RESEARCH IN THE ISOXAZOLE SERIES.

XXXI.* BASICITIES OF PHENYLISOXAZOLES

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The ionization constants of 14 phenylisoxazoles in acetic acid were determined by a spectrophotometric method. The ionization constants of 4-R-3,5-diphenylisoxazoles correlate well with the Hammett σ_m constants of substituents R.

The basicities of isoxazole derivatives were studied in [2-5], but the pK_a values of some phenylisoxazoles were presented only in [3]. In all cases the basicities were determined by a spectrophotometric method using acetic acid [2, 3] or aqueous [4, 5] solutions and the Hammett acidity function for the calculation of the ionization constants. The criterion of the applicability of this function to the selected class of compounds is the magnitude of n in the equation

$$H_0 = pK_a - n\lg \ ([\text{cation}]/[\text{base}]).$$

A base is assumed to be a Hammett base if $0.8 \leq n \leq 1.20$ [6-8]; in particular, it has been shown [4] that isoxazole derivatives are bases of this type. The doubts with respect to the correctness of the results obtained with acetic acid solutions [4] that have appeared recently are, in our opinion, groundless. Graphical evidence for this is offered by the pK_a values of 3,5-dimethyl-4-nitroisoxazole (I), determined in various media – -6.39 (method A) and -6.57 (method B†) in water and -6.17 in acetic acid, which differ within the limits of experimental error‡ from the pK_a value of -6.43 acknowledged as absolute by Burton and co-workers [4]. The increased basicity of nitroisoxazole I [3], which has served as the main object of criticism of the use of acetic acid [4], was associated with the incorrectly selected acidity range (0.2-6.0 M solutions of sulfuric acid in acetic acid). The difference in the pK_a values obtained in the present research is due to the effect of the medium and is comparable in magnitude to the scatter in the pK_a values calculated by various methods. The low basicity of I provides evidence for a more marked change in the electron density on the nitrogen atom of the heteroring and might have been expected from the effect of the NO_2 group in the heteroaromatic system. When the refined pK_a value of I is used, the $\sigma_m - \Delta pK_a$ correction parameters for a series of 4-R-3,5-dimethylisoxazoles [3] are approximately $r = 0.945$ and $s = 0.217$.

The pK_a values of 14 phenylisoxazoles were determined to ascertain the effect of substituents in the heterocyclic ring on the electron density on the nitrogen atom (Table 1). We used glacial acetic acid as the solvent, since phenylisoxazoles are insoluble in water. Sulfuric acid served as the proton donor.

We also used the Hammett H_0 acidity function to determine the ionization constants. It is apparent from Table 1 that, except for V, large deviations from unity are not observed for the n criterion. Thus it may be supposed that the H_0 acidity function is applicable for the determination of the pK_a values of most isoxazoles

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*See [1] for communication XXX.

†All of the data in Table 1 were calculated by method A [8]: the ε value in glacial acetic acid was adopted for ε_B, the ε value in concentrated sulfuric acid was adopted for the ε_{BH^+} value, and the ε values at an acidity equal to $pK_a \pm 1.5$ H_0 units were adopted for ε_{BH^+} and ε_B, respectively, by method B [8]. The data obtained by method B are designated by asterisks.

‡The usual error in the determination for bases with $pK_a < 0$ is ± 0.1 pK_a units [13], and in some cases it is ± 0.2 pK_a units [8].

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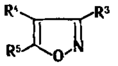
TABLE 1. UV Spectra and pK_a Values of Phenylisoxazoles and 3,5-Dimethyl-4-nitroisoxazole



Compound	R_3	R_4	R_5	λ_{max}, nm (lg ε)		pK_a	n
				in CH_3COOH	in 16.8 M soln. H_2SO_4 in CH_3COOH		
I	CH_3	NO_2	CH_3	264(3,74)	223(4,00)	−6,17±0,06	0,95
II	C_6H_5	H	H	251(3,88)	275(4,17)	−3,19±0,10	1,03
III	C_6H_5	H	CH_3	253(4,03)	273(4,28)	−2,38±0,02	0,85
IV	C_6H_5	H	Cl	250(4,01)	282(4,27)	−4,90±0,03	1,24
V	C_6H_5	NO_2	H	252(3,78)	283(3,98)	−7,90±0,17	1,43
VI	H	H	C_6H_5	262(4,27)	290(4,32)	−2,96±0,05	0,88
VII	CH_3	H	C_6H_5	262(4,27)	287(4,37)	−2,08±0,11	0,92
VIII	Cl	H	C_6H_5	261(4,31)	298(4,38)	−6,01±0,06	1,26
IX	H	Cl	C_6H_5	268(4,24)	307(4,28)	−5,16±0,06	1,26
X	Cl	Cl	C_6H_5	269(4,25)	313(4,25)	−7,70±0,22	0,99
XI	C_6H_5	H	C_6H_5	268(4,39)	312(4,47)	−3,05±0,05	1,03
XII	C_6H_5	CH_3	C_6H_5	267(4,29)	304(4,42)	−2,70±0,10	1,00
XIII	C_6H_5	C_6H_5	C_6H_5	275(4,23)	318(4,26)	−3,14±0,07 −3,00±0,07	1,05 0,88*
XIV	C_6H_5	Cl	C_6H_5	274(4,31)	319(4,38)	−4,68±0,04	1,16
XV	C_6H_5	Br	C_6H_5	273(4,27)	319(4,39)	−4.67±0,06	1,03

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*The pK_a and n values were obtained by the method in [8].

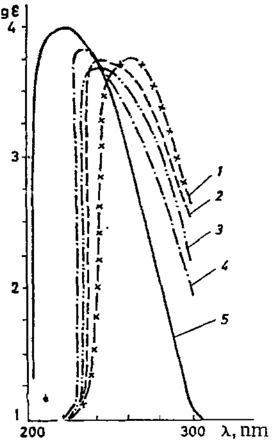

Fig. 1. Absorption spectra of 3,5-dimethyl-4-nitroisoxazole (I): 1) in CH_3COOH; 2) in a 7.00 M solution of H_2SO_4; 3) in an 8.00 M solution of H_2SO_4; 4) in a 9.25 M solution of H_2SO_4; 5) in a 16.80 M solution of H_2SO_4.

under our selected conditions. Judging from the n > 1.2 values for IV, VIII, IX, and V, the presence of acceptor substituents in the ring disrupts the usual protonation mechanism, and these substances can, strictly speaking, be distinguished from Hammett bases. According to our data, compounds that have two acceptor or two donor substituents best approximate Hammett bases: XI, XII, XIII, XV, and I have n values very close to unity.

It follows from the data obtained in this study that monosubstituted 3- and 5-phenylisoxazoles (II, VI) are weaker bases than the unsubstituted heterocycles [2, 4, 9], and II is weaker than VI. This is apparently associated with the −I effect of the phenyl group, which shows up most markedly in the 3-isomer. An increase in the number of phenyl groups does not lead to a sharp decrease in the basicity; a more complex dependence, which turns out to be a summation of the +M and −I effects of C_6H_5 groups, occurs here. The mono-, di-, and triphenylisoxazoles form the following series with respect to decreasing basicity: VI > XI > XIII > II. The presence in the molecule of two substituents with M and I effects with opposite signs, as, for example, in phenylchloroisoxazoles IV, VIII, and IX, gives a very complex overall effect, and the −I effect of chlorine plays the decisive role.

The electron-donor effect of the methyl group on the basicity of the isoxazole ring is identical, regardless of whether it is in the 3 or 5 position (compare II and III and VI and VII), and the difference between III and VII arises as a result of a change in the location of the phenyl group.

A good correlation between the ΔpK_a values (XI standard) and the σ_m substituent constants was found for a series of 4-substituted 3,5-diphenylisoxazoles (XI-XV); $\rho = 4.43$, $r = 0.997$, and $s = 0.09$ [10, 11]. The correlation is poorer in the case of σ_p constants ($\rho = 5.45$, $r = 0.966$, and $s = 0.293$).

There is evidently a certain analogy between the 4 position of the isoxazole ring (with respect to the nitrogen atom) and the meta position of a substituent in the benzene ring with respect to the reaction center.

EXPERIMENTAL

All of the isoxazole derivatives necessary for this study were obtained by described methods, and their physical constants were in agreement with the literature data.

Twice-distilled water was used for the determination of the pK_a value of isoxazole I; chemically-pure-grade glacial acetic acid, which was frozen out twice, was used for the remaining compounds. Analytical-grade 94% sulfuric acid (for the Saval test), the concentration of which was determined by indicator titration, served as the proton donor. The H_0 acidity function for acetic acid solutions of sulfuric acid was taken from [3]. The H_0 acidity function for aqueous solutions of sulfuric acid was taken from [12].

The UV spectra were recorded with a Perkin–Elmer 402 spectrophotometer in 1-cm-thick quartz cuvettes in a thermostatted block at $25 \pm 0.1°$. The solutions over the investigated concentrations ($2.5 \cdot 10^{-5}$ mole/liter) obeyed the Lambert–Beer law. The wavelengths at which the maximum on the absorption curve of the protonated (unprotonated) form is found under the minimum on the absorption curve of the other form [13] were used as the analytical wavelengths. The characteristic pattern of the UV spectra of a compound in solutions with various acidity is shown in Fig. 1. The calculations were made for a series of 11 solutions with different H_0 values. All of the results were treated statistically by the method of least squares; this made it possible to obtain the pK_a and n values and evaluate their confidence interval at a fixed reliability (α) of 0.95.

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