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Tautomeric pyridines. Part XXIV¹. Tautomeric equilibria for 3-ethoxycarbonyl-, 3-ethoxycarbonyl-6,7-methylenedioxy-, and 3-cyano-4-quinolone

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Abstract. Ultraviolet spectra and pK_a values for the title compounds and their *O*- and *N*-ethyl derivatives show that in each case the quinolone form is favoured in aqueous solution. The results are compared qualitatively with those for 4-quinolone and for findings in the gas phase.

4-Quinolone was early shown² to prefer the oxo-form, but little systematic work has been done on the effect of substituents on this equilibrium^{2,3}, although considerable progress has been made in explaining the effects of substitution on the tautomeric equilibria of 4-pyridone/4-hydroxypyridine³. Kay and Taylor⁴ state that the 3-ethoxycarbonyl derivative 1 exists in the oxo-form shown under all conditions investigated, but this assertion is not conclusively proved by the spectroscopic evidence quoted. Baker and Bramhall⁵ state that 4-hydroxyquinoline-3-carboxylic esters exist in the hydroxy-form, again without conclusive evidence. Somewhat similar compounds have been investigated by Staskun⁶, but none of this work gave quantitative estimates for the equilibrium constants. The present investigation was undertaken because of the pharmaceutical importance of compounds in this series⁷.



Preparation of compounds

The 4-quinolones were converted to their N-ethyl derivatives by refluxing with triethyl phosphate⁸. The 4-ethoxy compounds were prepared from the action of sodium ethoxide on the corresponding 4-chloro compounds which were made from the 4-hydroxy derivatives or by ring closure of (anilinomethylene)malonates⁹ in phosphorus oxychloride.

UV spectra of monocations

For each of the three series of compounds 1-3, 4-6 and 7-9 (Table I), the UV spectra of the monocations of the potential-

ly tautomeric compound and the two fixed models are similar, indicating that, within each series, the monocations possess similar structures. The absorption maxima of the cations of the three series (3-ethoxycarbonyl, 3-cyano and 6,7-methylenedioxy) of substituted quinolones are all shifted to longer wavelength in comparison with those of the 4-quinolone monocation (λ_{max} . 228, 302 nm; log ε 4.73, 3.85)¹⁰. This shift is small in the 3-CO₂Et and 3-CN series groups (approximately 16 and 10 nm for the lower and upper wavelength bands, respectively), but *ca.* 30 nm for both bands in the 3-ethoxycarbonyl-6,7-methylenedioxy compounds.

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UV spectra of neutral species

The UV spectra of the neutral 3-ethoxycarbonyl- and 3cyano-4-quinolones (1 and 7) closely resemble those of the corresponding N-ethyl derivatives, 2 and 8, but are dissimilar to the 4-ethoxy derivatives, 3 and 9 (see Tab. 1). Although in the 3-ethoxycarbonyl-6,7-methylenedioxy series, these distinctions are less pronounced, the spectra do indicate the preponderance of the quinolone form for each series of compounds in aqueous solution by factors of ≥ 10 .

The spectra of the neutral species of the 4-ethoxy-3-ethoxycarbonyl (3) and -3-cyano compounds (9) are very similar but that for the 4-ethoxy-3-ethoxycarbonyl-6,7-methylenedioxy compound (6), is bathochromically shifted with respect to the other two. The spectra of the neutral, fixed 1-ethyl derivatives of the 3-CO₂Et and 3-CN series are also similar. Again, the 6,7-methylenedioxy group causes a bathochromic shift for compound 5 compared with 2.

Ultraviolet spectra of anions

The UV spectrum of the anion of the $3\text{-}CO_2\text{Et}$ derivative 1 resembles that of the neutral species, in that both show two main regions of absorption at 225–260 and 310–323 nm, but significant bathochromic shifts occur for both complex bands for the anion (Fig. 1). The spectrum of the monocation is considerably simpler (Fig. 1). The spectra of the anion, cation and neutral species of 3-cyano-4-quinolone (7) and 3-ethoxycarbonyl-6,7-methylenedioxy-4-quinolone (4), show a similar trend (cf. Tabs I and II).



Fig. 1. Ultraviolet spectra of the cationic (---), anionic (---) and neutral (---) species of 3-ethoxycarbonyl-4-quinolone (1).

pK_a measurements

The pK_a values of the weakly basic compounds 7 and 8 were determined in aqueous sulphuric acid, employing the H_o acidity function. Graphs of extinction coefficient against H_o , at fixed wavelength, showed a marked solvent effect;

absorbance readings were obtained by the back-extrapolation of measurements from the first ten minutes. In each of the three series, the pK_a of the tautomeric compounds 1, 4, 7 is much closer to that of the corresponding *N*-ethyl fixed form (2, 5, 8) ($\Delta pK_a - 0.12, -0.04, +0.53$), than to that of the appropriate ethoxy derivative (3, 6, 9) ($\Delta pK_a > 2$ units). This shows that all three tautomeric compounds exist predominantly in the quinolone forms (1a, 4a, 7a) in aqueous solution, as previously indicated

however, compound 9 hydrolysed much more rapidly, and

by the UV spectral comparisons. Quantitative values of pK_T for the hydroxyquinolinequinolone equilibrium, obtained by subtraction of the fixed model pK_a values¹³, are -4.73, -3.01 and -2.06 for compounds 7, 1 and 4 respectively, (cf. 4-quinolone pK_T -4.22^{14} corrected¹⁵ from 30° to 20°C). The 3-CN substituent produces a greater preponderance of the quinolone form compared with the parent compound; however, $3-CO_2Et$, although it is also electron-withdrawing, leads to a greater proportion of the hydroxy-form. The 6,7methylenedioxy group produces a somewhat greater swing back towards the hydroxy-form.

Effect of substituents on pK_a values

Considerable insight is gained into the position of tautomeric equilibria by considering the effect of substituents on pK_a values¹⁶. Compared with *N*-methyl-4-quinolone (11)* (2.41 \pm 0.03; value from ref. 14 corrected¹⁵ from 30°C to 20°C) the electron-withdrawing 3-carboethoxy group in 2 and 3-cyano groups in 8 decrease the ionisation constants (Tab. III) by 1.54 and 3.96 pK units, respectively. The smaller drop for CO₂Et probably reflects in part intramolecular hydrogen bonding in the cation 13. The simultaneous presence of both the 6,7-methylenedioxy and 3-ethoxycarbonyl groups (5) causes a decrease of only 0.38 pK units relative to 11.



The effect of these substituents on the ethoxy fixed forms, **3**, **6** and **9**, is to decrease the pK_a values by 2.75, 2.54 and 3.45 pK units respectively compared with 4-methoxyquinoline (**12**) (6.63¹⁴ corrected¹⁵ from 30° to 20°C). Again, the effect of cyano is greater than that of ethoxycarbonyl (*cf.* the

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situation in pyridine: pK_a of 3-cyano 1.35¹⁷ of 3-ethoxy-carbonyl 3.35¹⁸).

The tautomeric equilibrium of 4-pyridones is significantly influenced by the electronic effects of substituents at the 2-position, but much less by those at the 3-position¹⁹. Whereas a 2-substituent affects the acidity of the nearby NH of the protonated form much more than that of the distant OH, a 3-substituent usually has less differential effect. However, the hydroxy-form can be effected by intramolecular hydrogen bonding²⁰. Thus, the diethoxycarbonyl derivative **14** exists in the hydroxy-form in non-polar solvents²¹, although mainly in the oxo-form in the solid (and probably in polar solvents). Replacing the phenyl groups by 2-pyridyl (as in **15**) or 2-quinolyl groups adds an electronwithdrawing effect which displaces the tautomerism, and these compounds exist in the hydroxy form even in the solid state²⁰.



Table III Basicity measurements.

Com- pound No.	Substituents	pK _a ª	λ (nm)	Conc. 10 ⁻⁴ M
1	3-CO ₂ Et	0.99 ± 0.04 ^b	309	0.510*
2	3-CO ₂ Et-1-Et	0.87 ± 0.02^{h}	246	0.3258
3	3-CO₂Et-4-OEt	$3.88 \pm 0.03^{\circ}$	286	1.6758
4	3-CO ₂ Et-6,7-OCH ₂ O	$2.07 \pm 0.03^{\circ}$	261	0.077 ^b
5	3-CO ₂ Et-1-Et-6,7-OCH ₂ O	2.03 ± 0.03^{d}	264	0.302 ^b
6	3-CO2Et-4-OEt-6.7-OCH2O	4.09 ± 0.03°	250	0.247 ^b
7	3-CN	-2.08 ± 0.02^{r}	314	1.1201
8	3-CN-1-Et	$-1.55 \pm 0.06^{\circ}$	317	0.804'
9	3-CN-4-OEt	$3.18 \pm 0.05^{\circ}$	312	0.932 ¹

^a At 20°C. ^b In standard HCl. ^c Formic acid, acetic acid, KOH buffer. ^d KCl, HCl buffer. ^c Citric acid, NaOH buffer. ^f In standard H_2SO_4 . ^g Stock solution contained 1% EtOH. ^h Stock solution contained 8% EtOH. ⁱ Stock solution contained 2% EtOH.

Tautomeric equilibria in non-aqueous media

Spectra for all nine compounds were compared in H_2O , $(CD_3)_2SO$, MeOH, CH_3CN , $CHCl_3$ and C_6H_6 . Little significant change in the spectra with differing solvent polarity was observed for the 3-ethoxycarbonyl- and 3-cyano-derivatives 1–3, 7–9, or for the 3-ethoxycarbonyl-6,7-methylenedioxy fixed forms 5, 6. 3-Ethoxycarbonyl-6,7-methylenedioxy-4-quinolone (4) (with the least strongly biased tautomeric equilibrium of the three series in aqueous solution) was more sensitive: the intensity of the absorption in the region 320–340 nm, characteristic of the quinolone form, decreased with decreasing solvent polarity, while absorptions near 290 and 300 nm increased in intensity. A similar series of spectra was observed for various MeOH/ C_6H_6 mixtures (Fig. 2), with an isosbestic point at 306 nm.



Fig. 2. UV spectra of 3-ethoxycarbonyl-6,7-methylenedioxy-4-quinolone in MeOH: benzene mixtures (A) 80%, (B) 50%, (C) 20%, (D) 10%, (E) 1% MeOH.

The absorptions at 288 and 302 assigned to the hydroxyform differ from those of the ethoxy model which has broad absorptions of roughly equal intensity centred at 295 and 338. This discrepancy is probably a consequence of steric inhibition of the ethoxy-group/ring resonance by the ethoxycarbonyl group.

Comparison of spectra²² of the pyrimidine (16) and 3ethoxycarbonyl-4-hydroxypyridine in *n*-hexane, various ethers and in MeOH and also in mixtures of these solvents, showed conversion from mainly lactim in the less polar media into lactam, in MeOH. Intramolecular hydrogen bonding (16a) stabilises the lactim in the less polar solvents.



The recently-developed CI/CID/MIKE (Chemical Ionisation/Collision-Induced Dissociation/Mass-analysed Ion Kinetic Energy) mass spectrometry²³ shows some preponderance of the quinolone form (**10a**) in the gas phase tautomeric equilibrium of 4-quinolone, indicating little change compared with aqueous solution data^{14*}. 3-Ethoxycarbonyl- and 3-ethoxycarbonyl-6,7-methylenedioxy-4-quinolone show a predominance of the hydroxy-forms, **1b** and **4b**, in the gas phase, presumably due to snhanced stabilisation of the hydroxy-form by hydrogen bonding. The presence of some hydrogen bonding in aqueous solution has been proposed to account for the lower values pf pK_T for these compounds compared with 4-quinolone (see above). No firm

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Table I UV spectral maxima (nm) and extinction coefficients (log s) for substituted 4-quinolones and their ethylated derivatives in buffered aqueous solutions.

						ž	tutral sp	ecies								Monoe	cations		
Compound No.	Substituents	Hq	Conc. of end soln. 10 ⁻⁴ M	~	log ɛ	~	log e	~	log c	~	3 gol	~	log e	Hd	Conc. of end soln. 10 ⁻⁴ M	~	log s	~	log e
-	3-CO ₂ Et	8.02ª	0.337	225	4.36	247	4.30	253	4.27	310	4.07	323	3.92	0.30 ^d	0.337	244	4.70	300	3.70
7	3-CO ₂ Et-1-Et	9.45ª	0.286	226	4.36	249	4.28	256	4.26	315	4.12	328	4.02	0.10 ^d	0.286	245	4.67	306	3.82
ŝ	3-CO ₂ Et-4-OEt	8.01 ^a	0.450			236	4.68			286	3.78		-	- 1.41°	0.450	242	4.66	310	3.76
4	3-CO ₂ Et-6,7-OCH ₂ O	7.40 ^h	0.312	257	4.49	266	4.51	319	3.94	334	3.88			0.30d	0.312	260	4.65	338	3.94
5	3-CO ₂ Et-1-Et-6,7-OCH ₂ O	7.53 ^b	0.303	261	4.54	270	4.55	323	4.02	337	4.00			0.30^{d}	0.303	262	4.67	342	3.97
9	3-C0 ₂ Et-4-OEt- 6,7-OCH ₂ O	9.57ª	0.269	250	4.68			295	3.87	338	3.85			0.30 ^d	0.269	258	4.57	345	4.11
٢	3-CN	6.05°	0.450	224	4.44	245	4.33	251	4.27	303 sh 312	4.01 4.03	325	3.90	4.69°	0.899	243	4.75	309	3.67
œ	3-CN-1-Et	5.30°	0.346	225	4.39	249	4.27	255	4.25	310 sh 318	4.06 4.10	330	4.01	- 4.82°	0.346	246	4.69	315	3.78
6	3-CN-4-0Et	8.08ª	1.006			236	4.79			281	3.88	324	3.28	0.30 ^d	0.265	242	4.79	308	3.72
Sodium bor	rate, HCl buffer. ^b Tris(hy	lroxymet	thyl)aminom	ethane,	HCI bu	ffer.	° Citric	acid, N	VaOH b	uffer. "	In stan	dard H	ן כ	• In stands	ird H ₂ SO ₄ .				

Table II UV spectral maxima (nm) and extinction coefficients (log ε) for substituted 4-quinolones in aqueous solutions.

					-
	log e	3.77		3.74	
	۲	1338 sh		333	
	logε	3.89		3.89	
	X	325 sh		318	
	log c	4.00	3.87	3.95	
ions	۲	304	305 sh	304	
An	logε	4.34	4.02	4.34 4.36	
	Y	259	293 sh	250 sh 255	
	log c	4.35	4.55	4.43	
	~	225	273	229	
	Concn. of end soln. 10 ⁻⁴ M	0.337	0.312	0.899	
	Hd	12.59ª	12.58ª	11.66ª	
	Substituents	3-CO ₂ Et	3-CO ₂ Et-6,7-OCH ₂ O	3-CN	
	Compound No.	_	4	7	

^a In standard NaOH.

conclusions could be drawn for 3-cyano-4-quinolone in the gas phase, in contrast with the marked predominance of the quinolone form (7a) in aqueous solution.

Experimental

UV spectra were recorded on a Unicam S.P. 800A spectrophotometer. Work at fixed wavelength was carried out on a Pye/Unicam SP6-500 UV spectrophotometer fitted with a thermostatted cell compartment. pH Readings were carried out using a Pye Model 290 pH meter. pK_a determinations were by the standard UV spectroscopic technique²⁴.

Preparation of compounds

The following were prepared by the literature methods indicated: 3-ethoxycarbonyl-4-quinolone, m.p. 278-280°C (lit.²⁵ m.p. 269-270°C); 3-cyano-4-quinolone, m.p. 306-308°C (lit.²⁶ m.p. 301°C); 3-ethoxycarbonyl-6,7-methylenedioxy-4-quinolone, m.p. 300-302°C (lit.²⁷ m.p. 301-302°C); 4-chloro-3-ethoxycarbonylquinoline, m.p. $43-45^{\circ}$ C (lit.²⁸ m.p. $44-45^{\circ}$ C, lit.²⁹ m.p. $46-47^{\circ}$ C); 4-ethoxy-3-ethoxycarbonylquinoline, m.p. $32-33^{\circ}$ C (lit.²⁸ m.p. 32-34°C).

Preparation of N-ethyl 4 quinolones

The quinolone (0.01 mol) and potassium carbonate (0.01 mol) in triethyl phosphate (0.03-0.05 mol) were refluxed for 30 min, poured into water (50 ml), and the whole kept 12 h at 0°C. The quinolones precipitated on standing: 3-ethoxycarbonyl-1-ethyl-4-quinolone, m.p. 108-110°C (lit.³⁰ 110-111°C); 3-ethoxycarbonyl-1-ethyl-6,7methylenedioxy-4-quinolone m.p. 177° C (lit.²⁷ m.p. $177-178^{\circ}$ C); 3-cyano-1-ethyl-4-quinolone, m.p. $234-236^{\circ}$ C (lit.³¹ m.p. 236° C).

4-Chloro-3-ethoxycarbonyl-6,7-methylenedioxyquinoline

Diethyl [(3,4-methylenedioxyanilino)methylene]malonate (30.73 g, 0.1 mol) was refluxed for 1 h in polyphosphoric acid (2 g) and phosphorous oxychloride (46.0 g, 0.3 mol). Ethanol (80 ml) was added at 20°C: the hydrochloride (30 g, 95%) separated on cooling. It was dissolved in water (150 ml) and neutralised with 10% NaHCO3: the chloroquinoline precipitated (25 g, 89.4%), m.p. 111-112°C (lit.⁹ m.p. 111-112°C).

4-Chloro-3-cyanoquinoline hydrochloride (0.7 g, 66%) was prepared from the 4-hydroxy derivative by the above method, an amorphous solid, m.p. 172-174°C.

Anal. Calcd. for C₁₀H₆Cl₂N₂ C, 53.4; H, 2.7; N, 12.5; Cl, 31.5. Found: C, 53.3; H, 2.6; N, 12.5; Cl, 31.6.

4-Ethoxyquinolines

The 4-chloro-3-ethoxycarbonyl compound (0.01 mol) was refluxed with ethanolic sodium ethoxide (from 50 ml EtOH and 0.28 g Na) for 2 h. The solvent was evaporated off and the residue extracted with hot light petroleum (b.p. 40-70°C). 4-Ethoxy-3-ethoxycarbonyl-6,7-methylenedioxyquinoline (0.28 g, 19.5%) separated on cooling, and crystallised as needles from light petroleum, m.p. 76°C (lit.³² 85-85.5°C). 4-Chloro-3-cyanoquinoline hydrochloride (0.0023 mol) was refluxed with ethanolic sodium ethoxide (from 10 ml ethanol and 0.12 g Na) for 2 h. The salt was filtered off and the solvent evaporated off. On treating the residue with water (2 ml), the 3-cyano-4-ethoxyquinoline (0.35 g, 77.8 %) separated as needles, m.p. 88-90°C.

Anal. Calcd. for C₁₂H₁₀N₂O: C, 72.7; H, 5.1; N, 14.1. Found: C, 72.5; H, 5.5; N, 14.3.

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An improved synthesis of 1,2,3-butatrienyl ethers

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Abstract. A modified synthetic route to 1,2,3-butatrienyl ethers 3 is presented. It involves hydroxyalkylation of 2-propynyl ethers with an aldehyde or a ketone, followed by trimethylsilylation of the hydroxy ether 1 and 1,4-elimination of Me₃SiOH from 2 with ethyllithium.

Introduction

Cumulenic ethers with the system C=C=C=C=OR were synthesised some years ago^{1,2} by 1,4-elimination of HOR⁴ from bis-ethers 2, using alkali amides in liquid ammonia or butyllithium in ether.

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