Enamine–Imine Tautomerism of Benzyl- and Phenacyl-quinolines

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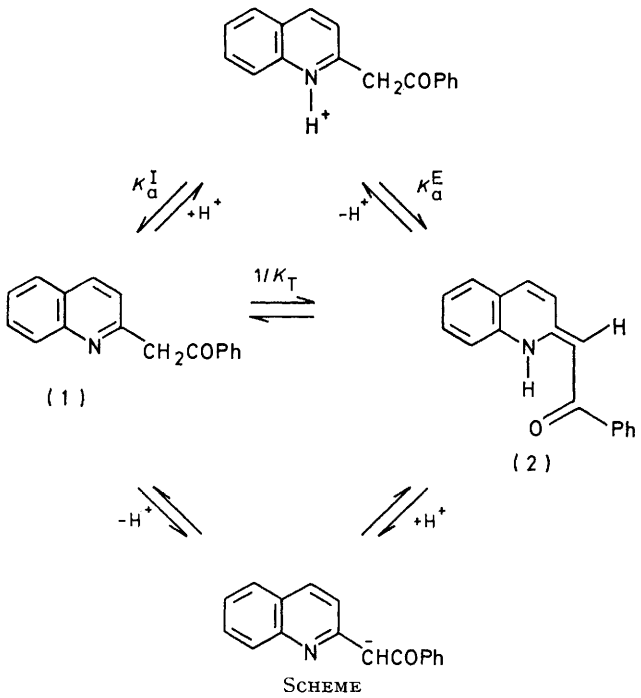
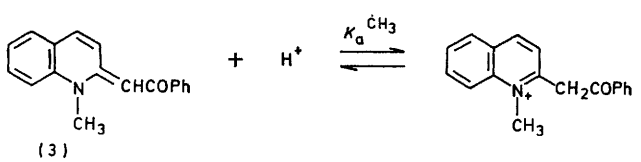
Measurements of tautomeric constants K_T for enamine–imine equilibria of 2-benzyl-, 2-phenacyl-, and 4-phenacyl-quinolines give values of log K_T of 8.7, −1.1, and 1.8 respectively, which may be compared with values for the corresponding 2- and 4-pyridines. For the stable enamine of 2-phenacylquinoline a test of the assumptions on which evaluations of K_T are usually based, that *N*-methyl and *N*-H enamines have the same pK_a values and extinction coefficients, shows differences of two units in pK_a values and 30% in extinction coefficients. For the *N*-methyl enamine, however, the n.m.r. spectrum points to a *trans*-arrangement of nitrogen and carbonyl group rather than the hydrogen-bonded *cis* conformation likely for the *N*-H compound. Interference with nitrogen-carbonyl conjugation through interaction of the *N*-methyl group with a hydrogen at the 8-position of the remote quinolyl ring is suggested as destabilising the *cis*-conformation in the *N*-methyl case.

As a preliminary to kinetic measurements pK_a values of 2- and 4-phenacylquinolines (1) have been measured and equilibrium constants ($1/K_T$) for tautomerisation to the corresponding enamine (2) determined (see Scheme).



SCHEME

The results are of interest both in providing a comparison with the corresponding measurements for 2- and 4-phenacylpyridines,[1] and because for 2-phenacylquinoline the stability of the enamine tautomer makes possible a test of the usual assumption made in deriving tautomerisation constants, namely, that the pK_a values for protonation of the enamine and of its *N*-methyl derivative (3) are the same.[2]



The pK_a values for protonation of 2-benzylquinoline and its *N*-methyl-enamine have also been measured, and allow a comparison of substituent effects upon tautomerisation of 2-methylquinolines and 2- and 4-methylpyridines.

RESULTS

The pK_a values for protonation and deprotonation of 2- and 4-phenacyl- and 2-benzyl-quinolines and their *N*-methyl-enamine derivatives are shown in Table 1, while details of absorption spectra for neutral, cationic, and anionic species, are given in Table 2. Because of its low solubility the extinction coefficient of *N*-methyl-2-benzylquinoline had to be measured indirectly and is less accurate than other values.

TABLE 1

pK_a Values of benzyl- and phenacyl-quinolines and their *N*-methyl derivatives at 25 °C [a]

	Parent		*N*-Methyl
	$-H^+$	$+H^+$	$+H^+$
2-$PhCOCH_2$	13.29 [b]	3.73 [b]	5.90 [c,d]
4-$PhCOCH_2$	12.37 [b]	5.24 [b]	7.02 [c]
2-$PhCH_2$		5.17	13.9 [e]

[a] In aqueous media and ionic strength 0.1 except as indicated. [b] Values corrected to refer to principal tautomer only. [c] Solutions contained 0.4% CH_3OH. [d] Ionic strength 0.15—0.17. [e] Uncertainty ±0.1.

TABLE 2

Principal absorption maxima of benzyl- and phenacyl-quinolines and their *N*-methyl derivatives in aqueous solution

		Parent		*N*-Methyl [a]	
	Species	$\lambda_{max.}$/nm	$10^{-4}\varepsilon$	$\lambda_{max.}$/nm	$10^{-4}\varepsilon$
2-$PhCOCH_2$	Neutral	444	2.15	445 (sh)	2.92
		423	2.25 [b]	429	3.20
	Cation	317	1.30	323	1.42
	Anion	398	2.29		
4-$PhCOCH_2$	Neutral	456	0.018_3 [c]	465	3.75
		341	0.45		
	Cation	313	0.89	317	1.12
	Anion	406	1.91		
2-$PhCH_2$	Neutral	315	0.53	415	3.0 [d]
	Cation	319	1.00	317	0.99

[a] Except for 2-$PhCH_2$, *N*-methyl solutions contained 0.4% CH_3OH. [b] Apparent extinction coefficient uncorrected for the presence of 8% of non-absorbing imine tautomer. [c] $10^{-4}\varepsilon$ in methanol is 0.035. [d] Indirectly estimated; probable error ±0.4; see Experimental section.

For 2-benzylquinoline, for which the aromatic imine tautomer is the more stable, a tautomeric constant K_T was

calculated from equation (1), where $pK_a^{CH_3}$ and pK_a^I are the pK_a values of the *N*-methyl derivative of the enamine

$$\log K_T = pK_a^{CH_3} - pK_a^I \quad (1)$$

and of the stable imine. The same relationship was used for 4-phenacylquinoline, although in this case a small amount of enamine is present so that the p*K* determined is an apparent value, pK_{app}, related to the true value by equation (2). In principle K_T may be determined by

$$K_a^I = K_T K_{app}/(1 + K_T) \quad (2)$$

iteration; in practice it was sufficiently large that corrections to K_{app} and K_T from equation (1) were less than 2%.

For 4-phenacylquinoline K_T was additionally determined from the apparent extinction coefficient ε of its weak principal absorption maximum at 456 nm, with the assumption [2] that the molar extinction coefficient of the enamine tautomer was the same as that of its *N*-methyl derivative, ε_{CH_3}, at the corresponding absorption maximum (465 nm); *i.e.* $K_T = (\varepsilon_{CH_3} - \varepsilon)/\varepsilon$.

For 2-phenacylquinoline the principal tautomer is the enamine (or enaminone) 2-benzoylmethylene-1,2-dihydroquinoline (2), as is shown by the similarity of its absorption spectrum to that of its *N*-methyl derivative.[3] In this case K_T was derived from the relationship (3), where pK_a^E is

$$\log K_T = pK_a^E - pK_a^I \quad (3)$$

the directly measured pK_a value of the enamine and pK_a^I was estimated from a plot of pK_a values of 2-substituted quinolines against 2-substituted pyridines using the pK_a of 2-phenacylpyridine (5.03).[1] For the substituents H, Me, $PhCH_2$, CH_2CH_2OTs, MeS, MeO, and Br a least-squares correlation gave pK_a (quinoline) = 0.90 pK_a (pyridine) +0.31 and $pK_a^I = 4.82 \pm 0.07$. Ionisation constants were taken from the literature [4] or, for CH_2CH_2OTs, measured directly. The apparent value, pK_{app}, of pK_a^E was corrected for the small amount of imine tautomer taking $K_a^E = K_{app}/(1 + K_T)$.

For 2-phenacylquinoline a qualitative investigation of the solvent dependence of the u.v.–vis spectrum showed only minor changes between water, methanol, Me_2SO, dioxan, and chloroform. However, in cyclohexane, the imine absorption was reduced by 50% and a broad peak of equal intensity appeared at 405 nm, presumably due to the enol. By contrast, 4-phenacylquinoline showed no absorption above 350 nm in cyclohexane, its behaviour in this respect being similar to that of 4-phenacylpyridine.[1]

Spectra in aqueous acidic solutions indicated C and N rather than O-protonation in all cases. However in 0.1N-HCl 2-phenacylquinoline showed a weak absorption at 390 nm ($\varepsilon \sim 200$) not seen with the *N*-methyl derivative or the corresponding 4-quinolines. Possibly this was due to a small amount of protonated enol. For acyclic enaminones O-protonation is normal [5] and in trifluoroacetic acid solution has been seen also for 2-quinolylenaminones.[6]

DISCUSSION

Table 3 compares enamine ⇌ imine tautomerisation constants log K_T for phenacylquinolines and phenacylpyridines, obtained from measurements of pK_a values and extinction coefficients (ε). A positive log K_T indicates predominance of the imine tautomer, with the aromatic heterocyclic ring intact. Values for the 2- and 4-phenacylpyridines and 4-phenacylquinoline are noticeably similar, with the aromatic imine favoured by a factor of 50—500. For 2-phenacylquinoline, however, K_T differs by 10^3—10^4 and it is the enamine that predominates ($K_T = 0.08$). Since in the related tautomerism of quinolones and hydroxyquinolines log K_T values for the 2- and 4-positions are nearly equal [7] (−3.9 and −4.2), as they are in the corresponding thiones,[7] the difference between 2- and 4-phenacylquinolines is perhaps unexpected. However factors controlling these equilibria are relatively complex [1,8] and no obvious explanation presents itself.

The satisfactory agreement between K_T values from pK_a and spectrophotometric measurements seen in Table 3 supports the assumptions on which their derivation is based, that the pK_a values and extinction coefficients of enamine tautomers and their *N*-methyl derivatives are the same. For 2-phenacylquinoline, however, the enamine is the stable tautomer and the assumptions may be tested. From Table 1 it can be seen that in this instance the pK_a of the *N*-methyl derivative (5.90) exceeds that of the enamine (3.73) by more than two units, a difference leading to an error of a factor of 150 in an estimated K_T. From Table 2 it is also apparent that the extinction coefficient of the *N*-methyl derivative (3.2×10^4) exceeds that of the enamine (2.4×10^4, after correction for the small amount of imine tautomer).

TABLE 3

Estimated tautomerisation constants log K_T for 2- and 4-phenacyl-pyridines [a] (Py) and -quinolines (Q)

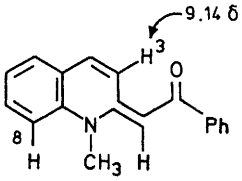
Method	4-Py	2-Py	4-Q	2-Q
pK_a [b]	2.65	2.35	1.78	−1.09
ε [c]	2.6 [d]	2.25 [d]	2.31	

[a] Pyridine data from A. R. Katritzky, H. Z. Kucharska, and J. D. Rowe, *J. Chem. Soc.*, 1965, 3093. [b] From difference of observed pK_a from that estimated for the unstable tautomer [equations (1) and (3) of text]. [c] From the difference in extinction coefficient of the phenacyl pyridine or quinoline from that of its *N*-methyl enamine. [d] Calculated from extinction coefficients at absorption maxima in reference cited above.[a] Values of log K_T reported were 2.41 and 2.75 for the 4- and 2-pyridines respectively.

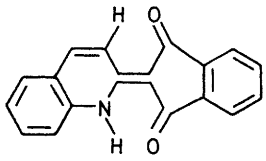
These discrepancies, especially in the pK_a values, are large, but they may not be general. For 2-phenacylquinoline itself the likely conformation of the enaminone group is the hydrogen-bonded *cis-s-cis* form (2). This is indicated in chloroform solution by the broad, barely detectable, low-field N-H signal [3,6] in the n.m.r. spectrum (δ *ca.* 16), and although the conformation in aqueous solution may differ the similarity of the u.v.–vis spectra in chloroform and water does not suggest it. A marked difference in the n.m.r. spectrum of the *N*-methyl-enamine from that of the *N*-H is that the quinolyl 3-H doublet normally appearing at δ 6.9 [3,6] is shifted downfield to δ 9.14. A reasonable explanation is that the conformation of the *N*-methyl-enamine is not *cis-s-cis* but *trans-s-cis* and that the downfield shift is a result of the proximity of the carbonyl group to the C(3) hydrogen in this conformation (4). A similar low-field shift is

seen in quinophthalone (5) (δ 8.6) and the related quinonaphthalone (δ 9.7),[9] and if aliphatic enaminones may be taken as a guide the higher extinction coefficient of the *N*-methyl than *N*–H compound is also consistent with a change from *cis* to *trans* conformation [10] (although, strictly, the reported spectra are for *trans-s-trans* conformations in the aliphatic series).

If this interpretation is correct a point illustrated by the results is that while enaminone extinction coefficients may change with conformation by no more than 30—40%, ionisation constants can be highly sensitive to a conformation change. It follows that agreement between tautomeric constants estimated from pK_a values and from extinction coefficients where *N*-methyl and *N*-H enaminones differ in conformation would be quite fortuitous, and that the substantial agreement seen for 4-phenacylquinoline and 2- and 4-phenacylpyridines in Table 3 suggests that in these cases the *N*-H and *N*-methyl conformations are the same. Possibly the *cis-s-cis* conformation is less favourable in the *N*-methyl derivative of 2-phenacylquinoline because of steric interaction of the methyl group with the remote aromatic ring; for full conjugation the *N*-methyl group, the carbonyl group, and the quinolyl C(8)-hydrogen should be in plane. In 2-phenacylquinoline the *N*-methyl group would be flanked by both a *cis-s-cis* carbonyl and a buttressing hydrogen atom.



(4)



(5)

Combining the tautomeric constants for 2-phenacyl- and 2-benzyl-quinoline with Katritzky's measurements for 2-methylquinoline [11] and for the corresponding 2- and 4-substituted pyridines [11,12] allows a comparison of the effect of phenyl and benzoyl substituents in the different series, and the relevant log K_T values are collected in Table 4. The expected large stabilising effect of

TABLE 4

Tautomerisation constants log K_T [a] of 2- and 4-substituted pyridines and quinolines

Substituent	4-Py	2-Py	2-Q
CH_3	13.4	14.0	9.6
$PhCH_2$	9.7	11.9	8.7
$PhCOCH_2$	2.6	2.3	−1.1

[a] log K_T = log([imine]/[enamine]). All values except 2-phenacylquinoline from log K_T − p$K_a^{CH_3}$ − pK_a. Data from ref. 11 except for 2-benzyl- and 2-phenacyl-quinolines.

benzoyl on the enamine tautomer is seen for both quinoline and pyridines. For the phenyl substituent, however, it is noticeable that the effect on the quinoline is relatively small. As usual K_T values are based on pK_a values of the *N*-methyl-enamines and it is possible that buttressing by the 8-quinolyl hydrogen again destabilises the *cis-s-cis* conformation. Such an effect should be small or negligible in the unsubstituted quinaldine but may become appreciable when H is replaced by a larger substituent. For polycyclic heterocycles in general, where tautomeric constants involving a bulky side-chain adjacent to a hetero atom flanked by a ring junction are based on pK_a values of *N*-alkyl derivatives the possibility of inter-ring steric interactions should be borne in mind.

EXPERIMENTAL

^{1}H N.m.r. spectra were measured on a Perkin-Elmer R-12 (60 MHz) spectrometer and u.v. spectra on a Perkin-Elmer–Hitachi 124 spectrophotometer equipped with a thermostatted cell compartment. Preparative t.l.c. (p.l.c.) was carried out with Merck Kieselgel $60PF_{254+366}$ silica gel.

2-Phenacylquinoline.—Quinaldyl-lithium from quinaldine (2-methylquinoline) and a two-fold excess of butyl-lithium was treated with methyl benzoate following a standard procedure.[13] The product was taken up in chloroform; it crystallised upon evaporation and addition of light petroleum. It was purified by two crystallisations (EtOH) and p.l.c.: m.p. 112—114 °C (lit.,[3] 114—115 and [14] 110—113).

N-Methyl-2-phenacylidene-1,2-dihydroquinoline (4).—This compound was obtained by Alt's method for the corresponding *N*-ethyl derivative [15,16] as yellow needles, m.p. 112—114° (from methanol) (lit.,[16] 108—109 °C) (Found: C, 82.6; H, 5.8; N, 5.4. $C_{18}H_{15}NO$ requires C, 82.73; H, 5.79; N, 5.36), δ ($CDCl_3$) 3.6 (3 H, s), 5.9 (1 H, s), 9.15 (1 H, d, *J* 9 Hz, H-3), and 7.3—8.3 (9 H, m).

4-Phenacylquinoline.—Lepidyl sodium was prepared from lepidine (4-methylquinoline) and sodamide in liquid ammonia and treated with ethyl benzoate.[17] The product was purified by p.l.c. and crystallised from diethyl ether as needles, m.p. 116—117 °C (lit.,[18] 116.2—117.8), δ($CDCl_3$) 4.8 (2 H, s), 9.0 (1 H, s *J* 4.5 Hz, H-2), and 7.5—8.4 (10 H, m).

N-Methyl-4-phenacylidene-1,4-dihydroquinoline.— This compound was prepared in the same way as the *N*-methyl-2-derivative above. Purification by p.l.c. using $CHCl_3$–CH_3OH (9 : 1) and isolation by evaporation from the same solvent mixture gave an orange powder, m.p. 141—143 °C (decomp.) (Found: C, 82.75; H, 5.25; N, 5.7. $C_{18}H_{15}NO$ requires C, 82.73; H, 5.79; N, 5.36), δ($CDCl_3$) 3.6 (3 H, s), 6.9 (1 H, s), 7.1 (1 H, d, *J* 7.5 Hz, H-3), 8.6 (1 H, d, *J* 7.5 Hz, H-2), and 7.3—8.3 (9 H, m).

2-Benzylquinoline Methiodide.—2-Benzylquinoline [19] when heated with methyl iodide in ether gave the methiodide as yellow plates, m.p. 210—220 °C (decomp.) (from EtOH) [lit.,[20] 220 °C (decomp.)] (Found: C, 56.6; H, 4.55; N, 3.95; I, 35.35. $C_{17}H_{16}NI$ requires C, 56.61; H, 4.46; N, 3.87; I, 35.17).

Samples of 2-(2-pyridyl)ethyl tosylate and 2-(2-quinolyl)-ethyl tosylate were prepared from the corresponding alcohols using toluene-*p*-sulphonyl chloride, and recrystallised from light petroleum (b.p. 60—80 °C); m.p.s were: 2-pyridyl, 43—44 °C (lit.,[21] 44°) and 2-quinolyl, 90—93 °C (decomp.).

The n.m.r. spectra of the compounds showed the characteristic chemical shifts and coupling constants reported previously,[3,6] save for the marked downfield shift of the 3-quinolyl hydrogen in the *N*-methyl derivative of 2-phenacyl quinoline.

For measurements of pK_a values and u.v.–vis spectra

aqueous solutions were prepared by diluting a stock solution in 0.2N-HCl, or, occasionally, in methanol, with an appropriate buffer; where methanol was used its concentration did not exceed 0.4%. For 2-phenacylquinoline the spectrum was as reported previously [3] and similar to those of its *N*-methyl derivative, the *N*-methyl derivative of 4-phenacylquinoline, and other structurally related enaminones.[6]

Measurements of pK_a values were made spectrophotometrically using formate, acetate, phthalate or imidazole buffers, or dilute sodium hydroxide, as appropriate. Mean values were based on 5—10 individual measurements which were weighted on the assumption that the absorption measurements were of equal precision. Standard deviations were less than 0.05 pK units save in the cases of 2-phenacylquinoline (0.1) and 2-benzylquinoline methiodide in sodium hydroxide. Measurements of pH were made with a Radiometer PHM26 pH meter; usually, measured values differed from calculated values incorporating activity coefficients by not more than 0.05 units. The ionic strength was normally maintained at 0.1 with added sodium chloride, and thermodynamic pK_a values should be *ca.* 0.1 units less than those in Table 1 for proton addition and 0.1 units greater for proton loss.

For 2-benzylquinoline methiodide ionising in sodium hydroxide the pK_a could not be estimated with usual accuracy because of the instability and low solubility of the conjugate base. Measurements were made in the absorbance range 0—0.2 using 5-cm cells, and at high base concentrations direct measurements were supplemented by extrapolations from methanol–water mixtures. The extinction coefficient of the conjugate base was not measured directly but adjusted to give pK_a values independent of hydroxide concentration.

The pK_a values are listed in Table 1. In addition, pK_a values of 4.68 and 4.79 were measured for 2-quinolyl- and 2-pyridyl-ethyl tosylates respectively.

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