PROTOLYSIS CONSTANTS OF PYRIDAZIN-6-ONE DERIVATIVES

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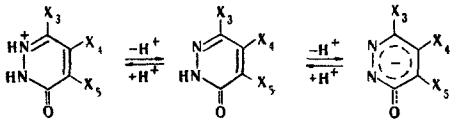
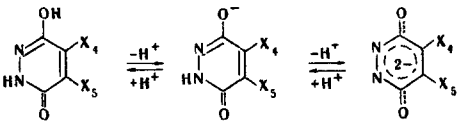
The protolysis constants of pyridazin-6-one and some of its derivatives have been determined by the spectrophotometric method. The influence of substituents on the value of the protonation constants is discussed.

For the successful development of the synthesis of new pyridazin-6-one derivatives, which possess various biological activities [1], all-round physicochemical investigations of these substances are required, in particular the study of tautomeric-protolytic equilibria among the substituted pyridazin-6-ones. In aqueous solutions of the pyridazin-6-ones equilibria exist either between the N-protonated cation a and the neutral molecule b or between the neutral molecule b and the anion c, depending on the acidity of the medium [2].



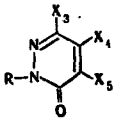
a b c

In the case of the 3-hydroxy derivatives (X_3 = OH), it has been shown [3] that the neutral molecule exists in the hydroxy-oxo form b and is therefore capable at higher pH values of splitting off another one or two protons, forming the corresponding monoanion c' or the dianion d':



b c d

Although the general features of the protonation of the pyridazin-6-ones and 3-hydroxypyridazin-6-ones have been investigated previously [2, 3], concrete values of pK_a were determined only for individual compounds of this series, and the accuracy of the figures obtained, particularly in the case of the cationic forms, is a matter of doubt. Consequently, we have undertaken a more detailed study of the protolysis of pyridazin-6-one derivatives on a relatively large number of compounds and in a wide range of pH values. The compounds studied in the present work correspond to structure A:



A

R=H, CH_3, C_6H_5;
X_3=H, CH_3, OCH_3, OH, Cl;
X_4=H, OH, NH_2;
X_5=H, NH_2, Cl.

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TABLE 1. Protolysis Constants of Pyridazin-6-one Derivative (in water)

Compound	R	X_3	X_4	X_5	$pK^{\oplus}_{NH}$	pK_{NH}	pK_{OH}	$pK^{\oplus}_{NH_3}$
I	H	H	H	H	−1,03±0,01	10,52±0,03	—	—
II	H	CH_3	H	H	−0,61±0,04	10,83±0,06	—	—
III	H	OCH_3	H	H	−1,03±0,01	10,79±0,04	—	—
IV	H	Cl	H	H	−1,86±0,01	8,91±0,03	—	—
V	H	OH	H	H	−0,95±0,08	>12	5,65±0,03	—
VI	H	H	NH_2	Cl	−1,77±0,02		—	
VII	CH_3	OH	H	H	−1,02±0,07	—	5,62±0,03	—
VIII	CH_3	OCH_3	H	H	−1,20±0,06	—	—	—
IX	C_6H_5	H	NH_2	Cl	−1,71±0,02	—	—	
X	C_6H_5	H	OH	Cl		—	2,93±0,06	—
XI	C_6H_5	H	NH_2	NH_2	−4,40±0,05	—	—	1,24±0,04

Transition from the cationic form to the less protonated forms b, c, c', and d' is characterized by a gradual bathochromic shift of the absorption band in the electronic spectra from 260 to 320 nm, and we used this for the spectrophotometric determination of the corresponding value of the basicity constants pK. We assigned figures obtained for the pK constants to definite protolytic equilibria, and these are given in Table 1. The constant $pK^{\oplus}_{NH}$ corresponds to the protonation of the nitrogen atom of the ring in position 2, pK_{NH} to the deprotonation of the nitrogen atom in the position 1, pK_{OH} to the formation of a phenolate anion, and $pK^{\oplus}_{NH_3}$ to the protonation of an amino group in a side chain.

Our measurements have shown that the $pK^{\oplus}_{NH}$ values for the majority of compounds studied are between −0.60 and −1.20, and only when strong electron-accepting substituents are present in position 3, 4, or 5 [Cl or NH_3^+ in the case of compounds (IV, VI, IX, and XI)] are more negative values obtained. This shows that the value of $pK^{\oplus}_{NH}$ given in the literature [2] for (V) (−2.2) is erroneous.

By means of the spectrophotometric method it was not possible to determine the pK_a values for all the expected protolytic transitions of compound (I-XI). For example, for compound (VI) the values of pK_{NH} and $pK^{\oplus}_{NH_3}$ are close to one another, which prevents the determination of the separate values of the corresponding constants.

Voluminous substituents in the ortho position relative to an amino group (compounds IX and XI) prevent the conjugation of the latter with the π-electronic system of the ring, in consequence of which the protonation of an amino nitrogen is not reflected in the nature of the electronic absorption spectrum. In the case of compound (XI), the two positively charged amino groups nevertheless affect the electronic system of the pyridazinone molecule. The inadequate solubility of compounds (IX) and (XI) in water did not permit the corresponding constants to be determined by the potentiometric titration of solutions of these substances.

For the determination of the protolysis constants $pK^{\oplus}_{NH}$ and pK_{NH} of compounds (I-V) it was not possible to find a linear correlation with the corresponding values of the σ constants, but a qualitative interconnection between the values of the protolysis constants and the polar effect of a substituent is observed, i.e., with an increase in the electron-accepting properties of the substituent X_3 the acidity of the compound increases.

The pK values obtained permit an idea to be obtained of the features of the electronic structure of the pyridazinone system and have been used in a study of the mechanism of the electrochemical reduction of pyridazin-6-one derivatives at a dropping mercury electrode [4].

EXPERIMENTAL

The spectrophotometric measurements were performed on $1 \cdot 10^{-4}$ M and $2 \cdot 10^{-4}$ M aqueous solutions of compounds (I-XI). To create the necessary pH values of the solutions investigated, borate, acetate, and glycine buffer solutions were used. To determine the $pK^{\oplus}_{NH}$ constants, solutions of hydrochloric and sulfuric acids were used, the H_0 functions of which were determined as described by Paul and Long [5]. The spectra were taken on a Specord UV VIS automatic spectrophotometer (GDR) and the pH values of the medium were determined on an LPU-01 instrument at 20°C. The calculations of the values of the constants were performed by means of known formulas [6] with corrections for the ionic strength of the solution.

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