Pergamon

Tetrahedron, Vol. 52, No. 36, pp. 11929-11946, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00690-4

Determination of the pK_a Values for Polycationic Species Derived from 9-Hydroxy and 9-Aminothiazolo[5,4-*b*]quinolines. A Problem related to the Tautomerism of these Systems

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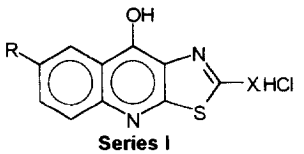
Abstract: Protonation constants of polycationic species derived from the tricyclic system thiazolo[5,4-*b*]quinoline-compounds **1-5 (a-c)**, **6 (a,b)**, and **7a** have been determined with a limit of error of ±0.5 pK_a units, by differential pulse polarography (DPP). The assignment of these values to the charged centres in each one of the species in equilibrium was possible from the calculated values for the enthalpies of the different species in solution, by using the force field MMP2 integrated in the software package PCMODEL. A plot of the calculated enthalpies *versus* the observed pKa for the compounds belonging to each one of the series, shows a good linear correlation which demonstrates the goodness of the assignment. The IR, ^{13}C, and ^{15}N NMR spectra for these compounds demonstrate their existence in the hydroxy form, this being a not very general modification in systems related to 4-quinolones and that, without doubt, is set by the presence of the fused thiazole ring.

INTRODUCTION

In the scope of a program directed to the synthesis of systems structurally related with proflavin, 9-aminoacridine, quinacrine and amsacrine, whose ability as double helix DNA intercalators[1] is well known,[2] the derived forms of the thiazolo[5,4-*b*]quinoline system from the series I, II, and III, compounds **1-3 (a, b, c)**, **4-5 (a, b, c)**, and **6 (a, b)-7a**, respectively, were obtained[3] (Scheme 1).

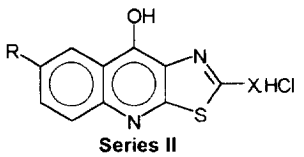
The presence of the 2-X-substituted thiazole ring in one of the extremes of the chromophore (Series I) modifies largely the chemico-physical properties of these systems related to the derived forms of acridine, while it allows the easy introduction of a side chain at the 2-position of the tricyclic system (series II). Specifically, the ethylene chain acts as a short spacing key among the chromophore and a basic centre which could be protonated at the physiological pH.[4-8] So that, the intercalation between the base pairs of double helix DNA

could be co-operatively linked to the interaction of the cationic centre with the phosphates on the external side of the receptor.[7] Identical philosophy has lead us to prove the incorporation of an analogous spacing key of *N,N*-dialkylaminoalkylidenamino at the 9-position of the tricyclic system (Series III), for which the presence of the hydroxyl group in the Series I predecessors (compounds **1a** and **1b**) is not a prerequisite for the synthesis.[3]



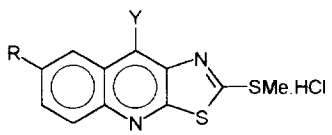
Series I

Compound	**1a**	**1b**	**1c**	**2a**	**2b**	**2c**	**3a**	**3b**	**3c**
R	H	Me	F	H	Me	F	H	Me	F
X	SMe	SMe	SMe	Cl	Cl	Cl	SO_2Me	SO_2Me	SO_2Me



Series II

Compound	**4a**	**4b**	**4c**	**5a, 5b, 5c**
R	H	Me	F	H, Me, F
X	$NH(CH_2)_2NEt_2$	$NH(CH_2)_2NEt_2$	$NH(CH_2)_2NEt_2$	N N–Me



Series III

Compound	**6a**	**6b**	**7a**
R	H	Me	H
Y	$NH(CH_2)_3NEt_2$	$NH(CH_2)_3NEt_2$	$NMe(CH_2)_3NMe_2$

Scheme I

In order to have a chemico-physical characterization previous to the biological assays, the experimental study of the pK_a of these compounds, using DPP, was undertaken.[9,13]

DPP technique was chosen instead of the spectrophotometric methods due to the own structural complexity of the chromophores which does not allow a clear assignment of the absorbances, due to the species which take part in every acid-base equilibria.[14]

DPP allows the obtention of polarograms (current-potential plots at the dropping mercury electrode) when a pulse train of constant amplitude is superimposed to a steadily varying with the time potential program, in the buffer solution containing the sample (Figure 1). A plot of the influence of pH on the peak potentials obtained, gives various linear regions whose intersection points can be associated to the pK_a value of each one of the chromophore electroactive centres.

This technique has been applied in the 0.5-12 pH range, which has allowed the determination of pK_a values for the compounds belonging to the series I and III (three pK_a) and II (four pK_a). In the case of compounds **1-5**, these values can be due to the existence in solution of two tautomeric forms for each compound. Obviously, compounds **6a-b**, and, unequivocally, compound **7a**, do not present this duality and, for a correct assignment of the centres responsible for the pK_a values, an evaluation of the relative stabilities of the species involved in the different acid-base equilibria should allow to find a linear correlation between both descriptors. The theoretical study of these equilibria has been carried out by the energetic minimization of the established structures by using the mechanical molecular force field MMP2,[15] updated for the treatment of conjugated π systems[16] and integrated in the software package PCMODEL.[17]

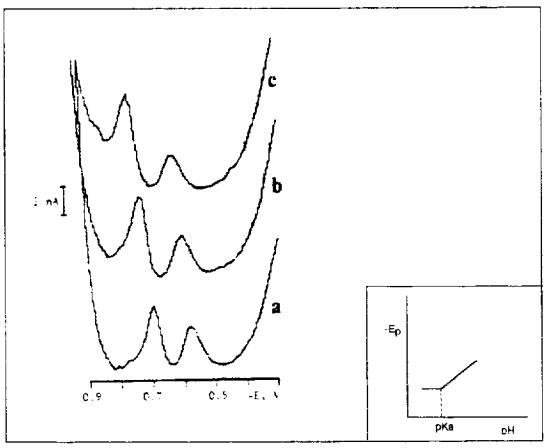


Figure 1. Polarograms on DME by means of DPP. Compound **1c**; concentration 6.0 10^{-6} mol.L^{-1}; buffer : Britton-Robinson 0.1 mol.L^{-1}; MeOH 6%; a) pH 2.0; b) pH 2.5; c) pH 3.0; V, 10 mV.s^{-1}; t_g 0.5 s.

Similarly, for the compounds belonging to the series I and II, the hypothesis of a participation of hydroxy or oxo forms in solution could be proved for a tentative assignment of the active centres responsible for the pK_a values. The theoretical calculation of the relative stabilities of the involved species under the basis of one and another structural hypothesis, should define the correlative analysis of the observed pK_a. The absence of a good linear correlation could then be originated either by an erroneous assignment of the pK_a values to active centres defined in an structure or because the structural hypothesis on the nature of the responsible tautomeric form was false.

In all the studied cases, the elaboration of the results has showed the coherence of all the data with a supposed hydroxy form in solution. This conclusion is in agreement with the NMR data for these compounds (hydrochlorides) in a solution of deuterochloroform or methanol-d_4 which support the same hypothesis.

RESULTS AND DISCUSSION

pK_a Values.

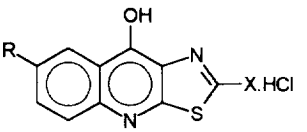
Series I

The obtained pK_a values for the compounds of this series are summarized in Table 1, and they have been tentatively assigned to the acid-base equilibria shown in Figure 2.

In order to establish the acid-base equilibria which occur in solution, we have compared the series of values of the observed pK_a with models found in the literature.[18] This shows that the thiazole nitrogen is less basic than the pyridine one. Nevertheless, and as these models could not be completely related to our compounds, if we consider the interaction between both rings in the studied molecules, the difference in energy among the species B (pyridine nitrogen protonated) and the equally hypothetical species B' with the thiazole nitrogen, instead of the pyridine nitrogen, protonated, has been calculated with the MMP2 force field. The

determined energies for the monoprotonated type B species are much lower, 20-30 kcal/mol, than those for the species B'. It is for this reason that the B species could be responsible for the noted pK_{a1} and pK_{a2} values.

Table 1. Observed pKa values for the 9-hydroxythiazolo[5,4-*b*]quinolines **1-3 (a, b, c)**.



Compound	R	X	pK_{a1}	pK_{a2}	pK_{a3}
1a	H	SMe	0.9	5.9	9.2
1b	Me	SMe	0.8	4.6	9.9
1c	F	SMe	a	5.7	10.5
2a	H	Cl	a	5.9	9.5
2b	Me	Cl	1.0	5.0	11.0
2c	F	Cl	a	4.9	11.2
3a	H	SO_2Me	a	5.2	7.6
3b	Me	SO_2Me	1.5	4.0	8.1
3c	F	SO_2Me	a	5.5	6.5

[a]Lower than 0.5.

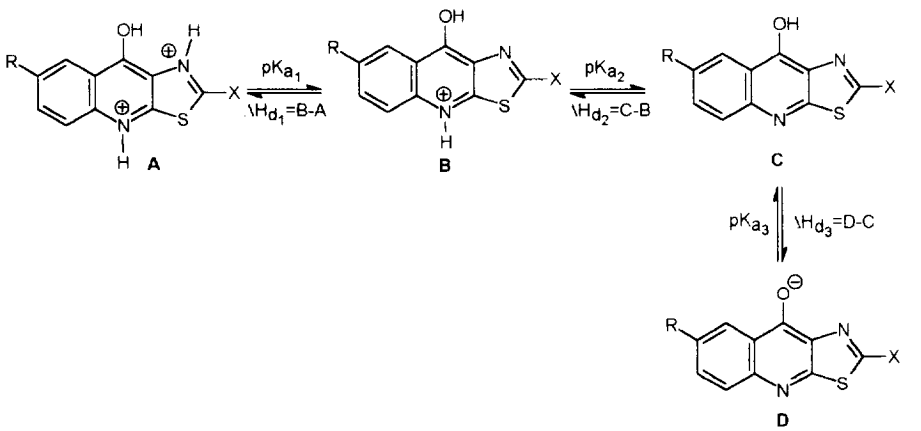


Figure 2. Proposed acid-base equilibria for compounds **1-3 (a, b, c)** of Series I.

Table 2 shows the relative stabilities of the participant species using two types of alternative combinations (hydroxy or oxo forms) for the reasons advanced earlier.

The $\Delta H_{di}/pK_{ai}$ linear regression analysis, on the basis of the pK_a assignment referred in Table 1 and the ΔH_{di} values calculated for the hydroxy forms of the group of considered compounds (Table 2), gives an

acceptable linear correlation (r=0.952), the equation of the line being ΔH_d=(7.2 ± 0.5)·pK_a - (36 ± 3). It does not occur the same when the pK_a values are confronted with the ΔH_{di} values calculated for the forms (Table 2) (r = 0.655; ΔH_d = (-1.3 ± 0.3)·pKa + (2 ± 2).

Table 2. Relative stabilities (ΔH_{di}, kcal/mol) calculated by using the force field MMP2 for the hydroxy and oxo forms of compounds **1-3 (a-c).**

			ΔH_{d1} [a]		ΔH_{d2} [b]		ΔH_{d3} [c]	
Compound	**R**	**X**	**OH**	**CO**	**OH**	**CO**	**OH**	**CO**
1a	H	SMe	-36.5	-6.2	4.2	0.0	27.2	-11.9
1b	Me	SMe	-36.6	-4.8	3.9	-0.2	27.0	-12.3
1c	F	SMe	-36.5	-0.1	6.8	0.1	24.8	-12.6
2a	H	Cl	-38.1	-8.6	5.6	4.0	40.6	-16.3
2b	Me	Cl	-38.4	-7.0	5.3	3.7	41.0	-16.7
2c	F	Cl	-38.1	-7.6	8.2	4.0	38.0	-16.9
3a	H	SO_2Me	-30.6	-1.2	1.6	-3.1	28.4	-9.4
3b	Me	SO_2Me	-30.9	0.2	0.7	-3.4	29.0	-9.8
3c	F	SO_2Me	-30.9	-1.2	4.4	-3.0	26.1	-10.0

[a]ΔH_{d1}=B-A; [b]ΔH_{d2}=C-B; [c]ΔH_{d3}=D-C (see Table 1).

Series II.

The obtained pK_a values for the compounds belonging to this series are shown in Table 3, and they have tentatively assigned to the acid-base equilibria depicted in Figure 3.

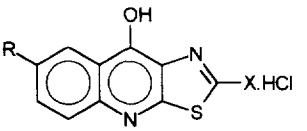
The nature of the species B, C, and D should correspond to the proposed structures (Figure 3) taking into account the pKa values found in the literature for model compounds.[18,19]

The relative stabilities of the species A-F and the corresponding oxo tautomers have been calculated by using the mechanical molecular force field MMP2,[15-17] and they are summarized in the Table 4.

The ΔH_{di}/pK_a linear regression analysis, taking as ΔH_{di} the calculated values for the hydroxy forms, gives a satisfactory correlation coefficient (r=0.930) for the line ΔH_{di} = (6.7 ± 0.6)·pK_a - (53 ± 5), while the linear correlation for the oxo forms is not acceptable (r=0.790; line: ΔH_{di} = (4.2 ± 0.7)·pK_a - (42 ± 5)).

Once again, the pKa assignment to the electroactive centres which are present in the species in equilibria is in accordance with the existence of hydroxy tautomers in solution.

Table 3. Observed pKa values for the 9-hydroxythiazolo[5,4-*b*]quinolines **4-5 (a, b, c)**.



Compound	R	X	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}	pK_{a5}
4a	H	$NH(CH_2)_2NEt_2$	---[a]	4.7	---[b]	9.3	---[b]
4b	Me	$NH(CH_2)_2NEt_2$	---[a]	4.7	---[b]	8.4	10.5
4c	F	$NH(CH_2)_2NEt_2$	---[a]	5.0	---[b]	8.3	10.3
5a	H	—N N—Me	---[a]	3.2	---[b]	8.6	11.0
5b	Me	—N N—Me	---[a]	5.0	---[b]	10.0	11.0
5c	F	—N N—Me	1.7	4.4	---[b]	8.0	10.0

[a]Lower than 0.5. [b]These pK_a can not be evaluated because a positive change of slope in the curve -Ep/pH was unobserved.

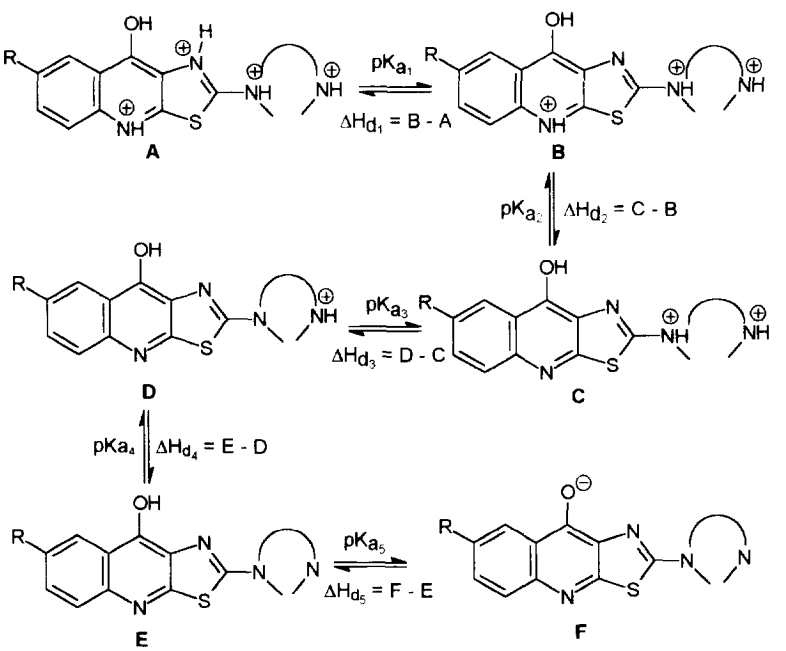
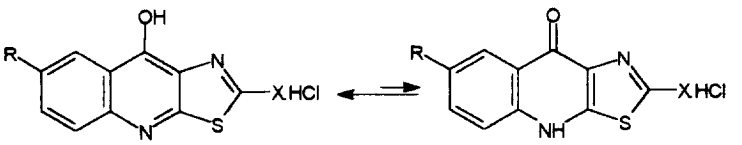
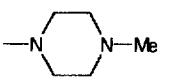
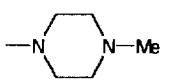
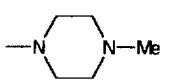


Figure 3. Proposed acid-base equilibria for compounds **4-5 (a, b, c)** of series II

Table 4. Relative stabilities (ΔH_{di}, kcal/mol) calculated by using the force field MMP2 for the hydroxy and oxo forms of compounds **4-5 (a-c).**



Comp.	R	X	ΔH_{d1}[a]		ΔH_{d2}[b]		ΔH_{d3}[c]		ΔH_{d4}[d]		ΔH_{d5}[e]	
			OH	**CO**	**OH**	**CO**	**OH**	**CO**	**OH**	**CO**	**OH**	**CO**
4a	H	$NH(CH_2)_2NEt_2$	-74.4	-52.8	-15.7	-22.8	2.1	-10.6	-1.0	-0.1	29.2	5.3
4b	Me	$NH(CH_2)_2NEt_2$	-73.3	-54.2	-17.2	-18.7	2.5	-10.7	-2.5	0.2	32.2	4.5
4c	F	$NH(CH_2)_2NEt_2$	-74.6	-51.9	-16.2	-21.9	2.5	-11.5	-0.7	0.1	29.3	4.6
5a	H		-53.3	-39.8	-23.0	-34.2	-3.2	-1.8	1.7	2.1	16.1	-8.6
5b	Me		-52.7	-38.6	-23.0	-34.2	-2.6	-0.4	1.4	3.9	17.0	-11.5
5c	F		-52.7	-38.5	-24.1	-34.3	-3.4	-2.3	1.1	2.1	15.5	-9.7

[a]ΔH_{d1}=B-A; [b]ΔH_{d2}=C-B; [c]ΔH_{d3}=D-C; [d]ΔH_{d4}=E-D; [e]ΔH_{d5}=F-E (see Table 1).

Series III

The obtained pK_a values for the compounds belonging to this series are shown in Table 5, and they have been tentatively assigned to the acid-base equilibria among the species **A-E** depicted in Figure 4. In the case of **7a**, only four constants should be apparent taking into account its structure.

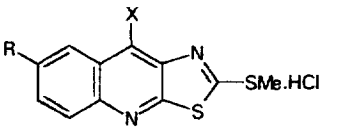
On the analogy with the data included in Table 3, the assignment of pK_a to the equilibria shown in Figure 4 has been tentatively carried out.

The relative stabilities of the species A-F were calculated, as in the former cases, using the mechanical force field MMP2.[15-17] The obtained results are summarized in Table 6. The correlation coefficient for the $\Delta H_{di}/pK_a$ linear regression, taking as ΔH_{di} the calculated values for the hydroxy tautomers, is very satisfactory ($r=0.990$) for a line $\Delta H_{di} = (6.8 \pm 0.4) \cdot pK_a - (46 \pm 2)$.

It is well established in the literature that the effect of the substituents over the acidity occurs in the same way in gaseous phase than in aqueous solution.[20] The employed method to evaluate the relative energies for the different species involved in the acid-base equilibria does not take into account the intermolecular Coulomb forces. This, at the concentrations at which the pK_a were measured and in aqueous medium, where the

solvating effects can minimize this kind of interactions, could not be important for the correct evaluation of the enthalpies of the species in solution. The same cannot be said for the mixture entropy, and the mentioned solvating effects must be different when going from series I to series II and III, which have alkyl chains with polar extremes. According to this, the overall obtained results stands properly for the second law of thermodynamics ($\Delta H = -RT \cdot \ln K_a + T\Delta S$), the Coulomb factors being responsible for the observed differences among the ideal and real parameters of these solutions.

Table 5. Observed pK_a values for the 9-[N,N-dialkylaminoalkylideneamino]thiazolo[5,4-*b*]-quinolines **6a**, **6b**, and **7a**.



Comp.	R	X	pK_{a1} [a]	pK_{a2} [b]	pK_{a3} [c]	pK_{a4} [d]	pK_{a5} [e]
6a	H	$-NH(CH_2)_3NEt_2$	1.0	5.9	---[f]	7.5	>12
6b	Me	$-NH(CH_2)_3NEt_2$	1.0	5.3	---[f]	7.9	>12
7a	H	$-NMe(CH_2)_3NMe_2$	0.9	4.1	---[f]	6.5	[g]

[a]ΔH_{d1}=B-A; [b]ΔH_{d2}=C-B; [c]ΔH_{d3}=D-C; [d]ΔH_{d4}=E-D; [e]ΔH_{d5}=F-E; [f]These pK_a have been unobserved because a net and positive change of the slope value in the -Ep/pH curve has been not noted within the pH ranges used. [g]This compound should have only four pK_a.

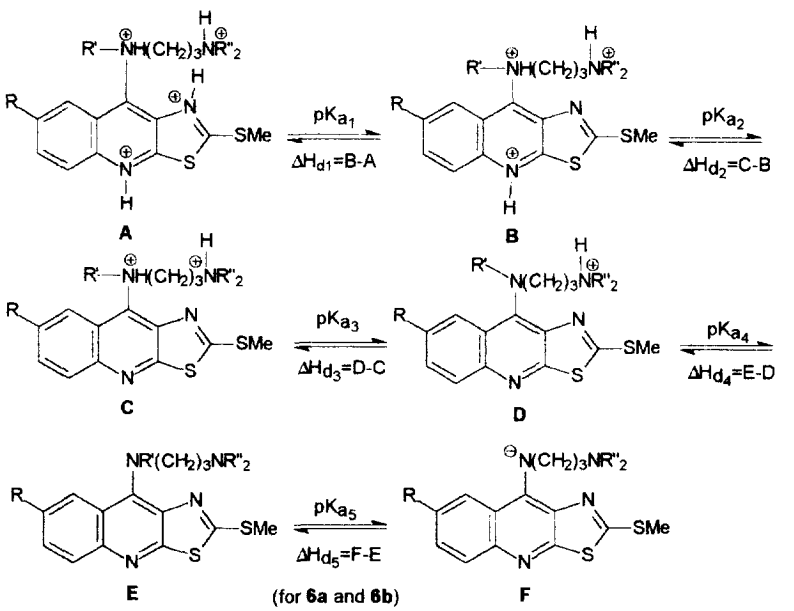
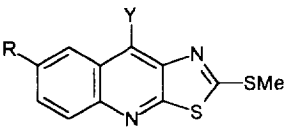


Figure 4. Proposed acid-base equilibria for compounds **6a** (R' = H, R" = Et), **6b** (R' = H, R" = Et), and **7a** (R' = R" = Me) of series III

Table 6. Relative stabilities (ΔH_{di}, kcal/mol) calculated by using the force field MMP2 for the compounds **6a**, **6b**, and **7a**..



Compound	R	Y	ΔH_{d1} [a]	ΔH_{d2} [b]	ΔH_{d3} [c]	ΔH_{d4} [d]	ΔH_{d5} [e]
6a	H	$-NH(CH_2)_3NEt_2$	-42.0	-8.9	-10.7	5.0	-2.2
6b	Me	$-NH(CH_2)_3NEt_2$	-40.2	-7.1	-11.3	5.6	-2.8
7a	H	$-NMe(CH_2)_3NMe_2$	-39.1	-12.4	-1.9	-0.9	---

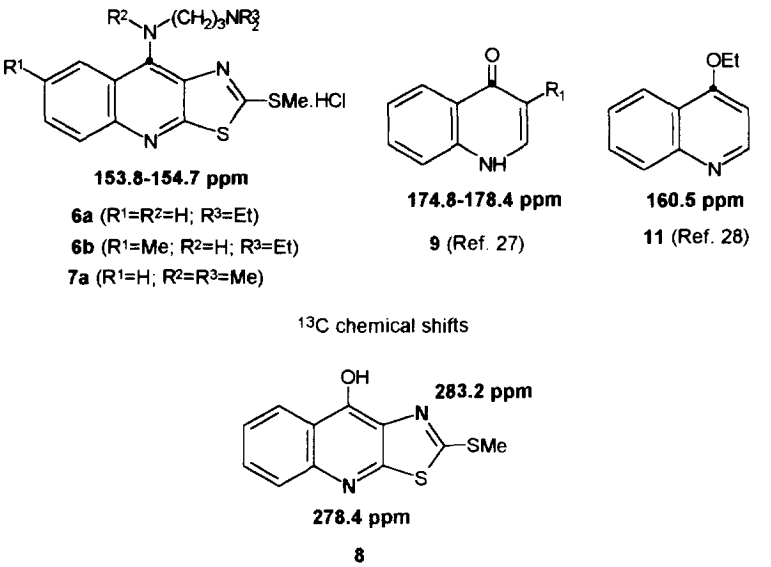
[a]ΔH_{d1}=B-A; [b]ΔH_{d2}=C-B; [c]ΔH_{d3}=D-C; [d]ΔH_{d4}=E-D; [e]ΔH_{d5}=F-E

Structural assignment.

All new compounds gave correct elemental analysis and their structures were unambiguously confirmed by IR, ^1H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra. Compounds **1-5** (**a-c**) are all present in the hydroxy form as evidenced from their IR spectra, observed ^{13}C NMR chemical shifts for the carbon C-9 (150.6-167.4 ppm), and the ^{15}N NMR spectrum of the 9-hydroxy-2-methylthiothiazolo[5,4-*b*]quinoline **8** which was the free base precursor of the hydrochloride **1a**.

For some time, it was generally agreed that the 2- and 4-pyridones, and 2- and 4-quinolones, exist in that form and not as the alternative 2- and 4-hydroxy isomers.[21] But this situation depends on the backbone structure, on the phase and the solvent in which the situation is investigated.[22] The presence or absence of the carbonyl group stretching frequency for 2- and 4-pyridones, and 2- and 4-quinolones, is an useful experimental criterion to study the hydroxy-oxo tautomerism of six-membered heterocycles containing one or more carbonyl groups in the ring.[23] The N-H and C=O stretching vibrations of lactams[24] give rise to bands in the same regions as those for secondary amides (1.680-1.630 cm^{-1} in solid state or 1.700-1.665 cm^{-1} in solution),[25] and an unsaturation results in an increase in the carbonyl stretching vibration frequency by about 15 cm^{-1}.[26] The absence of a strong absorption at 1.715-1650 cm^{-1} in the IR spectra of the studied compounds **1-5** (**a-c**) supports the predominance of the hydroxy tautomer in solution.

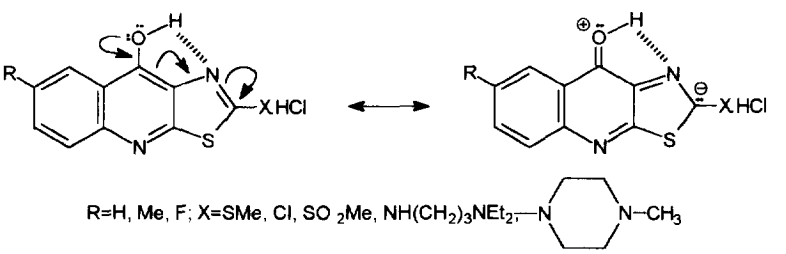
The observed ^{13}C chemical shifts for the carbon C-9 (150.6-167.4 ppm) in the compounds **1-5** (**a-c**) as well as in their precursor free bases (157.5-164.7 ppm)[3] are in agreement with a predominance in all cases of the hydroxy tautomer in solution. These values are clearly similar to the observed chemical shifts for the 9-aminothiazolo[5,4-*b*]quinoline hydrochlorides **6a**, **6b** and **7a** (153.8-154.7 ppm), and they are clearly different of the data reported for the oxo derivative **9** which presents a +15 ppm higher chemical shift than the corresponding ethoxy derivative 11 (Scheme 2).



Scheme 2

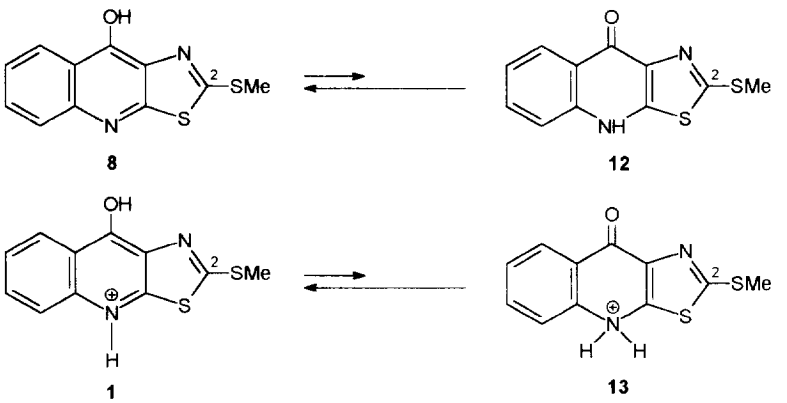
On the other hand, the ^{15}N NMR chemical shifts are of considerable value in studies of tautomerism of the type hydroxyquinoline-quinolone,[29] because large upfield shifts by *ca.* -150 ppm are found[30,31] when a compound exists in a tautomeric form with a hydrogen on a sp^3 nitrogen. The ^{15}N spectrum of the compound **8**[3,32] shows two singlets at 278.4 ppm and 283,2 ppm[33] which can be assigned to quinoline and thiazole nitrogens, respectively, by comparison with the ^{15}N chemical shifts reported for acridine (283.0 ppm)[34] and benzothiazole(319.3 ppm).[35] The observed ^{15}N chemical shifts for the compound **8** correspond unequivocally to two sp^2 nitrogen atoms because a sp^3 protonated nitrogen (NH form) should show a significant small ^{15}N chemical shift (by *ca.* -150 ppm).

The predominance of the hydroxy form in all studied compounds could be reasonably justified by an intramolecular hydrogen bonding between the OH group and the thiazole nitrogen, and by an stabilization of the hydroxy form by resonance (Scheme 3).



Scheme 3

In order to test this hypothesis, an energy optimization by the semiempirical method AM1[36] of the free bases and hydrochlorides in their hydroxy (**8, 12**) and oxo forms (**1, 13**) (R=H; X=SMe) was carried out (Scheme 4), and the atomic partial charges on atom C-2 were calculated by means of the algorithm RESCHA[37] for conjugated systems containing charged and backdonating atoms.[37c] This procedure is reported as an empirical method and gives more satisfactory results than *ab initio* methods[38] and semiempirical procedures.[36] The results of these calculations have been summarized in the Table 7.



Scheme 4

Table 7. Relative stabilities, $\Delta\Delta H_f$(kcal/mol), and atomic partial charges at atom C-2, Q_{C-2}, calculated by the semiempirical AM1 method and the algorithm RESCHA, respectively, for the compounds **1**, **8**, **12** and **13**.

Compound	$\Delta\Delta H_f$ (kcal/mol)[a]	Q_{C-2}
8	0	0.074
12	3.4	0.094
1	0	0.074
13	39.9	0.223

[a]Calculated for each pair oxo-hydroxy forms as the difference between the corresponding enthalpies of formation.

In all cases, the calculated enthalpies of formation for the oxo forms were higher than the calculated ones for the hydroxy tautomers. Thus, the thermodynamic equilibrium would favour the hydroxy forms. On the other hand, the calculated atomic partial charges at atom C-2 were significantly lower for the hydroxy forms than for the oxo tautomers, according to the hypothesis of a conjugative donating effect +K of the hydroxy group on carbon atom C-2 which would favour the hydroxy forms by resonance (Scheme 3).

Conclusions. We present here the assignment of the observed pK_a to acid-base pairs in equilibrium by means of a linear regression, in related structural series, of the relative stabilities of the implied species with the

observed pK_a. In all cases, the acid-base equilibria stablished for hydroxy forms were better than the corresponding equilibria for carbonyl tautomers. The structural assignment was unambiguously determined from their IR, ^1H, ^{13}C and ^{15}N NMR data showing only the hydroxy tautomers to be present in solution as predominant forms.

EXPERIMENTAL SECTION

Apparatus

A Metrohm E 626 Polarecord equipped with a Metrohm 663 VA stand was used for the DPP measurements, and a Metrohm E 510 pH-meter was also used.

Electrodes and electrochemical cell

The electrochemical cell consisted of a multimode Metrohm 6.1246.020 Hg electrode equipped with a Metrohm 6.1226.030 capillary tube and operated in the DME mode, a Metrohm 6.0728.000 Ag/AgCl/3 $mol.L^{-1}$ KCl reference electrode, and a Metrohm 6.1247.000 auxiliary glassy carbon electrode, in a Metrohm 6.1415.0210 vessel.

A Metrohm AG-9100 combined electrode was used for pH measurements.

Reagents and solutions. Procedure.

DP polarograms were recorded in $6.0x10^{-6}$ $mol.L^{-1}$solutions of each compound in a Britton-Robinson buffer solution containing each component acid at 0.1 $mol.L^{-1}$ (supporting electrolyte) and with a 6% content in methanol. The prepared solutions (25 mL) were transferred into the electrochemical cell and deareated by passing an argon stream through them for 15 min. Polarograms were recorded at 25 ± 1 °C keeping an inert atmosphere in the cell, with ΔE = -50 mV, v = 10 $mV.s^{-1}$, and td = 0.5 s.

All starting thiazolo[5,4-*b*]quinolines as free bases were prepared according to the previously described procedure.[3] IR spectra were recorded as KBr solid pellets or as $CHCl_3$ solutions in 0.1 mm NaCl cells with compensation. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75.5 MHz, respectively, in $CDCl_3$ or CD_3OD solutions with TMS as internal reference. Full assignment of ^{13}C NMR signals were carried out with the aid of 2D heteronuclear ^1H-^{13}C correlations.

Preparation of thiazolo[5,4-*b*]quinoline hydrochlorides from free bases. General Procedure. A stream of gaseous dry hydrogen chloride was passed trough a solution of the free base (0.752 mmol) in anhydrous benzene (5 mL) until the precipitation of a white solid was finished. The crude solid was separated by filtration, dried under vacuum at room temperature for 12 h., and purified, when it was necessary, by recrystallization or preparative TLC chromatography.

9-Hydroxy-2-methylthiothiazolo[5,4-*b*]quinoline hydrochloride, 1a. White solid (100%). Mp 163-5. IR ($CHCl_3$) ν 3660, 3400, 2400, 1620, 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.96 (3H, s), 7.91 (1H, ddd, ^3J = 8.4, 6.9, ^4J = 1.5 Hz), 8.04 (1H, ddd, ^3J = 8.7, 6.9, ^4J = 1.2 Hz), 8.54 (1H, ddd, ^3J = 8.7, ^4J = 1.5, ^5J = 0.6 Hz), 8.56

(1H, ddd, ^3J = 8.4, ^4J = 1.2, ^5J = 0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 116.1, 122.8, 124.9, 125.4, 129.0, 133.1, 138.6, 141.4, 144.8, 155.4, 171.6. Anal. Calcd. for $C_{11}H_6N_2S_2OCl$: C, 46.39; H, 3.19; N, 9.84. Found: C, 46.48; H, 3.16; N, 9.75.

9-Hydroxy-7-methyl-2-methylthiothiazolo[5,4-*b*]quinoline hydrochloride, 1b. White solid (100%). Mp 173-4. IR ($CHCl_3$) ν 3680, 3400, 2400, 1610, 1580, 1510 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.70 (3H, s), 2.96 (3H, s), 7.87 (1H, dd, ^3J = 8.7, ^4J = 1.5 Hz), 8.28 (1H, bs), 8.46 (1H, d, ^3J = 8.7 Hz), 9.50 (1H, bs). ^{13}C NMR ($CDCl_3$) δ 15.2, 22.0, 123.2, 124.0, 125.1, 136.3, 139.1, 139.4, 140.1, 153.6, 158.3, 171.5. 2D Correlation ^1H-^{13}C ($CDCl_3$) δ 7.87-136.3; 8.28-124.0, 8.46-123.2. Anal. Calcd for $C_{12}H_{11}N_2S_2OCl$: C, 48.24; H, 3.71; N, 9.38. Found: C, 48.53; H, 3.76; N, 9.25.

7-Fluoro-9-hydroxy-2-methylthiothiazolo[5,4-*b*]quinoline hydrochloride, 1c. White solid (100%). Mp 175-7. IR ($CHCl_3$) ν 3680, 3300, 2400, 1630, 1560, 1520 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.89 (3H, s), 7.52 (1H, ddd, ^3J = 9.3, 8.5, ^4J = 2.8 Hz), 7.94 (1H, dd, ^3J = 9.7, ^4J = 2.8 Hz), 8.06 (1H, dd, ^3J = 8.5, ^4J = 5.4 Hz) ^{13}C NMR ($CDCl_3$) δ 15.3, 108.0, 119.9, 125.8, 131.0, 142.3, 143.0, 155.6, 160.7, 172.8. Anal. Cald. for $C_{11}H_8N_2S_2OFCl$: C, 43.64, H, 2.66; N, 9.25. Found: C, 43.50; H, 2.46; N, 9.44.

2-Chloro-9-hydroxythiazolo[5,4-*b*]quinoline hydrochloride, 2a. This compound was purified by a preparative tlc (hexane:ethyl acetate: 70/30, v/v). White solid (96%). Mp 151-3. IR ($CHCl_3$) ν 3680, 3400, 2400, 1590, 1550 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.70 (1H, ddd, ^3J = 8.4, 6.9, ^4J = 1.2 Hz), 7.83 (1H, ddd, ^3J = 8.7, 6.9, ^4J = 1.5 Hz), 8.10 (1H, ddd, ^3J = 8.7, ^4J = 1.2, ^5J = 0.6 Hz), 8.38 (1H, ddd, ^3J = 8.4, ^4J = 1.5, ^5J = 0.6 Hz), 8.91 (1H, bs). ^{13}C NMR ($CDCl_3$) δ 124.8, 125.1, 127.4, 128.8, 130.7, 134.2, 140.4, 147.2, 156.5, 159.6. Anal. Calcd. for $C_{10}H_5N_2SOCl_2$: C, 43.97; H, 2.21; N, 10.26. Found: C, 43.58; H, 2.00; N, 9.97.

2-Chloro-9-hydroxy-7-methylthiazolo[5,4-*b*]quinoline hydrochloride, 2b. This compound was purified by preparative tlc (hexane/ethyl acetate: 85/15, v/v). White solid (97%). Mp 193-4. IR ($CHCl_3$) ν 3680, 3400, 2400, 1590, 1550 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.67 (3H, s), 6.53 (1H, bs), 7.78 (1H, dd, ^3J = 8.7, ^4J = 1.2 Hz), 8.18 (1H, d, ^3J = 8.7 Hz), 8.23 (1H, bs). ^{13}C NMR ($CDCl_3$) δ 22.0, 123.0, 124.0, 125.1, 136.4, 138.9, 139.6, 140.2, 142.1, 153.4, 158.4. Anal. Calcd. for $C_{11}H_7N_2SOCl$: C, 46.01; H, 2.81, N, 9.76. Found: C, 45.90; H, 3.01; N, 9.54.

2-Chloro-7-fluoro-9-hydroxythiazolo[5,4-*b*]quinoline hydrochloride, 2c. This compound was purified by preparative tlc (hexane/ethyl acetate: 85/15, v/v). White solid (97%). Mp 130-2. IR ($CHCl_3$) ν 3680, 3400, 2400, 1590, 1550 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.60 (1H, ddd, ^3J = 9.3, 7.7, ^4J = 2.8 Hz), 7.97 (1H, dd, ^3J = 9.6, ^4J = 2.8 Hz), 8.10 (1H, dd, ^3J = 9.3, ^4J = 5.2 Hz). ^{13}C NMR ($CDCl_3$) δ 108.3, 121.4, 126.0, 131.4, 133.2, 140.7, 144.1, 158.7, 160.9. Anal Calcd. for $C_{10}H_4N_2SOFCl_2$: C, 41.26; H, 1.73, N, 9.62. Found: C, 41.73; H, 1.62; N, 9.89.

9-Hydroxy-2-methylsulfonylthiazolo[5,4-*b*]quinoline hydrochloride, 3a. White solid (100%). Mp 204-5. IR (KBr) ν 3300, 2400, 1630, 1610, 1580 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.34 (3H, s), 7.73 (1H, ddd, ^3J = 8.7, 6.9, ^4J = 1.0 Hz), 7.77 (1H, ddd, ^3J = 8.4, 6.9, ^4J = 1.0 Hz), 8.13 (1H, ddd, ^3J = 8.4, ^4J = 1.0, ^5J = 0.6 Hz), 8.59 (1H, ddd, ^3J = 8.7, ^4J = 1.0, ^5J = 0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 41.5, 125.02, 125.03, 128.0, 128.3, 132.3, 139.3, 141.2, 147.9, 158.2, 169.6. Anal. Cald.for $C_{11}H_9N_2S_2O_3Cl$: C, 41.71; H, 2.86; N, 8.84. Found: C, 41.85; H, 2.89; N, 9.01.

9-Hydroxy-7-methyl-2-methylsulfonylthiazolo[5,4-*b*]quinoline hydrochloride, 3b. White solid (100%). Mp 193-4. IR (KBr) ν 3350, 2400, 1630, 1610, 1570, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.62 (3H, s), 3.33 (3H, s), 7.58 (1H, dd, ^3J = 8.4, ^4J = 1.5 Hz), 8.01 (1H, d, ^3J = 8.4 Hz), 8.34 (1H, bs). ^{13}C NMR ($CDCl_3$) δ 21.9, 41.6, 123.6, 124.9, 125.1, 126.9, 135.5, 139.0, 141.6, 145.3, 156.2, 158.9, 169.6. Anal. Calcd. for $C_{12}H_{11}N_2S_2O_3Cl$: C, 43.57; H, 3.35; N, 8.47. Found: C, 43.70; H, 3.40; N, 8.37.

7-Fluoro-9-hydroxy-2-methylsulfonylthiazolo[5,4-*b*]quinoline hydrochloride, 3c. White solid (100%). Mp 220-2. IR (KBr) ν 3300, 2400, 1630, 1590, 1550 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.53 (3H, s), 7.72 (1H, ddd, ^3J = 9.4, 9.3, ^4J = 2.8 Hz), 8.09 (1H, ddd, ^3J = 9.3, ^4J = 2.8, ^5J = 0.6 Hz), 8.24 (1H, ddd, ^3J = 9.4, ^4J = 5.2, ^5J = 0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 41.6, 108.4, 122.8, 123.0, 126.3, 131.9, 139.3, 141.7, 146.0, 158.3, 161.2, 170.6. Anal. Calcd. for $C_{11}H_8N_2S_2O_3FCl$: C, 39.47; H, 2.41; N, 8.37. Found: C, 39.80; H, 2.20; N, 8.59.

2-[2-(*N,N*-diethylamino)ethylamino]-9-hydroxythiazolo[5,4-*b*]quinoline hydrochloride, 4a. White solid (100%). Mp 214-5. IR ($CHCl_3$) ν 3360, 3320, 2400, 1605, 1550 cm^{-1}. ^1H NMR (CD_3OD) δ 1.43 (6H, t, ^3J = 7.2 Hz), 3.43 (2H, q, ^3J = 7.2 Hz), 3.45 (2H, q, ^3J = 7.2 Hz), 3.59 (2H, t, ^3J = 6.0 Hz), 4.04 (2H, t, ^3J = 6.0 Hz), 7.75 (1H, ddd, ^3J = 8.4, 6.9, ^4J = 1.2 Hz), 7.82 (1H, ddd, ^3J = 8.4, 6.9, ^4J = 1.5 Hz), 8.02 (1H, ddd, ^3J = 8.4, ^4J = 1.2, ^5J = 0.6 Hz), 8.31 (1H, ddd, ^3J = 8.4, ^4J = 1.5, ^5J = 0.6 Hz). ^{13}C NMR (CD_3OD) δ 9.3, 40.2, 49.0, 52.3, 125.2, 125.9, 126.5, 129.1, 129.7, 131.1, 142.6, 144.5, 158.2, 167.6. Anal. Calcd. for $C_{16}H_{21}N_4SOCl$: C, 54.46; H, 6.00; N, 15.88. Found: C, 54.60; H, 6.01; N, 15.83.

2-[2-(*N,N*-diethylamino)ethylamino]-9-hydroxy-7-methylthiazolo[5,4-*b*]quinoline hydrochloride, 4b. White solid (97%). Mp 226-7. IR ($CHCl_3$) ν 3360, 3320, 2620, 1605, 1550 cm^{-1}. ^1H NMR (CD_3OD) δ 1.03 (6H, t, ^3J = 7.2 Hz), 2.57 (3H, s), 2.58 (4H, q, ^3J = 7.2 Hz), 2.73 (2H, t, ^3J = 5.7 Hz), 3.54 (2H, t, ^3J = 5.7 Hz), 7.44 (1H, dd, ^3J = 8.7, ^4J = 1.5 Hz), 7.86 (1H, d, ^4J = 1.5 Hz), 7.87 (1H, d, ^3J = 8.7 Hz). ^{13}C NMR (CD_3OD) δ 9.3, 21.8, 40.1, 49.2, 52.1, 123.9, 125.5, 126.4, 129.2, 133.3, 139.9, 141.0, 144.5, 167.4, 168.7. Anal. Calcd. for $C_{17}H_{23}N_4SOCl$: C, 55.65; H, 6.32; N, 15.27. Found: C, 55.80; H, 6.18; N, 15.19.

2-[2-(*N,N*-diethylamino)ethylamino]-7-fluoro-9-hydroxythiazolo[5,4-*b*]quinoline hydrochloride, 4c. White solid (97%). Mp 214-6. IR (CH_3OH- ethyl acetate with compensation) ν 3360, 3320, 2480, 1630, 1550 cm^{-1}. ^1H NMR (CD_3OD) δ 1.42 (6H, t, ^3J = 7.3 Hz), 3.44 (4H, q, ^3J = 7.3 Hz), 3.58 (2H, t, ^3J = 6.3 Hz), 4.04 (2H, t, ^3J = 6.3 Hz), 7.56 (1H, ddd, ^3J = 9.2, 8.0 Hz, ^4J = 2.8 Hz), 7.85 (1H, ddd, ^3J = 9.9, ^4J = 2.8, ^5J = 0.6 Hz), 8.00 (1H, dd, ^3J = 8.0, ^4J = 5.1 Hz). ^{13}C NMR (CD_3OD) δ 9.3, 39.9, 49.2, 52.3, 108.5, 119.5, 126.2,

127.5, 131.0, 141.9, 144.0, 158.8, 162.3, 168.2. Anal. Calcd. for $C_{16}H_{20}N_4SOFCl$: C, 51.82; H, 5.44; N, 15.11. Found: C, 51.53; H, 5.57; N, 14.89.

9-Hydroxy-2-(4-methylpiperazine-1-yl)thiazolo[5,4-*b*]quinoline hydrochloride, 5a. White solid (100%). Mp > 300. IR (KBr) ν 3660, 3400, 2420, 1600, 1550 cm^{-1}. ^1H NMR ($CDCl_3$) d 3.12 (3H, s), 3.32 (4H, t, ^3J = 5.0 Hz), 3.80 (4H, t, ^3J = 5.0 Hz), 7.54-7.64 (2H, m), 7.99 (1H, dd, ^3J = 7.2, ^4J = 1.5 Hz), 8.24 (1H, dd, ^3J = 7.5, ^4J = 2.0 Hz). ^{13}C NMR ($CDCl_3$) δ 45.8, 47.3, 55.1, 125.9, 126.2, 126.6, 128.4, 129.0, 129.5, 143.3, 145.3, 158.5, 169.2. Anal. Calcd. for $C_{15}H_{17}N_4SOCl$: C, 53.49; H, 5.09; N, 16.63. Found: C, 53.65; H, 5.20; N, 6.55.

9-Hydroxy-7-methyl-2-(4-methylpiperazine-1-yl)thiazolo[5,4-*b*]quinoline hydrochloride, 5b. White solid (100%). Mp >300. IR (KBr) ν 3660, 3400, 2420, 1600, 1550, cm^{-1}. ^1H NMR (CDCl3) δ 2.37 (3H, s), 2.57 (s, 3H), 2.57 (4H, t, ^3J = 5.0 Hz), 3.80 (4H, t, ^3J = 5.0 Hz), 7.44 (1H, dd, ^3J = 9.0, ^4J = 2.1 Hz), 7.80 (1H, d, ^3J = 9.0 Hz), 8.00 (1H, d, ^4J = 1.8 Hz). ^{13}C NMR ($CDCl_3$) δ 22.2, 45.8, 46.8, 54.9, 125.9, 126.0, 128.7, 129.1, 131.3, 136.2, 143.4, 145.9, 157.3, 169.2. Anal. Calcd. for $C_{16}H_{19}N_4SOCl$: C, 54.77; H, 5.46; N, 15.97. Found: C, 54.63; H, 5.57; N, 15.78.

7-Fluoro-9-hydroxy-2-(4-methylpiperazine-1-yl)thiazolo[5,4-*b*]quinoline hydrochloride, 5c. White solid (100%). Mp >300. IR (KBr) ν 3660, 3400, 2420, 1605, 1545 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.01 (3H, s), 3.73 (4H, t, ^3J = 12.6 Hz), 3.78 (4H, t, ^3J = 12.6 Hz), 7.56 (1H, ddd, ^3J = 9.4, 8.1, ^4J = 2.8 Hz), 7.91 (1H, dd, ^3J = 9.9, ^4J = 2.8 Hz), 8.04 (1H, dd, ^3J = 9.4 Hz, ^4J = 5.2 Hz). ^{13}C NMR ($CDCl_3$) δ 38.3, 39.8, 47.6, 102.2, 113.5, 119.7, 120.1, 124.3, 134.7, 136.4, 150.6, 155.3, 162.3. Anal. Calcd. for $C_{15}H_{16}N_4SOFCl$: C, 50.78; H, 4.55; N, 15.79. Found: C, 50.96; H, 4.70; N, 15.70.

9-[3-(*N,N*-diethylamino)propylamino]-2-methylthiothiazolo[5,4-*b*]quinoline hydrochloride, 6a. White solid (100%). Mp >300. IR ($CHCl_3$) ν 3450, 3210, 2620, 1610, 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.34 (6H, t, ^3J = 7.2 Hz), 2.32 (2H, quintet, ^3J = 5.7 Hz), 2.88 (3H, s), 3.29 (4H, q, ^3J = 7.2 Hz), 3.33 (2H, t, ^3J = 7.5 Hz), 4.40 (1H, t, ^3J = 5.7 Hz), 7.65 (1H, dd, ^3J = 8.4, 7.5 Hz), 7.90 (1H, dd, ^3J = 8.1, 7.5 Hz), 7.78 (1H, d, ^3J = 8.1 Hz), 8.58 (1H, d, ^3J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 9.2, 16.5, 26.3, 44.1, 50.6, 79.5, 117.1, 120.6, 124.9, 127.1, 130.1, 134.5, 138.7, 148.6, 154.7, 163.5. Anal. Calcd. for $C_{18}H_{25}N_4S_2Cl$: C, 54.46; H, 6.35; N, 14.11. Found: C, 54.63; H, 6.12; N, 13.95.

9-[3-(*N,N*-diethylamino)propylamino]-7-methyl-2-methylthiothiazolo[5,4-*b*]quinoline hydrochloride, 6b. White solid (100%). Mp >300. IR ($CHCl_3$) ν 3350, 3210, 2620, 1590, 1560 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.35 (6H, t, ^3J = 7.2 Hz), 2.34 (2H, quintet., ^3J = 5.7 Hz), 2.57 (3H, s), 2.87 (3H, s), 3.02 (4H, q, ^3J = 7.2 Hz), 3.29 (4H, t, ^3J = 5.7 Hz), 7.66 (1H, d, ^3J = 8.4 Hz), 7.71 (1H, d, ^3J = 8.4 Hz), 8.37 (1H, br s). ^{13}C NMR ($CDCl_3$) δ 9.2, 16.6, 21.6, 26.4, 44.1, 50.9, 77.7, 116.9, 120.3, 123.9, 130.0, 136.3, 136.8, 137.9, 148.1, 153.8, 163.3. Anal. Calcd. for $C_{19}H_{27}N_4S_2Cl$: C, 55.52; H, 6.62; N, 13.63. Found: C, 55.70; H, 6.42; N, 13.55.

9-[*N*-Methyl-3-(*N'*,*N'*-dimethylamino)propylamino]-2-methylthiothiazolo[5,4-*b*]quinoline hydrochloride, 7a. White solid (100%). Mp >300. IR ($CHCl_3$) ν 2620, 1590, 1560 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.41 (2H, quint., ^3J = 7.5 Hz), 3.31 (6H, s), 2.89 (3H, s), 3.69 (2H, t, ^3J = 7.5 Hz), 3.76 (3H, s), 4.42 (2H, t, ^3J = 7.5 Hz), 7.66 (1H, ddd, ^3J = 8.4, 6.9, ^4J = 1.2 Hz), 7.89 (1H, ddd, ^3J = 8.4, 6.9, ^4J = 1.2 Hz), 7.91 (1H, dd, ^3J = 8.4, ^4J = 1.2 Hz), 8.48 (1H, dd, ^3J = 8.4, ^4J = 1.2 Hz). ^{13}C NMR ($CDCl_3$) δ 16.9, 22.8, 43.5, 46.1, 50.5, 54.7, 120.1, 126.2, 129.2, 129.6, 134.6, 136.2, 139.8, 153.5, 154.3, 164.9. Anal. Calcd. for $C_{17}H_{23}N_4S_2Cl$:C, 53.32; H, 6.05; N, 14.63. Found: C, 53.17; H, 5.89; N, 14.75.

Acknowledgements. Financial support from the Comisión Interministerial para la Ciencia y Tecnologia (CYCIT; Grant No. PB90-0043) is gratefully acknowledged as well as Universidad Complutense de Madrid for its NMR Service support. R. F.-G. gratefully acknowledges the Fundación Uriach for a grant.

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(*Received in UK* 8 *May* 1996; *revised* 23 *July* 1996; *accepted* 25 *July* 1996)