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The Spectra, Ionization, and Deuteriation of Oxazoles and Related Compounds

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The ^{1}H n.m.r. spectra of oxazole, its derivatives, and some related compounds in non-polar, polar, and protonating media are discussed. The hitherto undetermined pK_a values for oxazole (0·8, now measured by the chemical shifts of H-2 in acidic media) and its derivatives show that the nucleus is far less basic than previously supposed, primarily owing to the powerful inductive effect of the oxygen atom. The ultraviolet spectra of 2,5- and 2,4-diphenyloxazole indicate through-conjugation only in the former. This fact and other data suggest that oxazoles should be considered more as conjugated dienes than as fully aromatic compounds. The rates for the 2-deuteriation of simple oxazoles increase with the alkalinity; oxazole also undergoes 5- but not 4-deuteriation under extreme conditions. On these grounds, the electron-distribution of the three carbon atoms of oxazole is clearly in the order 4 > 5 > 2. This is confirmed by the chemical shifts of the respective protons and the pK_a values of 2-, 4-, and 5-carboxyoxazole. Isoxazole (pK_a −2·03) is a much weaker base than previously reported.

ALTHOUGH the organic chemistry of the oxazole series has been well developed [1] little is known of those physical properties reflecting electron distribution in the ring system. In the present work we examine some aspects of the aromaticity and π-electron distribution in oxazoles as revealed by their ^{1}H n.m.r. spectra. ultraviolet spectra, ionization constants, and rates of deuteriation; we compare these properties with those of appropriate derivatives of imidazole, 1,2,4- and 1,3,4-oxadiazole, 1,2,4-triazole, and thiazole. Most of the required compounds were prepared by known methods [2-20] indicated in Table 1.

^{1}H *N.m.r. Spectra.*—The only reported ^{1}H n.m.r. spectra of oxazoles were incomplete data for the parent (I; $R^1 = R^2 = R^3 = H$) and its 4-methyl, 4,5-dipropyl, and 4,5-diphenyl derivatives.[21,22] To these we added the spectra in Table 1, where assignments were based on three criteria: the known [23,24] signal broadening by a ring nitrogen, the replacement of ring-protons by methyl groups, and the spin–spin coupling constants. Thus the broad signals shown by oxazole at τ 1·75 and 2·75 were assigned to H-2 and H-4 respectively on the basis of previous reports [21,22] and by comparison with the methyloxazoles; and the triplet centred at τ 2·03 was assigned to H-5, coupled equally to H-2 and H-4 ($J_{2,5} = J_{4,5} = 0·8$ c./sec.). These coupling constants were slightly lower than the corresponding values in 1-methylimidazole [25] (1·0 c./sec.) and substantially lower than in thiazole [23,24] (3·5 c./sec.), thereby indicating greater bond polarization by the strongly electronegative oxygen atom than by sulphur or nitrogen.[26] The apparent lack of 2,4-coupling was attributed to nitrogen perturbation.

In 2-methyloxazole (I; $R^1 = Me$, $R^2 = R^3 = H$),

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TABLE 1

Chemical shift data (τ) and ionization constants

Oxazole	Ref.[a]	Solvent	ν_2 [b]	ν_4 [b]	ν_5 [b]	pK_a [c]
Unsubst.	2	CCl_4	2·05	2·91	2·31	0·8 ± 0·2 [d]
		D_2O	1·75	2·75	2·03	
		5N-DCl–D_2O	0·11	1·99	1·46	
		CF_3CO_2H	0·34	2·06	1·63	
2-Me-	2	CCl_4	*7·63*	3·18	2·59	— [e]
		D_2O	*7·56*	2·83	2·22	
		5N-DCl–D_2O	*7·09*	2·21	1·72	
4-Me-	3	CCl_4	2·23	*7·89*	2·73	1·24 ± 0·04 (235)
		D_2O	1·90	*7·83*	2·41	
		5N-DCl–D_2O	0·25	*7·60*	1·78	
2,4-Me_2-	3	CCl_4	*7·78*	*7·94*	2·86	2·91 ± 0·05 (235)
		D_2O	*7·60*	*7·91*	2·57	
		5N-DCl–D_2O	*7·15*	*7·65*	2·15	
2,5-Me_2-	4	CCl_4	*7·71*	3·58	*7·78*	— [e]
		D_2O	*7·61*	3·36	*7·74*	
		5N-DCl–D_2O	*7·18*	2·61	*7·54*	
2,4,5-Me_3-	5	CCl_4	*7·72*	*8·04*	*7·85*	3·56 ± 0·05 (245)
		D_2O	*7·68*	*8·01*	*7·85*	
		5N-DCl–D_2O	*7·23*	*7·76*	*7·63*	
2-Ph-	6	$CDCl_3$	—	2·74	2·26	
4-CO_2H-	2	D_2O	1·46	—	1·73	*3·41* ± 0·03 (250)
4-CO_2Et-	2	$CDCl_3$	1·80	—	2·09	
		D_2O	1·34	—	1·60	
		10N-DCl–D_2O	0·25	—	0·98	
4-CO·NH_2-	7	CCl_4	1·71	—	2·13	
		D_2O	1·53	—	1·74	
4-Ph-	8	$CDCl_3$	2·09	—	2·09	−1·21 ± 0·05 (315)
4-*p*-NO_2·C_6H_4-	9	$(CD_3)_2SO$	1·08	—	1·40	
5-Ph-	10	$CDCl_3$	2·10	2·66	—	0·26 ± 0·04 (285)
5-*p*-Cl·C_6H_4-	10	$CDCl_3$	2·06	2·64	—	0·16 ± 0·02 (293)
5-*p*-MeO·C_6H_4-	10	$CDCl_3$	2·13	2·75	—	0·70 ± 0·05 (300)
5-*p*-NO_2·C_6H_4-	10	$(CD_3)_2CO$	1·64	1·90	—	−0·19 ± 0·03 (335)
2-CO_2H-5-Ph-	10	$(CD_3)_2CO$	—	2·32	—	−1·87 ± 0·06 (280)
						1·78 ± 0·04 (280)
2-CO_2H-5-*p*-Cl·C_6H_4-	10	$(CD_3)_2CO$	—	2·45	—	−1·81 ± 0·04 (340)
						1·68 ± 0·05 (325)
2-CO_2H-5-*p*-MeO·C_6H_4-	10	$(CD_3)_2CO$	—	2·32	—	
2-CO_2H-5-*p*-NO_2·C_6H_4-	10	$(CD_3)_2CO$	—	1·85	—	1·54 ± 0·03 (350)
2-CO_2Et-5-Ph-	10 [f]	$CDCl_3$	—	2·50	—	—
2-CO_2Et-5-*p*-Cl·C_6H_4-	10 [f]	$CDCl_3$	—	2·46	—	— [g]
2-CO_2Et-5-*p*-MeO·C_6H_4-	10 [f]	$CDCl_3$	—	2·59	—	—
2-CO_2Et-5-*p*-NO_2·C_6H_4-	10 [f]	$CDCl_3$	—	1·99	—	— [g]
2-Ph-5-*p*-NO_2·C_6H_4-	11	Me_2SO	—	1·90	—	— [g]
4-CO_2H-2-Ph-	6	D_2O	—	—	—	3·41 ± 0·05 (290)
4-CO_2H-2-Me-	2	—	—	—	—	−0·66 ± 0·02 (234)
						3·54 ± 0·04 (240)
4-CO_2Et-2-Me-	2	$CDCl_3$	*7·50*	—	1·83	−0·89 ± 0·02 (240)
		D_2O	*7·45*	—	1·58	*3·54* ± 0·04 (240·5)
5-Ac-4-Me-	12	CCl_4	2·05	*7·51*	—	−0·97 ± 0·05 (262)
		D_2O	1·48	*7·48*		
Oxime deriv.						0·18 ± 0·01 (285)
TSH deriv.[h]	—	$(CD_3)_2SO$	1·76	*7·62*	—	—
5-CO_2H-4-Me-	3	D_2O	1·75	*7·57*	—	−0·72 ± 0·06 (244)
						2·83 ± 0·02 (244)
5-CN-4-Me-	7	MeOD	1·59	*7·60*	—	— [i]
5-CO·NH_2-4-Me-	7	$CDCl_3$	2·18	*7·49*	—	— [i]
5-CO_2Et-4-Me-	7	CCl_4	2·04	*7·53*	—	−0·89 ± 0·04 (240)
		CD_3OD	2·01	*7·52*	—	
5-CO_2Me-4-Me-	—	CCl_4	2·01	*7·54*	—	−1·00 ± 0·05 (249)
		CD_3OD	1·58	*7·45*	—	
4-Me-5-Ph-	13	CCl_4	2·14	*7·55*	—	1·09 ± 0·02 (260)
4,5-Me_2-	14	CCl_4	2·31	*7·92*	*7·76*	2·05 ± 0·01 (253)
4-Me-5-*p*-NO_2·C_6H_4-	—	$(CD_3)_2CO$	1·62	*7·45*	—	0·39 ± 0·04 (335)
5-Ac-1,4-Me_2-	12	CCl_4	*7·55*	*7·65*	—	0·21 ± 0·02 (264)
		D_2O	*7·45*	*7·55*	—	
PH deriv.[j]	—	$(CD_3)_2CO$	*7·56*	*7·55*	—	
TSH deriv.[h]	—	$(CD_3)_2SO$	*7·60*	*7·85*	—	
DNP deriv.[k]	—	$(CD_3)_2SO$	*7·50*	*7·50*	—	—
5-CO_2H-2,4-Me_2-	3	D_2O	*7·54*	*7·65*	—	0·38 ± 0·06 (250)
						3·03 ± 0·05 (250)
5-CO_2Et-2,4-Me_2-	3	D_2O	*7·45*	*7·60*	—	0·28 ± 0·03 (250)
2,4-Me_2-5-Ph-	15	CCl_4	*7·55*	*7·64*	—	2·45 ± 0·04 (270)
2,4-Me_2-5-*p*-NO_2·C_6H_4-	—	$(CD_3)_2SO$	*7·46*	*7·55*	—	1·69 ± 0·03 (350)
4-Ac-2,5-Me_2-	4	CCl_4	*7·60*	—	*7·65*	0·20 ± 0·04 (260)
Oxime deriv.	4	$CDCl_3$	*7·59*	—	*7·75*	1·28 ± 0·01 (230)
4-CO_2H-2,5-Me_2-	4	D_2O	*7·47*	—	*7·59*	0·27 ± 0·04 (245)
						4·12 ± 0·04 (250)

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TABLE 1 (*Continued*)

Oxazole	Ref.[a]	Solvent	ν_2 [b]	$\nu\nu_4$ [b]	ν_5 [b]	pK_a [c]
4-CO_2Et-2,5-Me_2-	4	$CDCl_3$	*7·50*	—	*7·77*	0·15 ± 0·04 (244)
4-CO_2H-2,5-Ph_2-	10[f]	—	—	—	—	−1·32 ± 0·05 (335)
						3·35 ± 0·05 (320)
5-CO_2H-2,4-Ph_2-	10[f]	—	—	—	—	−1·44 ± 0·06 (325)
						ca. 2·4
1,2,4-*Oxadiazole*			ν_5	ν_3	ν_2	
3-Me-	16	CCl_4	1·36	*7·59*	—	—[e]
3,5-Me_2-	17	D_2O	*7·35*	*7·67*	—	—[e]
		CD_3OD	*7·37*	*7·62*	—	
5-Me-3-Ph-	18	CD_3OD	*7·35*	—	—	
1,3,4-*Oxadiazole*						
2,5-Me_2-	19	D_2O	*7·40*	—	*7·40*	—[e]
1,2,4-*Triazole*			ν_2	ν_5	ν_4	
4-Me-	20	D_2O	1·5	1·5	*6·18*	—[l]
Isoxazole	—[m]					−2·03 ± 0·03 (260)

[a] To preparation or source. [b] Chemical shifts of methyl protons in italics. [c] Measured in aqueous media at 20° spectrometrically (analytical wavelength given) by methods described by A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Methuen, London, 1962; values of < -1 represent H_0 values for half-protonation calculated at nine points within the range $H_0 = pK_a \pm 0·8$; acidic pK_a values in italics. [d] Determined by ^{1}H n.m.r. spectra (see text) at 33°. [e] Too little spectral change on protonation for pK_a measurement. [f] Kindly supplied by the author. [g] Too insoluble in water for measurement. [h] Toluene-*p*-sulphonylhydrazone of above ketone. [i] Unstable in acid. [j] Phenylhydrazone of above ketone. [k] 2,4-Dinitrophenylhydrazone of above ketone. [l] See ref. 20. [m] Made by Mr. B. W. Arantz by the method of P. J. Tarsio and L. Nicholl, *J. Org. Chem.*, 1957, **22**, 192.

the methyl group was not observed to couple with H-5 which was split into a doublet (J 0·9 c./sec.) by H-4. However, in 2,4-dimethyloxazole (I; $R^1 = R^2 = Me$, $R^3 = H$) coupling occurred between Me-4 and H-5 which appeared as a quartet (J 1·3 c./sec.); in 4-methyloxazole (I; $R^1 = R^3 = H$, $R^2 = Me$) H-5 appeared as a quintet (J 1·1 c./sec.) on account of coupling with both H-4 and H-2. Similar splitting occurred in 2,5-dimethyloxazole and the other derivatives in Table 2 but the presence of electron-withdrawing or electron-releasing groups had little if any effect on the J-values.

TABLE 2

Coupling constants for oxazoles (c./sec.)

Oxazole	Solvent	
Unsubst.	D_2O	$J_{4,5}$ 0·8; $J_{2,5}$ 0·8
	5N-DCl	—[a]
2-Me-	D_2O	$J_{4,5}$ 0·9
	5N-DCl	1·2
4-Me-	CCl_4 or D_2O	$J_{2,5}$ 0·8; $J_{Me,5}$ 1·1
	5N-DCl	0·8 1·3
2,5-Me_2-	CCl_4 or D_2O	$J_{5\text{-}Me,4}$ 1·2
	5N-DCl	1·3
2,4-Me_2	CCl_4	$J_{4\text{-}Me,5}$ 1·0
	D_2O	1·2
	5N-DCl	1·4
2-Ph-	$CDCl_3$	$J_{4,5}$ 0·9
4-*p*-NO_2·C_6H_4	$CDCl_3$	$J_{2,5}$ 1·0
4-$CONH_2$-	D_2O	$J_{2,5}$ 0·9
4-CO_2H-	D_2O	$J_{2,5}$ 1·0
4-CO_2Et-	D_2O	$J_{2,5}$ 0·9
	5N-DCl	1·0

[a] Unresolved.

The progressive introduction of methyl groups into oxazole caused the expected upfield shift of proton signals relative to those of the parent; electron-withdrawing substituents caused a shift in the opposite direction. These substituent effects (Table 1) appeared to be transmitted inductively, but two notable exceptions were 4-carboxy- and 4-ethoxycarbonyl-oxazole (I; $R^1 = CO_2Et$, $R^2 = R^3 = H$) in which H-2 and H-5 were shifted to the same extent. A phenyl group in the 4- or 5-position had little effect on the chemical shift of H-2 but a *p*-nitrophenyl group, especially at the 4-position, produced an appreciable downfield shift of H-2.

Protonation had little effect on the coupling constants for oxazoles but caused considerable changes in the chemical shifts for the ring protons (Table 3). Such changes for H-2 were particularly marked compared with related heterocycles;[21,22,27] the changes for H-4 and H-5 were less pronounced and quite close. This was consistent with part of the positive charge residing on the oxygen atom in such oxazolium cations.

TABLE 3

Downfield shifts (p.p.m.) on protonation or change in solvent

	From D_2O to 5N-DCl–D_2O						From CCl_4 to D_2O					
Oxazole	H-2	H-4	H-5	Me-2	Me-4	Me-5	H-2	H-4	H-5	Me-2	Me-4	Me-5
Unsubst.	1·64	0·76	0·57	—	—	—	0·30	0·16	0·28	—	—	—
2-Me-	—	0·62	0·50	0·47	—	—	—	0·35	0·37	0·07	—	—
4-Me-	1·64	—	0·63	—	0·23	—	0·33	—	0·32	—	0·06	—
2,4-Me_2-	—	—	0·42	0·45	0·26	—	—	—	0·29	0·18	0·03	—
2,5-Me_2-	—	0·75	—	0·43	—	0·20	—	0·22	—	0·10	—	0·04
2,4,5-Me_3-	—	—	—	0·45	0·25	0·22	—	—	—	0·04	0·03	0·00
4-CO_2Et-	1·09	—	0·62	—	—	—	0·46	—	0·49	—	—	—

[27] B. Bak, J. T. Nielsen, J. Rastrup-Andersen, and M. Schottländer, *Spectrochim. Acta*, 1962, **18**, 741.

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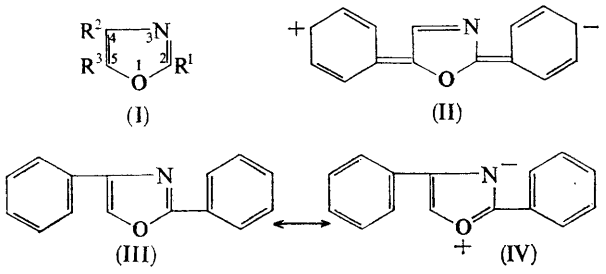
(τ *ca.* 0·2); change of solvent had little effect on methyl protons. The individual spectra of 1,2,4-oxadiazoles,[28] imidazoles,[25,29] and triazoles [25] have been discussed elsewhere.



Ionization and Ultraviolet Spectra.—The only published information on the ionization of oxazoles, derived from their solubility in acids and the hydrolysis of their salts,[30] was thought to indicate that oxazoles and pyridines were bases of comparable strength. This suggestion can be accepted no longer in view of the pK_a values in Table 1, which indicate that oxazoles are about 10,000 times weaker as bases than the corresponding pyridines.

The measurement of pK_a values for simple oxazoles was complicated by a lack of ultraviolet absorption above 250 mμ and by the very small differences between

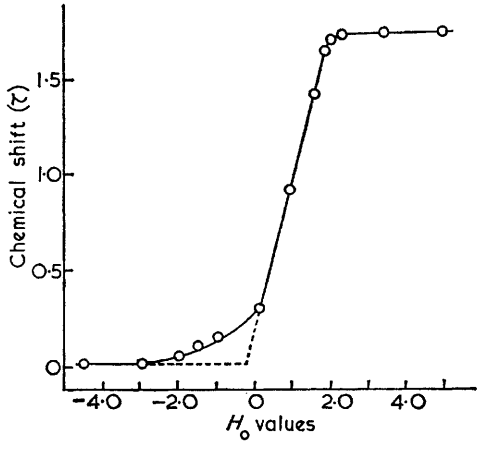


FIGURE 1 Plot of pH or H_0 against the chemical shift of the H-2 signal in fresh DCl–D_2O solutions of oxazole at 33°

the spectrum of each neutral molecule and its cation; the low basic strengths precluded satisfactory titration. Hence we determined the pK_a value of oxazole (which has only end-absorption above 205 mμ [3,31]) from a plot (Figure 1) of the chemical shifts of H-2 against the pH or H_0 values [32] of appropriate solutions. The result (0·8 at 33°) was in tolerable agreement with a figure (0·6) derivable from the pK_a values of substituted oxazoles in Table 1.

The feeble basic strength of oxazole and its derivatives relative to 1-methylimidazole (pK_a 7·44),[33] pyridine (5·2), or thiazole (2·44) [34] indicated the dominating inductive effect of the powerfully electronegative

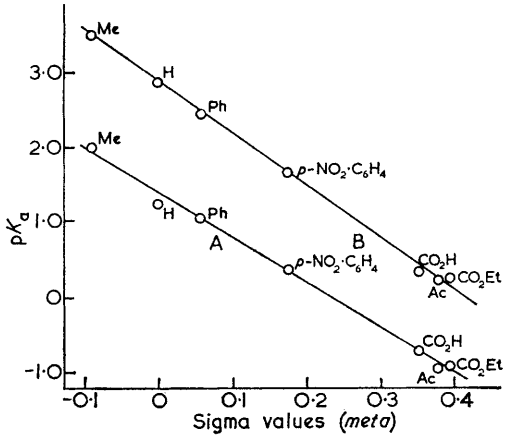


FIGURE 2 Plots of pK_a values for 4-methyl- (A) and 2,4-dimethyl-5-substituted-oxazole (B) against the Hammett (*meta*)-sigma constants.

oxygen atom. This effect, seen to perfection in isoxazole (pK_a −2·03; *cf.* +1·3 reported earlier [35]), was clearly more important in oxazole than any base-strengthening effect from delocalization of the oxygen lone pair; indeed such delocalization appeared to be minimal in view of the spectral evidence below.

The effects of 5-substitution on the basic strengths of 4-methyl- and 2,4-dimethyl-oxazole are summarized in the closely rectilinear plots of Hammett substituent constants (σm) [36] *versus* pK_a values in Figure 2. From these data and from Table 1 it was evident that the introduction of a 2-methyl group increased the pK_a of an oxazole by an abnormally high increment (*ca.* 1·6 units), whereas a 4-methyl group (also adjacent to the site of protonation) produced a much smaller increase (*ca.* 0·6), comparable with that from a 5-methyl group. Although we cannot explain these observations, it is interesting that methyl substituents in the weakly basic five-membered heterocyclic ring of indole also caused abnormal changes in apparent pK_a when the H_0 scale was used.[36] Other oxazoles bearing an electron-withdrawing 4-substituent (Ac, CO_2H, CO_2Et) had pK_a values very similar to those of the respective 5-isomers, a fact readily explained in terms of stabilization of the cation by hydrogen-bonding with the carbonyl group of the 4-substituent. However, with 4- and 5-*p*-nitrophenyloxazole, in both of which such bonding was impossible, the 4-isomer was the weaker base. The stability of the oxazoles during pK_a measurement

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was confirmed by the normality of their ^{1}H n.m.r. spectra under conditions of comparable or greater acidity.

The acidic pK_a values of the carboxyoxazoles furnished a direct guide to the electron distribution over the three carbon atoms: the acidic strength of the isomers was in the order 2 > 5 > 4, the reverse to that expected if the acid-weakening effect of the hydrogen-bonding between each acid group and the adjacent O and/or N atoms was the determining factor. The above order was parallel to the ease of decarboxylation [37] and was in full agreement with the rates of base-catalysed deuteriation at C-2, C-4, and C-5 reported below.

Although the ultraviolet spectra of many oxazoles have been recorded and discussed,[38,39] no conclusions as to the nature of the bonding in this system have been reached. With this in mind, we examined the spectra of phenyl- and diphenyl-oxazoles (Table 4). The curve for 2,5-diphenyloxazole (I; $R^1 = R^3 = Ph$, $R^2 = H$) showed two main peaks of which the high-intensity one at 314 mμ (log ε 4·34) must have arisen from an extended conjugation as in structure (II); *cf.* 2,5-diphenylfuran, 2,5-diphenyl-1,3,4-oxadiazole, and *p*-terphenyl.[40,41] The spectrum of 2,4-diphenyloxazole (III) showed no such high-intensity peak above 276 mμ, and was clearly an approximate superimposition of the 2- and 4-phenyloxazole absorptions. This suggested that canonical structures such as (IV) contributed little to the oxazole resonance, and hence to the conclusion that an oxazole should be considered more as a conjugated diene than as a fully aromatic system. A similar probability has been postulated for 1,2,4-oxadiazoles.[42]

TABLE 4

Ultraviolet spectra in methanol

Oxazole	$\lambda_{max.}$ (mμ)	ε
2-Ph-	263	16,290
4-Ph-	243	17,420
5-Ph-	267	19,370
	261	19,800
2,4-Ph_2-	276	17,200
	232	17,500
2,5-Ph_2-	244	12,100
	314	22,080

Base-catalysed Deuteriation.—The discovery [43] of the importance of a labile 2-H in thiamine stimulated interest in the acidity of *C*-protons in such 5-membered heterocyclic cations,[44,45] and comparative rates for the deuteriation of thiazolium and oxazolium cations have been measured.[21] In addition, it was reported [22] that 1-benzylimidazole underwent deuteriation in CH_3OD six times faster than oxazole and eight times faster than thiazole. We made similar measurements in CH_3ONa–CH_3OD of known [46] pH or H_-. In the range 13·0—14·6, rapid deuteriation of oxazole occurred (Table 5; Figure 3) but 1-benzylimidazole was unchanged. Since the imidazole (pK_a 6·7) was a much stronger base than either oxazole (0·8) or thiazole (2·4) it seemed that the earlier results [22] represented a comparison of the deuteriation rates for neutral oxazole and thiazole with that for the small proportion of 1-benzylimidazolium cation present in a CH_3OD solution.

TABLE 5

Deuteriation rates [a] in 1·43 M-NaOMe–CH_3OD (H_- 14·4)

	10^4k (sec.$^{-1}$)	$t_{\frac{1}{2}}$ (min.)
Oxazole	6·8	17·0
4-Me-	4·8	24·0
5-Ph-	13·0	9·0
5-*p*-ClC_6H_4-	19·2	6·0
5-*p*-$MeOC_6H_4$-	6·9	16·7
5-Me-4-Ph-	4·2	27·0
1,2,4-Triazole	—	—
1-Me	6·5	17·6

[a] Accuracy better than ±20%.

Of the oxazoles available for deuteriation, those bearing strongly electron-withdrawing substituents (Ac, CO_2Et, CN) in the 4- or 5-position proved too unstable for measurement under alkaline conditions; conversely, 2-methyloxazoles were too inactive to incorporate deuterium into the methyl group. The rates for 2-deuteriation of the remaining oxazoles in CH_3ONa–CH_3OD ($H_- \sim 14·4$) are in Table 5 and rate profiles for deuteriations in aqueous alkali are shown in Figure 3. Under extreme alkalinity (CH_3ONa in CD_3SOCD_3: $H_- \sim 16·8$) [46] oxazole underwent instantaneous 2-deuteriation and a slower 5-deuteriation ($t_{\frac{1}{2}}$ 50 min. at 33°), indicating that electron-density at the three carbon atoms of oxazole was in the order 4 > 5 > 2. This was consistent with the pK_a values of the three monocarboxyoxazoles (above) but at variance with an order (5 > 4 > 2) predicted [47] from molecular orbital calculations.

The marked effect of substituents on the 2-deuteriation of oxazole was evident in a 40% decrease of rate for 4-methyloxazole, a 90% increase for 5-phenyloxazole, a 300% increase for 5-*p*-chlorophenyloxazole, and other such figures (Table 5), all consistent with the electronic nature of each group. Similarly, the replacement of C-5 in oxazole by a powerfully electron-withdrawing nitrogen atom to give 1,2,4-oxadiazole (V) increased the deuteriation rate at pH 14 by some 12,000% (derived from the experimental value for 3,5-dimethyl-1,2,4-oxadiazole by multiplying first by

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80, the rough factor determined below for the relative deuteration rates of =CMe– and =CH– in the same molecular environment, and then by 2 to allow for the effect of the second methyl group). However, the further replacement of the oxygen atom by NMe as in 1- or 4-methyl-1,2,4-triazole (VI) (VII) [20,25] resulted in a

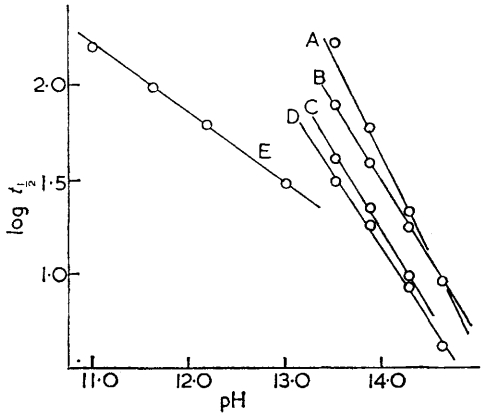
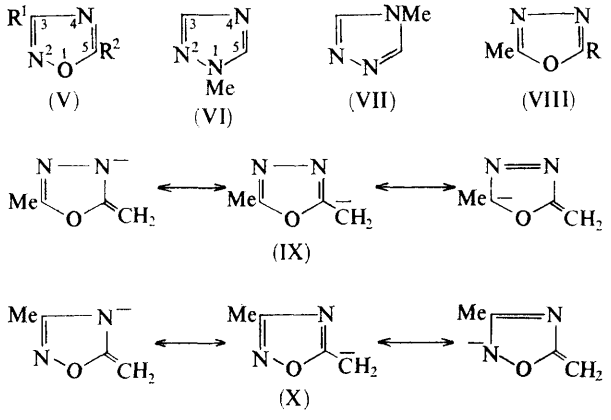


FIGURE 3 Plots of pH value against log $t_{\frac{1}{2}}$ values for base-catalysed deuteriations of 4-methyloxazole (A), 1-methyl-1,2,4-triazole (B), 4-methyl-1,2,4-triazole (C), oxazole (D), and 3,5-dimethyl-1,2,4-oxadiazole (E)

reduced =CH– deuteration rate, comparable with that for oxazole (Figure 3).



The simple oxadiazoles were too unstable under alkaline conditions for measurement of rates for base-catalysed deuteriation: 3-methyl-1,2,4-oxadiazole (V; R^1 = Me, R^2 = H) decomposed [28] into acetonitrile and sodium cyanurate before any deuterium exchange could be observed and published observations [48] insured a similar result with 2-methyl-1,3,4-oxadiazole (VIII; R = H).[49] However, 3,5-dimethyl-1,2,4-oxadiazole (V; R^1 = R^2 = Me) deuteriated satisfactorily from pH 9 to 13 (Figure 3). In addition, the deuteriation rate was measured for 5-methyl-3-phenyl-1,2,4-oxadiazole (V; R^1 = Ph, R^2 = Me) in 0·4M-piperidine–CH_3OD to permit direct comparison with a rate similarly determined [44] for 3-phenyl-1,2,4-oxadiazole (V; R^1 = Ph, R^2 = H). The latter compound underwent deuteriation at C-5 *ca.* 80 times faster than did its homologue at the 5-CH_3, thus providing a rough factor for comparing the deuteriation rate of a ring proton with that of a corresponding methyl group. 2,5-Dimethyl-1,3,4-oxadiazole (VIII; R = Me) failed to deuteriate at pH 7—14, probably owing to stabilization of the anion (IX) by only one ring nitrogen instead of two as in the anion (X) of the isomeric 1,2,4-oxadiazole. This situation was formally similar to that postulated [33] for the transition states in nucleophilic displacement reactions of tetrazoles and triazoles.

EXPERIMENTAL

Analyses were done by Dr. J. E. Fildes and her staff. ^{1}H n.m.r. spectra were measured (33°) at 60 or 100 Mc./sec. against tetramethylsilane or sodium 3-trimethylsilylpropanesulphonate. Ultraviolet spectra were recorded on a Spectracord-4000 and peaks were checked on an Optica manual instrument.

5-Methoxycarbonyl-4-methyloxazole.—Methyl chloroacetate [50] (55 g.), formamide (36 g.), and 98% formic acid (100 g.) were heated under reflux for 4 hr. The cooled mixture was added to ice–water (150 ml.), adjusted to pH 7 with 2N-sodium hydroxide at <40°, and then saturated with sodium chloride. Ether extraction and distillation gave the *oxazole* (57%), b.p. 104°/18 mm., m.p. 60° (from light petroleum–ethyl acetate or by sublimation at 100°/50 mm.), $\nu_{max.}$ 1730 cm.$^{-1}$ (C=O) (Found: C, 51·3; H, 4·8. $C_6H_7NO_3$ requires C, 51·1; H, 5·0%).

Hydrazones of 5-Acetyl-2,4-dimethyloxazole.—The acetyloxazole [11] was converted by the usual method into its yellow *phenylhydrazone*, m.p. 96—97° (from ethanol) (Found: C, 68·4; H, 6·7; N, 18·4. $C_{13}H_{15}N_3O$ requires C, 68·2; H, 6·6; N, 18·4%); red *2,4-dinitrophenylhydrazone*, m.p. 204—205° (from acetone–dimethylformamide) (Found: C, 49·0; H, 3·9; N, 21·7. $C_{13}H_{13}N_5O_5$ requires C, 48·9; H, 4·1; N, 21·9%); and colourless *toluene-p-sulphonylhydrazone*, m.p. 179—180° (from methanol) (Found: C, 54·7; H, 5·4; N, 13·7. $C_{14}H_{17}N_3O_3S$ requires C, 54·8; H, 5·5; N, 13·7%).

5-Acetyl-4-methyloxazole Toluene-p-sulphonylhydrazone.—The *hydrazone* had m.p. 209—210° (from acetone) (Found: C, 53·3; H, 5·1; N, 14·1. $C_{13}H_{15}N_3O_3S$ requires C, 53·3; H, 5·2; N, 14·3%).

4-Methyl- and 2,4-Dimethyl-5-p-nitrophenyloxazole.—Potassium nitrate (0·011 mole) in 85% sulphuric acid (10 ml.) was added dropwise to 4-methyl-[13] or 2,4-dimethyl-5-phenyloxazole [15] (0·01 mole) in 98% sulphuric acid (10 ml.) at 0—5°. The mixture was maintained at 25° for 1 hr. and then at 70° for 10 min. It was poured into ice (200 g.) and adjusted to pH 2·0 with solid potassium carbonate. The precipitate was recrystallized from ethanol. The monomethyl compound (75%) had m.p. 118—119° (lit.,[51] 118—119°) and the dimethyl compound (85%) m.p. 168—169° (lit.,[52] 169—170°).

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Deuteration Rates.—The concentration of each CH_3ONa–CH_3OD solution or other alkaline medium was determined by titration and the H_- value read from Bowden's tables;[46] no correction for isotopic effect was attempted. Oxazole (*ca.* 75 mg.) was added to CH_3ONa–CH_3OD (0·5 ml.; H_- ~14·4) preheated to 33°. At intervals after mixing, the ^1H n.m.r. spectrum was recorded. The first-order rate constant for deuteration was determined from the slope of the rectilinear plot: log ratio of height H-2 signal (τ *ca.* 1·7) to height of H-4 signal (τ *ca.* 2·7) *versus* time. The $t_{\frac{1}{2}}$ was reproducible within ±20%. Other rates were determined similarly except for 4-methyl-1,2,4-triazole in which the equal mobility of H-3 and H-5 caused a loss of rectilinearity as the reaction progressed; for comparative purposes, the rate determined from the early part of this plot was divided by 2. No such factor was used in comparing rates for 3-phenyl-1,2,4-oxadiazole and its 5-methyl derivative; the reported ratio (80 : 1) was simply based on the observed $t_{\frac{1}{2}}$ for complete deuteriation of each compound.

To check that ring fission had not occurred during measurements, the complete ^1H n.m.r. spectrum of each solution was recorded at the end of each run. Control runs in comparable non-deuteriated media insured that changes in the ratio of peak heights were due to deuteriation.

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