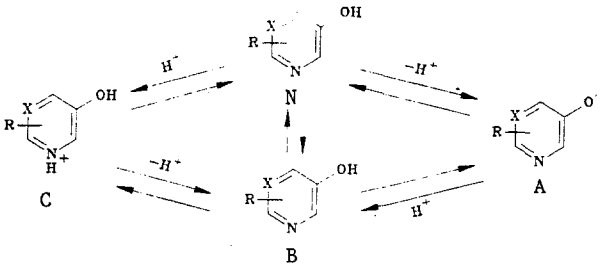
TABLE 1. UV Spectral Absorption Data for Compounds I and II

Compound	pK_{HA} (50% EtOH) [17]	pK_{BH^+} (CH_3NO_2) [17]	λ_{max}, nm				Relative concentration of tautomeric forms in aqueous solution at	
			N form	C form	A form	B form	pH 3,10	pH 7,05
Ia	9,49	11,85	216, 278	222, 283	236, 298	246, 314	C	N—B, 1 : 1
Ib	—	13,63	211, 285	225, 295	239, 307	248, 323	C	N—B, 1 : 3
Ic	—	—	210, 280	230, 291	240, 303	250, 321	C	N—B, 1 : 1
Id	—	—	212, 284	227, 288	243, 301	251, 318	C	N—B, 1 : 2
IIa	7,54	8,21	214, 273	223, 285	238, 304	325	N—B, 50 : 1	N—B—A*
IIb	—	—	217, 281	220, 291	237, 310	320	N—B, 30 : 1	N—B—A*
IIc	8,27	10,24	218, 276	230, 285	244, 300	250, 319	N—B, 6 : 1	N—B—A*
IId	8,84	11,18	273	229, 287	244, 306	260, 325	C	N—B, 1 : 3
IIe	—	—	264, 317	—	215, 284	—	N	N—A*
IIf	8,50	9,20	260, 303	—	294	335	N—B	N—A*
IIg	8,12	8,72	204, 246, 299	229, 271, 323	226, 240, 331	350	N—B	N—A*

*It was not possible to determine the relative concentrations of these forms.

using UV spectroscopy [3-6]; it was found that, depending on the pH of the medium, compounds of the type I could exist in equilibrium of neutral (N), cationic (C), anionic (A), and bipolar (B) forms [3, 4, 7].

It was also found that the ratio of the N and B forms in neutral aqueous solution was approximately 1:1 in the case of compound Ia [3-5, 8, 9], 1:1.5 for 3-hydroxy-6-methylpyridine [3], and 1:2 for 3-hydroxy-2-hydroxymethylpyridine [3]. The value of the equilibrium constant $K_B = f_B/f_N$ (where f_B and f_N are the mole fractions of the bipolar and neutral forms, respectively) for compound Ia has been determined by a variety of different methods and is in the range 0.88-1.3 [3-5]. In contrast to the case with substituted pyridines I, the acid-base equilibria involving 5-hydroxypyrimidines II have been examined only for the unsubstituted derivative IIa; according to its UV spectral data, the equilibrium for this compound is shifted in favor of the N form (N:B = 50:1), which is observed in more acidic solutions (pH 4.30) than in the case of compound Ia [4, 7].



I X=CH, a R=H, b R=2,6-$(CH_3)_2$; c R=2-$CH_2C_6H_5$, d R=2-t-C_4H_9; II X=N, a R=H, b R=2-CH_3, c R=4,6-$(CH_3)_2$, d R=2,4,6-$(CH_3)_3$, e R=2-C_6H_5, f R=2-C_6H_5 and 4,6-$(CH_3)_2$, g R=4-C_6H_5

In the present paper we have utilized the UV absorption spectra of these types of compounds to compare and contrast the behavior of alkyl-substituted 3-hydroxypyridines Ia-d and methyl(phenyl)-substituted 5-hydroxypyrimidines IIa-g in buffered aqueous solutions and in solvents of differing polarities and at a variety of phase compositions.

The positions of the absorption maxima characteristic of the different tautomeric forms of compounds Ia-d and IIa-g are given in Table 1. Spectral band assignments were made based on analysis of the UV spectra of the different compounds in different media and also taking into account the literature data for compounds Ia and IIa; the assumptions were also made that in aqueous solutions at pH 11 all of the compounds existed in their anionic forms, and that in chloroform and DMSO solutions they existed primarily in their corresponding neutral forms [9]. We note in this regard that the bands of the different tautomeric forms overlap each other to a significant extent, especially in the case of compounds IIe-g, and that it is therefore difficult to resolve these bands for different forms using conventional UV spectral acquisition parameters. For this reason, in analyzing the spectra of the phenyl-substituted 5-hydroxypyrimidines IIe, f, g we utilized their first and second differential

TABLE 2. pH Dependence of the Composition Forms of Compounds I and II in Aqueous Solution

Compound	pH of the aqueous solution				
	−0,45	1,75	3,10	7,05	11,0
Ia	C	C	C	N + B	A
Ib	C	C	C	N + B	A
Ic	C	C	C	N + B	A
Id	C	C	C	N + B	A
IIa	C	N	N+B	N+B+A	A
IIb	C	C	N+B	N+B+A	A
IIc	C	C	N+B	N+B+A	A
IId	C	C	C	N + B	A
IIe	N	N	N	N + A	A
IIf	N	N	N+B	N + A	A
IIg	C	C	N+B	N + A	A

(derivative) spectra [10], and we also analyzed in detail the spectra of these compounds and their derivatives upon stepwise gradual acidification and basification of neutral aqueous solutions.

It was found that all of the newly studied 3-hydroxypyridines IIb-d, as well as the previously studied compound Ia, contain a bipolar form B in addition to their neutral form in neutral aqueous solution. The concentration of the B form at pH 7.05 varies in the series Ia ≈ Ic < Id < Ib (Table 1). As discovered previously, introduction of one methyl group in the 6-position of 3-hydroxypyridine shifts the N ⇆ B equilibrium in favor of the B form [3]. Two methyl groups in the 2- and 6-positions of the pyridine ring in compound Ib result in further displacement of the substituted 3-hydroxypyridines toward predominantly the B form. The effect of a 2-t-Bu group on the acid-base equilibrium behavior of 3-hydroxy pyridines is approximately the same as the effect of a 2-CH_2OH group (cf. compounds Id and [3]).

In acidic solution (pH 3.10) all of the derivatives Ia-d are completely protonated (Table 2), while in basic solution (pH ≥ 9) these compounds exist in the form of mixtures of the N and A forms, with form A the exclusive species present at pH 11.0.

In other solvents ($CHCl_3$, DMSO, alcohol) form B was not observed in the case of compounds Ic and d, while in alcohol solutions of compounds Ia, b substantial quantities of this form are present (Fig. 1).

In the solid state compounds Ia-d exist primarily in their N forms, although the nature of their absorption curves (Fig. 2) and analysis of their differential (derivative) spectra lead us to conclude that other forms of the compounds are also present in the solid state; the possible existence or formation of ion pairs linked by strong intermolecular hydrogen bonds of the type $^+NH...O^-$ [11] must also be taken into account (for the solid state).

Since the presence of intermolecular hydrogen bonds can be detected easily by IR spectroscopy, we investigated the IR spectra of compounds Ia-d in the solid state and also of dilute solutions of compound Ia in chloroform. The IR spectra of compounds Ib-d in the solid state contain, in addition to broad intense bands in the 2500-2700 cm^{-1} region, broad absorption bands in the 1700-2000 cm^{-1} region as well. Analogous bands have been detected previously for compound Ia and their appearance was ascribed to the formation of ion pairs linked by strong intermolecular hydrogen bonds of the designated type, namely $^+NH...O^-$ [11]. The fact that these hydrogen bonds are indeed intermolecular in nature is supported by the observation that the 1700-2000 cm^{-1} absorption band which is present in the spectrum of a 1% chloroform solution of compound IIa disappears when the solution is diluted tenfold.

In contrast to 3-hydroxypyridines, the IR spectra of 5-hydroxypyrimidines IIa-f in the crystalline state contain only low intensity bands in the 1700-2100 cm^{-1} region (Fig. 3, curves c-g), which suggests that compounds of the type II are less susceptible to hydrogen bond formation involving proton transfer; this is further consistent with the lower basicity of type II compounds compared to I. The UV spectra of compounds of the type II in the crystalline state contain primarily bands due to their respective N forms.

Using the UV absorption spectra of compounds IIa-f in buffered aqueous solutions it is possible to compare the pH dependent behavior of compounds I and II in solution.

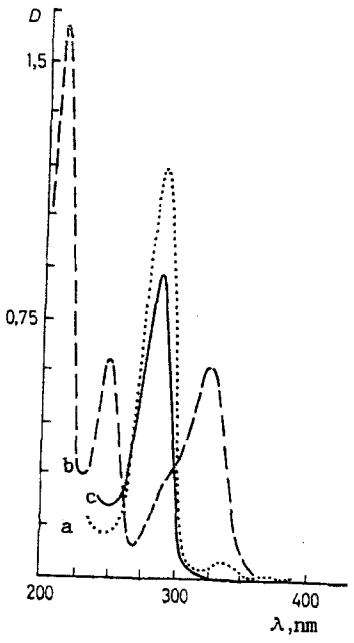


Fig. 1

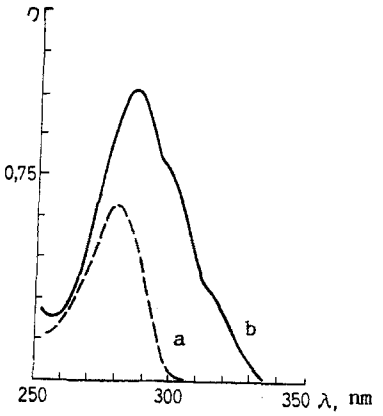


Fig. 2

Fig. 1. UV absorption spectra of 2,6-dimethyl-3-hydroxypyridine (Ib) in alcohol (a), water (pH 7.05) (b), and chloroform (c).

Fig. 2. UV absorption spectra of 2-benzyl-3-hydroxypyridine (Ic) in chloroform (a) and in KBr (b).

As mentioned above, compound IIa exists in solution at pH 4.30 as a mixture of its N and B forms in a 50:1 ratio [4]. We have found that this ratio remains practically unchanged as the solution acidity is increased to pH 3.10, although at pH 1.75 form B could no longer be detected; in more acidic media (pH −0.45) compound IIa exists in its C form. In neutral solution (pH 7.05) the absorption bands of three forms, N, B, and A, are observed, while the concentration of the B form is lower in neutral solution than at pH 3.10. An analogous pattern was observed for compounds IIb, c, and g (Tables 1, 2), although the concentration of the B form for compound IIc was 15% at pH 3.10. Compound IId is of special importance among the pyrimidine derivatives studied. This compound exists in its C form even at pH 3.10, while at pH 7.05 it exists as a 1:3 mixture of the N and B forms. In the pyridine series the same ratio of forms was observed in the case of 2,6-dimethyl-3-hydroxypyridine (Ib). The UV spectra of compound IId in aqueous solution were recorded over the entire pH range from −0.30 to 11.00; in the pH range 4.00-8.00 the spectral measurements were made in 0.1-0.5 pH intervals. The observed spectral changes in the pH range 3.10-7.55 are illustrated in Fig. 4. At pH values lower than 3.55 compound IId exists in the C form; in the range $4.00 < pH < 5.05$ absorption bands of the N, C, and B forms are observed, at $5.05 \leq pH < 7.40$ the N and B forms, at $7.40 < pH < 7.55$ forms N, B, and A are observed, and finally at pH 7.75 only the absorption bands of the A form are present. The largest concentration of the B form was found at pH 6.10 (N:B ratio equal to 1:4).

Introduction of a phenyl group into the pyrimidine ring (compounds IIe-g) leads to a significant shift of the N ⇆ B equilibrium in favor of the neutral form. In neutral solution these compounds exist only in their N and A forms, and in more acidic media predominantly in the N forms. It was not possible to obtain the completely protonated C forms for compounds IIe and f (Table 2), even at pH −0.45, apparently due to the reduced basicity of these compounds, the result of the phenyl group influence.

We have demonstrated in the present study that substituted 5-hydroxypyrimidines II are capable to existing in B forms. The amount of the B form increases in the transition from the unsubstituted derivative to the mono-, di-, and trimethyl substituted 5-hydroxypyrimidines. The pH ranges in which the B forms are found depend on the nature of the compound and the type of substitution. The maximum concentration of the B form in the case of 3-hydroxypyridines is observed in neutral solutions; in contrast, the maximum concentration of the B form is observed in acidic solutions (pH ~3-4) for 5-hydroxypyrimidines, and

Fig. 3. IR spectra of KBr pellets in the region 3600-1700 cm^{-1}: a) 3-hydroxypyridine (Ia); b) 3-hydroxy-2,6-dimethylpyridine (Ib); c) 2-phenyl-4,6-dimethyl-5-hydroxypyrimidine (IIf); d) 2-methyl-5-hydroxypyrimidine (IIb); e) 5-hydroxypyrimidine (IIa); f) 4,6-dimethyl-5-hydroxypyrimidine (IIc); g) 2,4,6-trimethyl-5-hydroxypyrimidine (IId).

at pH 6.10 in the case of compound IId which is consistent with the basicity pattern of these compounds.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 325 or Specord IR-75 spectrophotometer in the form of either KBr pellets (1:800) or $CHCl_3$ solutions. UV spectra and their first and second derivative spectra were measured on a Beckman DU-8 spectrophotometer in aqueous solutions (pH −0.30-11.00), $CHCl_3$, DMSO, alcohol ($c = 10^{-4}$ mole/liter; d = 1 cm), and also in KBr pellets (0.1:800 mg).

Buffer solutions were prepared as follows: pH −0.45 from 0.1 N HCl solution; pH 1.75 in 0.1 N potassium tetraoxalate solution; in the range pH 2.0-8.0 by mixing 0.4 N Na_2HPO_4 and 0.3 N citric acid solutions at various ratios; in the range pH 8.0-9.2 by mixing 0.1 N borax and 0.1 N HCl solutions; pH 9.2-12.0 by mixing 0.1 N borax solution with 0.1 N NaOH. The pH values of the buffers were measured using an ÉV-74 universal ion meter at 20°C.

The relative concentrations of the different tautomeric forms of compounds I and II were measured based on their UV absorption spectra, according to the following procedure: the values of the extinction coefficients for the absorption band maxima were determined from chloroform solutions for the N form, from aqueous solutions at pH −0.45 for the C forms, and from pH 11.00 solutions for the A forms. In the case of overlap of bands due to different tautomeric forms the contributions of adjacent or overlapping bands were estimated using the assumption that the parameters of the bands (half-width, asymmetry coefficient, etc.) were approximately the same as the corresponding parameters for the same bands in the corresponding form of compound Ia, which were determined in [3]. The relative concentrations of the different forms were determined with an accuracy of ±10%, although in the case of weak bands the accuracy was substantially poorer (±25%). The validity of this approach was confirmed using 3-hydroxypyridine Ia as an example; a N:B ratio of 1:1 was determined for this compound at pH 7.05 using this method, which is analogous and consistent with the results reported in previous studies [3-5]. For methyl substituted 5-hydroxypyrimidines the form of their absorption bands was assumed to be similar to the pyridine derivatives. Values of their extinction coefficients were determined in the same way as for the methyl substituted 3-hydroxypyridines.

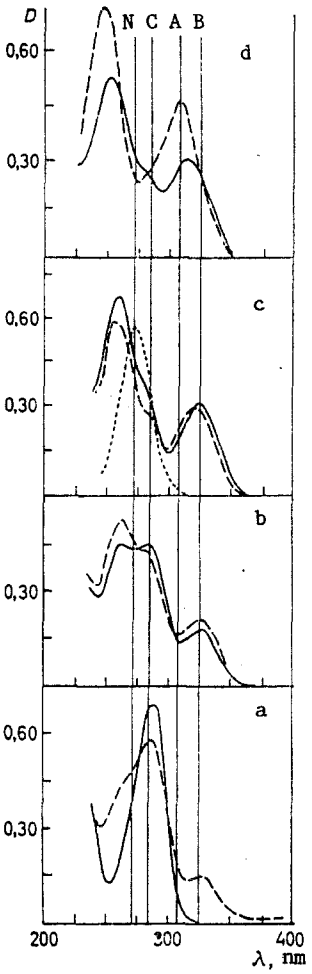


Fig. 4. UV absorption spectra of 2,4,6-trimethyl-5-hydroxypyrimidine (IId) in aqueous buffer solutions: a) —— at pH 3.10; --- at pH 4.55; b) —— at pH 4.80; --- at pH 5.05; c) —— at pH 6.10; --- at pH 7.05; ····$CHCl_3$; d) —— at pH 7.40; --- at pH 7.95. N, neutral form; C, cationic, A, anionic; B, bipolar.

Reagent Ia was obtained from the RIAP plant in Kiev, compounds Ib-d were synthesized according to [12], IIa according to [13], IIc, d, f according to [14], and IIg according to [15]. The compounds were purified by distillation, recrystallization, or column chromatography, as appropriate. The melting points of the purified compounds agreed with their literature values.

5-Hydroxy-2-methylpyrimidine (IIb). A mixture of 2.0 g (11 mmole) 5-bromo-2-methylpyrimidine and 3.24 g (60 mmoles) sodium methoxide in 100 ml absolute methanol was heated in an autoclave at 180°C for 7 h. The reaction mixture was diluted with 70 ml water, acidified with 2 N HCl to pH 2-3, and extracted with hot chloroform for 10 h. The chloroform solution was dried and evaporated, and the residue was subjected to column chromatography on silica gel with chloroform eluent. Yield 0.5 g (40%) of compound IIb, mp 175-179°C; literature mp 173°C [16].

5-Hydroxy-2-phenylpyrimidine (IIe). A mixture of 2.2 g (9.3 mmoles) 5-bromo-2-phenylpyrimidine and 2.5 g (47 mmoles) sodium methoxide in 80 ml absolute methanol was heated in an autoclave at 180°C for 7 h. The reaction mixture was diluted with 50 ml water, acidified with 2 N HCl to pH 2-3, and extracted with chloroform; the chloroform solution was dried and evaporated, and the residue was separated on a silica gel column with chloroform and chloroform–acetone (4:1) eluents. Yield 1.15 g (73%) of compound IIe, mp 150-153°C; literature mp 148-151°C [16].

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OXIDATION OF HYDROXYAMINO- AND NITROSOPYRIMIDINES. SYNTHESIS OF 2- AND 4-NITROPYRIMIDINES

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Oxidation of phenyl- and methyl-substituted 2- and 4-hydroxyamino- and -nitrosopyrimidines has given the azoxy- and nitropyrimidines, respectively. The behavior of the nitropyrimidines obtained towards reduction and nucleophilic substitution is considered.

Electrophilic substitution in pyrimidines is difficult. Nitration of pyrimidines is facilitated by the presence in the ring of strongly electron-donating substituents, to give 5-nitropyrimidines only [1]. Pyrimidines with a nitro-group in even-numbered positions in the ring have until recently been difficult to obtain, being synthesized by oxidation of S,S-dimethyl-N-(2-pyrymidinyl)sulfilimine [2] or 5-dimethylamino-7-hydroxy[1,2,5]oxadiazolo[3,4-d]pyrimidine 1-oxide [3], or by oxidative photolysis of aryl-2-azidopyrimidines [4].

α-Nitroazines have been obtained from nitroso- and aminoazines by treatment with strong oxidizing agents such as ozone [2, 5], sodium hypochlorite [2], permaleic acid [6], trifluoroperacetic acid [7], H_2O_2 in concentrated sulfuric acid [8, 9], and oxygen in sodium hydroxide solution [10].

In the course of earlier investigations, it was shown that oxidation of hydroxyaminopyrimidines with activated MnO_2, Ag_2CO_3, or $BaMnO_4$ affords the 2- and 4-nitrosopyrimidines [11]. The object of the present investigation was to study further the behavior of phenyl-

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