INVESTIGATION OF PYRIMIDINE-4-CARBOXYLIC ACIDS

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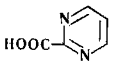
The effect of various substituents in the 6 position on the ionization constants of pyrimidine-4-carboxylic acids was studied and compared with the effect of substituents on the dissociation constants of the corresponding meta-substituted benzoic acids.

A number of pyrimidine-4-carboxylic acids and pyrimidine-2- and 4-carboxylic acids were synthesized in order to study the effect of substituents on the ionization constants of the acids; the pK_a values of the acids, which have not been reported for most of the pyrimidinecarboxylic acids described in the literature, were also determined.

We selected these compounds for the investigations because the evaluation of the above-indicated substituent effect is quantitative, since it is expressed by accurate pK_a values of the acids and, in addition, because small amounts of the substances are required for these investigations.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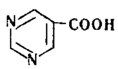
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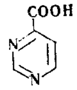
III

In comparing the pK_a values of the unsubstituted pyrimidinecarboxylic acids, it is seen that the ionization constants are somewhat greater for acids I (2.99) and III (2.98), in which the carboxyl groups are in the 2, 4, and 6 positions, with the most reduced electron density than for pyrimidine-5-carboxylic acid (II) (3.16) and are approximately an order of magnitude greater than the ionization constant of benzoic acid [1].

It is interesting to compare the effect of substituents in 6-substituted pyrimidine-4-carboxylic acids (IV-XII) with the effect of substituents in meta-substituted benzoic acids [1] on the ionization constants of these acids (the pK_a values of the acids are presented in Table 1).

As in the case of meta-substituted benzoic acids, the effect of substituents in IV-XII should be considered to be the overall result of conjugation (C) and inductive (I) effects, with predominance of one or the other effect as a function of the character of the substituent and the effect of the nitrogen heteroatoms. In acids IV and IX, the hydroxyl and chloro groups, just as in the corresponding benzoic acids, display electron-acceptor properties and increase the dissociation constants of the acids. The pK_a values of the acids demonstrate that the hydroxyl group has an identical effect on IV and m-hydroxybenzoic acid, while the effect of chlorine in m-chlorobenzoic acid is manifested more strongly than in IX. The methyl group in V exhibits the same electron-donor action as in m-methylbenzoic acid. The methoxy group in VI is exhibited as an electron donor, while it has electron-acceptor properties in the corresponding benzoic acid. This indicates that the mechanisms for transfer of the effect of the methoxy group differ – the +C effect predominates in the pyrimidine ring, while the I effect prevails in the benzoic acid.

The SH group in VII has an electron-donor (although weak) effect, while a considerable electron-acceptor effect (a Hammett σ_{μ} constant of +0.25) is displayed in m-mercaptobenzoic acid.

The sharp decrease in the ionization constant of VII (pK_a 6.25) is apparently explained by the formation of salt A rather than by the electron-donor effect of the NH_2 group.

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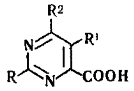
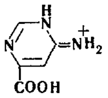
TABLE 1. Ionization Constants (pK_a) of Pyrimidine-4-carboxylic Acids



Comp.	R	R¹	R²	pK_a	Ionization constant	pK_a of benzoic acids
III	H	H	H	2,98	$1{,}05 \cdot 10^{-3}$	4,17
IV	H	H	OH	2,83*	$1{,}48 \cdot 10^{-3}$	4,12
V	H	H	CH_3	3,07	$8{,}51 \cdot 10^{-4}$	4,28
VI	H	H	OCH_3	3,68	$2{,}09 \cdot 10^{-4}$	4,09
VII	H	H	SH	3,02	$9{,}55 \cdot 10^{-4}$	
VIII	H	H	NH_2	6,25	$5{,}62 \cdot 10^{-7}$	4,82
IX	H	H	Cl	2,80	$1{,}59 \cdot 10^{-3}$	3,82
X	OH	H	OH	2,66*	$2{,}19 \cdot 10^{-3}$	
XI	SH	H	OH	2,72	$1{,}55 \cdot 10^{-3}$	
XII	Cl	H	Cl	2,81	$1{,}91 \cdot 10^{-3}$	

*The pK_a values according to [2] are as follows: 2.80 for IV, and 2.8, 2.4, and 2.07 for IX.



A

The character of the effect of the second substituent in the 2 position in acid X is the same as for the 6 position in IV. In XI, the SH group in the 2 position also increases the acidity, in contrast to VII, where it exerts a weak electron-donor effect.

The chlorine in the 2 position in XII does not exert an additional effect, since it is, as it were, blocked by the nitrogen heteroatoms, which is interesting and requires checking in other compounds.

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 compounds were obtained via the methods in [3-5] (I), [6,7] (II), [8-10] (III), [11] (IV), [12] (V), [13] (VII and VIII), [14] (X and XI), and [15] (XII).

6-Chloropyrimidine-4-carboxylic Acid (IX). A 3.95-g (28 mmole) sample of calcined potassium carbonate was added to a suspension of 8.05 g (57 mmole) of IV in 100 ml of water, and the solution was evaporated on a water bath to dryness to give 9.25 g of the potassium salt of acid IV. The salt was refluxed in a mixture of 76 ml (0.5 mole) of phosphorus oxychloride and 4.8 ml (0.04 mole) of dimethylaniline for 3 h. The excess phosphorus oxychloride was removed by vacuum distillation, the residue was poured slowly over ice with vigorous stirring, and the mixture was extracted with ether. The ether extract was dried over sodium sulfate. Removal of the ether gave 4 g (50%) of yellow crystals of IX with mp 132-133° (from petroleum ether). Found: C 37.96; H 2.05; N 17.60%. $C_5H_3N_2ClO_2$. Calculated: C 37.87; H 1.90; N 17.67%. The amide of acid IX was obtained as white crystals with mp 162-163° (from alcohol). Found: C 38.47; H 2.55%. $C_5H_4N_3OCl$. Calculated: C 38.11; H 2.55%.

6-Methoxypyrimidine-4-carboxylic Acid (VI). A solution of 0.5 g (3.3 mmole) of IX in 20 ml of absolute methanol was added to sodium methoxide (from 0.1 g of sodium and 5 ml of methanol). Sodium chloride precipitated immediately, and heating was observed. The suspension was refluxed for 40 min, the methanol was removed by vacuum distillation, and the residue was dissolved in 8 ml of water. The solution was heated to 50° and acidified to pH 3 with concentrated HCl to give 0.2 g of a precipitate with mp 235° (from water). The precipitate was purified by vacuum sublimation to give a substance with mp 198°. Found: C 46.53; H 4.17; N 18.16%. $C_6H_6N_2O_3$. Calculated: C 46.75; H 3.92; N 18.17%.

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