4. *Tautomerism of* N-*Heteroaromatic Aldoximes.*

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The ionisation constants of a number of *N*-heteroaromatic aldoximes and of their *O*- and nuclear *N*-alkyl derivatives have been measured in aqueous solution at 20°. The ultraviolet spectra of the aldoximes have been obtained in water and ethanol, and their infrared spectra in carbon tetrachloride. In aqueous solution a small amount of the zwitterionic N–H tautomer co-exists with the predominant enol form, and tautomeric equilibrium constants have been calculated from both the ionisation constants and the spectroscopic data. The low values of the tautomeric constants, relative to those of the corresponding hydroxy-compounds, are ascribed to restricted conjugation between the aldoxime group and the nucleus.

N-Heteroaromatic aldoximes possess a basic ring nitrogen atom and an acidic exocyclic hydroxyl group, and, like the analogous *N*-heteroaromatic hydroxy-compounds,[1-3] the neutral enolic form (*e.g.*, I) exists in tautomeric equilibrium with the corresponding zwitterionic (*e.g.*, IIa) or " quinonoid " form (*e.g.*, IIb). The equilibrium of the *N*-heteroaromatic aldoximes has now been investigated with the methods employed in previous studies of tautomerism.[1-3]

The ionisation constants of pyridine-2-, -3-, and -4-aldoxime and quinoline-4-aldoxime, and of their nuclear *N*-methyl derivatives, have been measured in aqueous solution at 20°,

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[1] Mason, *J.*, 1957, 4874.
[2] Mason, *J.*, 1957, 5010.
[3] Mason, *J.*, 1958, 674.

and tautomeric equilibrium constants (K_t = [N–H form]/[O–H form]) have been calculated according to the equation [3]

$$K_t = 1/(K_1/K_{NMe} - 1) \qquad (1)$$

where K_1 and K_{NMe} are the ionisation constants of the conjugate acids of the aldoxime and of its nuclear *N*-methyl derivative respectively. The results are in Table 1. The infrared spectra of the aldoximes have been measured in carbon tetrachloride solution in the 3 μ region, and their visible and ultraviolet spectra, together with those of the nuclear *N*-methyl derivatives, in aqueous and in ethanol solution. The spectral data are recorded in Table 2 and Figs. 1 and 2.

TABLE 1. *Ionisation constants of some* N-*heteroaromatic aldoximes and of their* O- *and nuclear* N-*alkyl derivatives in water at 20°, and the concentration of measurement. The tautomeric equilibrium constants* (K_t = [NH-*form*]/[OH-*form*]) *of the aldoximes and of the corresponding hydroxy-compounds.*

Compound	pK_1	pK_2	Concn. (10^{-3}M)	log K_t Aldoxime	log K_t [c] Hydroxy
Pyridine-2-aldoxime [a]	3·63 ± 0·02	10·14 ± 0·02	20	−4·37	2·96
O-n-propyl ether	3·58 ± 0·05		5		
1-methiodide [b]	8·00 ± 0·01		20		
Pyridine-3-aldoxime [a]	4·10 ± 0·01	10·36 ± 0·03	10	−5·12	−0·08
O-n-propyl ether	4·12 ± 0·04		5		
1-methiodide [b]	9·22 ± 0·03		10		
Pyridine-4-aldoxime [a]	4·77 ± 0·01	9·99 ± 0·01	20	−3·80	3·29
O-n-propyl ether	4·81 ± 0·04		5		
1-methiodide [b]	8·57 ± 0·02		20		
Quinoline-4-aldoxime	4·55 ± 0·04	10·42 ± 0·05	0·1	−3·77	3·88
1-methiodide [b]	8·32 ± 0·04		5		

[a] After the completion of this work, spectroscopically determined pK_a values were reported (cf. ref. 6); for pyridine-2-aldoxime, 3·60 and 10·8, -3-aldoxime, 3·94 and 10·32, and -4-aldoxime, 4·58 and 9·91. [b] From the pH of half-neutralised solutions, Ginsberg and Wilson (cf. ref. 8) report pK_a 8·0, 9·2, 8·6, and 8·3 for pyridine-2-, -3-, and -4- and quinoline-4-aldoxime respectively. [c] Quoted from ref. 3.

In carbon tetrachloride solution the *N*-heteroaromatic aldoximes absorb near 3600 cm.$^{-1}$, owing to the O–H stretching vibration, but no N–H group absorption is observed, and they exist, therefore, predominantly in the enolic form (*e.g.*, I) in non-polar solvents. Quinoline-2- and pyridine-2-aldoxime have the *trans*- or *syn*-configuration,[4] since the infrared absorption corresponds to that [1] of a free O–H group (Table 2). The ionisation

TABLE 2. *Frequency of the* O–H-*stretching vibration absorption of some* N-*heteroaromatic aldoximes in carbon tetrachloride solution* (ν_{OH})*; their ultraviolet absorption band maxima, and those of the corresponding nuclear* N-*methyl derivatives; and the tautomeric equilibrium constants* (K_t = [NH-*form*]/[OH-*form*]) *calculated from the spectra. Values in italics refer to shoulders.*

Compound	ν_{OH} (cm.$^{-1}$)	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$	Solvent	log K_t
Pyridine-2-aldoxime	3596	*355*; 277; 239	*0·15*; 3·88; 4·02	pH 6·9	−4·1
		279; 240	3·89; 4·01	EtOH	
1-methochloride		335; *285*; 220	4·26; *3·72*; 3·71	pH 11	
Pyridine-3-aldoxime	3591	*275*; 243	*3·67*; 4·06	pH 7·2	
		275; 245	*3·68*; 4·06	EtOH	
1-methochloride		*335*; 288; 242	*3·62*; 4·17; 4·11	pH 12	
Pyridine-4-aldoxime	3590	*340*; 246	*0·50*; 4·10	pH 7·4	−3·8
		248	4·11	EtOH	
1-methochloride		336; 239	4·34; 3·78	pH 11	
Quinoline-4-aldoxime	3591	312; 234	3·81; 4·29	pH 7	
		327; 241	3·95; 4·35	pH 1	
		323; 235	4·26; 4·36	pH 13	
1-methochloride		387; 246	4·31; 4·33	pH 12	
Quinoline-2-aldoxime	3593				

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[4] Hanania and Irvine, *Nature*, 1959, **183**, 40.

constants indicate (Table 1) that in neutral aqueous solution the enolic form of the aldoximes predominates over the zwitterionic form by a factor of 10^4—10^5, a conclusion which is supported by the ultraviolet evidence. Pyridine-2- and -4-aldoxime in neutral aqueous solution give spectra showing a low-intensity shoulder at long wavelengths, at a position similar to that of the first high-intensity band in the spectrum of the zwitterionic form of the corresponding *N*-methyl derivative (Figs. 1 and 2). The shoulder is due to absorption by the small amount of the zwitterionic form of the aldoxime in equilibrium with the enolic form, for the shoulder is not observed in ethanol solution where tautomerism to the zwitterion is suppressed. It is improbable that the shoulder arises from a forbidden transition in the enolic form, as the absorption would then appear in both ethanol and aqueous solution. If it is assumed that the long-wavelength absorptions of the zwitterionic species of an aldoxime and its *N*-methyl derivative have the same maximum extinction coefficient, the intensity of the shoulder gives the fraction of the aldoxime present as the zwitterionic form in aqueous solution. The values of the tautomeric equilibrium constants for pyridine-2- and -4-aldoxime so obtained (Table 2) show satisfactory agreement with those calculated from the ionisation constants of the compounds (Table 1). The 3-isomer and quinoline-4-aldoxime are less soluble in water, and the visible and ultraviolet absorption curves of these compounds could not be followed to low enough extinction values to derive tautomeric equilibrium constants by the spectroscopic method.

FIG. 1. *Ultraviolet absorption spectra of pyridine-*2-*aldoxime* —— *in water* (pH 6·9) *and* . . . . *in ethanol, and of its* 1-*methochloride* — — — *at* pH 11.

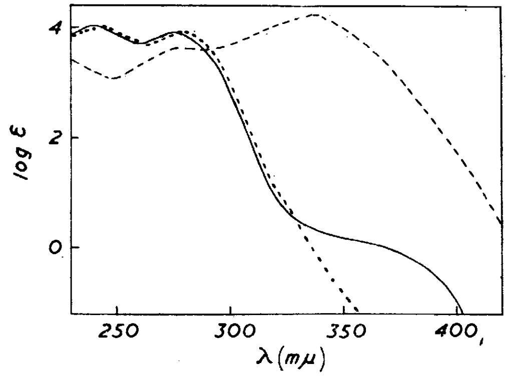
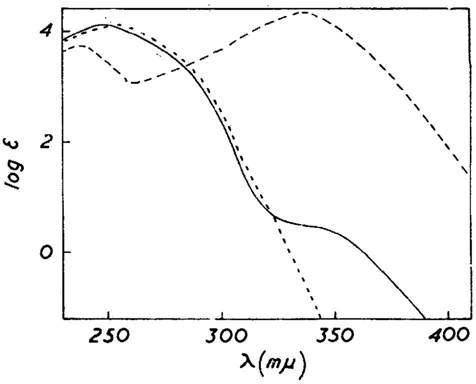


FIG. 2. *Ultraviolet absorption spectra of pyridine-*4-*aldoxime* —— *in water* (pH 7·4) *and* . . . . *in ethanol, and of its* 1-*methochloride* — — — *at* pH 11.



The tautomerism of the *N*-heteroaromatic aldoximes, like that of the corresponding hydroxy-compounds, involves the ionisation of a proton from an oxygen to a nitrogen atom, and tautomeric equilibrium constants of similar magnitude might be expected in the two series. However, the constants are 10^5—10^7 times larger in the hydroxy- than in the aldoxime series (Table 1), indicating that relative to the enolic forms the zwitterionic species in the hydroxy-series are 7—10 kcal./mole more stable than their aldoxime analogues in aqueous solution. The oxygen atom of the hydroxyl group in the aldoximes is bonded to nitrogen, as opposed to carbon in the hydroxy-compounds, and the aldoximes should have the greater acidity in consequence, nitrogen being more electronegative than carbon. Hydroxylamine ($pK_a = 12{\cdot}5$—13)[5] is a stronger acid than methyl alcohol, but phenol is some six times stronger an acid than α-benzaldoxime (pK_a 10·75),[6] and in the *N*-heteroaromatic series the enolic hydroxy-compounds[3] are more acidic by 1—2 pK_a units than the aldoximes. The smaller relative acidity of the oxime group in aromatic systems suggests

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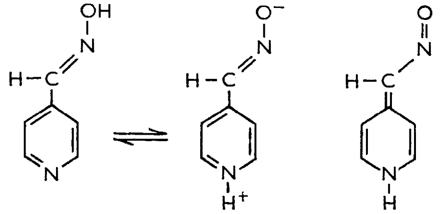
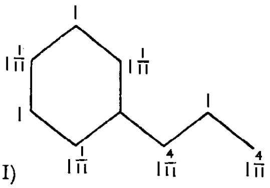
[5] Charles and Freiser, *Analyt. Chim. Acta*, 1954, **11**, 101.
[6] Cecchi, *Ricerca sci.*, 1958, **28**, 2526.

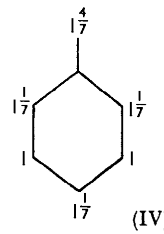
that the lone-pair electrons of the oxygen atom in the aldoximes are less effectively conjugated with the nucleus than the corresponding electrons in the phenols, particularly when the oxygen atom carries a formal negative charge, a conclusion which is consistent with the low values of the tautomeric equilibrium constants in the series of *N*-heteroaromatic aldoximes.

The zwitterionic forms of *N*-heteroaromatic hydroxy-compounds derive stability from the delocalisation of lone-pair electrons from the negatively charged oxygen atom into the nucleus,[3] the stabilisation being particularly effective when the positively charged nitrogen atom occupies a starred (conjugated) position in the nucleus. If conjugation between the exocyclic atoms and the nucleus were complete, that is, if all resonance integrals in the π-electron system system were equal, a smaller fraction of the oxygen lone-pair electrons would be delocalised into the nucleus of the pyridinealdoximes, which are hetero-analogues of the cinnamyl anion, than into the nucleus of the hydroxypyridines, which are hetero-analogues of the benzyl anion, since only three-elevenths of the negative charge are located in the nucleus of the cinnamyl anion (III), in contrast to three-sevenths in the benzyl anion (IV). [Relative charge distributions are shown in (III) and (IV).] According to the considerations presented previously,[3] the tautomeric equilibrium constants of pyridine-3-aldoxime and 3-hydroxypyridine would then be of the same order of magnitude, the nuclear nitrogen atom occupying an unstarred position in both these compounds, and the difference between the free energies of tautomerism of pyridine-3- and -4-aldoxime would be seven-elevenths of the corresponding free-energy difference between 3- and 4-hydroxypyridine. However, the tautomeric constant of pyridine-3-aldoxime is 10^{-5} that of 3-hydroxypyridine, and the difference between the tautomeric free energies of pyridine-3- and -4-aldoxime is little more than half of the theoretical value, suggesting that conjugation between the exocyclic atoms and the nucleus is less effective in the zwitterionic forms of the *N*-heteroaromatic aldoximes than in those of the corresponding hydroxy-compounds.


(I) (IIa) (IIb)



(III)



(IV)

The restricted conjugation in the aldoximes implies that in the cases where the nitrogen atom occupies a starred position in the nucleus, resonance between the zwitterion (*e.g.*, IIa) and the quinonoid form (*e.g.*, IIb) is limited, the structure of the N–H tautomer approximating closely to the former (*e.g.*, IIa). Thus, in contrast to the corresponding pyridones, the nuclear *N*-methyl derivatives of pyridine-2- and -4-aldoxime cannot be extracted from alkaline solution with chloroform or ether, indicating that they are particularly polar, (*e.g.*, IIa), and the alkaline solutions show no absorption in the red region, where the nitroso-group has a characteristic absorption band, suggesting that the quinonoid structure (*e.g.*, IIb) contributes little to the resonance hybrid of which the N–H tautomer is composed.

The acetamidopyridines are isoconjugate with the pyridinealdoximes, and conjugation between the exocyclic atoms and the nucleus appears to be limited in the zwitterion or acetylimino-species of the former compounds.[7] In the pyridone acylimines it is possible that one lone-pair of the exocyclic nitrogen atom conjugates with the nucleus and the other with the carbonyl group,[7] but a similar restriction of conjugation between the exocyclic group and the nucleus cannot occur in the zwitterionic forms of the pyridine-aldoximes. As in other acyclic π-electron systems, it is probable that there is an alternation

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[7] Jones and Katritzky, *J.*, 1959, 1317.

of bond character in the exocyclic group of the *N*-heteroaromatic aldoximes, the exocyclic C–C and N–O bonds being largely single, and the C–N link being largely a double bond, so that interaction between the oxime portion and the nucleus is small.

EXPERIMENTAL

Materials.—The pyridinealdoximes and their *O*-n-propyl ethers were commercial specimens. The former were recrystallised from water, and the latter redistilled. Quinoline-2- and -4-aldoxime, and the aldoxime methiodides, were prepared according to Ginsberg and Wilson,[8] their method B being adopted for the latter compounds. Quinoline-2-aldoxime methiodide could not be prepared, as noted previously.[8]

Spectra.—Infrared spectra were obtained by using dilute carbon tetrachloride solutions of the aldoximes in a 5 cm. cell with a Mervyn N.P.L. grating spectrophotometer. Visible and ultraviolet absorption curves were measured with a Hilger Uvispek quartz spectrophotometer, in the solvents listed in Table 2.

Ionisation Constants.—These were determined by potentiometric titration, with a Cambridge pH meter with glass and calomel electrodes, except for quinoline-4-aldoxime, the constants of which were measured spectroscopically at 280—350 mμ with 0·01M-acetate and -borate buffers for the acidic and basic pH ranges respectively.

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[8] Ginsberg and Wilson, *J. Amer. Chem. Soc.*, 1957, **79**, 481.