# INVESTIGATION OF PYRIMIDINE-5- AND PYRIMIDINE-2-CARBOXYLIC ACIDS

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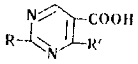
The dissociation constants of pyrimidine-5- and pyrimidine-2-carboxylic acids were determined to ascertain the effect of the character of the substituent and its position in the pyrimidine ring. This effect was compared with the effect of substituents on the dissociation constants of the corresponding benzoic acids.

In order to ascertain the effect of substituents in the pyrimidine ring, in a previous communication [1] we described the effect of substituents on the ionization constants of pyrimidine-4-carboxylic acids. In the present study, we have investigated the effect of substituents in pyrimidine-5- and pyrimidine-2-carboxylic acids. As compared with pyrimidine-2- and pyrimidine-4-carboxylic acids, pyrimidine-5-carboxylic acid is the weakest acid, which is explained by the peculiarity of the 5 position in the pyrimidine ring [1]. The $pK_a$ values were determined for the pyrimidine-5-carboxylic acids obtained since, except for isoorotic acid (VI), there are no data on the ionization constants of these acids (Table 1) in the literature.

It is interesting to compare acids II-IV with the corresponding para-substituted benzoic acids [2]. The hydroxyl group in II exerts the same +C effect as in the corresponding benzoic acid (the changes in the $pK_a$ values are +0.33 and +0.37, respectively). It would seem that this contradicts the generally acknowledged data, according to which 2- and 4-hydroxypyrimidines exist in the lactam form. The ring nitrogen atoms are apparently protonated in aqueous solutions under the conditions of titration of the acids, and the equilibrium is shifted to favor the hydroxy form. The amino group in acid IV has a considerably greater effect on the ionization constant than in p-aminobenzoic acid (the changes in the $pK_a$ values are +1.31 and +0.75, respectively). The $NH_2$ group in V has a still greater effect, and the $pK_a$ changes by +2.46. The decrease in the ionization constants of IV and V under the influence of amino groups is in conformity with the

TABLE 1. Ionization Constants of Pyrimidine-5-carboxylic Acids (I-VIII)



| Compound | R | R′ | $pK_a$ | $pK_a$ of benzoic acids |
|---|---|---|---|---|
| I | H | H | 3,16 | 4,17 |
| II | OH | H | 3,49 | 4,54 |
| III | $SC_2H_5$ | H | 3,39 | |
| IV | $NH_2$ | H | 4,47 | 4,92 |
| V | H | $NH_2$ | 5,62 | 5,00 |
| VI | OH | OH | 4,32* | |
| VII | SH | OH | 3,87 | |
| VIII | Cl | Cl | 3,10 | |

*According to the literature [3], the $pK_a$ is 4.16.

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increase in the basicity of 2-amino- and 4-aminopyrimidines as compared with pyrimidine (the $pK_a$ values are 3.54 and 5.71, respectively, as compared with 1.30 for pyrimidine). This increase in the basicity is due to the existence of the amines in the imino form, which promotes their more facile protonation. The second hydroxyl group in isoorotic acid (VI) increases the $pK_a$ as compared with acid II by almost one order of magnitude, which, in contrast to orotic acid [1], is explained by the formation of a strong hydrogen bond between the carboxyl group and the C = O group in the 4 position. As compared with VI, the SH group in acid VII, like that in p-mercaptobenzoic acid, exhibits an electron-acceptor effect due to the free d orbitals of the sulfur atom.

The chlorine atoms in 2,4-dichloropyrimidine-5-carboxylic acid (VIII) have almost no effect on the ionization constant as compared with unsubstituted acid I. No explanation has yet been found for this fact, if one takes into account that the chlorine in o-chlorobenzoic acid very markedly increases the ionization constant of the acid as compared with benzoic acid ($pK_a$ 2.89).

We examined the transfer of the substituent effect from the 5 position in pyrimidine-2-carboxylic acid (IX) ($pK_a$ 2.99, $K = 1.02 \cdot 10^{-3}$) only in the case of 5-bromopyrimidine-2-carboxylic acid (X) ($pK_a$ 2.80, $K = 1.58 \cdot 10^{-3}$), in which the bromine, as in p-bromobenzoic acid [2], increases the ionization constant only slightly.

## EXPERIMENTAL

The $pK_a$ values of the pyrimidinecarboxylic acids were determined by potentiometric titration with an LPU-01 potentiometer at 20° in aqueous solutions. The investigated compounds were obtained via the methods in [4,5] (I), [6,7] (II and III), [7] (IV and VI), [10] (VII), [11] (VIII), [12] (IX), and [13] (X).

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