Keto–Enol and Imine–Enamine Tautomerism of 2-, 3- and 4-Phenacylpyridines

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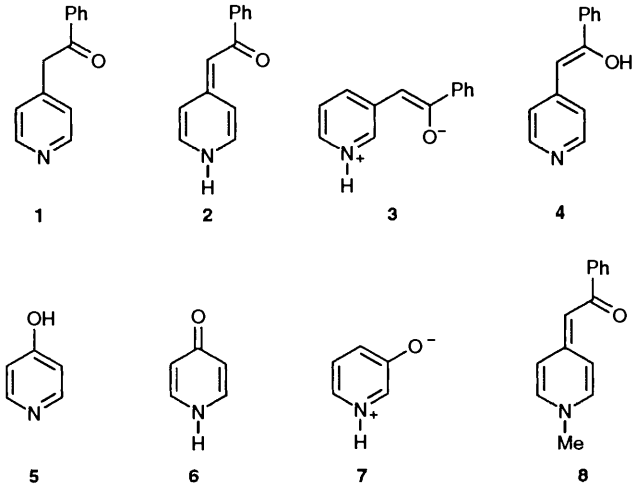
Equilibrium constants for keto–enol tautomerisation and migration of hydrogen from carbon to nitrogen to form enamine or zwitterion tautomers have been measured for 2-, 3- and 4-phenacylpyridines ($PyCH_2COPh$) in aqueous solution at 25 °C. Relative tautomeric stabilities fall in the order ketoimine > enamine > enol and (for the 3-isomer) enol > zwitterion. Values of pK_T, $(-\log K_T)$ where K_T = [enamine (or zwitterion)]/[imine] or [enol]/[ketone], are 1.05, 5.87 and 2.42 for the enamine or zwitterion tautomerism and 2.0, 4.86 and 4.4 for keto–enol tautomerism of the 2-, 3- and 4-isomers respectively. For the enamines K_T was determined kinetically by quenching the enolate anion at a pH below its pK_a and monitoring its relaxation to the ketoimine spectrophotometrically: combining rate constants for this process and the reverse reaction measured by halogen trapping of the enol or enamine gave K_T. Values are compared with results of earlier indirect measurements by Katritzky. For the 3-isomer, the *N*-methyl-3-phenacylpyridinium ion was taken as a model for the zwitterion tautomer and a ratio of enol to zwitterion concentrations of 10:1 was derived from kinetic and equilibrium ionisation measurements corrected for a methyl substituent effect. The unusually large enol content of 2-phenacylpyridine in non-polar solvents was measured spectrophotometrically and extrapolated to water. For the 4-isomer the enol content could be obtained from a correlation of pK_as of phenacylpyridine enols and vinylogously related phenols. Acidic and basic pK_as of all tautomers are reported including kinetically determined values for O-protonation of the enaminones. Proton activating factors for ionisation and tautomerisation have been calculated and are compared with values for the vinylogous hydroxypyridines. The influence of charge delocalisation and electrostatic interactions on the stability of enolate and carboxylate anions is discussed.

Recent studies of the tautomerism of aldehydes and ketones have provided quantitative measurements of the enol contents of representative structures in aqueous solution including acetone,[1] acetophenone[2] and acetaldehyde.[3] In this paper we report a corresponding study of the tautomerism of the three α-heterocyclic ketones, 2-, 3- and 4-phenacylpyridine.[4] As illustrated for the 4-isomer (**1**), these ketones differ from their non-heterocyclic analogues in forming an enamine (**2**) or, in the case of the 3-isomer, a zwitterionic (**3**) as well as enol (**4**) tautomers. These structures are (nearly) vinylogously related to the phenolic, pyridone and zwitterion tautomers of the hydroxypyridines,[5] *e.g.* **5**, **6** and **7**. They are designated keto-imine (**1**), enolimine (**4**) and enaminone (**2**) or, more briefly, keto, enol and enamine.

Tautomeric constants (K_T) for the phenacylpyridines can be measured kinetically. The stable forms of all three isomers in water are ketoimines (*e.g.* **1**) but these are acidic enough to yield enolate anions in dilute aqueous sodium hydroxide. Quenching the anions in acidic or buffer solutions leads to kinetically controlled protonation on nitrogen or oxygen to form an enol or enamine tautomer, followed by slower relaxation to the thermodynamically stable keto form, a process which may be monitored spectrophotometrically. A rate constant for this process may be combined with that for the reverse enolisation (or enamine formation), measured by trapping the enol or enamine with halogen, to yield the tautomeric constant as a ratio of forward and reverse rate constants.[6]

The tautomeric constant so determined is an effective value referring principally to the more stable of the minor tautomers (among enol, enaminone or zwitterion) since these are rapidly equilibrated under the conditions of quenching. In the case of 2- and 4-phenacylquinolines in aqueous solution, the enamines are known to be more stable than the enols,[6] and Katritzky has shown the same to be true of 2- and 4-phenacylpyridines.[7] Katritzky obtained approximate values of K_T by measuring

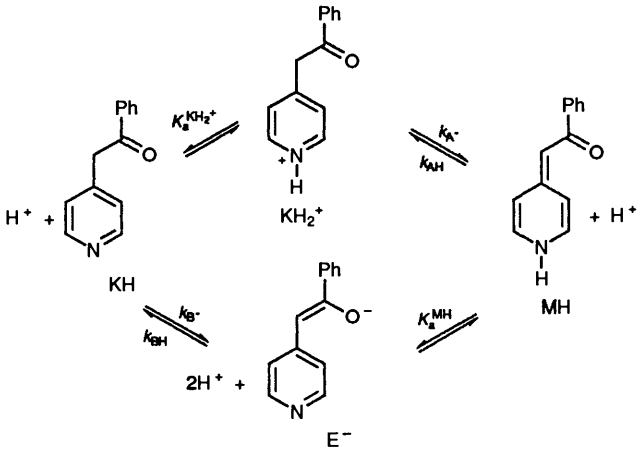


pK_as and extinction coefficients of *N*-methylenaminones, taking these as models for the N–H species.[7] In this paper we compare his results with the values obtained kinetically, and extend the measurements to the less easily accessible enol tautomers.

Kinetic and ionisation studies of phenacylpyridines have also been reported by Bunting and Stefanidis,[8] who examined in detail structure–reactivity relationships for reactions of these substrates with base. In this paper we consider mainly tautomeric equilibria.

Results

4-Phenacylpyridine.—Measurements of pK_as for protonation and deprotonation of 4-phenacylpyridine gave values (4.63 and 12.74 respectively) in satisfactory agreement with those found by Katritzky (4.93 and 12.46). From the presence of a weak



Scheme 1

absorption in the UV–VIS spectrum (λ_{max} = 405 nm) similar to that of the corresponding *N*-methylenaminone (**8**) Katritzky inferred that in aqueous solution, 4-phenacylpyridine exists in equilibrium with a small amount of enaminone.[7] We have measured an equilibrium constant for the tautomerisation by combining forward and reverse rate constants for the process as described above. Rate constants for conversion of ketoimine to enaminone in strong acid solutions and acetic acid or lutidine buffers were measured by trapping the latter with iodine or bromine.[6,9] Rate constants for the reverse reaction were obtained by quenching a solution of the anion of 4-phenacylpyridine in dilute NaOH into acidic or buffer solutions at pHs below its pK_a and monitoring disappearance of the initially formed enaminone.

The experimental measurements yield second order rate constants for general catalysis by buffer base (k_{GB}) or buffer acid (k_{GA}) together with (first order) buffer independent rate constants (k_0) or rate constants for catalysis by hydrogen (k_H) or hydroxide (k_{OH}) ions. The rate constant k_0 may include contributions from H^+, OH^- or water reactions or a combination of these ($k_0 = k_{H_2O}[H_2O] + k_H[H^+] + k_{OH}[OH^-]$). Usually either the general acid or general base term is dominant for a particular buffer, but for lutidine significant catalysis by both buffer species was observed and values of k_{GA} and k_{GB} had to be separated from measurements at different buffer ratios based on eqn. (1) as described previously.[6]

$$k_{obs} = k_0 + k_{GB}[lut] + k_{GA}[lutH^+] \quad (1)$$

Rate constants for general acid and general base catalysis may be related to the 'molecular' rate and equilibrium constants for ionisation and tautomerisation shown in Scheme 1. In this scheme, ketoimine and enaminone tautomers are denoted KH and MH respectively and their common conjugate acid and base KH_2^+ and E^-. Acid dissociation constants for the protonated ketoimine (KH_2^+) and enaminone (MH) are then $K_a^{KH_2^+}$ and K_a^{MH} respectively. The rate constants k_{A^-} and k_{B^-} refer to rate determining transfer of a proton from carbon by attack of buffer base (or hydroxide ion or water) upon protonated and neutral ketoimine respectively. The rate constants k_{AH} and k_{BH} refer to the reverse protonation steps.

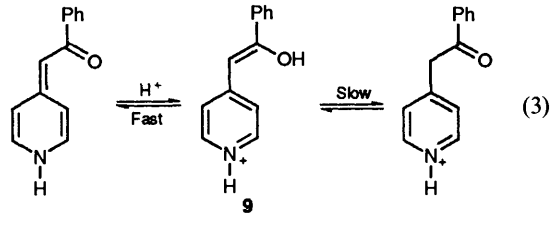
The experimental rate constants for general acid and general base catalysis are related to the molecular rate constants as $k_{GB} = k_{B^-}$ and $k_{GA} = k_{A^-}K_a/K_a^{KH_2^+}$ for reaction of enaminone to ketoimine and $k_{GB} = k_{BH}K_a^{MH}/K_a$ and $k_{GA} = k_A$ for conversion of ketoimine to enaminone, where K_a is the ionisation constant of the buffer acid. These relationships allow the molecular rate constants to be evaluated from buffer measurements for ketonisation and halogenation, and values for different acid and base catalysts are listed in Table 1.

Ratios of experimental rate constants k_{GA} or k_{GB} in the two directions yield an equilibrium constant K_T = [MH]/[KH] = 3.8 × 10^{-3} (pK_T = 2.42) for the interconversion of ketoimine and enaminone tautomers. The constant K_T may also be expressed in terms of the rate constants and dissociation constants of Scheme 1 as shown in eqn. (2). Once K_T is known therefore rate constants for both ketonisation and enolisation may be derived from measurements for one reaction only.

$$K_T = \frac{k_{A^-}K_a^{KH_2^+}}{k_{AH}K_a} = \frac{k_{B^-}K_a}{k_{BH}K_a^{MH}} \quad (2)$$

Buffer-independent rate constants (k_0) and first order rate constants from measurements in strong acid or sodium hydroxide solutions are listed in Table 2. A plot of the values for sodium hydroxide against [OH^-] gave a straight line with slope (k_{B^-} for hydroxide ion) and intercept (k_{BH} [H_2O] for H_2O) yielding a basic ionisation constant for 4-phenacylpyridine $K_b = k_{B^-}/k_{BH}$ = 3.6 × 10^{-2} consistent with that measured directly (5.5 × 10^{-2}).

First order rate constants from the measurements in acid solutions were independent of acid concentration at pH < 4, and this is consistent with a rapid protonation on oxygen of the enaminone reactant to form protonated enol (**9**) prior to ketonisation [eqn. (3)] as was previously observed for 2- and 4-phenacylquinolines.[6]



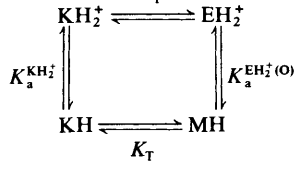
(3)

9

The reaction product at these low pHs is the protonated ketoimine, and combining the measured ketonisation rate constant with that for the reverse reaction yields a tautomeric constant for enolisation of this species as $K_{T'}$ = [EH_2^+]/[KH_2^+] = 1.38 × 10^{-3} (p$K_{T'}$ = 2.86). From these measurements also one obtains pK_a = 4.19 for protonation of the enaminone by making use of eqn. (4) and the thermodynamic

$$K_a^{EH_2^+(O)} = K_T K_a^{KH_2^+}/K_{T'} \quad (4)$$

cycle of Scheme 2, in which the cumbersome notation $K_a^{EH_2^+(O)}$ denotes the ionisation constant of O-protonated enaminone and K_T and $K_{T'}$ refer to tautomerisation of neutral and protonated ketoimines respectively.



Scheme 2

Unfortunately, K_T for enolisation of the neutral ketoimine could not be measured experimentally. However, a value was estimated from a correlation of pK_as of enols of phenacyl aryl ketones and the correspondingly substituted and vinylogously related phenols. This correlation is discussed below in connection with the tautomerism of 3-phenacylpyridine and, for reasons noted there, the value of pK_a = 8.3 derived for the 4-isomer probably represents an upper limit. Nevertheless, the value agrees quite well with that estimated (8.1) by assigning

Table 1 Rate constants[a] for reactions of 2-, 3- and 4-phenacylpyridines, their emaminone or zwitterion tautomers, their *N*-methylenaminones and conjugate acids and bases, with oxygen or nitrogen acids and bases in aqueous solution at 25 °C

		2-Phenacylpyridine				4-Phenacylpyridine				3-Phenacylpyridine					
		N–H		N–Me		N–H				N–Me		N–H			
Acid (AH or BH)	pK_a	k_{AH}[b,c]	k_{A^-}[b,d]	k_{AH}[b,c]	k_{A^-}[b,d]	k_{AH}[b,c]	k_{BH}[b,d]	k_{A^-}[b,c]	k_{B^-}[b,d]	k_{AH}	k_{A^-}	k_{AH}[b,c]	k_{BH}[b]	k_{A^-}[b,d]	k_{B^-}[b]
H_3O^+	−1.74	1.2×10^5	0.10/55.5	3.7×10^5	0.015/55.5	1.36×10^5		1.21×10^{-2}/55.5		6.24×10^6	6.55×10^5/55.5	6.37×10^6		1.16×10^{-4}/55.5	
$ClCH_2CO_2H$	2.86	9.6×10^3	5.8	5.5×10^4	1.66										
CH_3CO_2H	4.76	9.3×10^2	47	3.7×10^3	6.92					6.66×10^4	4.02×10^2	9.2×10^4		9.6×10^{-2}	
2,6-Lutidinium	6.77			17.8	5.29	1.04×10^2	2.02×10^5	54.6	0.217	1150	7.1×10^{-2}		1.49×10^5		
Boric acid	9.24									78.6	1.43				
Et_3NH^+	10.65			8.1	1.94×10^3										
H_2O	15.74			0.023/55.5	9.55×10^4		8.85/55.5		1.61×10^2	5.06/55.5	5300				1.97×10^{-2}

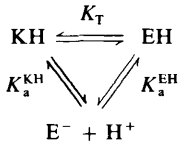
[a] Units $dm^3\ mol^{-1}\ s^{-1}$ including rate constants for H_2O. [b] AH and BH refer to acid indicated in subscripts to rate constants; A^- and B^- refer to conjugate base. [c] For reaction of acid with enamine. [d] For reactions of base with protonated or methylated imine. [e] For reaction of acid with enolate anion.

Table 2 Dependence upon pH of rate constants[a] from halogenation of phenacylyridines and/or quenching their enolate anions or *N*-methyl enaminones or *N*-methylpyridinium ions in aqueous acid or buffer solutions

	2-Isomer		2-NMe$^+$		3-Isomer		3-NMe$^+$ [b]		4-Isomer	
	pH	k/s^{-1}	pH	k/s^{-1}	pH	k/s^{-1}	pH	k/s^{-1}	pH	k/s^{-1}
Quenching	0.82	35.5	1.00	8.11	0.35	0.88	1.32	1.08	0.35	8.91
	1.0	35.6	1.30	8.81	0.60	0.87	2.52	1.13	0.60	8.74
	1.30	34.5	2.35	7.51	1.30	0.90	3.10	1.13	1.00	9.15
	1.70	33.8	2.76	10.50	2.30	0.91	6.10	4.42	1.40	8.81
	2.74	35	4.05	8.70	6.94	3.17	6.33	5.20	1.70	8.76
	3.39	18.7	5.85	0.48	11.40	14.9	6.87	5.32	2.00	8.68
	3.7(0)	13	6.20	0.25	11.70	16.0	7.26	5.78	2.52	8.70
			6.80	0.13	12.00	23.3	8.46	2.77	3.00	8.77
			7.40	0.090			9.64	3.06	10.70	3.8
			8.17	0.30			10.70	4.16	11.00	4.4
			8.52	0.49			10.70	5.72[c]	11.40	4.42
			9.12	1.31			10.90	4.99	11.70	5.43
			9.72	2.56			11.00	8.33[c]	12.00	6.48
			10.07	3.23			11.18	8.14	12.40	9.46
			10.83	36			11.30	12.3[c]	12.70	12.8
			10.23	5.27			11.70	29.5	13.40	21.0
			11.60	180						
Halogenation	4.64	0.2			0.52	1.13×10^{-4}	2.0	6.55×10^{-5}	1.00	11.9×10^{-3}
					0.92	1.21×10^{-4}	2.4	6.66×10^{-5}	1.40	12.2×10^{-3}
					1.40	1.12×10^{-4}	3.0	6.42×10^{-5}	6.56	0.59×10^{-3}
					1.96	1.17×10^{-4}	5.13	8.6×10^{-5}		
					2.30	1.16×10^{-4}	7.01	86×10^{-5}		
					4.3	2.0×10^{-4}	8.33	570×10^{-5}		
					4.70	1.64×10^{-4}				
					7.27	0.30×10^{-4}				

[a] Aqueous solution at 25 °. [b] Reaction of enolate zwitterion except as indicated. [c] Reaction of *N*-methylpyridinium ion with OH^-.

pK_a = 6.4 for N-protonation of 4-phenacylpyridine enol on the assumption that the ratio of σ constants for 3- and 4-enol substituents is the same as for the corresponding enolate anions.* Combining pK_a = 8.3 with pK_a = 12.74 for ionisation of the ketoimine in basic solutions yields a tautomeric constant for the ketoimine $K_T = 4 \times 10^{-5}$ (pK_T = 4.4) based on the thermodynamic cycle of Scheme 3 and $K_T = K_a^{KH}/K_a^{EH}$.



Scheme 3

3-*Phenacylpyridine*.—An important difference between 3-phenacylpyridine and its 4-isomer is that the enaminone tautomer is replaced by the zwitterion (**3**). The question then arises: is this or the enol the dominant minor tautomer? Solutions of 3-phenacylpyridine in dioxane or cyclohexane show a weak absorption with λ_{max}(319 or 322 nm respectively) at a slightly shorter wavelength than that of the enolate anion (338 nm). This is consistent with the presence of enol rather than zwitterion. Indeed, the spectrum differs from that of the zwitterion (**11**) derived from the *N*-methyl-3-phenacylpyridinium ion (**10**, λ_{max} = 354 nm) which should provide a model for **3**. However these spectra were measured in non-polar media and are not a reliable guide to aqueous solutions, in which only the spectrum of the ketoimine and no long wavelength absorption is apparent.

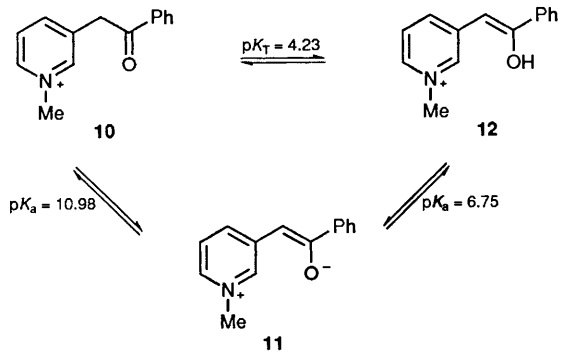
Katritzky measured acidic and basic pK_as for 3-phenacylpyridine as 4.87 and 13.71, and our own value for the latter (13.65) agrees well with his. Fortunately, the ketoimine is just acidic enough that quenching a solution in 0.1 mol dm^{-3} NaOH in excess acid or buffer yields sufficient concentration of the unstable tautomer to observe the ketonisation reaction. A tautomerisation constant could be measured in the usual way therefore by combining rates of ketonisation and halogen trapping. Measurements with lutidine buffers gave K_T = 1.48×10^{-5}. Rate measurements were also made for acetic acid buffers, HCl and NaOH, and molecular rate constants for these acids and bases are summarised in Table 1.

As for 4-phenacylpyridine, ketonisation rates in HCl solutions were independent of acid concentration, and a tautomeric constant $K_{T'} = [EH_2^+]/[KH_2^+] = 1.3 \times 10^{-4}$ (p$K_{T'}$ = 3.89) was obtained for enolisation of the protonated ketoimine [*cf.* eqn. (3)]. Likewise a pK_a for protonation of the predominant minor tautomer to form protonated enol (EH_2^+) could be determined as 5.84 from the cycle of Scheme 2 based on K_Ts for neutral and protonated ketoimines and pK_a = 4.87 for the 3-phenacyl pyridine ketoimine itself.

However, none of these measurements indicate whether the principal minor tautomer is enol or zwitterion and for this it is necessary to consider dissociation and tautomerisation of the *N*-methyl-3-phenacylpyridinium iodide (**10**), deprotonation of which provides a model for the corresponding reaction of the zwitterionic species (**3**).

N-*Methyl*-3-*phenacylpyridinium Ion*.—The pK_a for ionisation of *N*-methyl-3-phenacylpyridinium iodide (**10**) to form its *N*-methyl zwitterion (**11**) was measured as 10.98 (Scheme 4). Again this is in good agreement with Katritzky's value of 11.18.[7] A tautomeric constant for formation of the enol (**12**) was obtained by combining rate constants for quenching the zwitterion (**11**) at pHs < 11 and for halogenation of the cation (**10**). These measurements gave $K_T = [EMeH^+]/[KMeH^+] = 5.9 \times 10^{-5}$ (pK_T = 4.23). From the cycle of Scheme 4, one then obtains pK_a = 6.75 for the enol tautomer (**12**).

* This pK_a was earlier estimated[4] as 8.4 instead of 8.1 and the derived pK_T for the keto–enol tautomerisation as 4.2 instead of 4.4. The present values are preferred.



Scheme 4

Table 3 Comparison of pK_as of phenols ArOH and the vinylogous enols ArCH=C(OH)Ph in aqueous solution at 25 °C [a] (numbers refer to Fig. 1)

Ar		Phenol[a]	Enol[b]
Phenyl	(1)	9.95	9.6[c]
3-Pyridyl	(2)	8.44	8.79
N-Protonated	(3)	5.16	(6.85)[d]
N-Methylated	(4)	4.96	6.75
4-Pyridyl	(5)	7.75	(8.3)[d]
N-Protonated	(6)	3.27	4.19
2-Pyridyl	(7)	9.09	11.27
N-Protonated	(8)	0.70	2.51
N-Methylated	(9)	0.32	4.65
2-Pyrazyl	(10)	8.23	9.68[e]
1-Pyridinium	(11)	0.94	4.80
1-(4-Dimethylamino) pyridinium	(12)	3.88	7.65

[a] Data from the literature including ref. 14 for pyridinols and ref. 27 for pyridine *N*-oxides (points 11 and 12). [b] Data from this or ref. 10 except as indicated. Values in parentheses are derived from the correlation of Fig. 1. [c] Estimated as described in the Experimental. [d] Interpolated from correlation of Fig. 1. [e] Ref. 30.

The pK_a of the N-methylated enol cation (**12**) must be close to that of the corresponding N-H cation. However, a more precise estimate of the latter can be made by correcting the N-methyl pK_a for the substituent change between N-H and N-Me groups. This was achieved with the help of a correlation mentioned above between pK_as of phenacyl ketone enols and pK_as of vinylogously related phenols.

Relevant pK_as are listed in Table 3 and plotted in Fig. 1 with enols as ordinate and phenols as abscissa. The figure includes some large positive and negative deviations, *e.g.* for 2-pyridyl and protonated 2-pyridyl enols (points 7 and 8), but a satisfactory straight line may be drawn through the points for the enols of deoxybenzoin (point 1), *N*-methyl-3-phenacylpyridinium ion (point 4) and 1-phenacylpyridinium ion (point 9), of which the last is taken from the following paper.[10] The pK_as of these enols are plotted against pK_as of phenol, *N*-methylated pyridin-3-ol and pyridine-*N*-oxide respectively. The satisfactory correlation of these three points may be partly fortuitous but its use to determine the difference in pK_as of N-H and *N*-methyl-3-phenacylpyridinium ions is justified by the smallness of the difference found (0.1 log units) and the fact that a derived pK_a for 3-phenacylpyridine enol itself (see below) shows a good fit to the correlation (point 2). Thus from the slope of the line (0.53), the difference in pK_as of N-methylated and N-protonated pyridin-3-ol (0.2), and the pK_a the *N*-methyl-3-phenacylpyridinium enol (6.75), we obtain the pK_a for ionisation of the corresponding N-H ion to its zwitterion (**3**) as 6.85.

Comparison of this pK_a, for ionisation of 3-phenacylpyridinium enol to form a zwitterion, with the substantially smaller value of 5.84, obtained for its ionisation to the principal minor tautomer of 3-phenacylpyridine above, implies that the zwitterion is present in lower concentration than the enol. The proportion of zwitterion is not negligible, however, and strictly speaking the experimentally measured pK_a and pK_T are apparent values requiring correction for the ratio of the two tautomeric species. If $ZH^{\pm}$ is used to denote the zwitterion (**3**), and replaces MH in Scheme 2, we may combine $pK_a^{EH^{\pm}(O)}$ = 6.85 with pK_T = 3.89 for keto–enol tautomerisation of the protonated species and $pK_a^{KH^{\pm}}$ = 4.87 for *N*-protonation of the ketoimine to obtain $pK_T^{ZH^{\pm}}$ = 5.87 for tautomerisation of the ketoimine to zwitterion (in Scheme 2, $K_T^{ZH^{\pm}}$ replaces $K_{T'}$). Combining this with the apparent value pK_T^{app} = 4.82 for tautomerisation of 3-phenacylpyridine to an equilibrium mixture of enol and zwitterion and using the relationship $K_T^{app} = ([ZH^{\pm}] + [EH])/[KH] = K_T^{ZH^{\pm}} + K_T^{EH}$, we obtain pK_T^{EH} = 4.86 for tautomerisation to the enol alone. These values for the two tautomeric constants imply that the equilibrium mixture of minor tautomers contains 91% enol and 9% zwitterion.

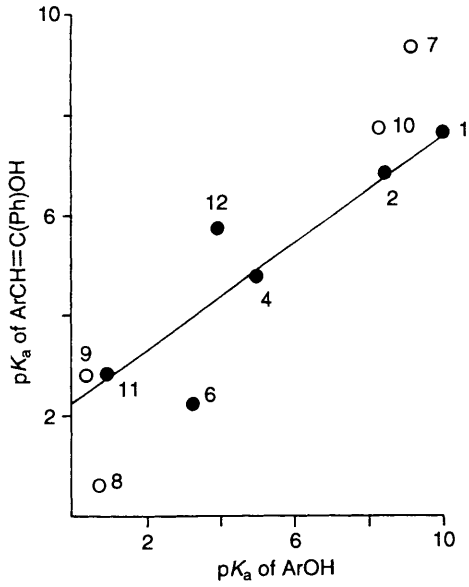


Fig. 1 Plot of pK_as of phenacyl ketone enols *versus* pK_as of the corresponding phenols in aqueous solution at 25 °C. Numbers refer to Table 3: (●) 3- and 4- substituents; (○) 2-substituents.

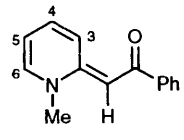
From Scheme 3 we further obtain pK_a = 8.79 for ionisation of 3-phenacylpyridine enol to its enolate anion. This value is well correlated by Fig. 1, as already noted. As we saw too, Fig. 1 also leads to the assignment of pK_a = 8.3 for the enol of 4-phenacylpyridine. However, this value may be less precise than that for the 3-isomer because the correlation appears not to accommodate large resonance effects. This is evident from the point for N-protonated 4-phenacylpyridine enol (point 6) which shows a substantial negative deviation. The resonance effect should be less important for the unprotonated enol, but the possibility of some deviation means that the assigned pK_a (8.3) is probably a maximum value.

Rate constants for tautomerisation of 3-phenacylpyridine methiodide in lutidine, borate and acetate buffers from kinetic measurements of bromination of (**10**) and 'quenching' the zwitterion (**11**) are summarised in Table 1. Buffer independent rate constants for reactions with hydrogen and hydroxide ions are shown in Table 2. The data from the latter table show that at low pH both halogenation and quenching reactions are pH independent reflecting reaction of the positively charged ketone or enol with water acting as a base according to the mechanism of eqn. (5), in which $ZMe^{\pm}$ represents the zwitterion (**11**).

$$KMeH^{+} \underset{\text{slow}}{\overset{OH^{-}}{\rightleftharpoons}} ZMe^{\pm} \underset{\text{fast}}{\overset{pK_a = 6.75}{\rightleftharpoons}} EMeH^{+} \qquad (5)$$

Above pH 6, reaction of the ketone with hydroxide ion becomes important and the rate of enolisation increases with pH. There is also a small increase in rate from catalysis by hydroxide ion for ketonisation. However, this increase rapidly 'peaks out', presumably because ionisation of the zwitterion (pK_a = 6.75) restores a pH-independent reaction. This pH-independence persists until the pK_a of the ketoimine is reached and the relaxation measurements begin to show the influence of the reverse hydroxide promoted ionisation of ketone (*i.e.* pH > 11). A small decrease in rate constants (0.3–0.4 log units) near pH 8 was probably an artefact of the borate buffers used for the measurements.

2-Phenacylpyridine.—For 2-phenacylpyridine the presence of enaminone as principal minor tautomer is apparent from a weak long-wavelength absorption in the UV–VIS spectrum at λ_{max} = 400 nm, close to that (410 nm) for the corresponding *N*-methylenanminone (**13**). Katritzky estimated K_T for ketoimine–enaminone tautomerisation (a) by comparing an apparent extinction coefficient for the enaminone in equilibrium with the ketoimine with the extinction coefficient of the *N*-methylenaminone, and (b) from the difference in pK_as of 2-phenacylpyridine and *N*-methylenaminone. These estimates presume that the methyl for hydrogen substitution in the enaminone leaves its extinction coefficient and basicity substantially unchanged.[7]



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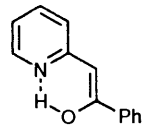

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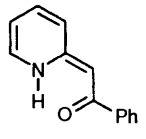

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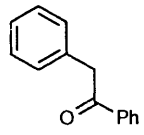

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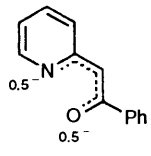

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Again, the tautomeric constant can also be measured kinetically by combining rate constants for iodination of 2-phenacylpyridine and reaction of the enaminone following quenching of the enolate anion. These rate constants were conveniently obtained using acetic acid buffers and gave $1/K_T$ = [KH]/[MH] = 11. The value is reported as $1/K_T$ as a reminder that K_T was defined by Katritzky[7] in the inverse sense (*i.e.* K_T = [KH]/[MH]) to that used here.* It differs significantly in magnitude from the values of 220 and 560 reported by Katrizky based on *N*-methyl pK_as and extinction coefficients respectively. The discrepancy between the kinetically measured pK_T and that based on pK_a measurements recalls a similar difference found for 2-phenacylquinoline[11] discussed below. The discrepancy with that based on extinction coefficients is more surprising and appears to represent partly an error of a factor of ten in a measurement of the apparent extinction coefficient of the N-H enaminone. Thus we found good agreement between our own and Katritzky's value of the extinction coefficient for the *N*-methylenaminone (2.66×10^4 mol^{-1} dm^3 cm^{-1} at λ_{max} = 402 nm compared with 2.49×10^4 mol^{-1} dm^3 cm^{-1} at 410 nm) but obtained 0.13×10^4 compared with 0.014×10^4 (both at 400 nm) for the apparent extinction coefficient of the enamine itself.

* And used in our previous papers.[6,11]

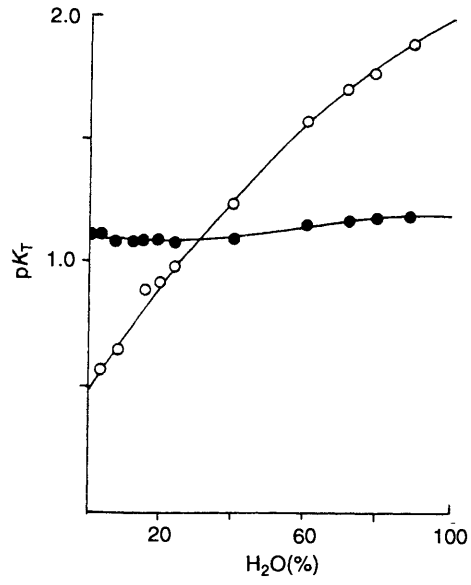


Fig. 2 Solvent dependence of tautomeric constants ($pK_T = -\log K_T$) for keto–enol (○) and keto–enamine tautomerism (●) of 2-phenacylpyridine in water–methanol mixtures at 25 °C

This may have arisen from an arithmetical slip or because the necessity to add a little base to catalyse equilibration of the tautomers was overlooked. Our own value of the apparent extinction coefficient yields $1/K_T$ = 19 rather than 220, which is in better agreement with kinetically determined value of 11, although the difference is still rather large.

In non-polar solvents such as cyclohexane or dioxane, 2-phenacylpyridine shows a quite different long-wavelength absorption from that shown in aqueous solution, with λ_{max} = 335 nm.[7,12] This is reasonably ascribed to the presence of the intramolecularly hydrogen-bonded enol (**14**) which would be expected to be stabilised relative to the ketoimine and (more polar) enaminone structures in such solvents.[13] We have evaluated K_T for the keto–enol equilibrium from absorbance measurements by determining an extinction coefficient for the enol in cyclohexane (ε = 17 200) and measuring apparent extinction coefficients in water–methanol mixtures.

The dependence of enol and enaminone K_Ts upon solvent composition in water–methanol mixtures is shown in Fig. 2. The value of K_T in pure water, [EH]/[KH] = 0.010, was obtained by extrapolation. It is subject to the approximations that the extinction coefficients in water and cyclohexane are the same and that enol formation in cyclohexane is complete. In cyclohexane the absorption spectrum of 2-phenacylpyridine showed no sign of ketoimine or enaminone peaks.

Kinetic measurements for ketonisation and enolisation in acetic acid, chloroacetic acid and lutidine buffers as well as hydrogen ion and hydroxide ion solutions gave the molecular rate constants shown in Table 1. Buffer independent rate constants and rate constants for reactions in solutions of strong acid are shown in Table 2. At low pH reaction of the enaminone again shows a pH independent reaction consistent with protonation occurring on oxygen, with pK_a = 3.57. As for 4-phenacylpyridine, this pK_a can be combined with K_T for enaminone formation and K_a for *N*-protonation of the ketoimine to yield $K_{T'}$ for keto–enol tautomerisation of *N*-protonated ketoimine ($pK_{T'}$ = 2.51) and a pK_a for *N*-protonation of the enol (pK_a = 4.52).

N-Methyl Enaminone of 2-Phenacylpyridine (**13**).—This substrate provides a model for the enaminone tautomer (**15**) of 2-phenacylpyridine. The pK_a for C-protonation to form the *N*-

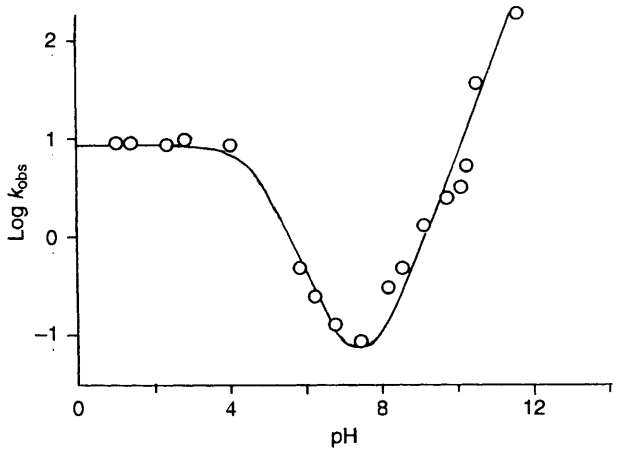
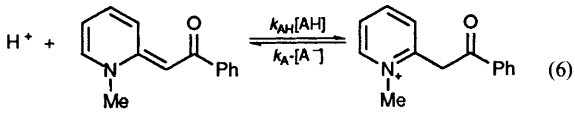


Fig. 3 Plot of log k *versus* pH for protonation of the *N*-methyl enaminone of 2-phenacylpyridine (pH < 7.4) and deprotonation of its conjugate acid (pH > 7.4) in aqueous solution at 25 °C



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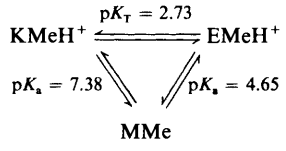
methylpyridinium ion [eqn. (6)] was determined as 7.49 in good agreement with Katritzky's value of 7.38.[7] At pHs below this pK_a, rate constants k_{AH} for protonation of the enaminone by various buffer acids and H_3O^+ were measured by monitoring a decrease in absorbance of enaminone reactant. At pHs above the pK_a reaction of the protonated enaminone with base gave rate constants k_A for proton removal by borate, triethylamine and hydroxide ions. For each of the buffers studied, values of both k_{AH} and k_{A^-} could be derived by combining the measured rate constant (k_{A^-} or k_{AH}) with the equilibrium constant for the reaction to obtain the other value from $K_a^{KMeH^+} = (k_{A^-}/k_{AH})K_a$, where K_a is the dissociation constant of the buffer acid. These rate constants are listed in Table 1 and yield an approximate Brønsted coefficient $\alpha = 0.52$ for the protonation reaction.

Buffer-independent rate constants were also obtained and used to construct the pH-profile shown in Fig. 3. As can be seen, at pHs above the pK_a of the substrate (7.38) the reaction is hydroxide-dependent reflecting proton abstraction from the protonated enaminone by OH^-. At pHs below the pK_a of the substrate it is H^+-catalysed corresponding to the reverse protonation reaction. Below pH 4.65, however, reaction of the enaminone with H^+ becomes pH-independent, presumably as a result of *O*-protonation of the reactant. This pH, which corresponds to the inflection point in the pH-profile may be identified with the pK_a for proton loss from the oxygen of the *N*-methylphenacylpyridinium enol. Combining this pK_a with that for C-protonation allows $pK_T = 2.73$ to be derived for keto–enol tautomerism of the *N*-methyl-2-phenacylpyridinium ion. These results are summarised in Scheme 5 where $KMeH^+$, $EMeH^+$ and MMe represent the N-methylated 2-phenacylpyridine and its enol and neutral enaminone forms respectively.*



Scheme 5

Enol Contents of 2- and 4-Phenacylquinolines.—For 2- and 4-phenacylquinolines the enol tautomer is again less stable than the enamine, and kinetic measurements yield keto–enamine tautomeric constants.[6] No measurements have been made of enol contents but these can be estimated, at least approximately. Thus from $pK_a = 6.21$ for N-protonation of 4-phenacylpyridine enol and a correlation of pK_as of 4-substituted pyridines and quinolines ($pK_a^Q = 1.07$, $pK_a^P = -0.55$) we obtain 6.1 as the pK_a of the corresponding phenacylquinoline enol. Combining this with $pK_T = 3.3$ for keto–enol tautomerism of the N-protonated ketone and $pK_a^{KH_2^+} = 5.24$ for the ketoimine[11] gives $pK_T = 4.2$ for 4-phenacylquinoline based on a thermodynamic cycle similar to that of Scheme 2 with the enol (EH) replacing the enamine (MH) tautomer. This value agrees satisfactorily with a value of 4.5 obtained by assigning a pK_a to the enol on the basis of Fig. 2 and using the cycle of Scheme 3.

A similar estimate can be made for 2-phenacylquinoline using a correlation between pK_as for N-protonation of 2-substituted pyridines and quinolines ($pK_a^Q = 0.9\ pK_a^P + 0.31$).[11] This gives $pK_a = 4.4$ for N-protonation of 2-phenacylquinoline enol from $pK_a = 4.52$ for the corresponding protonation of the phenacylpyridine enol. In the same way as for the 4-phenacylquinoline we then obtain $pK_T = 1.3$ from $pK_{T'} = 1.7$ for the keto–enol tautomerism and $pK_a = 4.82$ for the acid dissociation constant of the N-protonated ketoimine. This pK_T is probably less well-founded than that for the 4-isomer because intramolecular hydrogen bonding of the enols (*e.g.* **14**) may affect the correlation. Moreover, as the most stable tautomer for 2-phenacylquinoline is the enaminone the proportion of enol in solution will be less than implied by the keto–enol tautomeric constant had the ketoimine predominated.

Discussion

Keto–Enol and Imine–Enamine Tautomerism.—Keto–enol and imine–enamine (or zwitterion) tautomeric constants for 2-, 3- and 4- phenacylpyridines and 2- and 4-phenacylquinolines are summarised as values of pK_T ($= -\log K_T$)† in Table 4. In all cases except 2-phenacylquinoline the ketoimine is the most stable tautomer. For the 2- and 4-pyridyl and quinolyl compounds the enamine is more stable than the enol but for the 3-pyridyl isomer the enol is more stable than the zwitterion.

Keto–enol equilibrium constants for acetophenone[2] and deoxybenzoin (**16**) are also included in Table 4. Substitution of an α-phenyl group converting acetophenone to deoxybenzoin stabilises the enol by a factor of 650 ($pK_T = 5.15$ compared with 7.96) and the pyridyl and protonated pyridyl substitutions cause further stabilisation. If σ constants are assigned to 3- and 4-pyridyl and pyridinium nitrogen atoms,[14] ρ for enolisation is found to be ~0.5. This compares with $\rho = 0.76$ for enolisation of substituted phenylacetaldehydes in DMSO.[15]

Table 4 also shows that the enol content of 2-phenacylpyridine is unusually high with $pK_T = 2.0$ compared with 4.86 for the 3-isomer and ≥ 4.4 for 4-phenacylpyridine. This is almost certainly because of stabilisation of the enol by hydrogen bonding (**14**), which is also indicated by the low pK_a (4.52) for N-protonation of the enol compared with 5.8 and ≥ 6.2 for the 3- and 4-isomers respectively, as well as by the positive deviation of the pK_a for proton loss from the enol from the correlation of Fig. 1.

* Values of pK_T and pK_a for the O-protonated *N*-methyl enaminone reported previously[4] are in error.

† K_T = [enol]/[keto] or [enamine]/[imine]. Note that this relationship differs from previous papers[6,7,11] in which K_T was taken as [imine]/[enamine].

Table 4 Tautomeric constants (pK_T)[a] for enol and enamine formation from 2-, 3- and 4-phenacyl-pyridines and -quinolines (RCH_2COPh) in aqueous solution at 25 °C.

R	Enol			Enamine
	N[b]	N–H$^+$	N–Me$^+$	
H	7.94[c]	—	—	—
Phenyl	5.15[d]	—	—	—
4-Pyridyl	(4.4)[e,f]	2.86	—	2.42
3-Pyridyl	4.86	3.89	4.23	5.87[g]
2-Pyridyl	2.0	2.51	2.73	1.05
4-Quinolyl	(4.2)[e]	3.2	2.8	2.30
2-Quinolyl	(1.3)[e]	1.7	2.4	−1.09

[a] K_T = [enol]/[keto] or [enamine]/[imine]. [b] Unprotonated heterocycle or simple ketone. [c] Ref. 2. [d] A. J. Kresge, personal communication. [e] Estimated. [f] Lower limit. [g] pK_T For zwitterion formation.

Table 5 pK_as of keto, enamine and enol tautomers of 2-, 3- and 4-phenacylpyridines (PP) and 2- and 4-phenacylquinolines (PQ) in aqueous solution at 25 °C

	Keto[a]		Enamine[b]			Enol[c]	
	+H(N)	−H(C)	+H(O)	+H(C)	−H(N)	+H(N)	−H(O)
2-PP	5.03	13.27	3.57	6.08	12.22	4.52	11.10
3-PP	4.87	13.65	6.85	10.74	7.78	5.84	8.79
4-PP	4.63	12.74	4.19	7.05	10.32	6.21	(8.3)[d]
2-PQ	4.82	12.20	2.0	3.73	13.29	(4.4)[d]	(10.9)[d]
4-PQ	5.24	12.27	4.2	7.54	10.07	6.1	(8.1)[d]

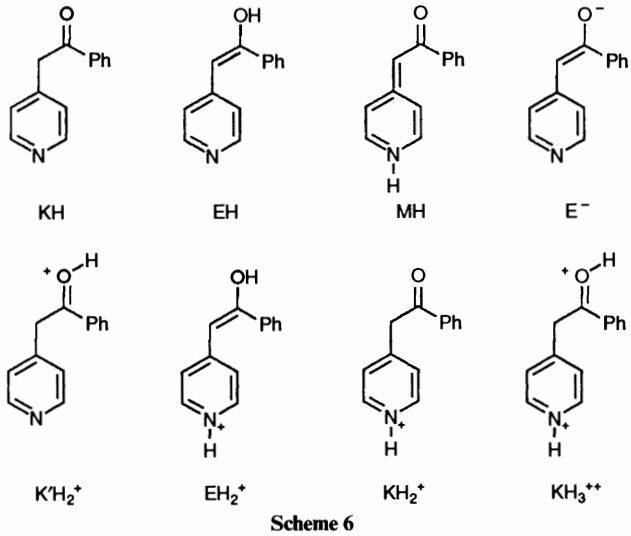
[a] pK_as for protonation on nitrogen and deprotonation from carbon. [b] pK_as for protonation on oxygen and carbon and deprotonation from carbon. [c] pK_as for protonation on nitrogen and deprotonation from oxygen. [d] Estimated as described in the text.

The values of pK_T = 1.05 and 2.42 for imine–enamine tautomerism of 2- and 4-phenacylpyridine respectively compare with −1.09 and 2.30 for the corresponding quinolines.[6,11] These variations in pK_T reflect the greater stability of the 2- than 4-enaminone and greater influence of benzo ring fusion on the 2- than 4-isomer. As for 2-phenacylquinoline,[6] there is quite a large discrepancy between K_T for the 2-phenacylpyridine measured directly (0.09) and that based upon a difference in pK_as of ketoimine and enaminone tautomers with the *N*-methyl derivative taken as a model for the latter ($K_T = 4.5 \times 10^{-3}$). This discrepancy almost certainly reflects a difference in configuration of the enaminones with a *Z*-configuration favoured by hydrogen-bonding in the case of the N-H enaminone (**15**) and disfavoured by steric interactions for the *N*-methyl enaminone (**13**). The difference in configuration is signalled by NOE measurements for **13** and the influence of the adjacent carbonyl group on the chemical shift of the hydrogen at the 3-position of the ring which is shifted 2 ppm downfield in (**13**) compared with a normal pyridine ring, as is observed for the corresponding quinoline.[11] For the 4-isomer, which can exist only in a single configuration, the discrepancy between the direct evaluation of $K_T = 2.6 \times 10^{-3}$ and that based on the pK_a of the *N*-methylenaminone ($K_T = 1.8 \times 10^{-3}$) is much smaller.

Tautomeric and Ionisation Constants.—Tautomeric constants for the three phenacylpyridines are shown in Table 4 and ionisation constants for protonation or deprotonation at oxygen or nitrogen atoms in Table 5. For each isomer these equilibria form a network of reactions and it is worth considering whether they can be represented systematically. Thus for simple ketones, where the only tautomers are keto and enol and these are associated with a common conjugate acid and conjugate base, all four species may be represented at the corners of a quadrilateral with ionisation equilibria occurring along the sides and the tautomerisation reaction along a diagonal as shown (for keto and enamine tautomers) in Scheme 1.

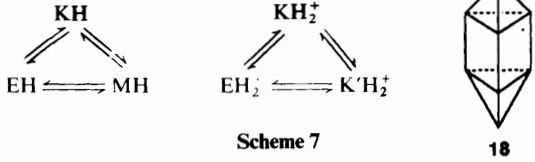
The phenacylpyridines exist as three tautomers, ketoimine, enolimine and enaminone (or zwitterion for the 3-isomer). These share a common anion (E^-), and each is associated with two conjugate acids, each of which in turn is common to two of the tautomers. Thus the enaminone (MH) and ketoimine (KH) yield the same N-protonated ketone (KH_2^+) by protonation respectively on carbon and nitrogen atoms. Similarly the enaminone (MH) and enol (EH) yield the same N-protonated enol (EH_2^+) by N- and O-protonation. All these species are collected in Scheme 6 for the example of 4-phenacylpyridine.

Scheme 6 also includes two species not encountered in this study because of their high acidity. These are the O-protonated and N,O-diprotonated ketoimines designated $K'H_2^+$ and KH_3^{++} respectively. It is helpful to take account of these in trying to represent systematically the eighteen tautomeric and ionisation equilibria interconnecting the set of structures.



Scheme 6

The tautomeric equilibria linking the three monoprotonated species are conveniently represented by placing the tautomers at the corners of a triangle as in Scheme 7. These triangles may



Scheme 7

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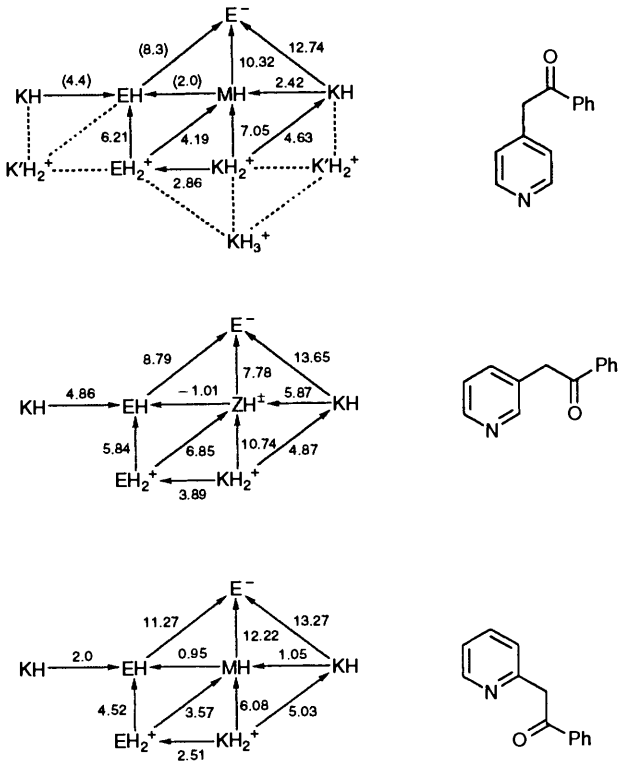
then be thought of as forming planes connected vertically by the ionisation reactions. If the neutral species are also linked to their common anion (E^-) and the monoprotonated structures to their common dication (KH_3^{2+}), it is not too fanciful to represent all eight species at the apices of a trigonal biprism (**18**) with the tautomerisation and ionisation reactions occurring along the edges.

Tautomeric and ionisation equilibria for each of the isomeric phenacylpyridines are shown based on this representation in Scheme 8. The 'biprism' is projected onto the plane of the paper so that tautomerisations are displayed horizontally. This allows only two of each group of three tautomerisation reactions to be displayed and the third is shown by 'folding out' the back of the biprism. In this way all reactions can be included in this scheme and there is only one redundancy ($K'H_2^+ = KH + H^+$ on the right and left vertical edges). Ionisation and tautomeric



Scheme 8

Table 6 PAFs[a] for ionisation of hydroxypyridines (HP) and phenacylpyridine enols (PPE) and ketones (PPK) in aqueous solution at 25 °C.

	HP[b]	PPE	PPK
2-Isomer	7.4×10^7	5.0×10^7	1.5×10^7
3-Isomer	8.7×10^2	1.4×10^2	8.1×10^2
4-Isomer	1.3×10^4	1.0×10^4	4.9×10^5

[a] Activating effect of N-protonation upon equilibrium dissociation of OH or CH hydrogen. [b] Data for hydroxypyridines from ref. 5.

constants are expressed as pK_as and pK_Ts with the direction of the reactions indicated by arrows. Estimated values are shown in brackets.

For 4-phenacylpyridine the reactions connecting the O-protonated and N,O-diprotonated ketoimine, $K'H_2^+$ and KH_3^{++} are shown as dotted lines. These are important species but less stable than the other protonated species and not normally implicated in acid-catalysed reactions.[16] By analogy with non-heterocyclic ketones (*e.g.* substituted acetophenones) pK_as for the deprotonation of $K'H_2^+$ and KH_3^{++} at oxygen might be ~ −5 and −7 respectively. However, no attempt was made to estimate these quantitatively and for 2- and 3-phenacylpyridine in Scheme 8 these equilibria are omitted. In other respects the 2- and 3-isomers match the 4-phenacylpyridine save that for the 3-isomer the enaminone tautomer is replaced by the zwitterion ($ZH^{\pm}$).

Resonance Stabilisation of Enolate and Carboxylate Anions.—Deserving comment are the pK_as for ionisation of the phenacylpyridines to form enolate ions. It is noticeable from Table 5 that pK_a = 13.27 found by Katritzky for the 2-phenacylpyridine is larger than that for its 4-isomer (12.74) and only slightly smaller than for its 3-isomer (13.65). It might have been expected that delocalisation of charge to the pyridyl nitrogen atom in the anion would have been most efficient for the 2-pyridyl ion (**17**) and that 2-phenacylpyridine should have been more acidic than both its 3- and 4-isomers. As seen in Table 5 a similar pattern of pK_as is observed for the enol tautomers of the phenacylpyridines and indeed for the vinylogously related pyridinols. For 2-phenacyl pyridine enol the high pK_a can be attributed partly to hydrogen bonding stabilisation of the enol (**14**) but this cannot be true of the 2-isomer of pyridinol which is unexpectedly less acidic (9.09) than not only the 4-isomer (7.79) but even the 3-isomer (8.84).

Phillips and Ratts[17] have suggested that this behaviour reflects an unfavourable electrostatic interaction between the two electronegative atoms (N and O) bearing the bulk of the negative charge in the anions (**17**). This destabilisation is greatest for the 2-isomer and apparently outweighs the advantages of resonance stabilisation in this case.

It is interesting to consider this suggestion in connection with the recent proposal that resonance is relatively unimportant in the stabilisation of carboxylate anions and that the greater acidity of acetic acid than methanol can be understood substantially in terms of the difference in inductive effects of the methyl group and acetyl group with a highly dipolar structure assigned to the latter.[18] This proposal does not take account of the electrostatic repulsion between the negative charges on the carboxylate oxygen atoms, and the analysis of Phillips and Ratts suggests that this might roughly balance the resonance stabilisation.

Proton Activating Factors.—Also of interest is the effect of protonation of the pyridyl ring upon keto–enol tautomerism and upon ionisation of the keto or enol tautomers. In general, electron-withdrawing substituents increase the enol content, presumably because of their unfavourable interaction with the keto group. Table 4 shows that with one exception enol contents are also increased as the phenyl group in deoxybenzoin (pK_T = 5.15) is replaced by the more electronegative pyridyl group, and the pyridyl group is replaced by protonated pyridyl. The exception is 2-phenacylpyridine where, as we have seen, the enol (**14**) is stabilised by hydrogen bonding. In this case the enol content of the neutral ketone is greater than that of the protonated species. The same appears to be true of 2-phenacylquinoline.

Not surprisingly, the effect of *N*-protonation upon *C*- and *O*-deprotonation of the keto and enol tautomers to their enolate anions is much greater than upon the keto-enol tautomerism itself. The relevant equilibria are summarised on the left and right hand sides of eqns. (7) and (8). As shown in eqn. (8) deprotonation of the *N*-protonated enol or keto tautomers at oxygen and carbon atoms respectively yield enaminone (MH).

$$EH \overset{-H^+}{\rightleftharpoons} E^- \underset{-H^+}{\rightleftharpoons} KH \qquad (7)$$

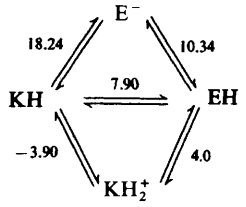
$$EH_2^+ \overset{-H^+}{\rightleftharpoons} MH \underset{-H^+}{\rightleftharpoons} KH_2^+ \qquad (8)$$

Stewart and Srinivasan drew attention to the effect of protonation at a non-reacting site upon a rate or equilibrium constant and called this a 'proton activating factor' (PAF).[19] This factor is measured as the ratio of equilibrium (or rate) constants for reactions of protonated and unprotonated reagents respectively. For the enol tautomers considered here the relevant equilibria lie to the left hand sides of eqns. (7) and (8) and PAF = $K_a^{EH_2^+(O)}/K_a^{EH}$. PAFs for ionisation of the 2-, 3- and 4-phenacylpyridine enols are compared in Table 6 and it can be seen that they range in value from 140 to 10^8. As expected, the largest activation is associated with protonation at the 2-

position. However, this is probably accentuated by hydrogen bonding which stabilises the enol reactant (**14**) in the direct ionisation of this species and the enaminone product (**15**) from reaction of the protonated enol.

Table 6 compares proton activating factors for ionisation of the phenacylpyridine enols with those of the vinylogous pyridinols. The effects are surprisingly similar in the two series, although one might have expected considerably larger values for the pyridinols. At least in the case of the 2-isomer, the expected difference may be masked by the contributions of hydrogen bonding in the enol and enaminone which are not present in the pyridinol and pyridone.

Table 6 shows that the range of proton activating factors for C–H bond ionisation of the ketones is a little smaller than for O–H ionisation of the enols. Thus PAF for the 2-isomer is smaller than for the enol while that for the 3- and 4-isomers is larger. The difference from the enols arises because protonation favours the enol over the ketone as we have seen. The difference between 2- and 4-isomers is also diminished because there is no hydrogen-bonding in the 2-ketoimine.



Scheme 9

Proton activating factors upon carbon–hydrogen bond breaking are of interest in relation to acid catalysis of this process. In principle catalysis may arise from protonation of the pyridyl nitrogen atom or of the keto oxygen atom in phenacylpyridines. The activating effect of O-protonation cannot be measured directly but is probably similar to that for acetophenone for which the activating factor for ionisation of the ketone may be derived from the pK_a values[2,20] shown in Scheme 9 and is greater than 10^{14}. This is much greater than 2×10^7 for N-protonation. Nevertheless for the phenacylpyridines it appears that acid-catalysis occurs with N-protonation rather than O-protonation because the poorer activating effect of N-protonation is more than offset by the greater basicity of nitrogen and hence greater concentration of N- than O-protonated substrate.[16]

Experimental

The isomeric phenacylpyridines were prepared by reaction of the appropriate picolyl anion with methyl benzoate making minor modifications of literature methods.[7,8,21–23] The picolyl anions were generated by reaction of the picoline with butyllithium in diethyl ether for the 2-isomer,[21,22] with potassium amide in liquid ammonia for the 3-isomer,[22] and with sodium hydride in 1,2-dimethoxyethane for the 4-isomer.[23] The products were purified by recrystallisation or chromatography on silica; they gave correct analyses and m.p.s. in satisfactory agreement with values in the literature; NMR spectra will be reported in a later paper.[24]

The 3-phenacylpyridine was methylated by treating 3-phenacylpyridine with methyl iodide in methanol for 24 h. The 3-phenacylpyridine methiodide was precipitated with diethyl ether and recrystallised from methanol–diethyl ether (despite apparent instability upon lengthy exposure to methanol); again the analysis was satisfactory. The *N*-methyl enaminone of 2-phenacylpyridine, [2-(benzoylmethylene)-1-methyl-1,2-dihydro-pyridine (**13**)], was prepared by stirring 2-picoline methiodide (2.36 g, 0.1 mol) with benzoyl chloride (2 cm^3) for two days in triethylamine (50 cm^3) with a catalytic amount of 2,6-dimethylaminopyridine. The reaction mixture was cooled, diluted with chloroform (100 cm^3), extracted with solvent and washed with saturated $NaHCO_3$ (5×50 cm^3) and dried. The solvent was removed and the product, which was obtained as a brown oil, was purified by flash chromatography on silica. Recrystallisation from ethyl acetate–light petroleum (b.p. 40–60 °C) after removing insoluble material by filtration gave yellow needles m.p. 115–119 °C (decomp.) (lit.[22] 117–119°) which slowly decomposed in air; $\delta_H(CDCl_3)$ 9.18–9.23 (1 H, s), 7.3–7.9 (8 H, m), 6.2–6.3 (1 H, m), 5.58 (=CH) and 3.52 (N–CH_3) (Found: C, 79.10; H, 6.20; N, 6.63. $C_{14}H_{13}NO$ requires C, 79.59; H, 6.44; N, 6.70%).

An NOE study of the *N*-methylenaminone of 2-phenacylpyridine (**13**) was undertaken to establish the configuration of the exocyclic double bond. Irradiation of the *N*-methyl hydrogens enhanced the vinyl hydrogen signal by 5% and 6-H by 13%; irradiation of the vinyl hydrogen enhanced the methyl signal by 13% and the *o*-hydrogens of the phenyl group by 13%; finally, irradiation of 3-H enhanced 4-H by 29% but had no effect on the vinyl hydrogen. These results are consistent with the *E*-configuration of the enaminone double bond shown in **13**.

Ionisation Constants.—Equilibrium constants for ionisation of 3- and 4-phenacylpyridines and 3-phenacylpyridine methiodide in aq. sodium hydroxide were measured spectrophotometrically. Extinction coefficients (ε) of enolate anions were determined at high hydroxide concentrations where ionisation was complete as 2.58×10^4 (λ_{max} = 352 nm) and 1.97×10^4 (λ_{max} = 354 nm) for the 4-isomer and 3-methiodide respectively. For the 3-isomer ionisation was not complete even at the highest base concentrations studied, and $\varepsilon = 1.2 \times 10^4$ (λ_{max} = 338 nm) were chosen to yield a constant pK_b from absorbance measurements over a range of hydroxide concentrations. Values of pK_b were based on eqn. (9) where A, A_{E^-} and A_{KH} are

$$pK_b = \log_{10}\{(A_{E^-} - A)/(A - A_{KH})\} - \log_{10}[OH^-]\} \quad (9)$$

respectively absorbances measured at different hydroxide but common substrate concentrations (A) and limiting absorbances at high (A_{E^-}) and low (A_{KH}) base concentration. Corrections for ionic strength were based on eqn. (10) where I is the ionic

$$pK_a = pK_a' + 0.512\,(\sqrt{I}/\sqrt{I} + 1) - I/10 \quad (10)$$

strength[25] and pK_a and pK_a' are the thermodynamic and measured pK_as respectively. The pK_as obtained for the 4- and 3-isomers and the 3-methiodide were 12.74 (12.60 at I = 0.14), 13.65 (13.49 at I = 0.5) and 10.98 (10.82 at I = 0.5). These compare with Katritzky's values of 12.46, 13.71 and 11.18 (ionic strength not reported).[7] A pK_a of 4.57 was also measured potentiometrically for protonation of 4-phenacylpyridine. This compares with 4.93 measured spectrophotometrically by Katritzky for an ionic strength of 1.0 which extrapolates to a thermodynamic value of 4.69 at zero ionic strength on the basis of eqn. (10) with the + sign replaced by − for the positively charged acid. A mean value of 4.63 was used in this paper. Katritzky's values of 5.03 and 4.87 were used for the acidic pK_as of 2- and 3-phenacylpyridine.

Kinetic Measurements.—Details of kinetic measurements were similar to those for the previous study of phenacylquinolines.[6] Measurements were made spectrophotometrically using a (Durrum D110) stopped flow or conventional UV–VIS spectrometer. Enolisation or 'enaminisation' of the stable ketoimine tautomers was measured by trapping the less stable enamine or enol with iodine or, at low pHs where iodination

Table 7 Slopes and intercepts for a plot of rate constants against base concentration at constant buffer ratio for ketonisation of 4-phenacylpyridine enaminone in lutidine buffers.

Slope/dm^3 mol^{-1} s^{-1}	Intercept (k_0/s^{-1})	R^a
406 ± 22	1.01 ± 0.35	4
182 ± 10	9.9 ± 5.6	1
82 ± 0.7	10.0 ± 4.0	0.25

[a] [lutH$^+$]/[lut].

Table 8 Slopes (k) of plots of first order rate constants against [CH_3CO_2H] in acetic acid buffers for the relaxation of the enaminone or iodination of the keto tautomer of 2-phenacylpyridine

R^a	pH	k(iodin^n)	k(relax^n)
4	4.02	—	820
1	4.64	58.4	870
0.25	5.18	36.5	940

[a] [CH_3COOH]/[CH_3COO^-].

becomes reversible, with bromine. In the reverse reaction enaminone or enol tautomers were generated by quenching their enolate anions in aqueous acidic buffers at pHs below the pK_a for enolate formation. Rapid protonation on nitrogen occurred, followed by relaxation to the stable carbon-protonated ketoimine, which was monitored spectrophotometrically. At sufficiently low pHs quenching led to rapid protonation of nitrogen and oxygen atoms and the rate measured corresponded to converting O-protonated enaminone (or N-protonated enol) to neutral of N-protonated ketoimine. Combination of forward and reverse rate constants then gave imine–enaminone (imine-zwitterion for the 3-isomer) or protonated keto–enol equilibrium constants depending on the pH-range investigated.

Kinetic measurements were made in HCl and NaOH solutions and in chloroacetic acid, acetic acid, lutidine and borate buffers. Typically, first order rate constants were measured at 4–6 buffer concentrations for each of 1–3 buffer ratios. Plots of these rate constants against buffer acid or buffer base concentration at a constant buffer ratio gave slopes and intercepts which are shown in Table 7 for the example of 4-phenacylpyridine enaminone reacting to ketoimine in lutidine buffers. Plotting the slopes (which here refer to base concentration) against the buffer ratio (R = [buffer acid]/[buffer base]) allows separation of specific rate constants for buffer base (57 mol^{-1} dm^3 s^{-1}) and buffer acid (104 mol^{-1} dm^3 s^{-1}) as a further slope and intercept. Alternatively, these rate constants could be obtained more precisely by iterative least squares fitting of the full set of data to an eqn. such as (1) in which k_0 depends on the buffer ratio but k_{GB} and k_{GA} do not. Commonly, values of k_0 could not be determined because their errors were too large. Reliable values that were obtained are summarised in Table 2 and were used for construction of pH profiles.

pK_Ts and pK_as of Enaminone and Zwitterion Tautomers.—As already noted, tautomeric constants for forming enaminone or zwitterion tautomers were obtained by combining rate constants for relaxation of these unstable tautomers with rate constants for halogenation of the ketoimine. For the reactions of 2-phenacylpyridine in acetic acid buffers the following slopes of plots of first order rate constants (k) against acetic acid concentration were recorded at different buffer ratios (R = [CH_3COOH]/[CH_3COO^-]) for the two types of measurement as shown in Table 8. The relaxation measurements needed to be corrected for O-protonation of the enaminone reactant (MH) with pK_a = 3.40 and those for the back reaction (iodination) are modified by protonation of the ketoimine product (KH) with pK_a = 5.03 as shown in Scheme 10. The relationship between the slope k of a plot of experimentally

$$EH_2^+ \overset{pK_2 = 3.40}{\rightleftharpoons} MH + H^+ \underset{k_{A^-}[A^-]}{\overset{k_{AH}[AH]}{\rightleftharpoons}} KH_2^+ \overset{pK_2 = 5.03}{\rightleftharpoons} KH + H^+$$

Scheme 10

measured rate constants against buffer acid concentration and the rate constant for reaction of the enaminone with acetic acid k_{AH} is then given by eqn. (11) in which the tautomeric constant K_T has to be guessed initially and then refined

$$k = k_{AH} \times \left\{ \frac{1}{(1 + [H^+]/10^{-3.40})} + \frac{K_T}{(1 + [H^+]/10^{-5.03})} \right\} \quad (11)$$

by iteration. This is easily done in practice because the contribution of the back reaction is small.

For halogenation of the ketoimine a correction to the corresponding slope k(hal) of the plot of observed first order rate constants against acetate concentration is necessary to allow for partial protonation of the reactant and this is given by eqn. (12) where $K_a^{KH_2^+} = 10^{-5.03}$ and K_a is the ionisation constant

$$k_{A-} = k(\text{hal}) \times (1 + K_a^{KH_2^+}/[H^+]) \quad (12)$$

of acetic acid. Finally, the average values of k_{AH} and $k_{A^-} K_a/K_a^{KH_2^+}$ at different pHs are combined to give K_T^{app} as in eqn. (13). As indicated by the superscript, this is still an apparent value embracing enol and enamine tautomers and must be corrected for the presence of a small amount of enol (pK_T^{EH} = 2.0) using the relationship $K_T^{app} = K_T^{MH} + K_T^{EH}$ to obtain K_T^{MH} = 0.09 and pK_T^{MH} = 1.05.

$$K_T^{app} = \frac{k_{A^-}(K_a^{AcOH}/K_a^{KH_2^+})}{k_{AH}} = 0.10 \quad (13)$$

The value of p$K_a^{EH_2^+(O)}$ = 3.40 for O-protonation of the enaminone to yield protonated enol as in Scheme 11 was found

$$EH_2^+ \underset{}{\overset{K_a^{EH_2^+(O)}/[H^+]}{\rightleftharpoons}} MH \xrightarrow{k_H[H^+]} KH$$

Scheme 11

from the pH-dependence of relaxation of the enaminone to ketoimine in dilute HCl soluions and chloroacetic acid buffers (corrected for buffer catalysis). A change from a pH-independent reaction at low pH to acid-catalysed reaction at high pH occurs when the pH is equal to this pK_a. Measured first order rate constants (k_{obs}) are included in Table 2 and gave a best fit to eqn. (14) with p$K_a^{EH_2^+(O)}$ = 3.40.

$$k_{obs} = \frac{k_H K_a^{EH_2^+(O)}}{1 + K_a^{EH_2^+(O)}/[H^+]} \quad (14)$$

As noted above, the corresponding pK_as for O-protonation of the 4-phenacylpyridine enaminone and 3-phenacylpyridine methiodide, and the effective equilibrium constant for N- or O-protonation of the equilibrium mixture of zwitterion and enol of 3-phenacylpyridine, were obtained by combining halogenation and relaxation rates at low pHs to give K_T for conversion of the protonated enaminone or zwitterion to protonated ketoimine. Then, combining K_T with $K_a^{KH_2^+}$ for the ketoimine gave the

appropriate K_a *via* the cycle of Scheme 2. As expected the protonation of the enaminone was associated with a shift in λ_{max} to lower wavelengths.[6]

Keto–Enol Tautomeric Constants. The characteristic UV spectrum with λ_{max} = 335 nm observed for 2-phenacylpyridine in non-polar media such as dioxane, cyclohexane and chloroform has been consistently ascribed to the enol structure (**14**).[7,11] This is confirmed by correlations of ^{1}H and ^{13}C NMR chemical shifts as described elsewhere.[24] The enol content of 2-phenacylpyridine in water was determined from measurements of apparent extinction coefficients (ε_{app}) at 335 nm in water–methanol mixtures taking the extinction coefficient of the enol from a measurement in cyclohexane ($\varepsilon = 1.72 \times 10^4$). It was assumed that the enol was fully formed in cyclohexane and that the extinction coefficient did not depend appreciably on solvent. The former assumption is consistent with the absence or very low intensity of enamine and ketoimine peaks at 400 and 255 nm respectively in cyclohexane solutions.

Apparent extinction coefficients in water–methanol mixtures can be corrected for the presence of the enaminone tautomer from measurements of its absorbance at λ_{max} = 410 nm (at which the enol did not absorb) and the ratio of enaminone absorbances at 335 and 400 nm based on the spectrum of the *N*-methyl enaminone in pure water (0.26).

Values of K_T were calculated as $x/(1 - x)$ with $x = \varepsilon_{app}/(1.72 \times 10^4)$ and are shown plotted as a function of solvent composition in Fig. 2. The value extrapolated to pure water is $K_T = 1.0 \times 10^{-2}$ ($pK_T = 2.0$). The increase in enol content in non-polar media is characteristic of intramolecularly hydrogen-bonded enols[13] and contrasts with the behaviour of simple keto–enol equilibria for which the enol content normally decreases as the solvent becomes less polar.[26] Also shown in the figure is the dependence upon water–methanol solvent composition of K_T for enaminone formation based on the kinetically measured value in pure water (0.09) and absorbance measurements at 400 nm. It is clear that K_T is practically independent of solvent composition. Combining the absorbance in water with K_T yields an extinction coefficient $\varepsilon = 1.83 \times 10^4$ for the enaminone which, as noted already, is considerably lower than the corresponding value of 2.49×10^4 for the *N*-methylenaminone.

Keto–enol equilibrium constants for 4-phenacylpyridine and the 3-phenacylpyridinium ion were based on assignments of pK_as of their enol tautomers. These were obtained from a correlation of pK_as of the enols of phenacyl ketones, ArCH=CH(Ph)OH, with pK_as of the vinylogously related phenols (ArOH) shown in Fig. 1. The relevant pK_as are listed in Table 3. Those for the phenols include values for pyridinols and N-protonated or N-methylated pyridinols[5] (entries 2–8 in the Table) which are corrected for pyridinol–pyridone tautomerism using eqns. (15) and (16) for neutral and charged species respectively. In these equations K_T = [pyridone]/[pyridinol] and pK_a^{app} is the experimentally measured pK_a; the pK_a for pyrazinol (no. 10) is also from ref. 5. Values for pyridine oxide and its dimethylamino derivative (11 and 12) are from the measurements of Gardner and Katritzky.[27]

$$pK_a^{EH} = pK_a^{app} - \log(1 + K_T) \quad (15)$$

$$pK_a^{EH_i^+(O)} = pK_a^{app} + \log(1 + 1/K_T) \quad (16)$$

Most of the pK_as for the phenacyl ketone enols are from the present or, for the 1-phenacylpyridinium ions (11 and 12), from the following paper.[10] That for deoxybenzoin (phenylbenzyl ketone) was assumed to be the same as for phenylacetaldehyde[28] (pK_a^{EH} = 9.6) on the basis that replacing the aldehyde hydrogen by phenyl has little effect upon the pK_a of other enols. This is illustrated by pK_as for formyl-[29] and benzoylfluorene[30] (7.41 and 7.53), acetaldehyde and acetophenone (10.50 and 10.34)[1,2] and isobutyraldehyde and isobutyrophenone (11.63 and 11.78).[31] Combination of the published pK_a = 16.1 for deoxybenzoin[32] with a value for the keto–enol tautomeric constant (pK_T = 5.15) measured by Kresge[33] yields the larger value of pK_a^{EH} = 11.0; however, it now seems likely that the pK_a for the ketone on which this is based is too high because of extrapolation to aqueous solution from measurements in predominantly organic solvents. The pK_a for 2-phenacylpyrazine enol was taken from unpublished work of Harcourt.[30] In Fig. 1 this and other *ortho*-substituted enols are shown as open circles and are not considered in assessing the slope of the plot.

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Paper 3/02167J
Received 15*th April* 1993
Accepted 14*th May* 1993