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ACID–BASE PROPERTIES AND STRUCTURES OF 5-HYDROXYPYRIMIDINE DERIVATIVES AND THEIR N-OXIDES

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UDC 547.854:543.257.1:541.623

The acid–base properties of some 5-hydroxypyrimidine derivatives and their N-oxides were investigated in comparison with the analogous 3-hydroxypyridine derivatives. It was found that 5-hydroxypyrimidines exist in the hydroxy form and are protonated at the nitrogen atom, whereas their N-oxides are protonated at the oxide oxygen atom, in contrast to the N-oxides of other diazines (pyridazine and quinoxaline). The character of the effect of ortho and para substituents (alkyl, benzyl, and phenyl) on the basicities and acidities of the indicated compounds was ascertained.

Virtually no data on the acid–base equilibria of 5-hydroxypyrimidine derivatives (I) are available; this is due to their low accessibility. At the same time, data on the acid–base transformations of 3-hydroxypyridine derivatives (II) [1-3], of which I are aza analogs, are available. In this connection, it seemed of interest to study the acidities and basicities of derivatives I and their 1-oxides (III) and to compare them with data on derivatives II.

The basicities of the selected compounds were studied in nitromethane, which is suitable for the determination of the pK_{BH^+} values of weak bases, which I and, particularly, III are, and was previously used for the investigation of derivatives II [1], pyrimidine, and 1,3,5-triazine [4]. To determine the acidities of I and III we used 50% alcohol, in which these compounds are more soluble than in water.

Before we discuss the data obtained, we must examine the tautomeric compositions and the direction of the protolytic reactions of the investigated compounds. Judging from the literature data and our data, derivatives I exist in the hydroxy form (IV) in the selected solvents. In fact, it is known that the tautomeric equilibria of I are shifted to favor the hydroxy form to a much greater degree than in the case of II (in aqueous solution the amount of the hydroxy form for 3-hydroxypyridine is ∿50%, as compared with 98% for 5-hydroxypyrimidine) [5]. The normal form of the titration curves [6] of derivatives I indicates that they are protonated at one of the nitrogen atoms (hydroxy form) rather than at the oxygen center (the zwitter-ion form). Finally, the introduction of a 5-hydroxy group has only a slight effect on the basicity of pyrimidine in nitromethane (the pK_{BH^+} of pyrimidine is

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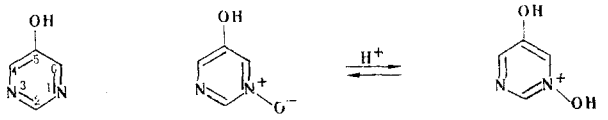
 0009-3122/83/1909-1012$07.50

TABLE 1. Effect of Methyl and Phenyl Groups on the Basicities of Pyridines and Pyrimidines and Their N-Oxides in Nitromethane

Pyridine			3-Hydroxypyridine			5-Hydroxypyrimidine			5-Hydroxypyrimidine 1-oxide		
X	pK_{BH^+} [21]	ΔpK^*	X	pK_{BH^+} [1]	ΔpK^*	X	pK_{BH^+}	ΔpK^*	X	pK_{BH^+}	ΔpK^*
H	11,95	0,00	H	11,85	0,00	H	8,21	0,00	H	6,55	0,00
2,6-Me_2	13,43	1,5	2,6-Me_2	13,63	1,8	4,6-Me_2	10,24	2,0	4,6-Me_2	8,48	1,9
2,4,6-Me_3	14,45	2,5		11,36		2,4,6-Me_3	11,18	3,0	2,4,6-Me_3	8,76	2,2
			2-Ph		−0,5	4-Ph	8,72	0,5			

*The change in the pK_{BH^+} value relative to the unsubstituted compound.

8.04 [4], and the pK_{BH^+} of 5-hydroxypyrimidine is 8.21), as one should expect [1, 6] if derivatives I exist in hydroxy form IV.*



IV V VI

It follows from the data in [7, 8] that when the nitrogen atom is oxidized, the tautomeric equilibria of hydroxy-substituted azines are shifted to favor the hydroxy from. This means that 5-hydroxypyrimidine N-oxide and its derivatives should exist in the hydroxy form (V) in solution and that their observed pK_{HA} values characterize the acidities of the hydroxy groups. As regards the protonation of these compounds, it may occur both at the $N_{(3)}$ atom and at the oxide oxygen atom. An examination of the form of the potentiometric titration curves of the investigated N-oxides (Tables 1 and 2) in nitromethane showed that they have increased slopes and additional potential differences at the half-neutralization points. The indicated distortions of the form of the titration curves are associated with a peculiarity of oxygen bases, viz., the tendency to form stable complexes† of the $B\cdots HB^+$ type in nitromethane and constitute evidence [6, 9] for the addition of a proton to the oxide oxygen atom to give a cation (VI). The reason for this is that the electron-acceptor N-oxide group (σ = 1.48 [10]) significantly weakens the basicity of the heterocyclic nitrogen atom, and the proton adds to the $N^+{-}O^-$ group. The decrease in the pK_{BH^+} values in nitromethane on passing from 5-hydroxypyrimidine (Ia) to its 1-oxide (IIa) (by 1.7 pK units) shows that the N-oxide group weakens the basicity of the azine nitrogen atom by a value that is much larger than 1.7 pK units.

Contradictory results were obtained in [11, 12] in a study of monoxides of p-diazines (pyridazine and quinoxaline) in aqueous media, in which the proton adds to the nitrogen atom. In addition to the spatial proximity of the electron-acceptor N-oxide and aza groups in pyrimidine, the reason for this difference may be the effect of the medium. In fact, in water the N-oxide group, which has a partial minus charge on the electronegative oxygen atom, is solvated strongly due to the formation of $HOH\cdots{}^-O{-}N^+$ hydrogen bonds, which lowers the basicity of this group relative to the nitrogen atom. In nitromethane, which is virtually incapable of forming such hydrogen bonds, the basicity of the N-oxide group increases as compared with the azine nitrogen atom [13] to such an extent that precisely the oxide oxygen atom becomes the protonation center. ‡

It follows from the data presented above that, under the experimental conditions, the investigated I and III derivatives exist in the hydroxy form and split out a proton from the hydroxy group; the protonation of I in nitromethane takes place at one of the nitrogen atoms, whereas the protonation of III takes place at the oxygen atom of the $N^+{-}O^-$ group.

*On passing from pyridine to the 3-hydroxypyridinium ion the basicity in nitromethane increases by 3.5 pK units [6], whereas for derivatives II the basicities are close to the basicity of pyridine (Table 1).

†The K_{BHB^+} values of the investigated 1-oxides of I range from 3.3 to 3.7.

‡A similar pattern was observed for the bifunctional p-$Me_2NC_6H_4P(Et_2)O$, which adds a proton at the nitrogen atom of the p-NMe_2 group in water but adds a proton at the oxide oxygen atom in nitromethane [15].

TABLE 2. Effect of Substituents in the 2 Position on the Basicities of 5-Hydroxypyrimidines and Their N-Oxides in Nitromethane

Substituents			5-Hydroxy-pyrimidine		5-Hydroxypyrimidine 1-oxide	
2-X	4-X	6-X	pK_{BH^+}	ΔpK^*	pK_{BH^+}	ΔpK^*
H	Me	Me	10,24	0,00	8,48	0,00
Me	Me	Me	11,18	0,9	8,76	0,3
Pr	Me	Me	11,84	1,6	—	—
i-Pr	Me	Me	11,17	0,9	8,88	0,4
t-Bu	Me	Me	11,42	1,2	—	—
C_5H_{11}	Me	Me	11,33	1,1	8,94	0,5
$PhCH_2$	Me	Me	10,55	0,3	8,02	−0,5
Ph	Me	Me	9,20	−1,0	—	—

*The change in the pK_{BH^+} values relative to the 4,6-dimethyl derivative.

An examination of the effect of o-methyl and phenyl groups on the basicities of mono- and diazines (Table 1) showed that in azines the steric hindrance created by ortho substituents is weakened significantly as compared with the aromatic ring [14] and that two methyl groups, regardless of whether they are in the ortho or para positions, increase the basicities of pyridine, 3-hydroxypyridine, and 5-hydroxypyrimidine (1.5-2 pK units) by a factor of approximately two as compared with three methyl groups (1 pK unit). As regards the 2-phenyl group, it decreases the basicities of 3-hydroxypyridines appreciably, evidently due primarily to the inductive effect of the ortho substituents in azines [16]. A phenyl ring in the 4 position increases the pK_{BH^+} value of 5-hydroxypyrimidine, since in this case a proton can add to the $N_{(1)}$ atom in the para position relative to the 4-Ph group, which is conjugated with the aza group of the electron-acceptor pyrimidine ring; in fact, the 2-Ph group, which is in the ortho position relative to both nitrogen atoms of derivatives I, decreases its basicity by 1 pK unit (Table 2).

The data in Table 2 make it possible to observe the effect of ortho substituents (2-X) on the basicities of 4,6-dimethyl-substituted I and its 1-oxide. In the I series this effect has primarily inductive character: Alkyl groups (the σ^* value for the H atoms is 0.49, whereas σ^* ranges from 0 to −0.15 for alkyl groups [17]) increase the basicities of derivatives I by 1-1.5 pK units (the 0.7 decrease in the pK_{BH^+} value on passing from the propyl group to the isopropyl group is possibly associated with the steric effect of a branched substituent), the phenyl group ($\sigma^* = 0.60$ [17]) decreases the pK_{BH^+} value by 1 pK unit, and the benzyl group ($\sigma^* = 0.20$) occupies an intermediate position.

In the series of III derivatives the effect of alkyl groups is weakened (ΔpK 0.3-0.5) because of the great distance between the 2-X substituent and the reaction center; the negative effect of the benzyl group (ΔpK = −0.5) is possibly associated with its steric effect in N-oxide III, in which steric interactions should be manifested to a greater degree than in pyrimidinium cations [14, 16].

On turning to an examination of the acidities of the investigated compounds in 50% alcohol, let us note that the introduction of a second nitrogen atom into the azine ring (the pK_{HA} value of 3-hydroxypyridine is 9.49, and the pK_{HA} value of 5-hydroxypyrimidine is 7.54) increases the acidity by 2 pK units; this is associated with the significant increase in the electron-acceptor character of the pyrimidine ring as compared with the pyridine ring. A similar phenomenon is observed on passing from phenol (pK_{HA} 9.99 in water [18]) to 3-hydroxypyridine (pK_{HA} 8.72 in water [18]). The further 2-pK unit increase in the acidity on passing from I to III is due to intensification of the electron-acceptor properties of the N-oxide group as compared with the azine N atom.

The effect of p-oriented alkyl and aryl substituents (2-X) on the acidities of the hydroxy groups of derivatives I corresponds to their effects in the benzene ring [the σ values of alkyl groups range from −0.13 to −0.20, σ (benzyl) = −0.10, and σ (phenyl) = −0.01]. The effect of an o-phenyl group (pK_{HA} values from 7.54 to 8.12) is considerably greater than that of a p-phenyl group (ΔpK 0.2), which may be associated both with hindrance to solvation of the 5-pyrimidinolate anion and with the formation of an intramolecular hydrogen bond between the hydroxy group and the π-electron system of the phenyl ring. How-

TABLE 3. Effect of Substituents on the Acidities of 5-Hydroxypyrimidines and Their N-Oxides in 50% Alcohol

Substituents			5-Hydroxypyrimidine		5-Hydroxypyrimidine 1-oxide	
2-X (p-X)	4-X (o-X)	6-X (o-X)	pK_{HA}	ΔpK*	pK_{HA}	ΔpK*
H	H	H	7,54	—	5,46	—
H	Ph	H	8,12	—	5,63	—
H	Me	Me	8,27	0,00	6,00	0,00
Me	Me	Me	8,84	0,6	6,83	0,8
Et	Me	Me	8,83	0,6	—	—
Pr	Me	Me	9,08	0,9	—	—
i-Pr	Me	Me	8,95	0,7	7,07	1,1
t-Bu	Me	Me	9,43	1,2	—	—
C_6H_{11}	Me	Me	8,89	0,6	6,88	0,9
$PhCH_2$	Me	Me	8,69	0,4	6,64	0,6
Ph	Me	Me	8,50	0,2	6,42	0,4

*The change in the pK_{HA} value relative to the 4,6-Me_2 derivative.

ever, in the analogous N-oxide system the o-phenyl group increases the pK_{HA} value to a lesser degree ($\Delta pK = 0.2$), and the solution of this problem requires additional study. The effects of para substituents in III are 0.2-0.4 units greater than in I; this is associated with the increased electron-acceptor character of the N-oxidated ring.

Thus we have investigated the acid–base properties of 5-hydroxypyrimidines and their N-oxides as compared with the analogous 3-hydroxypyridine derivatives. The effect of ortho substituents on the basicities of 5-hydroxypyrimidines has primarily inductive character. The effect of para substituents on the acidity of the OH group of 5-hydroxypyrimidines corresponds to their effect in the benzene ring. The increased effect of para substituents in 5-hydroxypyrimidine 1-oxide is explained by an increase in the electron-acceptor character of the N-oxidated ring. In the 3-hydroxypyridine, 5-hydroxypyrimidine, and 5-hydroxypyrimidine 1-oxide series the acidity of the hydroxy group increases substantially; this is associated with the introduction of electron-acceptor aza and N-oxide groups.

EXPERIMENTAL

The pK_{HA} values in 50% (by volume) alcohol were determined by potentiometric titration [19] with a 0.01 M solution of sodium hydroxide in the same solvent with the aid of glass (ÉSL-43-07) and ordinary silver chloride (ÉVL-1MZ) electrodes at solution concentrations of 0.001 g-mole/liter; the measuring system was calibrated with respect to aqueous buffer solutions (potassium biphthalate and sodium tetraborate), and the pK_{HA} values obtained are therefore relative values.

The pK_{BH^+} values in nitromethane were found by potentiometric titration with perchloro acid by the methods in [20, 21] with the aid of glass (ÉSL-43-07) and modified calomel electrodes at solution concentrations of 0.0025 g-mole/liter. The results obtained were reduced to the pK_{BH^+} value of diphenylguanidine (17.2) as the standard [20].

Compounds I were synthesized by the method in [22], and N-oxides III were synthesized by oxidation of the corresponding 5-hydroxypyrimidines with perbenzoic or p-nitroperbenzoic acid [23]. The homogeneity of the compounds obtained was monitored by thin-layer chromatography (TLC); the compounds were purified by sublimation in a stream of CO_2 and by recrystallization until they had constant melting points or the melting points were in agreement with the literature values [24].

The authors thank V. F. Sedova and V. P. Mamaev for providing the 4-phenyl-5-hydroxypyrimidine and its 1-oxide for the studies.

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SYNTHESIS AND STRUCTURE OF 1-(1-NAPHTHYL)DIHYDROURACIL DERIVATIVES

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UDC 547.854.2.83'652.1.07:548.737:543.422'51

The reaction of urea or thiocyanates in acidic media with N-(1-naphthyl)-α(and β)-methyl-β-alanines was used to synthesize 5(and 6)-methyl-1-(1-naphthyl)dihydrouracils and 5(and 6)-methyl-1-(1-naphthyl)-2-thioxodihydrouracils. The conformers of 6-methyl-1-(1-naphthyl)-2-thioxodihydrouracil were separated and subjected to x-ray diffraction analysis.

1-Aryldihydrouracil derivatives are of interest as stabilizers of the thermal-oxidative destruction of polymers [1].

The synthesis of 5(and 6)-methyl-1-(1-naphthyl)dihydrouracils I and II and 5(and 6)-methyl-1-(1-naphthyl)-2-thioxodihydrouracils III and IV was realized by heating N-(1-naphthyl)-α(or β)-methyl-β-alanines with urea or thiocyanates in acidic media.

We have observed for the first time that 1-(1-naphthyl)-substituted dihydrouracils I-IV are produced in the form of mixtures of conformers. Doubled signals of $-CH_2-\underset{|}{CH}-CH_3$ groups are observed in the PMR spectra of I-IV (Table 1) at 30°C. 6-Methyl-(1-naphthyl)-2-thioxodi-

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1267-1272, September, 1983. Original article submitted February 3, 1983.

 0009-3122/83/1909-1016$07.50