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THE TAUTOMERISM OF HETEROAROMATIC COMPOUNDS WITH FIVE-MEMBERED RINGS—I

5-HYDROXYISOXAZOLES–ISOXAZOL-5-ONES

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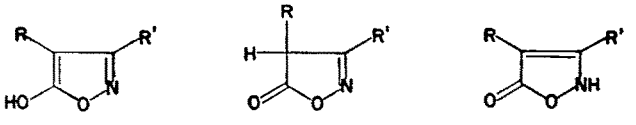
Abstract—Infra-red and ultra-violet spectra show that 3,4-dimethyl-5-hydroxyisoxazole exists in aqueous and chloroform solution, and in the solid phase in the OH form; and that 3-phenyl-, 4-bromo-3-phenyl-, and 4-methyl-3-phenyl-isoxazol-5-ones exist as mixtures of the CH and NH forms in solution, the proportion of the NH form increasing with the polarity of the solvent. The basicities of isoxazole and some of its derivatives are recorded. Isoxazol-5-ones are acids of comparable strength with carboxylic acids.

THE well-known reaction of β-ketoesters with hydroxylamine affords products which can be formulated as 5-hydroxyisoxazoles (I) or as 4H- (II) or 2H-isoxazol-5-ones (III)



I II III

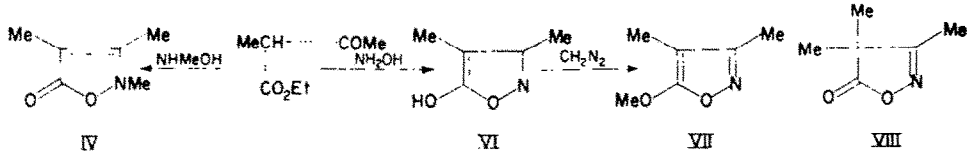
Early workers assigned structures on criteria now known to be unreliable, thus Uhlenhuth[1] favoured the NH structure (III) because the silver salt of 3-phenylisoxazol-5-one gave with methyl iodide a product (also obtained by methanol–sulphuric acid treatment of the isoxazolone) which he formulated as the N-methyl derivative (incorrectly, see below). Moureu and Lazennec[2] also preferred the NH structure on grounds of formation. Kohler and Blatt[3] found that 3,4-diphenylisoxazol-5-one when freshly dissolved in ethanol reacted with ca. 50 per cent of one molecule of bromine, but after standing with ca. 90 per cent and concluded that the solid was in the CH form (now disproved, see later) but that the OH form predominated in solutions; the NH form was held to be excluded by the results of ozonolysis. Confidence in the bromine titration method is undermined by the fact that 3-phenylisoxazol-5-one reacts rapidly with 1·9 moles of bromine.[4]

Physical methods were first used by Angyal and Le Fèvre[4]; the dipole moment of 3-phenylisoxazol-5-one (4·9 D) was nearer to that of the 4,4-dimethyl analogue (5·0 D) than to that of the 5-methyl compound (3·8 D) and although this was not regarded as conclusive evidence for the CH form, the infra-red spectra of the solids did show that the CH form (II) prevailed in the crystal. Infra-red spectral examination of the benzene solution in the 3800–2800 cm^{-1} region was stated to exclude the NH and the OH forms but this must be considered less conclusive because of poor solubility.

[1] R. Uhlenhuth, *Liebigs Ann.* **296**, 33 (1897).
[2] C. Moureu and I. Lazennec, *Bull. Soc. Chim. Fr.* (4) **1**, 1092 (1907).
[3] E. P. Kohler and A. H. Blatt, *J. Amer. Chem. Soc.* **50**, 504 (1928).
[4] C. L. Angyal and R. J. W. Le Fèvre, *J. Chem. Soc.* 2181 (1953).

Following work in this laboratory on potentially tautomeric pyridines and pyridine 1-oxides,[5] we have now studied the ultra-violet and infra-red spectra and basicities of a series of 5-hydroxyisoxazoles, or isoxazol-5-ones, and methylated derivatives of their three alternative tautomeric forms.

Preparation of compounds. Ethyl methylacetoacetate (V) and hydroxylamine afforded 3,4-dimethyl-5-hydroxyisoxazole (VI),[1] which gave a single methyl derivative



with diazomethane, shown to be 3,4-dimethyl-5-methoxyisoxazole (VII) by (a) the infra-red spectrum,[6] (b) methoxyl group shown by Zeisel analysis, and (c) non-identity with the N- and C-methyl derivatives. The silver and sodium salts of the isoxazolone also gave 3,4-dimethyl-5-methoxyisoxazole with methyl iodide. Diazoethane afforded the corresponding 5-ethoxy-derivative; this structure was confirmed by the infra-red spectrum. The acetoacetate (V) with N-methylhydroxylamine[7] gave unambiguously 2,3,4-trimethylisoxazol-5-one (IV); this use of N-methylhydroxylamine in isoxazolone synthesis is new although 2,4-diphenylisoxazol-5-one has been made analogously from phenylhydroxylamine.[8] Ethyl dimethylacetoacetate and hydroxylamine gave 3,4,4-trimethylisoxazol-5-one (VIII).[9]

The appropriate β-ketoesters and hydroxylamine gave 3-phenyl-,[10] 4-methyl-3-phenyl-,[11] and 4,4-dimethyl-3-phenyl-isoxazol-5-one.[11] 3-Phenylisoxazol-5-one with diazomethane,[12] or with methanol and sulphuric acid,[1] yielded 5-methoxy-3-phenyl-isoxazole,[13] but the sodium salt with methyliodide provided mainly the N-methyl derivative. 4-Methyl-3-phenylisoxazol-5-one with sodium ethoxide and methyl iodide gave the N-methyl derivative, the structure of which was proved by the infra-red spectrum, and a negative Zeisel analysis. Diazomethane afforded a mixture of ca. 35 per cent N-methyl and 65 per cent O-methyl derivative, as shown by infra-red spectroscopy; the methoxy- compound was isolated.

4-Bromo-3-phenylisoxazol-5-one[14] with diazomethane provided the N-methyl derivative. Bromine and 4-methyl-3-phenylisoxazol-5-one gave 4-bromo-4-methyl-3-phenylisoxazol-5-one; bromination of 3-phenylisoxazol-5-one gave the 4,4-dibromo-derivative[15] (*vide infra*).

Ultra-violet spectra (Table 1). The spectrum of 3,4-dimethyl-5-hydroxyisoxazole (Table 1, No. 4) as a neutral species resembles that of the 5-methoxy-analogue (No. 1) but differs from those of 2,3,4-, and 3,4,4-trimethylisoxazol-5-one (Nos. 3, 2). This

[5] J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.* 4375 (1957); R. A. Jones and A. R. Katritzky, *J. Chem. Soc.* 3610 (1958); 1317 (1959); In press (1960).
[6] A. R. Katritzky and A. J. Boulton, *Spectrochim. Acta* In press.
[7] *Beilstein Hauptwerk* **4**, 534.
[8] H. Rupe and J. Grünholz, *Helv. Chim. Acta* **6**, 102 (1923).
[9] P. Billon, *Ann. Chim.* (10) **7**, 357 (1927).
[10] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **24**, 502 (1891).
[11] A. Haller and E. Bauer, *C.R. Acad. Sci. Paris* **152**, 1446 (1911).
[12] E. Olivieri-Mandalà and A. Coppola, *Rend. Accad. Lincei* (5) **20** I, 248 (1911).
[13] P. Grünanger and M. R. Langella, *Gazz. Chim. Ital.* **89**, 1784 (1959).
[14] T. Posner, *Ber. Dtsch. Chem. Ges.* **39**, 3521 (1906).
[15] A. Meyer, *Ann. Chim.* (9) **1**, 315 (1914).

TABLE 1. ULTRA-VIOLET SPECTRA OF ISOXAZOLES AND ISOXAZOL-5-ONES

No.	Substituents at positions				Cyclohexane		Water		20 N H_2SO_4	
	2	3	4	5	λ(mμ)	ε × 10^{-3}	λ(mμ)	ε × 10^{-3}	λ(mμ)	ε × 10^{-3}
1	—	Me	Me	OMe	209	5·63	215	6·2	227	9·27
2	—	Me	Me_2	:O	— [a]		201	4·2	201	4·16 [d]
3	Me	Me	Me	:O	262	7·89	268	12·0	252	9·76
4	—	Me	Me	OH	213	6·58	224	6·25 [b]	236	8·64
5	—	Ph	H	OMe	236	15·4	239	16·0	— [e]	
6	—	Ph	Me	OMe	228	12·6	231	10·7	275	16·1
7	—	Ph	Me_2	:O	254	10·1	253	13·5	256	10·3
8	Me	Ph	Me	:O	280 231	6·95 10·6	281 243	10·4 8·65	271	11·6
9	—	Ph	H_2	:O	253	14·1	254	13·6 [b]	266	16·5
10	H	Ph	Me	:O	253	13·2	281 243	11·3 [b] 9·4	274	14·9
11	H	Ph	Br	:O	274 224	6·95 7·66	287 238	7·65 [c] 7·71		—
12	—	Ph	Br, Me	:O	273 223	7·42 7·71	281 219	6·69 6·09		—
13	—	Ph	Br_2	:O	290 226	6·47 8·30	— [f]			—
14	Me	Ph	Br	:O	291 238	7·8 8·95	291 246	10·2 8·02		—

[a] Band below solvent cut-off.
[b] Phosphate buffer pH 2 used, considerable proportion of anion present in water.
[c] Phosphate buffer pH 1·5.
[d] 10 N H_2SO_4 used to get sufficient transmission.
[e] Decomposed rapidly in acid.
[f] Decomposed.

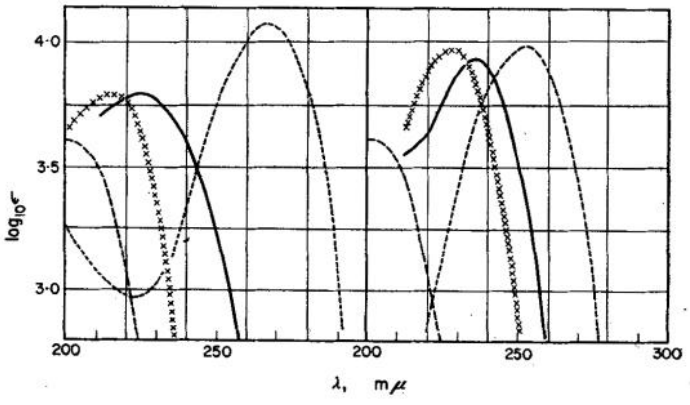
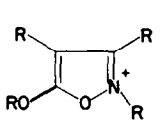


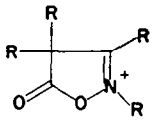
FIG. 1. Aqueous solutions; FIG. 2. Solutions in sulphuric acid.
——3,4-Dimethyl-5-hydroxyisoxazole; — — — — 3,4,4-Trimethylisoxazol-5-one;
× × × × 3,4-Dimethyl-5-methoxyisoxazole; ····· 2,3,4-Trimethylisoxazol-5-one.

holds for solutions in water (Fig. 1) and cyclohexane, and indicates that in both solvents the tautomeric compound exists predominantly in the hydroxy- form. The ultraviolet spectrum (Fig. 1) indicates that the proportion of the NH form does not exceed

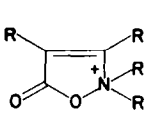
1 per cent and that that of the CH form does not exceed 20 per cent and is probably much lower. The spectra of the mono-cations of the 3,4-dimethyl series are shown in Fig. 2. Three structures are possible for these cations, (IX–XI); 5-methoxy- com-



IX

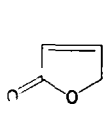


X

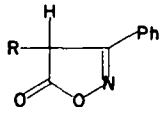


XI

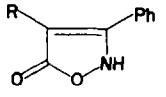
pounds must form cations of type IX, and 4,4-dimethyl- compounds must form cations of type X, but 2-methyl-, and potentially tautomeric compounds could form cations of all three types. Fig. 2 and Table 1 indicate that cations of structure IX are formed whenever possible; those of type XI should have U.V. spectra similar to XII, which shows only end absorbtion above 210 $m\mu$ in ethanol.[16]



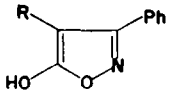
XII



XIII



XIV



XV

The spectra of aqueous solutions of neutral species in the 3-phenyl series are shown in Fig. 3, which indicates that 3-phenylisoxazol-5-one exists predominantly as the CH form (XIII, R = H) in equilibrium with ca. 30 ± 10 per cent of the NH form (XIV,

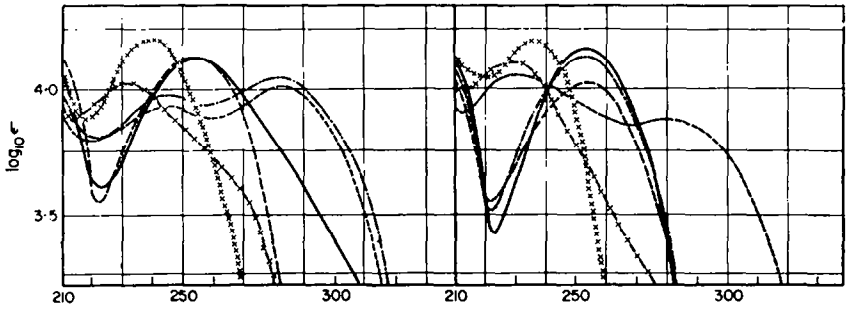


FIG. 3. Aqueous solutions; FIG. 4 cyclohexane solutions.
——3-Phenylisoxazol-5-one; —·—·—. 4-Methyl-3-phenylisoxazol-5-one; ·····4,4-Dimethyl-3-phenylisoxazol-5-one; × × × × 5-Methoxy-3-phenylisoxazole; —×—×—× 5-Methoxy-4-methyl-3-phenylisoxazole; ····· 2, 4-Dimethyl-3-phenylisoxazol-5-one.

R = H); the OH form (XV, R = H) cannot be detected, its proportion is probably less than 10 per cent. 4-Methyl-3-phenylisoxazol-5-one, on the contrary, exists predominantly in the NH form (XIV, R = Me); no contributions from the other forms (XIII, XV, R = Me) can be detected; they probably occur to an extent of less than 10 per cent. However, in cyclohexane (Fig. 4) both the potentially tautomeric compounds exist predominantly in the CH form; Fig. 4 indicates that the NH and OH forms certainly do not exceed 10 per cent. Using cyclohexane, diethyl ether, ethanol

[16] R. J. D. Smith and R. N. Jones, *Canad. J. Chem.* 37, 2092 (1959).

0·1 N sulphuric acid, and mixtures of adjacent pairs of these, solutions of each tautomeric compound in media of increasing polarity were prepared. 3-Phenylisoxazol-5-one shows a steady increase in the intensity of the NH peak with increasing solvent polarity, while with the 4-methyl homologue a gradual and apparently complete transition from CH to NH structure is observed (Figs. 5, 6).

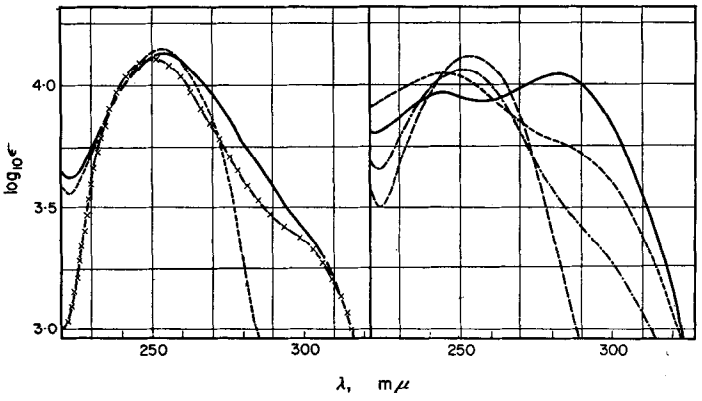


FIG. 5. 3-Phenylisoxazol-5-one; FIG. 6. 4-Methyl-3-phenylisoxazol-5-one.
——Aqueous sulphuric acid; —×—×—×— Ethanol–diethyl ether 1:1 + trace sulphuric acid; ····· Diethyl ether; —·—·—·— Cyclohexane–diethyl ether 1:1; — — — — Cyclohexane solution.

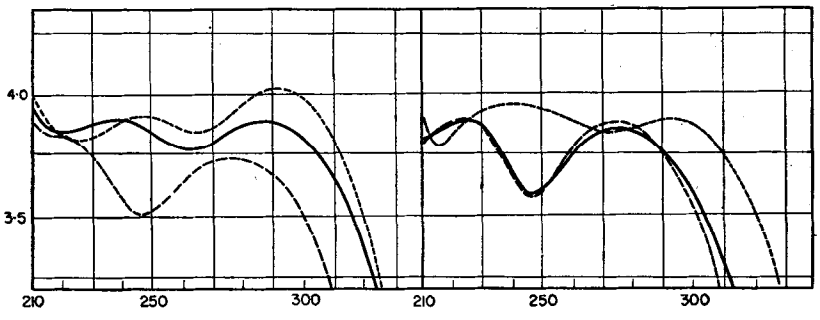


FIG. 7. Aqueous solutions; FIG. 8. Cyclohexane solutions.
——4-Bromo-3-phenylisoxazol-5-one; — — — — 4-Bromo-4-methyl-3-phenylisoxazol-5-one; ····· 4-Bromo-2-methyl-3-phenylisoxazol-5-one.

Considering the bromo-compounds of fixed structure, the expected bathochromic shifts of 3–11 mμ are found for 4-bromo-2-methyl-3-phenylisoxazol-5-one compared with the 2,4-dimethyl analogue in water and cyclohexane. More surprising are the larger shifts of 19–28 mμ for 4-bromo-4-methyl-3-phenylisoxazol-5-one compared with the 4,4-dimethyl analogue, and the second band found for the former compound above 210 mμ. This effect is presumably due to some specific interaction between the bromine atom and the phenyl ring (cf. Ref 17); the further large shift for the 4,4-dibromo-analogue (Table 1, No. 13) also indicates this. On the reasonable assumption that the spectrum of 4-bromo-5-methoxy-3-phenylisoxazole would be similar to that of its 4-methyl analogue, Figs. 7 and 8 show that 4-bromo-3-phenylisoxazol-5-one exists

[17] J. W. Smith and S. M. Walshaw, *J. Chem. Soc.* 3784 (1959).

predominantly as a mixture of CH and NH forms in aqueous solution but as the CH form in cyclohexane.

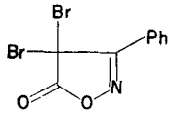
Infra-red spectra. Infra-red spectra demonstrate: (a) 5-hydroxy-3,4-dimethylisoxazole exists as such in the solid and in chloroform solution, (b) 3-phenylisoxazol-5-one exists in the CH form in the solid and chloroform, (c) 4-methyl-3-phenylisoxazol-5-one exists as the NH form in the crystal, as a mixture (ca. 1:2) of NH and CH forms in chloroform, and mainly as the CH form in tetrachloroethylene, (d) 4-bromo-3-phenylisoxazol-5-one exists as the NH form in the solid but mainly as the CH form in $CHCl_3$ solution.

These conclusions were reached by comparing the detailed spectra of the potentially tautomeric compounds with those of known structure. The spectra of compounds of the isoxazole structure are discussed elsewhere;[6] those of 2H- and 4H-isoxazol-5-ones are recorded in Tables 2 and 3 respectively.

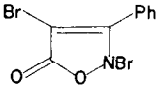
Some 2H-isoxazol-5-ones show νC=O absorption in chloroform as two partially resolved bands at 1740–1725 cm^{-1}; the cause of this splitting is not clear. The position is strongly dependent on the environment; in the less polar solvent C_2Cl_4, absorption is at ca. 1760 cm^{-1} and in the solid at ca. 1680 cm^{-1}. This behaviour is characteristic of a highly polarized C=O group.[18] The highest ring frequency, essentially νC=C, is shown as a strong band at 1645–1613 cm^{-1} (160–230) in solution and at somewhat lower frequencies in the solid phase. Four ring stretching modes and two C–H deformation modes are shown for the monosubstituted benzene rings as expected.[19] The 2H-isoxazol-5-one ring itself apparently absorbs (in addition to the νC=C band) at 1473–1463 cm^{-1} (35–50), 1377–1359 (25–70), 1296–1264 (10–45), 1197–1140 (35–60) and 1065–1036 (45–65), because these bands appear in all the compounds. Bands found only in the N—Me and others in the C—Me compounds, were assigned to corresponding modes as noted in Table 2.

4H-Isoxazol-5-ones show νC=O absorption at 1808–1793 cm^{-1} (410–600) except that the frequency is higher for Nos 5 and 13 with bromine α- to the C=O group. The highest ring frequency, essentially νC=N, absorbs at 1620 cm^{-1} (15) when not conjugated and at 1566–1553 cm^{-1} (15–30) when conjugated with a phenyl group. Other 4H-isoxazol-5-one ring bands are found at 1196–1151 cm^{-1} (70–170), 952–940 (5–25), and 900–872 (280–380). Most of the other bonds could be satisfactorily assigned to other structure groups within the various molecules as is briefly indicated in Table 3.

Dibromination of 3-phenylisoxazol-5-one yields a compound originally[15] for-



XVI



XVII

mulated as the 4,4-dibromo-derivative (XVI). Subsequently, formula XVII was proposed[4] because the compound liberated one equivalent of iodide in neutral solution. The infra-red spectrum (Table 3, No. 9) clearly confirms the original formulation (XVI); the chemical evidence can be reconciled with this, for bromine in XVI would be expected to be more reactive than that in XIV, (R = Br).

[18] L. J. Bellamy and R. L. Williams, *Proc. Roy. Soc.* A **255**, 22 (1960).
[19] A. R. Katritzky and J. M. Lagowski, *J. Chem. Soc.* 4155 (1958).

The infra-red spectrum of 3,4-diphenylisoxazol-5-one (KBr disk) has been published by Scarpati and Speroni[20]. A very strong band at ca. 1680, with a shoulder at ca. 1690 cm^{-1} and other bands at ca. 1600 (s), 1470 (m), 1340 (w), 1070 (w) and 990 cm^{-1} (w) show that this compound exists in the NH form in the crystalline phase and not the CH as earlier supposed.[3] The absence of strong absorption near 1800 and 880 cm^{-1} supports our conclusion.

Basicity determinations. Difficulty was encountered in applying the basicity method to the determination of tautomeric ratios in this series. Titration in aqueous

TABLE 4. BASE STRENGTHS OF ISOXAZOLES (pK_a OF CONJUGATE ACID)

	0·2 M solution[a]	0·38 M solution[a]	indicator[b]
Isoxazole	−1·96 ± 0·04	−2·28 ± 0·02	A
3-Methylisoxazole	−1·76 ± 0·02	−1·92 ± 0·03	A and B
5-Methylisoxazole	−1·72 ± 0·01	−1·95 ± 0·05	A and B
3,5-Dimethylisoxazole	−1·27 ± 0·02	−1·28 ± 0·02	B
3,4-Dimethyl-5-methoxy-isoxazole	−1·47 ± 0·01	−1·56[c]	B
2,3,4-Trimethylisoxazol-5-one	−1·24 ± 0·01	−1·32[c]	B
3,4-Dimethyl-5-hydroxyisoxazole	−0·66[c]	—	B

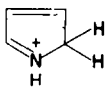
[a] Means of 3 or 4 determinations, and standard deviation of the mean.
[b] B represents 4-chloro-2-nitro-N-methylaniline, pK_a −1·37.[21] A represents N-(2′,4′-dinitrophenyl) morpholine, pK_a −2·21, which was determined by the spectrophotometric method using B as standard.
[c] Single readings, estimated errors 0·05.

solution could not be used as the basicities were too low. Usually the spectrophotometric method was inapplicable because of insufficient difference between the spectrum of the base and cation. Titration in non-aqueous solvents was avoided on account of the difficulties in relating the results to aqueous solutions. The indicator method of Lemaire and Lucas[21] was used: it consists in preparing a solution in acetic acid of the base together with half an equivalent of a strong acid. If the compound is considerably more basic than the solvent, the solution contains equal amounts of the base and its conjugate acid; if activities may be equated, then the acidity of the solution is equal to the pK_a of the base. Addition of a known small amount of a suitable indicator allows the determination of the acidity of the solution using the indicator spectrum. It was difficult to prepare solutions of perchloric acid in acetic acid free both from acetic anhydride (a powerful acetylating agent) and from water; therefore, sulphuric acid, treated as a monobasic acid, was used. (Some determinations were made in nitromethane in place of acetic acid, but concentration effects were found to be much greater). The values obtained (Table 4) varied with concentration, but values at the same concentration should be comparable. In the case of 2,3,4-trimethylisoxazolone, a value of −1·58 ± ·01 was obtained by the spectrophotometric method ($1·3 \times 10^{-3}$ M); this is in reasonable agreement with the results in Table 4.

As no base strengths of simple isoxazoles appear to have been reported, isoxazole and some methyl derivatives were measured. Isoxazole is a base of approximately the same strength as water (pK_a −2·35).[21] Substituting —O— for an adjacent —CH=CH— in pyridine thus lowers the basicity of the nitrogen atom by ca. 7 pK

[20] R. Scarpati and G. Speroni, *Gazz. Chim. Ital.* **89**, 1511 (1959).
[21] H. Lemaire and H. J. Lucas, *J. Amer. Chem. Soc.* **73**, 5198 (1951).

units. Isoxazole is a weaker base than pyrrole (pK_a −0·27)[22] although the aromaticity of pyrrole is destroyed on cation formation (XVIII)[23] but not that of isoxazole (cf.



XVIII

XIX

XIX). Methyl groups raise the basicity of isoxazole by ·2–·5 units, as expected. However, the basicity of 5-hydroxy-3,4-dimethylisoxazole is lowered ·8 unit by O-methylation and ·6 unit by N-methylation. This result is unexpected, as is the small difference between the basicities of the two methyl derivatives in view of the large preference for the hydroxy-form shown by 5-hydroxy-3,4-dimethylisoxazole.

TABLE 5. ACID STRENGTHS OF ISOXAZOLONES IN AQUEOUS SOLUTION

3-Substituent	Me	Ph	Ph	Ph
4-Substituent	Me	H	Me	Br
pK	6·1	4·01	4·73	2·3
Standard deviation	0·15	0·02	0·02	0·1
Method	potentiometric titration	spectrophotometric		

TABLE 6. THE TAUTOMERIC NATURE OF ISOXAZOL-5-ONES

Substituents at positions		Cyclohexane solution	Tetrachloroethylene solution	Chloroform solution	Aqueous solution	Solid state
3	4	(UV)	(IR)	(IR)	(UV)	(IR)
Me	Me	>80% OH	—	>98% OH	>80% OH	OH
Ph	H	>90% CH	—	>98% CH	70% CH + 30% NH	CH
Ph	Me	>90% CH	90% CH + 10% NH	70% CH + 30% NH	>90% NH	NH
Ph	Br	>90% CH	>95% CH	90% CH + 10% NH	20% CH + 80% NH	NH

The measured pK values for the isoxazolones as acids are recorded in Table 5; considered as analogues of phenol (pK 9·95) they are remarkably strong acids, comparable with carboxylic acids. In 1892, Hantzsch and Miolati[24] found pK 4·27 for 3-phenyloxazol-5-one by a conductivity method.

Conclusions. The results of this investigation are summarized in Table 6. Obviously, the balance between the various tautomers is a delicate one, and may depend on mesomeric, inductive, and steric effects. It is not possible to generalize on the basis of the four compounds so far studied: further work is in hand.

EXPERIMENTAL

Petroleum ether refers to the fraction of b.p. 60–80°, unless otherwise specified.

5-Hydroxy-3,4-Dimethylisoxazole.[1] This was crystallized from water and sublimed at 125° 0·1 mm and had m.p. 125–126° (lit.[1] m.p. 123–124°).

3,4-Dimethyl-5-methoxyisoxazole. Ethereal diazomethane (ca. 0·6 g) was added to 5-hydroxy-3,4-dimethylisoxazole (2·0 g) until the yellow colour persisted. After 5 min, the ethereal solution was

[22] N. Naqvi and Q. Fernando, *J. Org. Chem.* **25**, 551 (1960).
[23] R. J. Abraham, E. Bullock and S. S. Mitra, *Canad. J. Chem.* **37**, 1859 (1959).
[24] A. Hantzsch and A. Miolati, *Z. Phys. Chem.* (*Leipzig*) **10**, 19 (1892).

shaken successively with 2 N HCl (10 cc) and 2 N NaOH (10 cc), dried ($MgSO_4$) and distilled to give the *isoxazole* (1·1 g, 50%) b.p. 100° (bath)/15 mm, which formed prisms (from petroleum ether) m.p. 32–34° (Found: C, 56·5; H, 7·5; N, 10·6; MeO, 23·5. $C_6H_9NO_2$ requires: C, 56·7; H, 7·1; N, 11·0; MeO, 24·4%).

The neutral silver salt[1] of 5-hydroxy-3,4-dimethylisoxazole (1·6 g) was refluxed for 2 hr in ethanol (10 cc) with methyl iodide (1·5 g). After filtration, solvent was removed from the filtrate and ether (20 cc) added to the residue. The solution was extracted with 0·1 N NaOH (2 × 20 cc), dried ($MgSO_4$) and evaporated, to give an oil (0·3 g), shown to be crude methoxy- compound by the infra-red spectrum. The same methoxy-compound (ca. 10%) was also obtained by treatment of 5-hydroxy-3,4-dimethylisoxazole with methyl iodide and sodium ethoxide as in the preparation of 2,4-dimethyl-3-phenylisoxazol-5-one.

5-Methoxy-3,4-dimethylisoxazole in dil ethanol gave a *cadmium chloride complex* on mixing with saturated aqueous cadmium chloride, which crystallized as needles (Found: C, 22·4; H, 3·7; N, 4·4. $C_6H_9NO_2 \cdot CdCl_2 \cdot H_2O$ requires: C, 21·9; H, 3·4; N, 4·2%).

3,4-*Dimethyl*-5-*ethoxyisoxazole*. Diazoethane and 5-hydroxy-3,4-dimethylisoxazole gave the ethoxy-compound (80%), b.p. 110° (bath)/15 mm (Found: C, 59·6; H, 8·1; N, 9·4; $C_7H_{11}NO_2$ requires: C, 59·6; H, 7·9; N, 9·9%).

2,3,4-*Trimethylisoxazol*-5-*one*. N-Methylhydroxylamine[7] (16 g) in ethanol (40 cc) was added during ½ hr to ethyl methylacetoacetate (48 g) in ethanol (100 cc) and acetic acid (1 cc) at 25°. The whole was refluxed 4 hr and then distilled. Redistillation of the fraction of b.p. 148–151°/15 mm gave the *isoxazolone* (30·1 g, 68%), b.p. 108°/2 mm, which crystallized from benzene–petroleum ether (ca. 1 : 1) as prisms, m.p. 36° (Found: C, 5·70; H, 7·4; N, 10·8%).

3,4,4-*Trimethylisoxazol*-5-*one*. prepared by Billon's method,[9] had b.p. 101–102°/15 mm, n_D^{24} 1·4393 (lit.[9] b.p. 102–103°/15 mm).

3-*Phenylisoxazol*-5-*one*.[10] This formed plates, m.p. 151–153° (decomp) from chloroform (lit.[4] m.p. 151–152°).

4-*Methyl*-3-*phenylisoxazol*-5-*one*[11] had m.p. 121–122° (lit.[11] m.p. 123–124°).

4,4-*Dimethyl*-3-*phenylisoxazol*-5-*one*. Ethyl benzoyldimethylacetate (8·4 g), hydroxylamine hydrochloride (5 g), sodium acetate (1 g), water (15 cc) and ethanol (70 cc) were refluxed 3 hr, 12 N HCl (5 cc) was then added and the whole refluxed 30 min more. Volatile matter was removed to 80°/15 mm, water (20 cc) was added, and the mixture ether-extracted (2 × 20 cc). Evaporation of the dried ($MgSO_4$) extracts, and crystallization of the residue from ether, gave the isoxazolone (4·4 g, 61%) which sublimed at 100°/0·1 mm, m.p. 70° (lit.[11] m.p. 70–71°).

5-*Methoxy*-3-*phenylisoxazole*. Prepared from 3-phenylisoxazol-5-one and diazomethane,[12] this compound (m.p. 76–77° after 2 crystallizations from light petroleum) was identical with a sample prepared from the isoxazolone using methanol and sulphuric acid[1] (m.p. 77–78·5° after similar treatment), by the infra-red spectra. (Found: MeO, 16·7; Calc. for $C_{10}H_9NO_2$: MeO, 17·7%).

Treatment of 3-phenylisoxazol-5-one with methyl iodide and sodium ethoxide, as in the preparation of 2,4-dimethyl-3-phenylisoxazol-5-one, gave a viscous oil (80%) which did not solidify in 3 weeks. The infra-red spectrum showed that it contained 2-methyl-3-phenylisoxazol-5-one and 5-methoxy-3-phenylisoxazole in a proportion of ca. 9 : 1.

2,4-*Dimethyl*-3-*phenylisoxazol*-5-*one*. Methyl iodide (16 g, 7·0 cc) was added to 4-methyl-3-phenylisoxazol-5-one (17·5 g) in ethanolic sodium ethoxide (from 2·5 g Na and 150 cc EtOH) and the whole refluxed in 1½ hr. Ethanolic sodium ethoxide (from 2 g Na and 40 cc EtOH) and methyl iodide (12 g, 5·3 cc) were then added and refluxing continued for 1½ hr more. Volatile matter was removed to ca. 80°/15 mm, water (50 cc) added, and the whole ether-extracted (2 × 40 cc). The ethereal extracts were shaken with 2 N NaOH (50 cc), dried ($MgSO_4$) and the ether evaporated to give the *isoxazolone* (13·8 g, 73%), which separated as needles from benzene–petroleum ether (ca. 1 : 2), m.p. 66·5–67·5° after 3 crystallizations and sublimation at 80°/0·05 mm (Found: C, 70·3; H, 6·2; N, 7·4; OMe, 0·0. $C_{11}H_{11}NO_2$ requires: C, 69·8; H, 6·2; N, 7·4%).

5-*Methoxy*-4-*methyl*-3-*phenylisoxazole*. Diazomethane (ca. 1·0 g in ether) was added to a suspension of 4-methyl-3-phenylisoxazol-5-one (4·0 g) in ether (60 cc). The ethereal solution was then shaken with 2 N HCl (20 cc) and 2 N NaOH, (50 cc), the ether evaporated and the residue distilled 3 times (bath 105°; 0·05 mm) and crystallized from light petroleum (b.p. 40–60°). The *methoxy-compound* (0·1 g; 2·5%) had m.p. 30–32° (Found: C, 70·0; H, 6·5; N, 7·3%).

4-*Bromo*-2-*methyl*-3-*phenylisoxazol*-5-*one*. 4-Bromo-3-phenylisoxazol-5-one[14] (m.p. 120–121°

0·3 g; lit.[14] m.p. 121–122°) in ethanol (20 cc), treated with ethereal diazomethane (ca. 0·05 g), gave on evaporation of the solvents the N-*methyl derivative*, as needles (0·15 g, 48%), m.p. 106–107°, from ether–pet ether (ca. 1 : 2) (Found: C, 47·2; H, 3·3; N, 5·6. $C_{10}H_8BrNO_2$ requires: C, 47·2; H, 3·2; N, 5·5%).

4-*Bromo*-4-*methyl*-3-*phenylisoxazol*-5-*one*. Bromine (2·9 g) in chloroform (20 cc) was added over 5 min to 4-methyl-3-phenyl-5-isoxazolone (3·0 g) in chloroform (50 cc). The mixture was warmed to 50° for 10 min and the chloroform removed under reduced press. The residual *isoxazolone*, crystallized twice from petroleum ether, had m.p. 42–43° (3·1 g, 71%) (Found: C, 47·5; H, 3·5; N, 6·0%).

4,4-*Dibromo*-3-*phenylisoxazol*-5-*one*. This was prepared by the method of Meyer,[15] and had m.p. 76·5–77° (lit.[15] m.p. 76–77°).