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Tautomerism and Acidity in 4-Quinolone-3-Carboxylic Acid Derivatives

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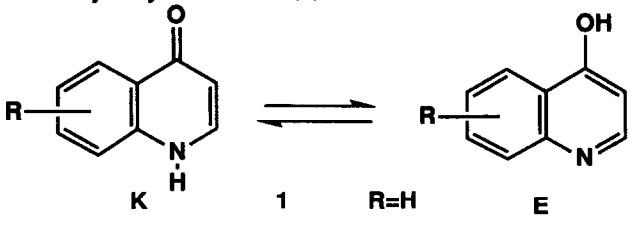
Abstract.—Prototropic tautomerism in 4-quinolone-3-carboxylic acid derivatives has been studied with particular emphasis on the influence of the ring substituents on the equilibrium. The techniques used include UV, ^{1}H-NMR , ^{13}C-NMR (solution) and ^{13}C-NMR CP/MAS (solid state) and semiempirical and *ab initio* calculations. The pK_a values of some quinolone derivatives have been determined and correlated with data obtained from semiempirical methods.

INTRODUCTION

Prototropic tautomerism of heteroaromatic compounds being an important phenomenon in many areas of chemistry and biology has been the subject of many studies.[1] Due to this, most problems of tautomeric equilibria are either solved or are easily predictable. However, there are still some cases where the position of the equilibrium is uncertain such as the keto-enol tautomerism of 4-quinolones especially in derivatives bearing ester or carboxy functions at the 3-position. In the case of the parent compound **1** only two tautomers are possible, the oxo or keto form (K) and the hydroxy or enol form (E).



The problem is more complicated when the heterocycle bears hydrogen bond acceptors such as CO_2R or CO_2H groups at the 3-position (Figure 1). In the first case three tautomers are possible, referred to as KK, KE and EK whilst for the 3-carboxylic acid derivatives as many as four forms have to be considered (KK, KE, EK(N) and EK(Z)). In both cases, the KE forms will not be taken into account since it is well known that in β-keto esters it is the carbonyl and not the ester group which is enolyzed. The zwitterion form EK(Z) does not exist in the gas phase, due to charge separation, but it is possible in solution and solid state.

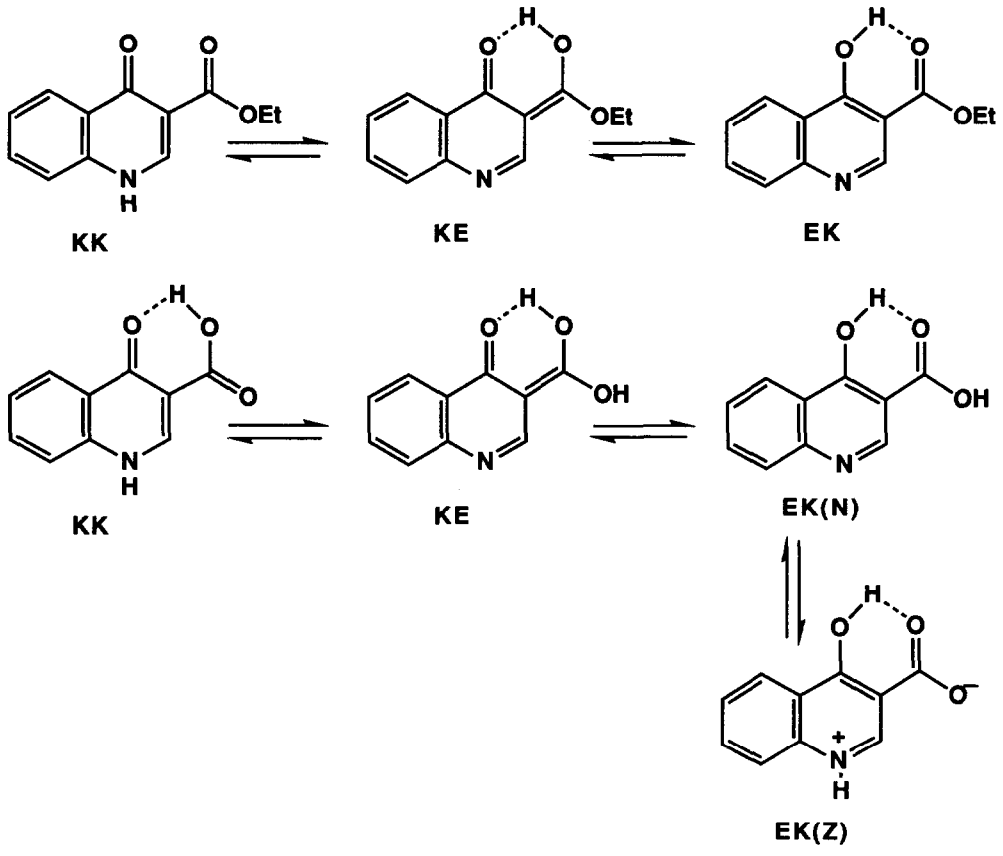


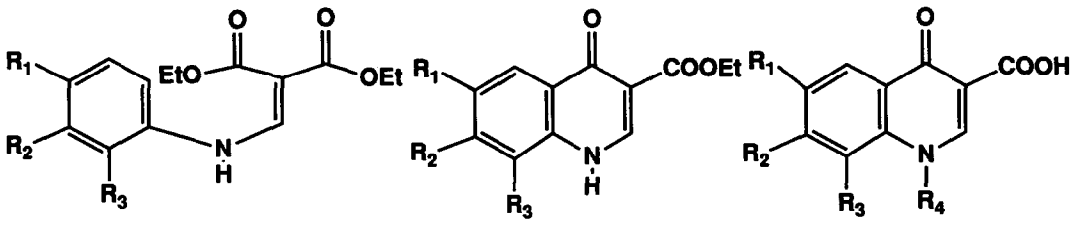
FIGURE 1

Previous literature results clearly indicate that in the parent compound the oxo form is by far preferred in solution.[2] However when the heterocycle bears hydrogen bond acceptors at position 3 such as CO_2R or CO_2H some authors suggest that intramolecular hydrogen bonding may stabilize the hydroxy form.[3] In the gas phase, the controversy appears already for 4-quinolone itself and the results depend on the technique used. According to metastable ion mass spectrometry the preferred form is the 4-hydroxy[4] whereas with photoelectron spectral studies the oxo form appears to be the more stable.[5] Results obtained using CID-MIKE spectrometry suggest the 4-oxo form for quinolone but the 4-hydroxy for the 3-ethoxycarbonyl compound.[6] Concerning MO calculations, only the parent compound **1** has been studied by PM3 and AM1[7] and the hydroxy form turned out to be the more stable.

With all these results in mind, in the present paper we have carried out a detailed study of the prototropic tautomerism in 4-quinolone and its 3-carboxylic acid derivatives in solution, solid state, and by means of semiempirical and *ab initio* methods. MO calculations have also been used to estimate the acidity of this system in the gas phase, results which have been correlated with experimental determinations in solution.

Synthesis

The quinolones used in this study were synthesized according to standard procedures starting from suitable anilines and diethyl ethoxymethylenemalonate.[8] Conversion to the 3-carboxylic acids was achieved in basic or acid medium (Figure 2). Some of these compounds had already been described, but since they are reported mainly in patents,[9] analytical and NMR data are included in the experimental part.



$R_1=R_2=R_3=H$	2	7	$R_1=F\ R_2=Cl\ R_3=R_4=H$	12
$R_1=F\ R_2=R_3=H$	3	8	$R_1=R_2=F\ R_3=R_4=H$	13
$R_1=F\ R_2=Cl\ R_3=H$	4	9	$R_1=F\ R_2=Cl\ R_3=H\ R_4=Bn$	14
$R_1=R_2=F\ R_3=H$	5	10	$R_1=R_2=R_3=H\ R_4=$ 	15
$R_1=R_2=R_3=F$	6	11		

FIGURE 2

Tautomeric Structure in Solution

The ^{13}C NMR data of the synthesized quinolones can be used to assign the tautomeric structure in solution. By comparison of the chemical shifts of compounds **8-11** (see experimental), with those previously described for N-Et and O-Et derivatives,[10] it is possible to establish the 4-oxo form as the only one present in DMSO, in good agreement with literature results.

Useful information concerning the tautomeric structure in water can be gained from UV spectroscopy (Table 1). The UV spectra of the neutral forms of the 3-carboxy derivative **12**, its corresponding ethyl ester **9** and that of its N-benzyl derivative **14**[8] are very similar, thus indicating the preponderance of the quinolone form in water. Besides, the fact that the basic pK_a values of the ester derivatives (<1) are much closer to that of the N-ethyl derivative (0.87) than to that of the O-ethyl compound (3.88) previously reported [3a] confirms the existence of the 4-oxo form in water for these compounds.

Tautomeric Structure in the Solid State

The ^{13}C-CP/MAS spectra of 4-quinolone **1** and its 3-ethoxycarbonyl derivative **7** (Table 2) indicate that both compounds exist, in the solid state, as a single tautomer since each carbon appears as a unique signal. In the case of **7** the signals corresponding to the methylene carbon and to the carbon at position 3 are split but this could be due to different conformations of the ethoxycarbonyl group.

By comparison of the chemical shifts of **1** and **7** with those of a model compound in which the prototropy is blocked, namely 1,4-dihydro-1-[(2-hydroxyethoxy)methyl]-4-oxo-3-quinolinecarboxylic acid **15**,[10] it can be concluded that both quinolones lie in the solid state, in the oxo form. There is also a good agreement with the results found in solution.

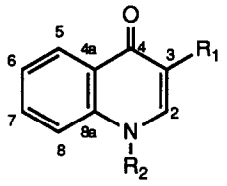
Table 1. UV Data and pK_a Values of 4-Quinolone Derivatives **7-14**

	pKa	λ_{max} (nm)								log ε_{max}								pH	Mol. form
7	0,99±0,05	[322]		[304]	298		241			[3,47]		[3,68]	3,70		4,72			Ho=-1	+
	10,32±0,18		[322]	308	[303]		[252]	246			[3,93]	4,10	[4,09]		[4,30]	4,34		4	0
		[336]	[322]	304		259				[3,80]	[3,92]	4,01		4,37				13	—
8	0,55±0,09	[325]	[314]		292		242			[3,55]	[3,61]		3,69		4,66			Ho=-2	+
	9,54±0,07	330	316	300		253	246			3,86	4,02	4,04		4,28	4,33			3	0
		[342]	328	302		260				[3,73]	3,83	3,96		4,38				12	—
9	0,36±0,08	[325]	[311]	298	[292]		246			[3,52]	[3,74]	3,84	[3,83]		4,74			Ho=-2	+
	8,76±0,03	331	318	302	259	251	[242]	[220]		3,88	4,00	4,01	4,47	4,43	[4,33]	[4,35]		2,13	0
		[342]	330	306	[294]	265	[248]	[242]	[232]	[3,73]	3,80	3,92	[3,83]	4,52	[4,27]	[4,27]	[4,32]	11	—
10	0,30±0,12		[316]	[301]	293	[282]	240				[3,45]	[3,72]	3,77	[3,70]	4,68			Ho=-2	+
	8,86±0,13	320	308	[300]		253	246	[232]		3,91	4,03	[4,01]		4,37	4,30	[4,24]		3	0
		[333]	[320]	304	[290]	260				[3,64]	[3,78]	3,88	[3,73]	4,35				11	—

11	-0,46±0,03	[320]		[303]	297		242			[3,51]		[3,71]	3,73		4,70		Ho=-3	+
	7,67±0,02	[320]	307	[302]		251	244			[3,93]	4,09	[4,07]		4,25	4,29		2	0
		[335]	[321]		303		257		[3,79]	[3,93]		4,01		4,33			10	—
12	5,91±0,05		328	314	302	[288]	258	250	[237]		3,81	3,94	3,94	[3,78]	4,54	4,53	[4,38]	4	0
	10,35±0,13	334	323	[312]	298	[288]	257	249		3,82	3,85	[3,74]	3,73	[3,69]	4,45	4,49		8	—
		[338]	[325]	318			260		[234]	[3,75]	[3,84]	3,86			4,50		[4,22]	13	2
13	5,92±0,06		[318]	306	[300]		252	244	230		[3,86]	4,00	[3,97]		4,38	4,36	4,33	3	0
	10,72±0,172		[324]	316	[294]	[280]	251	244			[3,85]	3,88	[3,75]	[3,61]	4,32	4,36		8	—
				316			254					3,93			4,37			13	2
14	5,65±0,13	333	320	308		262	254	[245]	[236]	3,96	4,04	3,98		4,48	4,47	[4,38]	[4,34]	3	0
		341	330	302	[290]	261	253			4,04	4,04	3,72	[3,61]	4,48	4,45			8	—
A	0,87±0,02			306				245				3,82				4,67		0,10	+
			328	315			256	249	226		4,02	4,12			4,26	4,28	4,36	9,45	0
B	3,88±0,03			310				242				3,76				4,66		Ho=-1,41	+
						286			236					3,78			4,68	8,01	0

A Ethyl 1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate[3a]. B Ethyl 4-Ethoxy-3-quinolinecarboxylate[3a].

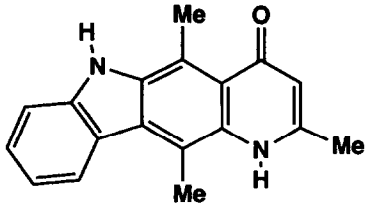
Table 2—. ^{13}C-NMR. Chemical Shifts (ppm) in Solid State and Solution of 4-Quinolone Derivatives



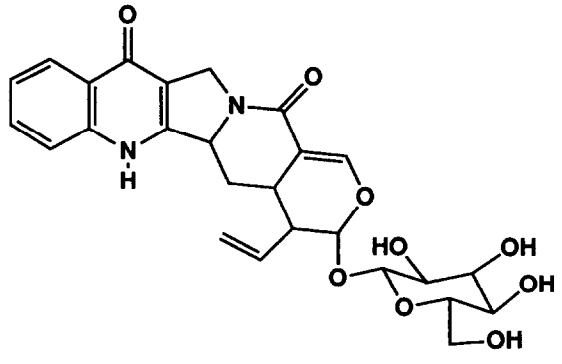
		C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a
R_1=R_2=H	**1**[a]	140.0	108.6	176.9	125.8	124.9	123.0	131.5	118.2	139.4
	1[b]	141.1	107.6	177.9	125.4	124.3	122.7	130.4	117.0	139.4
R_1=CO_2H R_2=HO⌐O⌐	**15**[a,c]	149.4	107.3	178.4	125.3	126.5	125.6	134.2	118.6	139.2
	15[b,d]	148.7	104.4	176.7	128.0	125.6	122.4	135.9	119.0	138.5
R_1=CO_2Et R_2=H	**7**[b,e]	148.7	107.5 106.1	174.8	129.3	127.2	125.4	132.3	118.5	138.5

[a] 20 MHz, DMSO-d_6. [b] 100 MHz, CP/MAS. [c] 165.9 (CO), 83.8 (NCH_2O), 70.3 (CH_2O), 59.9 (CH_2OH). [d] 170.3 (CO), 84.2 (NCH_2O), 70.8 (CH_2O), 61.8 (CH_2OH). [e] 164.6 (CO), 59.91 (59.17) (CH_2), 13.17 (CH_3).

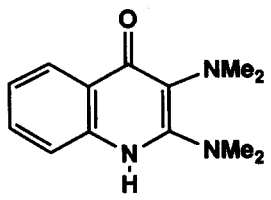
Finally it should be mentioned that no suitable crystals could be obtained for the compounds here reported and so, a search in the CSD[12] was carried out. In spite of the very large number of quinolones synthesized for antibacterial purposes, there are only X-ray data for sixteen of them, eleven compounds being N-substituted . In the other five structures in which the prototropic tautomerism is possible only the 4-oxo form has been observed (Structures **16-20**).



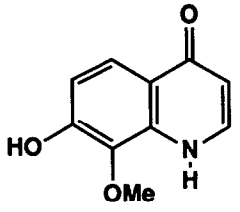
16[13]



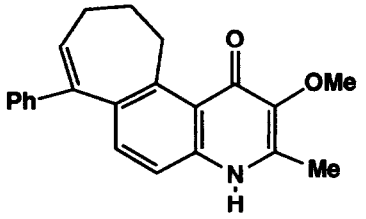
17[14]



18[15]



19[16]



20[17]

Theoretical Calculations of the Tautomerism of 4-Quinolones

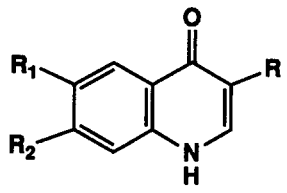
Tautomerism in heterocycles can also be studied by quantum-chemical calculations since the relative stability of two tautomers depends on the difference between their lowest energies.[18] For the present case, two different semiempirical methods were chosen: AM1,[19] which had proved useful for the study of tautomeric equilibria,[20] and PM3,[21] which has been recently shown to give good results in this type of studies.[15] In some cases, STO-3G *ab initio* calculations (Gaussian 80)[22] were also carried out.

AM1 calculations were done with the AMPAC program package[23] and PM3 calculations with the MOPAC[24] one. In all cases, the Chem QM interfase of the molecular modelling program Chem X[25] was used and full geometry optimizations with the Fletcher-Powell algorithm[26] were carried out. The input geometries were taken from the standard ones within Chem X assuming the planarity of the systems. In general, no significant differences were observed (in energy or geometry) between planar and fully optimized structures.

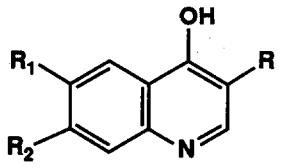
The results obtained for 4-quinolone **1** itself, its 3-carboxylic acid **12** and the 3-methoxycarbonyl derivative are gathered in Table 3. For the unsubstituted compound **1** there is a very small energy difference between both tautomers, the hydroxylic form being the most stable, when semiempirical methods are used, in agreement with previous results.[7] When the quinolone bears an ester or acid function at the 3-position the hydroxy form (EK) is still the more stable. However, the difference in energy between the KK and EK forms is larger for the ester than for acid **12**, probably due to the presence of a stabilizing hydrogen bond in the KK form of the acid, not possible in that of the ester. These energy differences between both tautomers become larger when one considers the *ab initio* calculation results, but again the hydroxylic form is the most populated.

The tautomeric preferences in 4-quinolones bearing halogen substituents were studied using only semiempirical methods since the results obtained for the parent compounds using these methods and *ab initio* calculations are qualitatively the same. PM3 and AM1 energy values for fluoroquinolones are given in Table 3. In all cases, the greater stability is predicted for the hydroxy form. A curious feature of these results is that whilst for the esters the difference in energy between both tautomers is around 5.5-6.5 kcal.mol^{-1} (independent of the method used), for the carboxylic acids this difference is somewhat greater with AM1 (~5 kcal.mol^{-1}) than with PM3 (~ 2 kcal.mol^{-1}). This may be explained assuming that these two methods consider the hydrogen bond present in tautomeric forms **a** in a different manner: thus, PM3 overestimates, in relation to AM1, the strength of this hydrogen bond, which would result in a smaller difference in energy between both tautomers. If one takes into account the geometries obtained from calculations, the averaged values for the distance H···O and for the angle H···O-H present in a hydrogen bond are 1.80 Å and 143° for PM3, and 2.02 Å and 137° for AM1 respectively. The crystallographic experimental data[27] show that the values for bond distances are between 1.7 and 2.1 Å and a typical hydrogen bond angle ranges from 155° to 180°, and so the results obtained with the PM3 method are in better agreement with experimental data.

Table 3 — Calculated Heats of Formation (kcal.mol^{-1}) and Dipole Moments (D) of 4-Quinolone Derivatives



a



b

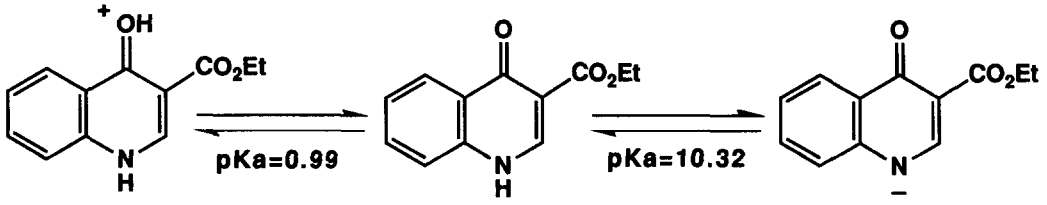
Comp.		AM1 ΔHf kcal.mol^{-1}	AM1 a-b kcal.mol^{-1}	AM1 μ D	PM3 ΔHf kcal.mol^{-1}	PM3 a-b kcal.mol^{-1}	PM3 μ D
R=H R_1=R_2=H	**1a**[a]	8.8	0.8	5.28	3.5	0.3	4.63
	1b[a]	8.0		1.91	3.2		2.07
R=COOH R_1=R_2=H	**12a**[b]	-81.0	4.3	8.07	-89.2	1.2	8.26
	12b[b]	-85.3		1.13	-90.4		0.56
R=CO_2Me R_1=R_2=H	**a**[c]	-72.5	6.0	5.43	-77.0	5.3	5.15
	b[c]	-78.5		0.40	-82.3		0.27
R=COOH R_1=F, R_2=H	**a**	-124.4	5.0	7.58	-131.4	1.8	7.66
	b	-129.4		0.74	-133.2		1.26
R=COOH R_1=F, R_2=Cl	**a**	-128.1	5.0	6.59	-136.4	1.9	7.07
	b	-133.1		1.49	-138.3		1.76
R=COOH R_1=R_2=F	**a**	-166.7	5.1	6.09	-173.6	2.1	6.10
	b	-171.8		1.97	-175.7		2.70
R=COOMe R_1=F, R_2=H	**a**	-116.3	6.4	5.50	-119.5	5.6	5.70
	b	-122.7		1.38	-125.1		1.85
R=COOMe R_1=F, R_2=Cl	**a**	-120.2	6.3	4.78	-124.6	5.6	5.27
	b	-126.5		2.28	-130.2		2.39
R=COOMe R_1=R_2=F	**a**	-158.8	6.3	4.52	-162.0	5.6	4.97
	b	-165.1		2.74	-167.6		3.32

[a] STO-3G calculations: (**a-b**)=8.1 kcal.mol^{-1}; **1a** μ=3.92 D; **1b** μ=2.06 D.[b] STO-3G calculations: (**a-b**)=11.5 kcal.mol^{-1}; **12a** μ=6.78 D; **12b** μ=1.21 D. [c] STO-3G calculations: (**a-b**)=16.6 kcal.mol^{-1}; tautomer **a** μ=3.87D; tautomer **b** μ=1.37D.

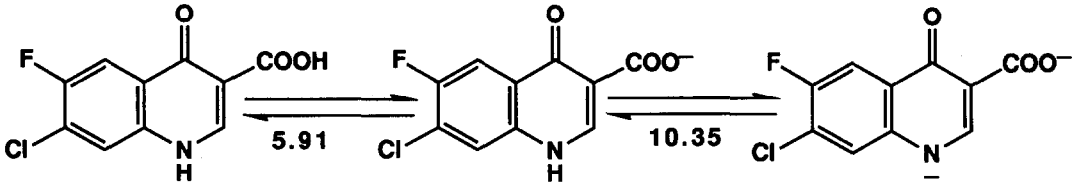
Concerning the tautomerism of quinolones, the overall conclusions of this experimental and theoretical study are: i) the difference in energy between both tautomers of unsubstituted quinolone, **1a** and **1b**, is very small which explains why both are observed in the gas phase depending on the technique used;[4,5,6] ii) since the oxo form **1a** is more polar than the hydroxy one **1b**, polar solvents or the solid state (which can be considered as a highly polar medium) favours the oxo tautomer (this work); iii) the presence at position 3 of a group able to act as a hydrogen bond acceptor with regard to the 4-OH group, stabilizes tautomer **b**, which should be dominat in the gas phase (Table 3); however, in solution in polar solvents, tautomer **a** becomes again the most stable due to its high dipole moment. The influence of solvent properties, polarity, for instance, on tautomerism of related compounds such 4-pyridones (stabilizing the oxo tautomer), is a well established fact.[28]

Acid base properties of 4-quinolones

Finally and in order to complete the structural properties of 4-quinolones, some of the previously reported techniques were used to study the acidity of these systems. For the experimental determination of the pK_a values, UV spectroscopy was used,[29] the data being gathered in Table 1. By intercomparison of the values, it has been possible to assign the ionization sequences. In the case of the ethyl 3-quinolinecarboxylate derivative **7**, the basic pK_a value (0.99) corresponds to the protonation of the neutral form to give the cation species and the next one (10.32) to the formation of the anion.



Some of the compounds studied have two ionizable groups. By comparison of the pK_a values of the acid **12** with those of its N-benzyl derivative **14** and the corresponding ester **9** the following ionization sequences can be written:

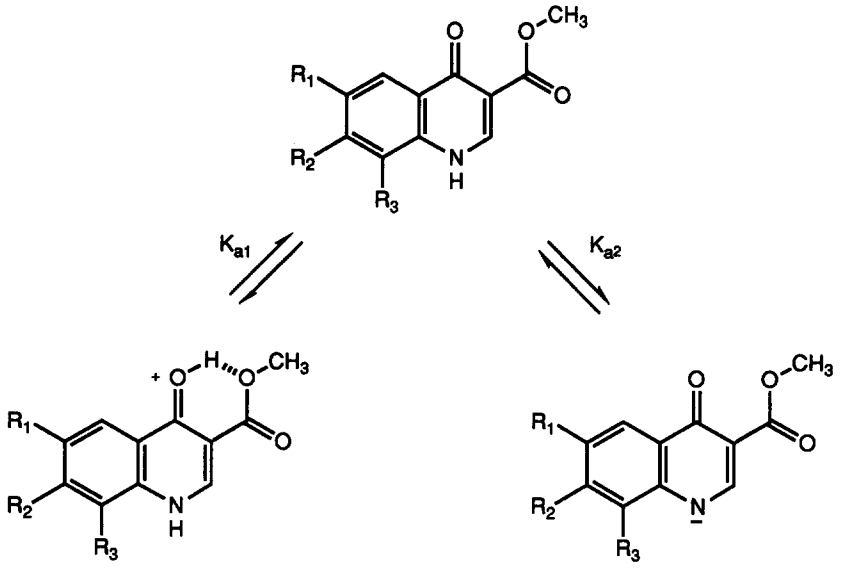


12

The successive introduction of halogen atoms in positions 6, 7 and 8 of the quinolone nucleus increases the acidity of the system, and so the pK_a corresponding to the deprotonation of the NH decreases from 10.32 in the unsubstituted compound **7** to 7.67 in the trifluoro derivative **11**.

The effect of the introduction of substituents on the acidity of the system has also been studied by PM3. For this purpose, the heats of formation of the protonated, neutral and anionic species of the 3-methyl esters (as model substances) of the halogen quinolones were calculated. From these data, the deprotonation energies of each process (ΔEd_1 and ΔEd_2), defined as the energy difference between the deprotonated and protonated species were estimated. The data are collected in Table 4 and again it can be seen how the introduction of halogen atoms increases the acidity of the system.

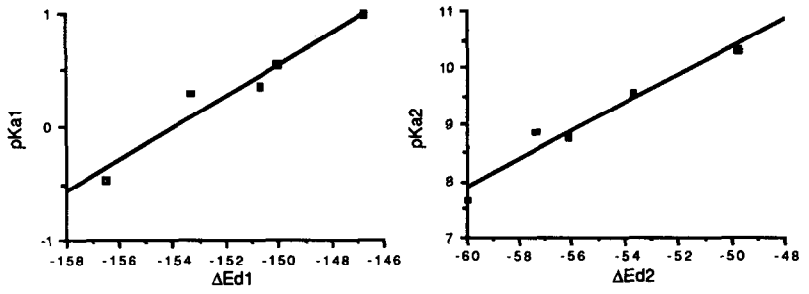
Table 4. Experimental (pK_a) and Calculated (ΔE_d kcal.mol^{-1}) Data of the Acidity of 1,4-Dihydro-4-oxo-3-quinolinecarboxylates **7-11**



Comp.		pK_{a1}	ΔE_{d1}*	pK_{a2}	ΔE_{d2}*
R_1=R_2=R_3=H	**7**	0.99	-146.76	10.32	-49.81
R_1=F R_2=R_3=H	**8**	0.55	-150.07	9.54	-53.70
R_1=F R_2=Cl, R_3=H	**9**	0.36	-150.70	8.76	-56.13
R_1=R_2=F R_3=H	**10**	0.30	-153.31	8.86	-57.39
R_1=R_2=R_3=F	**11**	-0.46	-156.46	7.67	-59.97

* Values of ΔEd correspond to the methyl esters.

These deprotonation energies, in the gas phase, can be correlated with the experimental pK_a values since they are related to the free energy of the process in aqueous solution.Thus, Figure 3 shows that there is a good lineal correlation between both kinds of parameters studied.



$pK_{a1}=0,14\Delta E_{d1}+21,59$ $r^2=0,94$ $\sigma=0,15$ $pK_{a2}=0,25\Delta E_{d2}+22,83$ $r^2=0,95$ $\sigma=0,25$

FIGURE 3

Acknowledgements.- We thank Dra. Isabel Sobrados (Instituto de Ciencia de Materiales. Sede C) for the register of the CP/MAS spectra, and Mrs. M. Bischler (University of Konstanz) for the pK_a determination values. The financial support from CICYT (project no. FAR 90-746) is gratefully acknowledged

EXPERIMENTAL

M.ps. were determined with a Reichert-Jung Thermovar and are uncorrected. ^{1}H-NMR were recorded at 293 K on a Varian XL-300 instrument operating at 300 MHz, using TMS as internal standard. ^{13}C-NMR were recorded at 293 K on a Bruker AM-200 spectrometer operating at 50 MHz under the following conditions: sweep width 16 kHz; pulse width 9 μs; acquisition time 1s. ^{13}C-CP/MAS NMR spectra were recorded on a Bruker-CXP-400 instrument operating at 100 MHz, under the following conditions: spinning rate 4.1 kHz; spectral width 50.0 kHz; acquisition time 5.0 s. Computational calculations were run on a VAX 9210 and on an Apple Macintosh IIfx computers, using the molecular modeling program CHEM-X.[25]

The NMR (^{1}H and ^{13}C) data of compounds **2-13** are collected in tables 5-8.

General procedure for the preparation of anilinomethylenemalonate derivatives **2-6**[8].- An equimolar mixture (0.1 mol) of the suitable aniline and diethyl ethoxymethylenemalonate was heated at 120-130°C during 3 h. After cooling, the solid was filtered off and crystallized from n-hexane.

Diethyl anilinomethylenemalonate **2.**- Yield : 50%, m.p.:49-50°C (Lit.[30] 49°C) (Found: C, 63.47; H, 6.51; N, 5.37 %. $C_{14}H_{17}NO_4$ requires: C, 63.86; H, 6.51; N, 5.32 %)

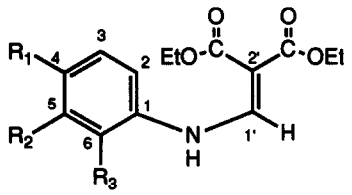
Diethyl 4-fluoroanilinomethylenemalonate **3.**- Yield: 79%; m.p.: 69-70°C (Lit.[9c] 77°C) (found: C, 59.99; H, 5.79; N, 4.97 %. $C_{14}H_{16}FNO_4$ requires: C, 59.78; H, 5.73; N, 4.98 %).

Diethyl 3-chloro-4-fluoroanilinomethylenemalonate **4.**- Yield: 80%; m.p.: 58-60°C (Lit.[8] 55-57°C) (Found: C, 53.32; H, 4.90; N, 4.23 %. $C_{14}H_{15}ClFNO_4$ requires: C, 53.26; H, 4.79; N, 4.44 %).

Diethyl 3,4-difluoroanilinomethylenemalonate **5**[9a].- Yield: 73%; m.p.: 77-79°C (Found: C, 56.36; H, 4.96; N, 4.80 %. $C_{14}H_{15}F_2NO_4$ requires: C, 56.19; H, 5.05; N, 4.68 %).

Diethyl 2,3,4-trifluoroanilinomethylenemalonate **6**[9b].- Yield: 80%; m.p.: 89-91°C (Found:C, 53.19; H, 4.40; N, 4.52 %. $C_{14}H_{14}F_3NO_4$ requires: C, 53.00; H, 4.45; N, 4.41 %).

Table 5. ^{13}C-NMR. Chemical Shifts (ppm) and ^{13}C, ^{19}F Coupling Constants (Hz) of Anilinomethylenemalonate Derivatives **2-6**[a]



Comp.		C-1	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	CO	CH_2	CH_3
R_1=R_2=R_3=H	**2**	139.2	117.0	129.6	124.7	129.6	117.0	151.6	93.7	168.8 165.5	59.8 60.1	14.2 14.1
R_1=F R_2=R_3=H	**3**	135.3	118.2	116.0	159.3	116.0	118.2	151.5	93.4	168.3 165.0	59.6 59.4	13.8 13.7
R_1=F R_2=Cl, R_3=H	**4**	136.3	116.9	117.3	155.3	122.3	119.2	151.5	94.9	168.7 165.3	60.4 60.1	14.3 14.1
R_1=R_2=F R_3=H	**5**	136.2	112.9	118.2	147.4	150.8	106.5	151.4	94.8	168.7 165.3	60.3 60.1	14.2 14.1
R_1=R_2=R_3=F	**6**	125.8	110.2	112.7	147.7	140.5	142.6	150.9	96.2	168.5 165.2	60.6 60.3	14.2 14.1

Comp.		C-1	C-2	C-3	C-4	C-5	C-6
R_1=F R_2=R_3=H	**3**	^4J=2.7	^3J=8.1	^2J=23.1	^1J=-244.5	^2J=23.1	^3J=8.1
R_1=F R_2=Cl, R_3=H	**4**	^4J=3.2	—	^2J=29.6	^1J=-247.2	^2J=19.2	—
R_1=R_2=F R_3=H	**5**	^4J=3.2 ^3J=8.1	^3J=6.0 ^4J=3.8	^2J=18.6 —	^1J=-246.5 ^2J=12.6	^2J=13.5 ^1J=-249.9	— ^2J=20.9
R_1=R_2=R_3=F	**6**	^4J=3.1 — ^2J=8.3	^3J=7.1 ^4J=4.1 —	^2J=18.7 — ^4J=3.9	1J=-248.4 ^2J=10.3 ^3J=2.3	^2J=13.5 ^1J=-252.6 ^2J=16.1	^3J=3.0 ^2J=12.6 ^1J=-251.2

a)50 MHz, $CDCl_3$

Table 6. ^{1}H-NMR. Chemical Shifts (ppm) and Coupling Constants (Hz) of Anilinomethylenemalonate Derivatives **2-6**[a]

Comp.	Aromatic	=CH	NH	CH_2	CH_3
2	7.10-7.40 (m)	8.57 (d)	11.07 (d)	4.33 (q) 4.27 (q)	1.37 (t) 1.33 (t)
3	7.10-7.20 (m)	8.47 (d)	10.73 (d)	4.27 (q) 4.23 (q)	1.37 (t) 1.33 (t)
4	6.93-7.27 (m)	8.37 (d)	11.00 (d)	4.33 (q) 4.23 (q)	1.40 (t) 1.37 (t)
5	6.77-7.33 (m)	8.40 (d)	11.03 (d)	4.33 (q) 4.27 (q)	1.37 (t) 1.33 (t)
6	6.97-7.10 (m)	8.40 (d)	11.00 (d)	4.33 (q) 4.27 (q)	1.37 (t) 1.33 (t)

[a] 90 MHz, $CDCl_3$, $J_{CH2,CH3}$=6 Hz. $J_{=CH,NH}$=12 Hz.

General procedure for the preparation of ethyl 1,4-dihydro-4-oxo-3-carboxylates **7-11**[8].- The corresponding diethyl anilinomethylenmalonate (0.1 mol) was suspended in diphenylether (40 ml) and heated at 250°C for 1 h. After cooling, the precipitate was filtered off, washed with n-hexane and crystallized from N,N-dimethylformamide.

Ethyl 1,4-dihydro-4-oxo-3-quinolinecarboxylate **7**.- Yield: 35%; sublimates at 220°C (Lit.[30] m.p.: 269°C) (Found: C, 66.72; H, 5.26; N, 6.80 %. $C_{12}H_{11}NO_3$ requires: C, 66.35; H, 5.10; N, 6.45 %).

Ethyl 6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate **8**.- Yield: 40%; sublimates at 220°C (Lit.[9c] m.p.: 313°C) (Found: C, 61.31; H, 4.62; N, 5.95 %. $C_{12}H_{10}FNO_3$ requires: C, 61.28; H, 4.28; N, 5.95 %).

Ethyl 7-chloro-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate **9**.- Yield: 56%; sublimates at 290°C (Lit.[8] m.p.>300°C) (Found: C, 53.50; H, 3.31; N, 5.55 %. $C_{12}H_9ClFNO_3$ requires: C, 53.45; H, 3.36; N, 5.19 %).

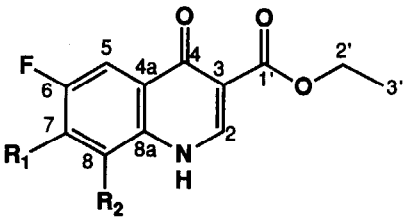
Ethyl 6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate **10**[9a].- Yield: 54%; sublimates at 225°C (Found: C, 56.70; H, 3.90; N, 5.35 %. $C_{12}H_9F_2NO_3$ requires: C, 56.92; H, 3.58; N, 5.53 %).

Ethyl 6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate **11**.- Yield: 66%; sublimates at 205°C (Lit.[9b] m.p.: 280°C) (Found: C, 53.01; H, 3.06; N, 5.28 %. $C_{12}H_8F_3NO_3$ requires: C, 53.15; H, 2.97; N, 5.16 %).

7-Chloro-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid **12**.- The ethyl quinolinecarboxylate **9** (3.0 g, 0.01 mol) was suspended in 2N NaOH solution (50 ml) and methanol (20 ml). The reaction mixture was refluxed for 3 h. After cooling, the methanol was eliminated under reduced pressure and the aqueous solution was neutralized with HCl. The solid was filtered and crystallized from N,N-dimethylformamide. Yield 2.2 g (82 %) of a white solid which sublimates at 260°C (Found: C, 49.39; H, 2.30; N, 6.10 %. $C_{10}H_5ClFNO_3$ requires: C, 49.71; H, 2.08; N, 5.80 %).

6,7-Difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid **13**.- This compound was obtained following the above procedure. Yield: 40%; m.p.: 274-276°C (Found: C, 53.02; H, 2.54; N, 6.08 %. $C_{10}H_5F_2NO_3$ requires: C, 53.35; H, 2.24; N, 6.22 %).

Table 7. ^{13}C-NMR. of Fluorine-containing 4-Quinolone Ester Derivatives **8-11**[a] (Chemical Shifts (ppm) and ^{13}C, ^{19}F Coupling Constants (Hz))



Comp.		C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-1'	C-2'	C-3'
R_1=R_2=H	**8**	148.4	108.8	176.3	126.9	112.7	165.9	130.9	125.3	139.9	171.0	68.1	15.8
R_2=Cl R_1=H	**9**	149.3	109.1	176.4	123.7	113.8	162.0	138.6	126.4	140.0	170.9	68.5	15.9
R_2=F R_1=H	**10**	149.5	109.0	176.3	121.4	112.4	161.1	156.0	115.8	141.2	171.0	68.6	15.9
R_1=H R_2=F	**11**	150.1	109.8	176.6	120.0	110.8	156.0	149.1	145.4	131.5	170.7	68.7	15.8

Comp.		C-4a	C-5	C-6	C-7	C-8	C-8a
R_1=R_2=H	**8**	—	^{2}J=24.9	^{1}J=-254.8	^{2}J=26.3	^{3}J=10.1	—
R_2=Cl R_1=H	**9**	^{3}J=9.1	^{2}J=25.1	^{1}J=-258.1	^{2}J=21.2	—	—
R_2=F R_1=H	**10**	—	^{2}J=22.35	^{1}J=-251.6 ^{2}J=15.0	^{1}J=-262.5 ^{2}J=14.7	^{2}J=21.2	^{3}J=11.4
R_1=H R_2=F	**11**	^{3}J=9.1	^{2}J=21.0 ^{4}J=5.0	^{1}J=-262.6 ^{2}J=9.3	^{1}J=-261.6 ^{2}J=13.5	^{1}J=-259.7 ^{2}J=13.1	—

a) 50 MHz. CF_3COOD.

Table 8. ^{1}H-NMR. Chemical Shifts (ppm) and Coupling Constants (Hz) of 4-Quinolone Derivatives **7-13**[a]

Comp.	H-2	H-5	H-6	H-7	H-8	CH_2	CH_3
7			7.93-8.77 (m)			4.73 (q)	1.57 (t)
8	8.87 (s)		8.23-8.37 (m)			4.30 (q)	1.03 (t)
9[b]	8.90 (s)	7.87 (d)	—	—	7.90 (d)	4.30 (q)	1.10 (t)
10[c]	8.87 (s)	7.90 (dd)	—	—	7.53 (dd)	4.20 (q)	1.03 (t)
11	9.00 (s)	7.83 (m)	—	—	—	4.23 (q)	1.07 (t)
12[d]	9.43 (s)	8.43 (d)	—	—	8.40 (d)	—	—
13[e]	8.97 (s)	8.30 (dd)	—	—	7.83 (dd)	—	—

a)90 MHz, CF_3COOH. b) $J_{H5,F}$=9Hz, $J_{H8,F}$=6Hz. c) $J_{H5,F6}$=9Hz, $J_{H5,F7}$=6Hz, $J_{H8,F6}$=6Hz, $J_{H8,F7}$=9Hz. d) $J_{H5,F}$=6Hz, $J_{H8,F}$=3Hz. e) $J_{H5,F6}$=9Hz, $J_{H5,F7}$=6Hz, $J_{H8,F6}$=6Hz, $J_{H8,F7}$=9Hz.

References

1. a) Katritzky, A. R.; Karelson, M.; Harris, P.A. *Heterocycles* **1991**, *32*, 329.
   b) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic Press: New York. 1976; p. 91.
2. a) Tucker, G.; Logan, J. *J.Chem.Soc.***1951**, 1923.
   b) Frank, J.; Katritzky, A.R. *J.Chem.Soc.Perkin Trans. II* **1976**, 1428.
3. a) Katritzky, A. R.; Ellison, J.; Frank, J.; Meszaros, Z. *J. Royal Nether.Chem. Soc.* **1981**, *100*, 30.
   b) Kay, I. T.; Taylor, P.J. *J. Chem. Soc. (c)* **1968**, 2656.
   c) Hearn, J.M.; Morton, R.A.; Simpson, J.C.E. *J.Chem.Soc.* **1951**, 3318.
4. Baldwin, M. A.; Langley, G.J. *J. Chem. Soc. Perkin Trans II* **1988**, 347.
5. Pfister-Guillouzo, G.; Guimon, C.; Frank, J.; Ellison, J.; Katritzky, A.R. *Liebigs Ann. Chem.* **1981**, 366.
6. Maquestiau, A.; Van Haverbeke, Y.; Flammang, R.; Mispreuve, H.; Katritzky, A. R.; Ellison, J.; Frank, J.; Meszaros, Z. *J. Chem. Soc. Chem.Commun.* **1979**, 888.
7. Fabian, W. M. F. *J. Comp. Chem.* **1991**, *12*, 17.
8. Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. *J. Med. Chem.* **1980**, *23*, 1358.
9. a)Jpn. Kokai Tokkyo Koho 79 14 978, **1979.**
   b)Irikura, T.; Koga, H.; Murayama, S. Fr. Demande 2 463 771, **1981.**
   c)Kaminsky, D. Fr. Demande 2 002 888, **1969**.
10. Katritzky, A.R.; Ellison, J.; Frank, J.; Rakoczy, P.; Radics, L.; Gacs-Baitz, E. *Org.Magn.Reson.* **1981**, *16*, 280.
11. De la Cruz, A.; Elguero, J.; Gotor, V.; Goya, P.; Martinez, A.; Moris, F. *J.Chem.Res. (S)* **1992**, in press.

12. Allen, F.H.; Bellard, S.A.; Brice, M.D.; Cartwright, B.A.; Doudag, A.; Higgs, H.; Hummelink, T.; Hummelink, P.T.G.; Kennard, O.; Motherwell, W.D.S.; Rodgers, J.R.; Watson, D.G. *Acta Cryst.* **1979**, *B35*, 2331.
13. Viossat, B.; Guyen-Huy, N.; Lancelot, J.C.; Benazeth, S.; Rault, S.; Robba, M. *Chem.Pharm.Bull.* **1987**, *35*, 1724.
14. Carte, B.K.; DeBrosse, C.; Eggleston, D.; Hemling, M.; Mentzer, M.; Poehland, B.; Troupe, N.; Westley, J.W. *Tetrahedron* **1990**, *46*, 2747.
15. Bouvy, A.; Janousek, Z.; Viehe, H.G.; Arietta, J.M. *Bull.Soc.Chim.Belg.* **1985**, *94*, 269.
16. Huang, S.; Lin, Y.; Long, K.; Yao, J.; Qian, J.; Fan, H. *J.Struct.Chem.* **1986**, *5*,1.
17. Kapadia, G.J.; Paul, B.D.; Silverton, J.V.; Fales, H.M.; Sokoloski, E.A. *J.Am.Chem.Soc.* **1975**, *97*, 6814.
18. Kwialtowski, J. S.; Zielinski, T. J.; Rein, R. *Adv. Quantum Chem.* **1986**, *18*, 85.
19. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J.J.P. *J. Am.Chem. Soc.* **1985**, *107*, 3902.
20. Katritzky, A.R.; Karelson, M. *J. Am. Chem. Soc.* **1991**, *113*, 1561.
21. Stewart, J.J.P. *J. Comp. Chem.* **1989**, *10*, 221.
22. Chandra, V.; Kollman, P. *QCPE Bull.* **1982**, *2*,117. QCPE program no. 446.
23. Dewar, M.J.S.; Stewart, J.J.P. *QCPE Bull.* **1986**, *6*, 24. QCPE program no. 506.
24. Stewart, J.J.P. *QCPE Bull.* **1989**, *9*, 10. QCPE program no. 455.
25. Chem-QM package. Chem-X molecular modelling program. Chemical Design Ltd., Oxford.
26. Fletcher, R.; Powell, M.J.D. *Comput. J.* **1963**, *6*, 163.
27. Khalil, M.; Woods, R.J.; Weaver, D.F.; Smith, V.H. *J.Comput.Chem.* **1991**, *12*, 584.
28. Karelson, M.M.; Katrizky, A.R.; Szafran, M.; Zerner, M.C. *J. Org. Chem.* **1989**, *54*, 6030.
29. Albert, A.; Serjeant, E.P. *UV Determination of Ionization Constants*; Chapman and Hall; London. 1971; p.171.
30. Riegel, B.; Lappin, G.R.; Adelson, B.H.; Jackson, R.I.; Albisetti, C.J.; Dodson, R.M.; Baker, R.H. *J.Am.Chem.Soc.* **1946**, *68*, 1264.