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TAUTOMERISM IN 2-KETOMETHYL QUINOLINES

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Dedicated to Professor E. C. Taylor for his sixty-fifth birthday

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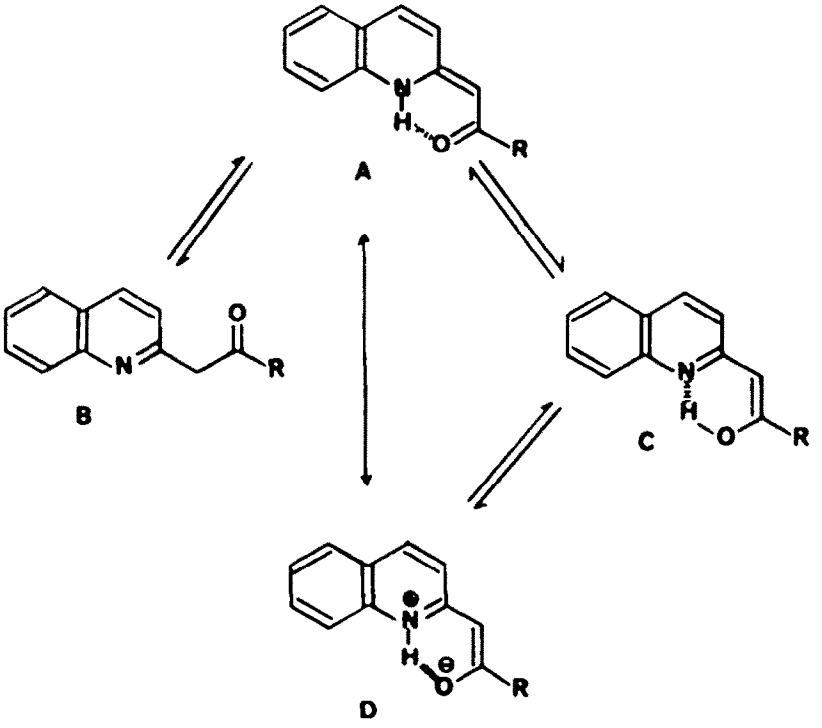
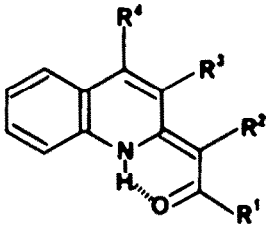
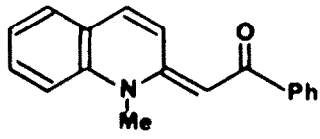
The i.r. solution spectra of a series of 2-ketomethylquinolines have been studied. Tautomeric ratios have been determined by n.m.r. spectroscopy. With one exception the compounds were substantially or exclusively in the enaminone forms. The only compound carrying an α-methyl group (18) proved to be solely in the ketone form.

Introduction





	R^1	R^2	R^3	R^4
1	Me	H	H	H
2	Et	H	H	H
3	Pr^i	H	H	H
4	Bu^t	H	H	H
5	COOEt	H	H	H
6	CN	H	H	H
7	Ph	H	H	H
8	Bu^t	H	Me	H
9	COOEt	H	Me	H
10	Ph	H	Me	H
11	Ph	H	Me	Ph
12	Ph	H	Ph	Ph
16	Me	COOEt	H	H
17	Me	CN	H	H



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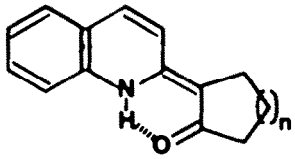
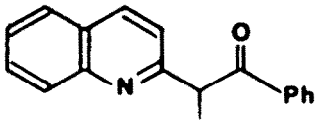


14 n=1
15 n=2



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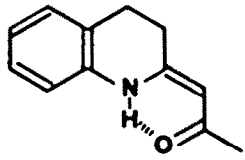

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There are several conflicting reports in the literature on the tautomerism of this group of compounds. Compound 1 was reported to show an 85:15 ratio of A:B by n.m.r. in carbon tetrachloride.[1] Compound 4 was examined by u.v. and n.m.r. in 25 solvents. In most cases form A was considered to be the main tautomer, mixed with 11.3 to 58.8% of form B.[2] In aqueous solution compound 7 was shown[3] by potentiometric titration to favour A over B with $pK_T = 1.09$.

Other workers suggested for compound 5 that the enol form C was dominant. One report used bromine titration in dry methanol and u.v. spectroscopy.[4] Another group studied the n.m.r. spectra and assigned a signal at δ6.38 (DMSO-d_6) or δ6.60 ($CDCl_3$) to the enol vinyl proton. They found no trace of a methylene signal and concluded that the compound was completely enolised.[5] Similarly, compound 7 was reported[6] to have 94% of form C in $CDCl_3$. The i.r. spectrum of 15 was said to show no carbonyl band, but υC=C at 1618 cm^{-1}. In consequence the structure was drawn in the enol zwitterion form D.[7]

These and other publications are notable for the lack of infra-red data relating to υN-H or υO-H or to the 1500-1600 cm^{-1} region. There is ample evidence[8-10] that enaminones show strong bands on either side of 1600 cm^{-1} for the coupled C=O/C=C system. Furthermore, any compound containing the simple ketone tautomer B would show its presence as a carbonyl band above 1700 cm^{-1}.

Discussion

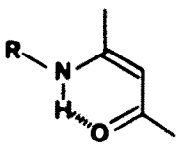
The results of our infra-red study of compounds 1 to 19 are given in Table 1.

Table 1 Infra-Red Bands [cm^{-1} (ϵ_A)] for the 1800-1500 cm^{-1} Region ($CHCl_3$)

Compound	C=O	C=O/C=C	Ar	C=C/C=O	COOEt
1	1720 (60)	1639 (500)	1584 (200)	1556 (590)	
2	1718 (80)	1637 (440)	1590 (210)	1556 (510)	
3	1712 (100)	1636 (530)	1593 (240)	1555 (560)	
4	1712 (90)	1636 (530)	1592 (240)	1554 (440)	
5		1636 (630)	1593 (500)	1574 (530)	1726 (300)
6		1636 (920)	1595 (350)	1572 (1080)	
7		1636 (630)	1590 (470)	1556 (730)	
8	1710 (50)	1636 (400)	1592 (380)	1560 (890)	
9		1636 (390)	1595 (260)	1575 (880)	1722 (320)
10		1635 (600)	1595 (440)	1563 (920)	
11		1616 (250)	1602 (650)	1550 (730)	
12		1613 (280)	1590 (730)	1545 (810)	
13 Z		1638 (s)	1596 (sh)	1562 (s)	
13 E		1603 (m)	1575 (sh)	1516 (vs)	
14	1740 (50)	1644 (550)	1598 (210)	1547 (550)	
	1747 (70)	1646 (510)	1596 (590)	1549 (250)*	
15	1715 (w)	1625 (sh)	1607 (s)	1544 (s)	
	1719 (120)	1642 (92)	1604 (330)	1551 (140)**	
16		1633 (490)	1591 (290)	1562 (150)	1682 (210)
				1518 (240)	
17		1636 (1260)	1593 (550)	1530 (540)	
18	1687 (250)		1602 (170)		
19		1609 (860)	1582 (960)	1553 (590)	

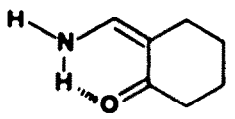
* Dioxane solution. $CHCl_3$ spectrum had an extra band at 1575 (340).

** Dioxane solution. $CHCl_3$ spectrum not well resolved.



20 a R=H

b R=p-tolyl



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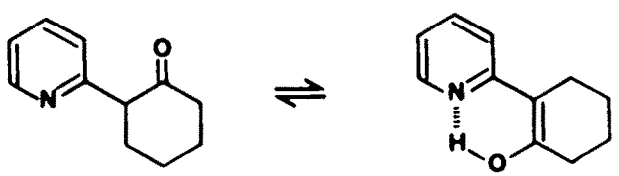
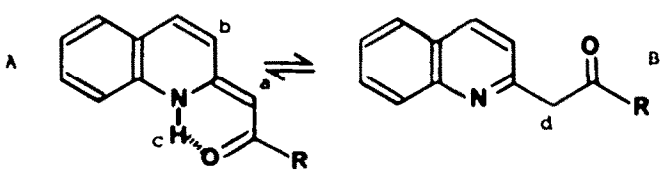
Typical cis-s-cis enaminone $\upsilon C{=}O$ and $\upsilon C{=}C$ vibrations for chloroform solutions have been reported[9] for **20a** at 1625 cm^{-1} (ϵ_A 680) and 1534 cm^{-1} (ϵ_A 660) and for **20b** at 1611 cm^{-1} (ϵ_A 780) and 1566 cm^{-1} (ϵ_A 560). Another group[10] gave the relevant bands for **21** at 1644 and 1585 cm^{-1}. For most of the entries in Table 1 the dominance of tautometric form A is clearly shown by comparison with these examples. In those cases with a significant proportion of tautomer B, weak unconjugated carbonyl bands were seen.

An interesting comparison is provided[11] by compound **22**.



22

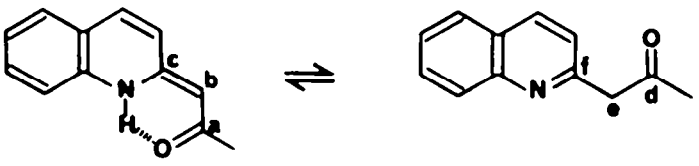
Table 2 ^{1}H n.m.r. Data (270 MHz)



Compound	Solvent	a	b	c	d	Ratio A:B
1	A	5.32	6.62	14.94	4.13	80:20
	B	5.34	6.71	15.00	4.05	76:24
2	A	5.32	6.61	15.00	4.10	76:24
	B	5.34	6.74	15.06	4.04	70:30
3	A	5.30	6.54	15.05	4.13	88:12
4	A	5.52	6.70	15.27	4.24	88:12
	B	5.52	6.82	15.44	4.20	55:45
5	A	6.33	7.05			100:0
	B	6.38	7.15	15.36		100:0
6	A	5.71	6.97	15.08		100:0
7	A	6.07	6.84		4.73	97:3
	B	6.16	6.95	15.83	4.67	96:4
8	A	5.53	2.20 (Me)	15.76	4.29	90:10
9	A	6.40	2.37 (Me)			100:0
10	A	6.08	2.31 (Me)	16.20		100:0
11	A	6.20		16.54		100:0
12	A	5.75		16.62		100:0
13	A	5.90	9.07	3.54 (Me)		100:0
14	A		6.61	13.80	3.52	80:20
	B		6.66	14.13		82:18
15	A		7.08	17.00	4.07	80:20
	B			16.53		87:13
16	A			17.45		100:0
17	A			15.90		100:0
18	A				5.15 (H)	0:100
19	A	5.88		12.84		100:0

* Solvents: A=$CDCl_3$, B=dioxane-d_8.

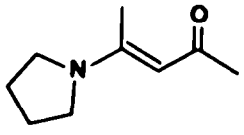
TABLE 3. ^{13}C n.m.r. Data ($CDCl_3$ 67.8 MHz)



Compound	a	b	c	d	e	f	Other
1	191.78	92.36	152.75	205.30	53.96	155.14	
2	195.68	95.16	152.93	207.85	52.86	156.96	
3	198.48	90.16	153.31	210.77	50.71	155.85	
4	200.52	88.01	153.80	212.40	47.09	156.19	
5	170.42	93.59	155.13				C=O 164.47
6	157.07	96.62	154.15				C-N 116.52
7	184.22	89.85	154.15		49.48	157.30	
8	201.65	84.07	153.81	212.34	45.68	153.81	
9	172.15	89.09	155.22				C=O 164.85
10	185.31	86.10	154.16				
11	185.09	86.04	154.26				
12	183.49	89.64	154.62				
13	186/97	90.95	153.56				
14	199.78	99.21	147.28	201.82	57.80	159.76	
15	178.17	98.97	156.23	210.19	57.88	160.43	
16	195.10	98.34	154.59				C=O 169.39
17	195.60	78.52	154.62				C-N 120.55
18				199.48	51.77	161.10	
19	189.53	92.44	158.88				

Here, the thermodynamic cost of disruption of the aromatic system to give an enaminone form would be greater than for the quinolines. The infra-red spectrum shows it to be a mixture of ketone, υC=O 1712 cm^{-1} (s) and enol υC=C 1644 cm^{-1} (s) with υC=C (aryl) 1600 cm^{-1} and only two very weak bands at 1575 and 1555 cm^{-1} between there and 1500 cm^{-1}.

The only example with an sp^3 tertiary nitrogen, compound **13**, clearly cannot adopt a planar cis-s-cis conformation. Its infra-red spectrum is more complex than the rest and probably shows the presence of both twisted cis-s-cis (Z) and planar trans-s-cis (E) forms.[8] The multiplicity of bands made it impossible to estimate the extinction coefficients. Evidence for the trans-s-cis form is provided by comparison with compound **23** which is reported[9] to show C=O 1621 cm^{-1} (ϵ_A 230) and C=C 1528 cm^{-1} (ϵ_A 1280) in chloroform.



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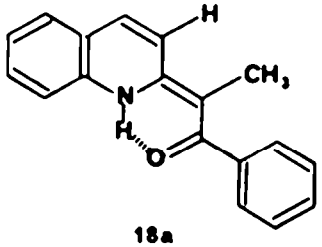

18a

Most compounds show a doublet in the ^1H n.m.r. spectrum between δ6.5 and δ7.1 clearly separated from the other aromatic protons which is assigned to the C3-H of the ring in form A. For compound **13** this signal is absent and is replaced by a downfield doublet at δ9.07 as would be expected for the trans-s-cis form.[17] Compounds having both C3-H and a vinyl proton showed equal integrals for the two signals.

The structure of the α-methyl derivative, compound **18** was a surprise. The parent, compound **7**, showed only a trace of the ketone form B, but **18** was the only compound studied to be 100% in form B. Our first idea was that steric interaction between C3-H and the methyl group in the enaminone structure **18a** had destabilised this form. Consequently compounds **8** to **12**, **16** and **17** were prepared. Of these all except **8** were 100% form A and the tautomeric ratio for compound **8** was essentially the same as the unsubstituted compound **4**. We conclude that part of the steric pressure against form **18a** is exerted between the phenyl and methyl groups with C3-H probably also contributing to the overall interaction.

Finally, we were able to hydrogenate compound **7** to obtain a small sample of the 3,4-dihydroderivative **19**. As expected, this gave a single tautomeric form with the infra-red bands close to those of compound **20b**. In spite of considerable effort we were unable to reveal any clear band for υN-H (or υO-H) in any compound. This must reflect the strength and symmetry of the intra-molecular hydrogen bond which results in a weak dipole.

Small differences between tautomeric ratios reported here and literature values[1,2,6] prompted us to check the effects of solvent and concentration on the results. Small changes in tautomeric ratios were seen for samples re-run in dioxane-d_8, see Table 2. The t-butyl derivative **6** was by far the most sensitive to this change, so it was a happy choice for the previous, very detailed, study.[2] However, a solution of compound **2** diluted 1 to 100 in deuterochloroform showed no change in the tautomeric ratio.

We conclude that, with the exception of compound **18**, the tautomeric systems studied were essentially in enaminone forms A with strong contributions from the mesomeric forms D.

Experimental

Infra-red spectra were run on a Perkin-Elmer PE 680 instrument linked to a 3500 data station and nuclear magnetic resonance spectra on a Jeol GX270 instrument, fitted with a 5 mm C/H probe. Tautomeric ratios were calculated from ^{1}H n.m.r. integrals. For compounds 1-4, 7 and 8 by comparison of the vinyl signal (a) of form A with half the methylene signal (d) of form B. For compounds 14 and 15 the C3-H signal at 6.61 and 7.08 respectively was taken to represent the enanminone form A. That all the other compounds were single tautomers was confirmed by the ^{13}C n.m.r. using a combination of broad band proton decoupled and DEPT experiments to determine carbon atom type.

The following compounds were prepared by literature methods: 1[12], 2[13], 3[13], 4[14], 5[15], 6[16], 7[17], 13[17], 14[18], 15[19], 16[20], 17[21]. They were purified via silica columns followed, for the solids, by recrystallisation to constant melting point.

1-(3-Methylquinolyliden-2-yl)-3,3-dimethylbutan-2-one (8). A solution of 2,3-dimethylquinoline (0.79 g, 0.005 mol) in dry THF (80 ml) was added dropwise over 10 mins. to sodium hydride (0.6 g, 0.025 mol) in THF (20 ml) with stirring under nitrogen. Methyl trimethylacetate (0.81 g, 0.007 mol) in THF (20 ml) was added and the mixture refluxed 48 hrs. The cooled solution was diluted with ether (50 ml) and extracted with dilute hydrochloric acid (3 x 40 ml). The acid solution was made basic with sodium carbonate and extracted with ether (3 x 50 ml). The combined organic extract was dried ($MgSO_4$), filtered and the solvent evaporated. The residue was chromatographed on a silica column with chloroform as eluent to give the butanone (0.31 g, 26%) m.p. 81° (from ethanol). Found: C, 79.9; H, 7.9; N, 5.8. $C_{16}H_{19}NO$ requires: C, 79.7; H, 7.9; N, 5.8%. By similar procedures were obtained:

2-(3-Methylquinolyliden-2-yl)-1-phenylethanone (10). 61%, m.p. 100° (from ethanol). Found: C, 82.2; H, 5.6; N, 5.3. $C_{18}H_{15}NO$ requires: C, 82.7; H, 5.8; N, 5.4%.

2-(3-Methyl-4-phenylquinilyliden-2-yl)-1-phenylethanone (11). 12%, m.p. 112° (from ethanol). Found C, 85.1; H, 5.85; N, 4.00. $C_{24}H_{19}NO$ requires: C, 85.5; H, 5.65; N, 4.15%.

2-(3,4-Diphenylquinolyliden-2-yl)-1-phenylethanone (12). 25%, m.p. 207° (from ethanol). Found: C, 87.3; H, 5.30; N, 3.35. $C_{27}H_{21}NO$ requires: C, 87.2; H, 5.25; N, 3.50%.

Ethyl (3-methylquinolyliden-2-yl) Pyruvate (9). A solution of diethyl oxalate (0.75 g, 0.005 mol) in dry ether (10 ml) was added to potassium ethoxide (0.01 mol from potassium (0.4 g) and ethanol (1.8 ml) in ether (20 ml)). A solution of 2,3-dimethylquinoline (0.79g, 0.005 mol) in ether (10 ml) was added dropwise and the mixture allowed to stand 5 days. The precipitate was collected rapidly and immediately added to dilute acetic acid. After stirring, the new precipitate was collected to give the keto-ester (0.35 g, 27%) m.p. 129-130° (from aqueous alcohol). Found: C, 70.2; H, 5.75; N, 5.30. $C_{15}H_{15}NO_3$ requires: C, 70.0; H,5.85; N, 5.45%.

1-Phenyl-2-(quinol-2-yl)-propan-1-one (18). A solution of compound 7 (2.5 g, 0.01 mol) in dry THF (50 ml) was added to sodium hydride (0.24 g, 0.01 mol) in THF (20 ml) and the mixture refluxed under nitrogen with stirring 3.5 hr. Iodomethane (1.4 g, 0.01 mol) in THF (20 ml) was added to the cooled product and the whole refluxed a further 5 hrs. The cooled solution was diluted with ether (50 ml) and extracted with dilute hydrochloric acid (3 x 50 ml). Aqueous sodium hydroxide was used to raise the pH to 6-7 and potassium carbonate was added before extraction with ether (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$) , filtered and the solvent removed to give the propanone (1.9 g, 72%) m.p. 94° (from ethanol). Literature [22] m.p. 100-101.5°. It gave the hydrochloride m.p. 184° (from ethanol). Found: C, 72.3; H, 5.50; N,4.45. $C_{18}H_{16}ClNO$ requires: C,72.6; H,5.40; N, 4.70%.

2-(3,4-Dihydroquinolyiden-2-yl)-1-phenylethanone (19). A mixture of compound 7 (1 g) and 10% Palladium on charcoal (0.5 g) in methanol (30 ml) was hydrogenated at room temperature and pressure for 18 hrs. After filtration the residue was chromatographed on a silica column using 1:1 dichloromethane/petroleum ether (b.p. 40-60°) as eluent to give the enaminone (0.19 g, 19%) m.p. 105-106° (from toluene). Found: C, 81.6; H, 6.20; N, 5.60. $C_{17}H_{15}NO$ requires: C, 81.9, H, 6.00, N, 5.60%.

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