INVESTIGATIONS IN THE ISOXAZOLE SERIES.

39.* THE PROTONATION OF 3-PHENYL-2-OXAZOLINES

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An unusually powerful influence of substituents in position 5 on the basicity of 3-phenyl-2-isoxazolines has been shown by a spectrophotometric method. The ^{13}C NMR spectra of 3-phenyl-2-isoxazoline, of its meta-nitro derivative, and of model compounds have been studied, and on this basis it has been concluded that protonation takes place at the nitrogen hetero atom.

The powerful influence of a substituent in position 5 on the basicity of two 3-phenyl-5-R-isoxazolines has been given two possible explanations [2]: either the oxygen atom transmits this influence, or these compounds form conjugate acids of the oxonium type. Both explanations emphasized the peculiarity of the heterocyclic fragment of the 3-phenyl-2-isoxazoline (I) molecule, which cannot be considered simply as a cyclic oxime (see [3]).

In the present investigation for a definite elucidation of the position of protonation, we determined the pK_a values of compound (I) and of five of its derivatives (Table 1).

In the study of basicity, glacial acetic acid was used as the solvent and sulfuric acid as the proton donor. To calculate the ionization constants we used Hammett's H_0 acidity function. The deviation of the criterion n from unity was in the usual range, and it may therefore be considered that the H_0 function is fully applicable to the series investigated.

The practically identical UV spectra of the bases (I-VI) in acetic acid, on the one hand, and of the corresponding conjugate acids in sulfuric acid, on the other hand, indicate identical protonation centers in compounds (I-VI). The pK_a values reveal an unusually powerful influence of alkyl and phenyl substituents on the basicity in the series investigated; these magnitudes for the tetramethylene derivative (II) and the 5,5-diphenyl derivative (VI) differ from one another by unity and by 0.5 from the pK_a value of compound (I).

For oxygen-containing bases, branching at the α-carbon atoms leads to a fall in basicity, since solvation and, consequently, the stabilization of the protonated forms are decreased [4].

Conversely, compounds (III) and (IV), containing long alkyl chains in position 5 are no more basic than (I), which is indirect proof of the protonation of compound (I-VI) at the nitrogen atom in each case.

Weighty arguments in favor of this hypothesis were obtained in an investigation of the ^{13}C NMR spectra of the isoxazoline (I) and its meta-nitro derivative (VII) (in the form of the bases and the conjugate acids) and of five model compounds: 2-methyl-3-phenyloxazolin-2-ium methosulfate (VIII), 5-methyl-3-phenylisoxazole (IX), 2,5-dimethyl-3-phenylisoxazolium methosulfate (X), tetrahydrofuran (XI), and O-ethyltetramethyleneoxonium hexachloroantimonate (XII) (Table 2).

Protonation caused considerable changes in the chemical shifts of the carbon atoms of both the isoxazoline and the benzene nuclei. The protonation and N-methylation of compound (I) exerted similar effects on the chemical shift of the $C_{(3)}$ carbon on the isoxazoline nucleus. A similar effect took place in the case of 5-methyl-3-phenylisoxazole (IX), for which N-protonation has been demonstrated previously [5]. This is in agreement with the hypothesis that the center of protonation in each of compounds (I) and (VII) is the nitrogen atom. Less indicative are the changes in the chemical shifts of the $C_{(4)}$ and $C_{(5)}$ carbon

*For communication 38 see [1].

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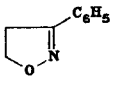
TABLE 1. UV Spectra and pK_a Values of 3-Phenyl-2-isoxazolines



Compound	x	R at the $C_{(x)}$ atom of the heterocycle	λ, nm (log ε)		pK_a
			CH_3COOH	16.8 N soln. of H_2SO_4 in CH_3COOH	
I	—	—	264 (4,12)	288 (4,20)	−2,35±0,07
II	4,5	$-(CH_2)_4-$	267 (4,05)	293 (4,13)	−1,85±0,05
III	5	n-C_4H_9	265 (4,13)	290 (4,19)	−2,14±0,05
IV	5	n-C_8H_{17}	265 (4,12)	290 (4,18)	−2,27±0,10
V	5	C_6H_5	265 (4,18)	293 (4,23)	−2,62±0,06
VI	5	$(C_6H_5)_2$	265 (4,19)	295 (4,22)	−2,90±0,08

TABLE 2. Carbon-13 Chemical Shifts in Compounds (I) and (VII-XII)

Compound	Solvent	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(1')}$	$C_{(2')}$	$C_{(3')}$	$C_{(4')}$	$C_{(5')}$	$C_{(6')}$	5-CH_3	2-CH_3
I	$CDCl_3$	156,8	35,2	69,2	129,5	126,2	128,7	130,0	128,7	126,7	—	—
I	A	166,1	36,8	73,3	122,2	131,2	131,5	138,1	131,5	131,2	—	—
I	CD_3OD	158,6	36,0	70,1	130,7	127,7	129,7	131,1	129,7	127,7	—	—
VII	$CDCl_3$	155,1	34,8	69,9	131,4	121,6	148,5	124,5	129,8	132,2	—	—
VII	A	164,7	37,0	73,9	124	125,9	149,7	131,7	133,2	137,0	—	—
VIII	CD_3OD	165,0	40,7	71,3	124,4	130,7	130,7	135,5	130,7	130,7	—	40,7
IX	$(CD_3)_2CO$	162,9	100,6	170,8	130,4	127,3	129,6	130,5	129,6	127,3	12,1	—
IX	A	161,8	106,0	178,3	122,3	131,6	130,0	136,4	130,0	131,6	13,8	—
X	B	159,7	107,4	174,3	122,3	129,4	129,7	133,2	129,7	129,4	12,1	39,7
XI	CD_2Cl_2	68,1	26,0	—	—	—	—	—	—	—	—	—
XII	CD_2Cl_2	72,6	26,5	—	—	—	—	—	—	—	—	—

atoms, for which the effects of N-methylation and protonation are different both for the isoxazoline derivative (I) and for the isoxazole derivative (IX). In both cases, $C(_4)$ experiences a large downfield shift on N-methylation, and $C(_5)$ on protonation. It is interesting that in their influence on the chemical shifts of the methylene carbons in the α- and β-positions to the oxygen of the heterocycle, the protonation of the isoxazolines (I) and (VII) is similar to the O-ethylation of tetrahydropyran (XI, XII). However, the lack of correspondence between the effects of N-methylation and N-protonation on the $C(_4)$ and $C(_5)$ chemical shifts in the isoxazole derivatives (IX) and (X) gives no grounds for considering this similarity as an argument in favor of the O-protonation of the isoxazoline derivatives (I) and (VII).

The changes in the chemical shifts of the carbon atoms of the benzene rings in compounds (I) and (VII), caused by protonation, agree far better with the hypothesis of protonation at the nitrogen atoms. Particularly characteristic are the appreciable shifts of the $C(_1')$ and $C(_4')$ signals upfield and downfield, respectively, which is observed not only on the protonation but also on the N-methylation of both the isoxazoline (I) and the isoxazole (IX) derivatives. By analogy with acetophenone [6], in the case of N-protonation this effect can be explained by an increase in the contribution of a resonance structure of type B for the cation as compared with the neutral molecule.

A B

EXPERIMENTAL

Derivatives (I-X) and (XII) were obtained by methods described in the literature, and their constants corresponded with those given [7-13].

To determine pK_a values of the isoxazolines we used glacial acetic acid of kh. ch. ["chemically pure"] grade that had been frozen out twice. The proton donor was 94% sulfuric acid of o.s.ch. ["particularly pure"] 12-4 grade, the concentration of which was determined by indicator titration. The acidity function H_0 for the solutions of sulfuric acid in glacial acetic acid was taken from [2].

UV spectra were obtained on a Perkin–Elmer 402 instrument in quartz cells with a layer thickness of 1 cm in a thermostated block at 25 ± 0.1°C. In the concentrations investigated ($1 \cdot 10^{-4}$-$2.5 \cdot 10^{-5}$ M), the solutions obeyed the Lambert–Beer law. As the analytical wavelengths we used those for which the differences in the optical densities were greatest and for which the maxima of the absorption curve of one of the forms lay above the minimum of the other. The calculation was performed for a series of 11 solutions with different values of H_0. All the results were treated statistically using the method of least squares. The values of pK_a and of n were obtained by this method and an estimate was made of their confidence interval at a predetermined reliability level of $\alpha = 0.95$.

^{13}C NMR spectra were taken on a Varian XL-100A instrument (25.2 MHz). The following were used as internal standards: for solvent A (concentrated H_2SO_4:CD_3COOD (4:3)), the signal of the methyl carbon in the acetic acid-d_4 (δ = 21.1 ppm, according to [14], calculated to the δ scale from the relation δ_{CS_2} = 192.8 ppm [15]); for solvent B [$(CD_3)_2CO$:D_2O (2:1)], the signal of the methyl carbon in the acetone-d_6 (δ = 29.2 ppm [15]); and for the other solvents, TMS.

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