Tautomeric Pyridines. Part XV.[1] Pyridone–Hydroxypyridine Equilibria in Solvents of Differing Polarity

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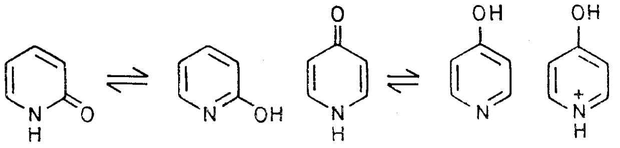
Tautomeric equilibria of the hydroxypyridine–pyridone type are investigated for five compounds: the proportion of pyridone form, dominant for H_2O solutions, falls roughly linearly with the solvent polarity as measured by Z. In cyclohexane solution, comparable amounts of both forms are present.

2- AND 4-pyridone exist predominantly in the oxo-forms (1a) and (2a) in aqueous solution: the hydroxy-forms (1b) and (2b) are minor components with pK_T values 3.0 and 3.3, respectively.[2,3] The effects of substituents on these tautomeric equilibria in aqueous solution are now well understood, and can be explained in terms of their relative effects on the acidity of the two protons in the conjugate acid [*e.g.* (3)].[3,4]


(1a) (1b) (2a) (2b) (3)

We have previously[5] investigated the dependence of such equilibrium constants on solvent polarity. For 6-chloro-2-pyridone and three different substituted 4-pyridones (and also 3-hydroxypyridine) we found that equations of type (1) held between K_T and Kosower Z solvent parameters for solvents α and β. The slopes a varied from 0.116 to 0.151. Because of the difficulties in applying the pK_a method in non-aqueous media, this investigation[5] was limited to compounds for which substituent effects had already caused considerable quantities of the hydroxy-form to occur in aqueous solution, and the u.v. method was utilised. It was pointed out that slopes of this order of magnitude would imply that 2- and 4-pyridone themselves should be predominantly in the hydroxy-forms (1b) and (2b) in hydrocarbon solvents, but that there appeared to be a tendency toward smaller slopes for compounds for which the oxo-form was more stabilised.

$$\log\,[K_{T(\alpha)}/K_{T(\beta)}] = a(Z_\alpha - Z_\beta) \qquad (1)$$

Since this previous work, it has become clear that 2- and 4-pyridone exist predominantly in the hydroxy-form (1b) and (2b) in the vapour phase: thus, u.v. comparison with fixed models[6] shows $[(1b)]/[(1a)] = 2.5 \pm 1.5$ at 120—140 °C, for the equilibrium in the vapour state and this is supported by previous[7] ionization potential measurements and is further confirmed by other mass spectrometric[8] studies. I.r. vapour phase measurements[9] while not conclusive[10] are certainly not incompatible.

In view of the expected similarity of tautomeric equilibria in the gas phase and in hydrocarbon solvents, we have reinvestigated some pyridones and quinolones lacking strongly electron donor or acceptor substituents

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[3] J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, 'The Tautomerism of Heterocycles,' Supplement No. 1 to *Adv. Heterocyclic Chem.*, 1976, ch. 2.

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[5] A. Gordon and A. R. Katritzky, *Tetrahedron Letters*, 1968, 2767.

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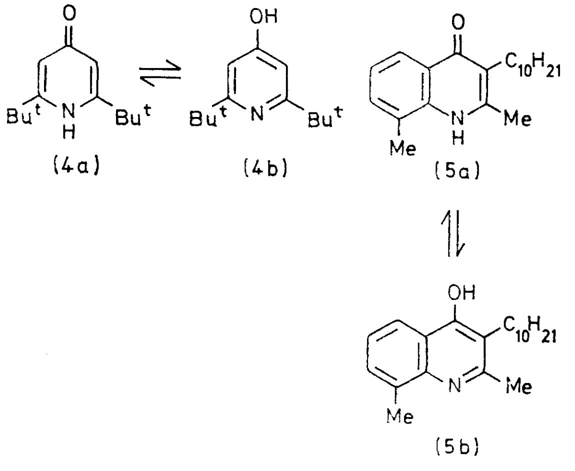
[8] A. Maquestiau, Y. Van Haverbeke, C. de Meyer, A. R. Katritzky, M. J. Cook, and A. D. Page, *Canad. J. Chem.*, 1975, **53**, 490.

[9] É. S. Levin and G. N. Rodionova, *Doklady Akad. Nauk S.S.S.R.*, 1965, **164**, 584 (*Doklady Chem.*, 1965, **164**, 910); 1967, **174**, 1132 (*Doklady Phys. Chem.*, 1967, **174**, 442); 1969, **189**, 326 (*Doklady Chem.*, 1969, **189**, 900).

[10] M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J.C.S. Perkin II*, 1972, 1295.

in non-polar media. As the unsubstituted compounds are sparingly soluble, we initially studied (4) and (5).


(4a) (4b) (5a) (5b)

EXPERIMENTAL

Compounds.—Commercial samples were sublimed to provide 2-pyridone, m.p. 106 °C (lit.,[11] 107 °C); 4-pyridone, m.p. 147—148 °C (lit.,[11] 148 °C); 4-quinolone, m.p. 196—197 °C (lit.,[11] 195—198 °C). A sample of 2,6-di-t-butyl-4-pyridone, m.p. 171—172 °C (lit.,[12] 170.5—172 °C) was supplied by Professor H. C. van der Plas.

3-*Decyl*-2,8-*dimethyl*-4-*quinolone*.—Sodium metal (0.8 g, 0.035 mol) was dissolved in EtOH (30 ml) and ethyl acetoacetate (4.55 g, 0.035 mol) added. The mixture was heated under reflux for 1.5 h then n-decyl bromide (8.4 g, 0.038 mol) was added and heating continued for 9 h more. After 12 h at 20 °C solid was filtered off and after removing solvent, the residue was distilled to give crude ethyl n-decylacetoacetate, b.p. 140—150 °C at 2 mmHg.

o-Toluidine (2.25 g, 0.021 mol) and ethyl-n-decylacetoacetate (5.7 g, 0.021 mol) were stirred at 20° for 10 days to give the crude crotonate. The crotonate (2.2 g) was heated in paraffin oil (25 ml) for 30 min at 240—245 °C. On cooling, the *quinolone* separated (0.4 g, 20%); it crystallised as plates, m.p. 165 °C (from ethyl acetate) (Found: C, 79.6; H, 9.6; N, 5.0. $C_{21}H_{31}NO$ requires C, 80.5; H, 9.9; N, 4.5%).

TABLE 1

U.v. absorption maxima (nm) and intensities (log ε) for pyridones and quinolones in solvents of varying polarity

	Water		EtOH		MeOH		MeCN		$CHCl_3$		1% EtOH 99% C_6H_{12}		C_6H_{12}	
	λ	log ε	λ	log ε	λ	log ε	λ	log ε	λ	log ε	λ	log ε	λ	log ε
2-Pyridone	293	3.77[a]	299	3.87[b]	297	3.80[c]	303	3.86[b]	296	3.81[b]	300	3.65[b]	295	3.68[b]
4-Pyridone	253	4.17[d]	257	4.26[b,e]	256	4.15[c]	256	4.18[b]	259	4.03[b]	258	2.77[b]	*f*	
2,6-Di-t-butyl-4-pyridone	*g*		*g*		258	4.17[h]	*g*		263	4.13[b]	251	3.38[b]	255	3.35[b]
4-Quinolone	*g*		317	4.08[b]	*g*				318	4.0[i]	*f*		*f*	
			330	4.12[b]					331	4.1[i]				
			318	4.15[j]			317	4.08[b]	319	4.05[b]				
			332	4.18[j]			330	4.12[b]	332	4.11[b]				
3-Decyl-2,8-dimethyl-4-quinolone	*g*		323	4.13[b]	*g*		322	4.10[b]	324	4.03[b]	*g*		321	3.95[b]
			336	4.13[b]			335	4.11[b]	338	4.08[b]			335	3.99[b]

[a] S. F. Mason, *J. Chem. Soc.*, 1957, 5010. [b] Present measurements were carried out in 1 cm cells with concentration in range 5×10^{-5}–10^{-4}M. [c] H. Specker and H. Gawrosch, *Ber.*, 1942, **75**, 1338. [d] S. F. Mason, *J. Chem. Soc.*, 1959, 1253. [e] Lit., log ε_{256} 4.16 (I. G. Ross, *J. Chem. Soc.*, 1951, 1374). [f] Insufficiently soluble for determination. [g] Not measured. [h] Ref. 12. [i] J. K. Landquist, *J. Chem. Soc.*, 1951, 1038. [j] J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.*, 1951, 3318.

RESULTS AND DISCUSSION

U.v. Spectra.—The u.v. spectrum of 2,6-di-t-butyl-4-pyridone varies considerably with solvent polarity (Figure 1). The spectrum in chloroform is very similar to the published spectrum[12] in methanol (Table 1) and these absorptions are similar to that found for 4-pyridone in polar solvents (Table 1). Undoubtedly in these polar solvents both compounds exist very predominantly in the pyridone form. Figure 1 clearly demonstrates that the extinction falls as the solvent polarity decreases.

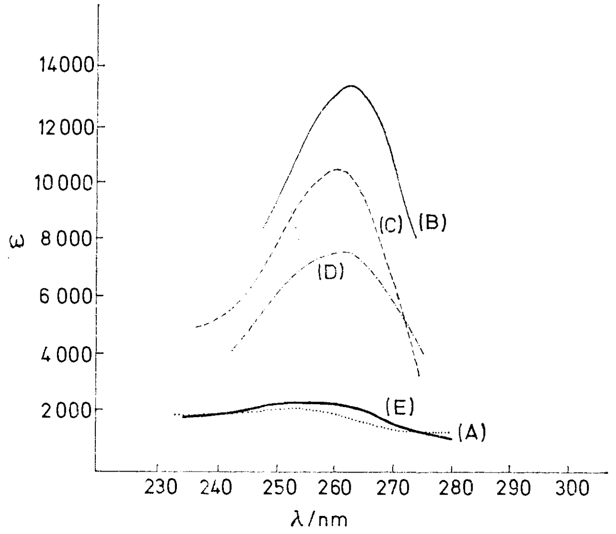


FIGURE 1 U.v. spectra of 2,6-di-t-butyl-4-pyridone: cyclohexane (A); chloroform (B); cyclohexane–ethanol (1 : 1) (C); cyclohexane–chloroform (90 : 10) (D); cyclohexane–ethanol (99 : 1) (E)

Similar behaviour is found for 4-pyridone (Figure 2) the log ε values for H_2O, EtOH, MeOH, and MeCN are all identical to within experimental error (Table 1), but the extinction falls significantly for $CHCl_3$ as solvent, and reaches a low value in cyclohexane (Figure 2). However,

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[11] L. Màzor, ' Szerveskémiai analitikai Kézikönyu,' Mùszaki Könyukiadó, Budapest, 1966.

[12] H. C. van der Plas and H. J. den Hertog, *Tetrahedron Letters*, 1960, 13.

for 2-pyridone the changes are much less, and do not show the same clear trend with solvent polarity.*

We have also investigated 3-decyl-2,8-dimethyl-4-quinolone (Figure 3) and 4-quinolone. In the decyl-4-quinolone, there is a clear sequence of decrease in extinction with solvent polarity, but no significant change for 4-quinolone.

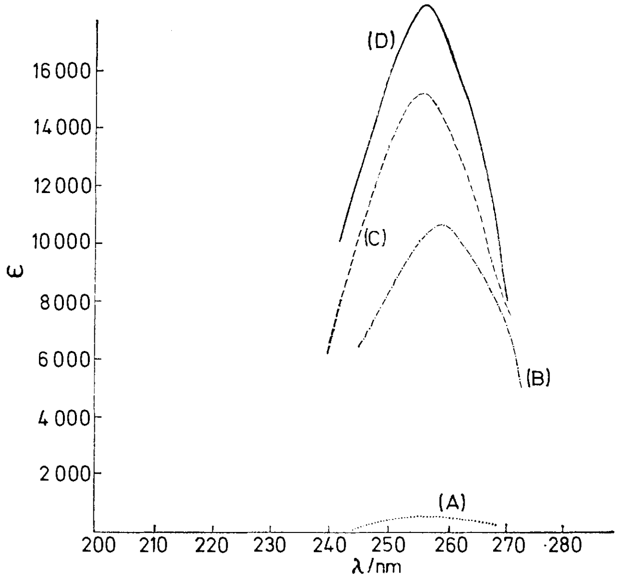

FIGURE 2 U.v. spectra of 4-pyridone: 1% EtOH–99% cyclohexane (A); chloroform (B); acetonitrile(C); ethanol (D)

Tautomeric Equilibrium Constants.—From the ε value at the absorption maxima given in Table 1 we have calculated K_T values (Table 2) using equation (2) and the values of ε_{OH} and ε_{NH} shown in Table 3, which were measured or estimated from the published work quoted. log K_T Values determined from u.v. data become increasingly inaccurate as log K_T varies from 0: at log K_T *ca.* 2 an uncertainty of *ca.* 0.3 units could occur, but

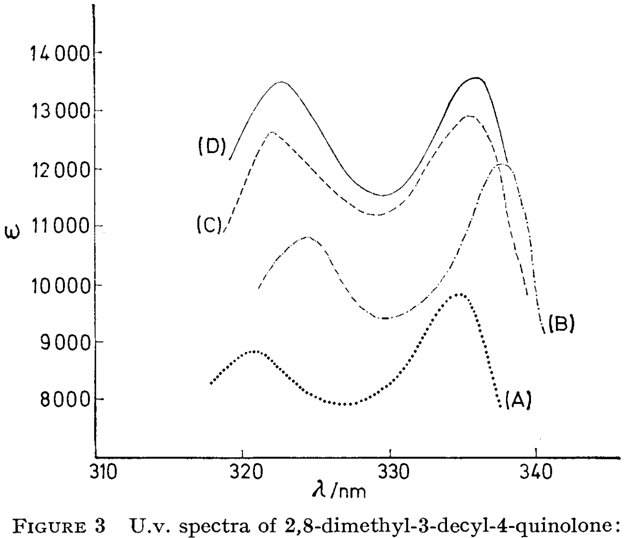

FIGURE 3 U.v. spectra of 2,8-dimethyl-3-decyl-4-quinolone: cyclohexane (A); chloroform (B); acetonitrile (C); ethanol (D)

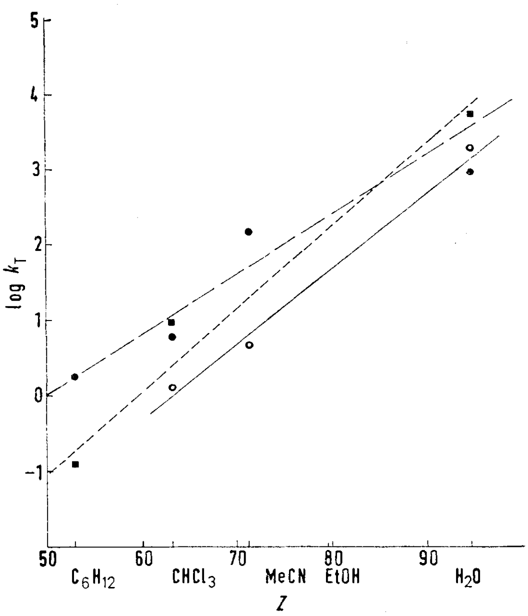

FIGURE 4 Plot of log K_T *vs.* Z for: 2-pyridone (●), 4-pyridone (○), and 2,6-di-t-butyl-4-pyridone (■)

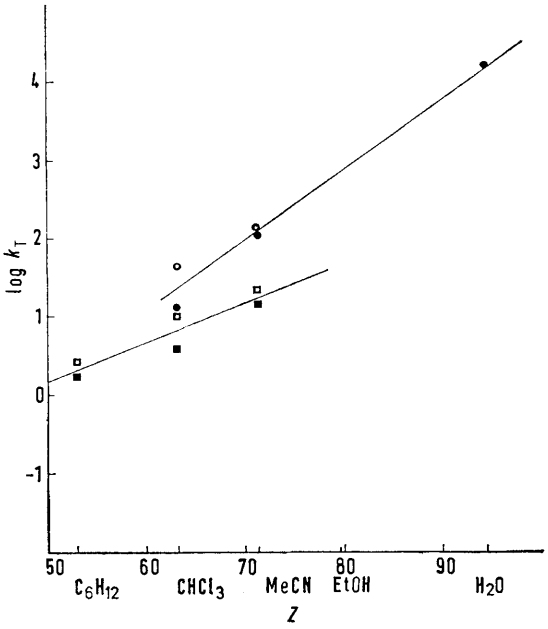

FIGURE 5 Plot of log K_T *vs.* Z for: 4-quinolone at 318 (●) and 331 (○) nm; 3-decyl-2,8-dimethyl-4-quinolone at 322 (■) and 335 (□) nm. The lines shown are based on averages for the measurements at the two wavelengths

$$K_T = (\varepsilon_{OH} - \varepsilon)/(\varepsilon - \varepsilon_{NH}) \qquad (2)$$

for smaller values of log K_T the uncertainty is considerably less than this. In Table 2 we also include values of log K_T for H_2O which are available in the literature and which were determined by the standard pK_a method.

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* *Note added in proof:* We now believe that under the conditions used in this paper 2-pyridone is still considerably dimerised accounting for its less regular behaviour.

TABLE 2

Tautomeric equilibrium constants for [NH]/[OH] equilibria

Compound	log K_T Values in Cyclohexane	Chloroform	Acetonitrile	Water from pK_a in water	Slope
2-Pyridone	0.24	0.78	2.17	2.96 [a]	0.08
4-Pyridone		0.11	0.66	3.29 [b]	0.10
2,6-Di-t-butyl-4-pyridone	−0.92	0.96		3.74 [c]	0.11
4-Quinolone		1.11 [d]	2.04 [d]	4.19 [b]	0.09
		1.63 [e]	2.12 [e]		
3-Decyl-2,8-dimethyl-4-quinolone	0.23 [g]	0.57 [g]	1.16 [g]		0.05 [i]
	0.42 [h]	0.99 [h]	1.33 [h]		

[a] Ref. 10. [b] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294. [c] Value for 2,6-dimethyl-4-pyridone, P. Bellingham, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1968, 866. [d] Value at 317 nm. [e] Value at 330 nm. [f] Value based on average for the measurements at 317 and 330 nm. [g] Value at 323 nm. [h] Value at 336 nm. [i] Value based on average for the measurements at 323 and 336 nm.

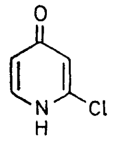
TABLE 3

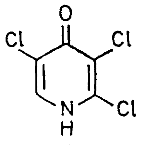
Spectroscopic data for tautomeric equilibrium constant determinations

	Model for C=O form					Model for OH form				
Compound	Nature	λ	ε	Solvent	Ref.	Nature	λ	ε	Solvent	Ref.
2-Pyridone	NH	299	7 500	EtOH	*a*	OEt	300	100	MeOH	*b*
	(*cf.* NMe	300	6 300	MeOH)	*b*	(*cf.* OEt	270	4 300	MeOH)	*b*
4-Pyridone	NH	257	18 400	EtOH	*a*	OEt	260	700	EtOH	*a*
	(*cf.* NMe	262	18 200	MeOH)	*b*	(*cf.* OMe	245	1 000	MeOH)	*b*
2,6-Di-t-butyl-4-pyridone	NH	258	14 800	MeOH	*c*			*d*		
4-Quinolone	NH	317	12 100	EtOH	*a*	OMe	318	1 000	EtOH	*e*
		330	13 300				330	100		
	(*cf.* NMe	325	12 800	EtOH)	*e*	(*cf.* OMe	283	7 900	EtOH)	*e*
		338	15 200							
3-Decyl-2,8-dimethyl-4-quinolone	NH	323	13 400	EtOH	*a*			*f*		
		336	13 500							

[a] This work. [b] H. Specker and H. Gawrosch, *Ber.*, 1942, **75**, 1338. [c] Ref. 12. [d] As for 4-pyridone. [e] J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.*, 1951, 3318. [f] As for 4-quinolone.

Variation of log K_T *with Solvent Polarity*.—We find that the best correlation is given by Kosower Z values[13] (E_T[13] gave distinctly curved plots). Figure 4 shows a plot of log K_T against Z. This plot includes data for 2-chloro- (6) and 2,3,5-trichloro-4-pyridone (7) which were previously reported[5] and incorporates the H_2O point for the pK_a method for the compounds presently investigated together with the K_T values for non-polar solvents determined by the u.v. method. Although some scatter occurs, it is evident that the same general pattern is found for all the compounds in Figures 4 and 5. For five of the compounds studied, the slopes of 0.05—0.11 for d log K_T/d Z are towards the lower end of the range 0.12—0.15 found previously[5] over a limited range of Z values.


(6)


(7)

We thank Dr. M. J. Cook for help in this investigation.

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[13] C. Reichardt, *Angew. Chem. Internat. Edn.*, 1965, **4**, 29.