DOI: 10.1002/ejoc.200800123

The Tautomeric Persistence of Electronically and Sterically Biased 2-Quinolinones

Jean-Noël Volle,[a,b] Ursula Mävers,[a] and Manfred Schlosser*[a,c]

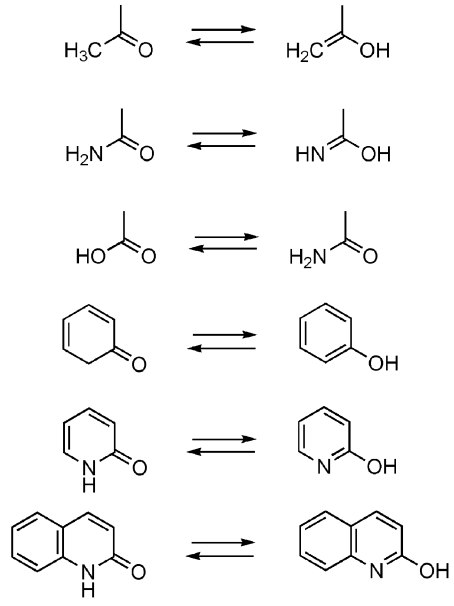
Keywords: Acidity constants / Amide–hydroxyimine tautomerism / 3-Fluoro-2(1*H*)-quinolinones / Keto–enol tautomerism / Knorr–Effenberger cyclizations

One dozen of tailormade model 3-fluoro-2(1*H*)-quinolinones were synthesized in order to be investigated by UV-, IR- and NMR spectroscopic techniques. All of these compounds were found to exist predominantly, if not exclusively, in the lactam (carboxamide, 1,2-dihydro-2-oxoquinoline) form. No tautomeric lactim (iminol, azaphenol) structure was detected.

Introduction

Keto/enol tautomerism remains a classic.[1] It typically manifests itself in the oxo/hydroxy olefin,[2–5] amide/hydroxy imine[6–8] and the degenerate carboxy/hydroxycarbonyl proton-shift equilibria, but also in phenol/cyclohexadienone,[9–10] 2-pyridinone/2-hydroxypyridine[11–16] and 2-quinolinone/2-hydroxyquinoline[16–18] equilibria (Scheme 1).

The position of such equilibria dictates not only the chemical reactivity of the respective compounds but also their behavior in living organisms. Molecular recognition,[19] including the base pairing in desoxyribonucleic acid, depends widely, though not alone,[20] on hydrogen bonding. Thus, the detailed knowledge of the tautomeric preferences and potentialities of all key components is a prerequisite for the rational design of the biological properties of an agonist or inhibitor. The structural analysis has also to take into account the physiological environment in which the compound is placed. Solvent[21–23] and phase effects can be critical. For example, an aqueous solution of 2-pyridone contains almost exclusively the amide form (K = 340,[24] $\Delta G°$ = 3.4 kcal/mol), whereas in the gas phase the 2-hydroxypyridine form is slightly favored (K = 2.2[25–26] $\Delta G°$ = 0.47 kcal/mol).



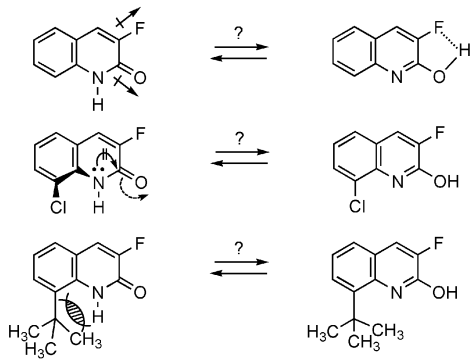
Scheme 1. Oxo/hydroxy olefin and carboxamide/hydroxyimine tautomerism in the aliphatic-acyclic and the aromatic or heterocyclic series.

Nitrogen-containing heterocycles play a privileged role in medicinal chemistry. Therefore, considerable efforts have been deployed to elucidate their tautomeric profiles.[26–31] In solution, as opposed to the gas phase, pyridines and quinolines carrying oxygen at the 2- or 4-position were found to exist as 2- or 4-pyridinones and 2- or 4-quinolinones rather than as 2- or 4-hydroxypyridines and 2- or 4-hydroxyquinolines. This assignment was based on the comparison of their UV[32–37] and IR[38–41] spectra, their dipole moments[42] and their dissociation constants[24,43] with data collected from model compounds where the lactam and lactim functions had been made immutable ("frozen") by *N*- and *O*-methylation, respectively. However, according to all available evidence, the relative thermodynamic stabilities of the oxo and hydroxy forms cannot be far apart. We won-

[a] Université, Section de Chimie,
1015 Lausanne, Switzerland
[b] Université, Institut Ch. Gerhardt, UMR5253 CNRS-ENSCM,
34296 Montpellier, France
[c] Ecole Polytechnique Fédérale, ISIC,
1015 Lausanne, Switzerland
Fax: +41-21-6939365
E-mail: manfred.schlosser@epfl.ch

dered whether or not a simple substitution bias would suffice to alter the tautomeric identity of the parent compounds.

We chose to probe, simultaneously or in parallel, three kinds of substitutive perturbations of 2-quinolinone. The first structural modification was subtle and, at the same time, quite precise. Although the hypothesis did not remain undisputed,[44] (*Z*)-2-fluoro-1-ethen-1-ol (i.e., fluoroacetaldehyde enol[45,46]) and 2-fluorophenol[47–49] were repeatedly apostrophed as entities stabilized by intramolecular hydrogen bonding. If such an interaction was really operative in the 3-fluoro-2-quinolinone series it would favor the lactim at the expense of the lactam form. The latter might be additionally disadvantaged by the close-to-parallel alignment of the C–F and C=O dipoles (Scheme 2). Next, we introduced into the 8-position heterosubstituents such as a chlorine atom the electron-withdrawing inductive effect of which should diminish the availability of the nitrogen lone pair and, as a corollary, weaken the amino-carbonyl resonance (Scheme 2). Finally, we placed a *tert*-butyl group at the 8-position. Owing to its bulkiness it should impede NH solvation and thus discriminate once more against the lactam form (Scheme 2).



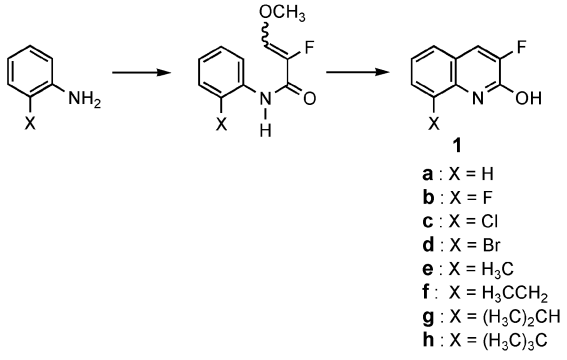
Scheme 2. Three structural modifications potentially causing the 2-quinolinone form to shift to its 2-hydroxyquinoline tautomer.

Despite numerous in-depth investigations into fluorine effects on keto/enol and related tautomeric equilibria, the subject has remained a controversial issue. According to Bumgardner et al., a fluorine atom at the 2-position of a *cyclic* 1,3-dicarbonyl compound does not noticeably alter the preference for the enol form whereas it reverses the equilibrium position and makes the keto form predominant upon fluorination of *acyclic* substrates.[50] This rule is at variance with earlier[51] but in agreement with later[52] findings. For example, the enol content of 3-fluoroacetonylacetone approximates 20%[52] in contrast to the 80% determined for the halogen-free analog.[53] Ethyl 2-fluoroacetoacetate and ethyl 2-fluorobenzoylacetate are enolized to the extent of 4% and < 3%, respectively,[52] less than half as much as the corresponding parent compounds.[53–54] Spectacular substituent effects on the oxo/enol equilibria of polyfluoroketones were reported by Lemal et al.[55] Whereas the enol forms of both cyclopentanone and 3*H*-heptafluoro-2-butanone were present only in undetectably small concentrations, 2*H*-nonafluorocyclohexanone, 2,2-H_2-hexafluorocyclopentanone, 2*H*-heptafluoropentanone and 2*H*-pentafluorocyclobutanone were enolized to the extent of 25, 13, 99 and >99.5%.[55]

The structures of uracil and of the cancer drug 5-fluorouracil have also been extensively investigated. According to an early ab initio calculation at the 3-21G level, the tautomeric population of the parent heterocycle and its fluorinated congener turned out to be almost identical.[56] The 2-hydroxy-4-oxo and the 4-hydroxy-2-oxo species, as the next-best tautomeric entities, proved to be already 17 and 20 kcal/mol less stable than the 2,4-dioxo form.[56] A later computational study using a more extended basis set maintained the qualitative order of stabilities but placed the 2-hydroxy-4-oxo and 4-hydroxy-2-oxo tautomers of uracil only 11 and 12 kcal/mol, respectively, and of 5-fluorouracil only 7 and 12 kcal/mol, respectively, above the 2,4-dioxo mark.[57] All data so far collected referred exclusively to the gas phase. More recently several attempts were made to mimic the aqueous medium by surrounding 5-fluoro-uracil with water molecules. Careful assessment of a 5-fluorouracil three water cluster brought the energy of the 2-hydroxy-4-oxo and 4-hydroxy-2-oxo relative to the 2,4-dioxo species down to 5 and 10 kcal/mol, respectively.[58] Thus, all evidence points at an effective stabilization of the 4-hydroxy-2-oxo relative to the 2,4-dioxo form by the 5-fluorine substituent. In combination with the other factors considered above this may suffice to close the gap between the two competing tautomeric species further and eventually give the preference to the lactime (hydroxyimine).

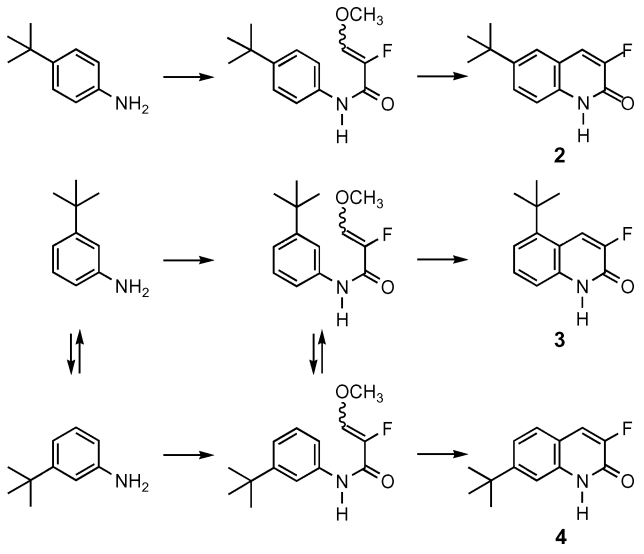
Synthesis of the Model Compounds

3-Fluoro-2(1*H*)-quinolinones can be readily made by a Knorr–Effenberger-type reaction[59–60] employing an aniline and a 2-fluoro-3-methoxyacrylic acid derivative which are first condensed to give a (*Z*/*E*) isomeric carboxamide intermediate to be subsequently cyclized under acidic conditions (Scheme 3).[61–63] This method was used to produce a series of 8-substituted 3-fluoro-2(1*H*)-quinolinones **1a**–**1h** in yields ranging from 51 to 88%.



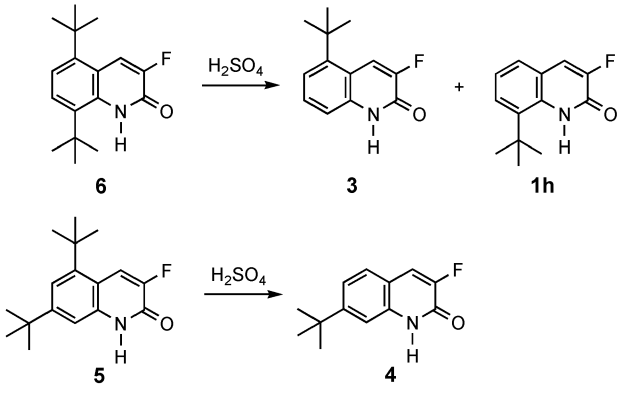
Scheme 3. 8-Substituted 3-fluoro-2(1*H*)-quinolinones by acid-catalyzed cyclization of *N*-(2-fluoro-3-methoxy-2-propenoyl)anilines.

For the sake of completeness, also the three other *tert*-butyl-substituted quinolinones **2**–**4** were prepared (Scheme 4). Whereas 4-*tert*-butylaniline afforded the 6-isomer **2** without any problem, the same sequence applied to the 3-*tert*-butylaniline produced an inseparable mixture of the 5- and 7-isomers **3** and **4**.



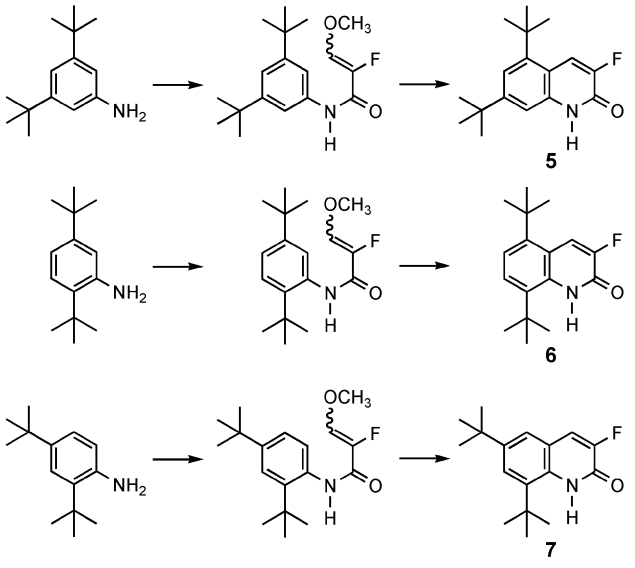
Scheme 4. Acid-catalyzed cyclization of *N*-(2-fluoro-3-methoxy-2-propenoyl)anilines affording 5-, 6- and 7-*tert*-butyl-3-fluoro-2(1*H*)-quinolinones.

Isomer **3** (82%) was isolated along with some 8-*tert*-butyl-2(1*H*)-quinolinone (**1h**; 11%) after treatment of 5,8-di-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone (**6**) with sulfuric acid (98%) (Scheme 5). A similar selective monodealkylation[64–66] applied to 5,7-di-*tert*-butyl-2(1*H*)-quinolinone (**5**) gave isomer **4** (14%).



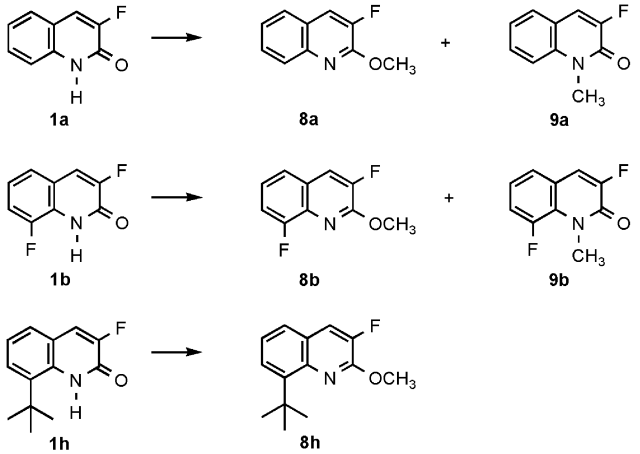
Scheme 5. Acid-catalyzed monodealkylation of di-*tert*-butyl-substituted quinolinones **5** and **6** producing 5-, 7- and 8-*tert*-butyl-3-fluoro-2(1*H*)-quinolinones **1h**, **3** and **4**.

The 5,7-, 5,8- and 6,8-di-*tert*-butylquinolinones **5** (51%), **6** (82%) and **7** (71%) were obtained in the usual way from the corresponding aniline and methyl 2-fluoro-3-methoxyacrylate (Scheme 6). The *N*-acryloanilides were again cyclized without prior isolation.



Scheme 6. Di-*tert*-butyl-3-fluoro-2(1*H*)-quinolinones **5**–**7** by condensation of 3,5-, 3,6- and 2,4-di-*tert*-butylaniline with methyl 2-fluoro-3-methoxy-2-propenoate and subsequent acid-catalyzed cyclization.

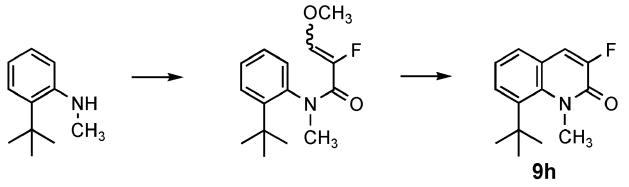
To prepare further model compounds for spectroscopic studies, the parent quinolinone **1a** and the 8-fluoro and 8-*tert*-butyl-substituted congeners **1b** and **1h** were consecutively treated with potassium hydride in dimethylformamide and dimethyl sulfate (Scheme 7). The first two compounds gave predominantly the *N*-methylated quinolinones **9a** (62%) and **9b** (77%) along with some of the *O*-methylated quinolines **8a** (8%) and **8b** (15%). The pairs of regioisomers were readily separated by column chromatography. In contrast, the 8-*tert*-butyl analog **1h** afforded exclusively the 2-methoxyquinoline **8h** (90%). Obviously, steric congestion prevented the access of the reagent to the nitrogen atom.



Scheme 7. Methylation of quinolinones **1a**, **1b** and **1h** giving rise to *O*-methylquinolinones **8a**, **8b** and **8h** and *N*-methylquinolinones **9a** and **9b**.

The missing *N*-methyl derivative of the quinolinone **9h** had to be accessed in a different way. To this end, 2-*tert*-butylaniline was *N*-methylated and deprotonated with po-

tassium hydride before being condensed with 2-fluoro-3-methoxyacryloyl chloride. Subsequent acid-mediated cyclization of the aniline-derived amide afforded the *N*-methylquinolinone **9h** in 37% over-all yield (Scheme 8).

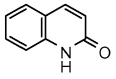
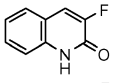
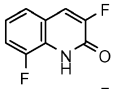
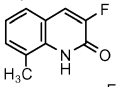
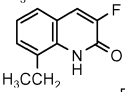
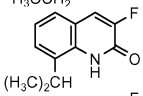
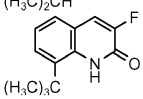
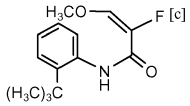


Scheme 8. Conversion of 2-*tert*-butyl-*N*-methylaniline into 8-*tert*-butyl-3-fluoro-1-methyl-2(1*H*)-quinolinone (**9h**).

Dissociation Constants

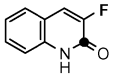
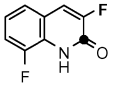
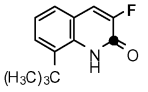
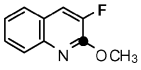
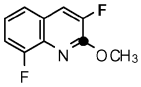
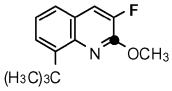
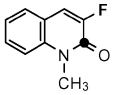
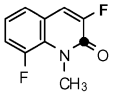
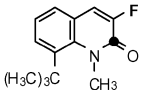
Attempts have previously been undertaken to deduce lactam/lactime equilibrium constants from a pK_a-comparison of 2-, 3- and 4-hydroxypyridines and -quinolines,[24,43] although the validity of such an approach remains questionable. The acidity data reported below (see Table 1), were only collected to probe substituent effects. The introduction of the first fluorine atom at the 3-position diminished the pK_a value by 1.0, the second one at the 8-position by even 1.5 units. The second substituent is *syn*-oriented with respect to the nitrogen and hence closer than the *anti*-oriented first one although both are equidistant in terms of the number of interposed bonds. Alkyl substituents at the 8-position either diminish the acidity slightly (ethyl and isopropyl) or do not affect it at all (methyl and *tert*-butyl). At first sight, the charge-stabilizing inductive electron-donating effect is largely offset by the steric hindrance to NH solvation which disfavors the acid form. However, the same dissociation constant as the one recorded for 8-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone was also found for the 6-*tert*-butyl isomer. The *N*-acryloylaniline precursors such as compound **10** proved to be considerably less acidic than the corresponding 2*H*-quinolinones. This was to be expected as the ring-open counterparts offer a less extensive area for charge delocalization and, in addition, the coplanarity of all resonance-active centers is not secured in such floppy structures.

Table 1. Dissociation constants pK_a of 2(1*H*)-quinolinone, 3-fluoro-2(1*H*)-quinolinone (**1a**), 8-substituted congeners thereof (**1b**, **1e**, **1f**, **1g**, and **1h**) and 2-*tert*-butyl-*N*-(2-fluoro-3-methoxyacryloyl)-aniline (**10**).

Comp.	Structure	pK_a
-		11.7[a]
1a		10.7
1b		9.22
1e		10.5
1f		10.7
1g		10.7
1h		10.5[b]
10		>12[d]

[a] Coinciding with a literature value.[24] [b] The same number was found for 6-*tert*-butyl- and 5,8-di-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone. [c] (*E*)-Isomer. [d] Not acidic enough to be assessed under the standard conditions applied.

Table 2. Comparison on the ^{13}C and ^{19}F chemical shifts of model quinolinones **1** with those of their *O*- and *N*-methylated derivatives **8** and **9**, respectively.

Comp.	Structure	$\delta^{13}C$ ($^2J_{CF}$)[a]	$\delta^{19}F$ [b]
1a		158.0 (26.4)	–132.0
1b		155.9 (27.8)	–128.6
1h		157.6 (27.8)	–132.9
8a		153.1 (13.8)	–138.6
8b		153.3 (14.4)	–136.8
8h		150.2 (13.2)	–140.4
9a		156.4 (26.4)	–128.9
9b		156.6 (26.4)	–127.0
9h		159.6 (26.4)	–132.2

[a] Chemical shifts (in ppm relative to tetramethylsilane) of the oxygen-bearing carbon nuclei at the 2-position and, in parentheses, vicinal C(2)–F coupling constants (in Hz). [b] Chemical shift (relative to Cl_3CF) of the fluorine nucleus at the 3-position.

Nuclear Magnetic Resonance Spectra

The ^{13}C signal of the C-2 nucleus reveals whether the latter is connected to a singly or doubly bonded oxygen.[67–70] In the same manner, the resonance frequency of the fluorine atom at the 3-position can tell whether the halogen is neighbored by a carbonyl or hydroxyl group.[71] When comparing the ^{13}C and ^{19}F NMR spectra of the three model quinolinones **1a**, **1b** and **1h** with those of their *O*- and *N*-methylated derivatives (**8** and **9**, respectively), the anticipated chemical shift differences were observed indeed (Table 2).

There was little difference ($\leq$ 2 ppm) between the ^{13}C frequencies of quinolinones **1** and the corresponding *N*-methyl derivatives **9** whereas the 2-methoxyquinolines **8** resonated at a 5 ($\pm$2) ppm higher field. The ^{19}F chemical shifts of the quinolinones **1** and their *N*-methyl congeners **9** were also quite similar ($\Delta\delta$ = 0.7–3.1 ppm), whereas those of the 2-methoxyquinolines **8** appeared again at a distinctly higher field ($\Delta\delta$ = 6.6–8.2 ppm). Most characteristic are the C(2)–F coupling constants. They fall for both quinolinones **1** and *N*-methylquinolinones **9** in the same narrow range of 26.4–27.8 Hz whereas they shrink to 13.2–14.4 Hz in the case of the *O*-methyl derivatives (see Table 2). Evidently compounds **1** exist predominantly or exclusively in the lactam form. The presence of minute proportions of the lactim (2-hydroxyquinoline) tautomers competing with the predominant lactam forms in a dynamic equilibrium can nevertheless not be ruled out.

Ultraviolet Absorption Spectra

The UV spectra of the quinolinones **1** were once again compared with those of the *O*- and *N*-methyl-substituted congeners **8** and **9**. The 2-methoxyquinolines **8** exhibit a UV profile that unmistakably features a triplet of maxima in the range of 300–320 nm followed by an abrupt drop to zero (Figures 1, 2, and 3). In contrast, the UV curves of the quinolinones **1** and their *N*-methyl derivatives level off only

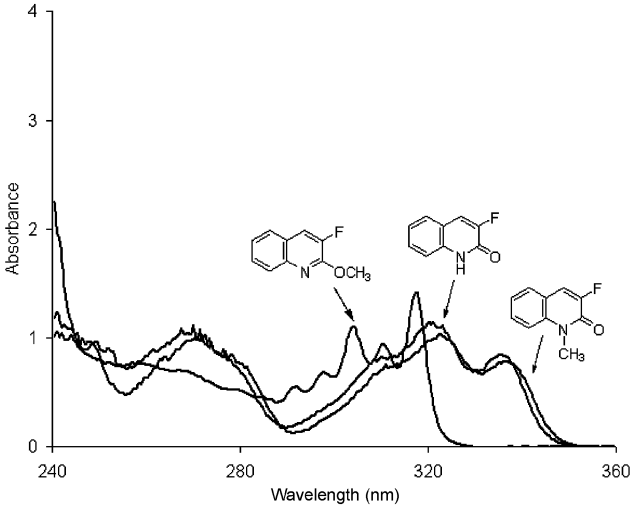


Figure 1. UV-absorption spectra of 3-fluoroquinolinone **1a**, 3-fluoro-2-methoxyquinoline (**8a**) and 3-fluoro-1-methyl-2-quinolinone (**9a**) (2×10^{-4} M concentrations in ethanol).

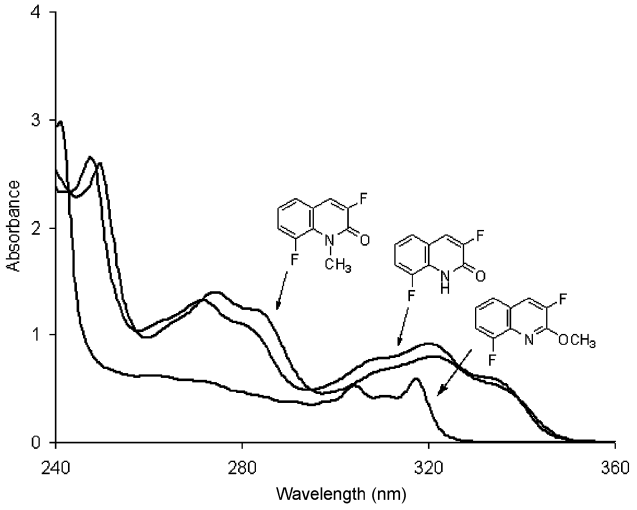


Figure 2. UV-absorption spectra of the 8-fluoro-substituted 2-quinolinone **1b**, 2-methoxyquinoline **8b** and *N*-methyl-2-quinolinone **9b** (2×10^{-4} M concentrations in ethanol).

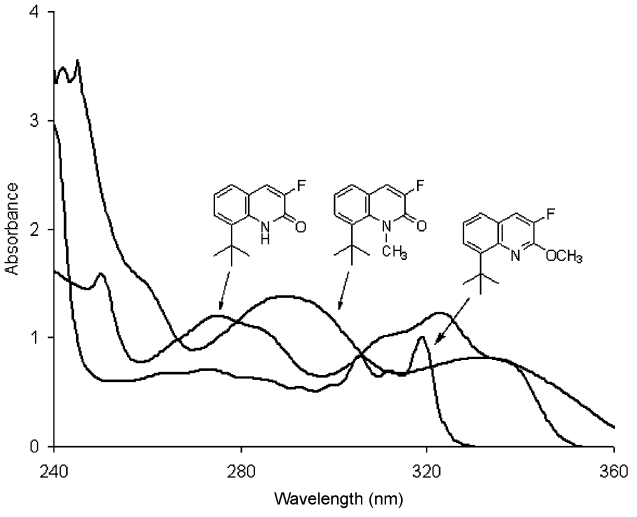


Figure 3. UV-absorption spectra of the 8-*tert*-butyl-substituted 2-quinolinone **1h**, 2-methoxyquinoline **8h** and *N*-methyl-2-quinolinone **9h** (2×10^{-4} M concentrations in ethanol).

at or beyond 350 nm. The spectra of the 8-unsubstituted or 8-fluorinated compound pairs **1a/9a** and **1b/9b** are virtually identical (Figures 1 and 2). In contrast, *N*-methylation of the 8-*tert*-butyl-substituted quinolinone **1h**, affording derivative **9h**, brings about a red shift of the long-wave absorption band (Figure 3). This spectral change has to be attributed to a structural distortion caused by the severe steric repulsion between the *tert*-butyl and *N*-methyl groups.

Infrared Absorption Spectroscopy

In principle, infrared (IR) spectra should offer the most unambiguous tool to differentiate between lactam and lactim tautomers. The stretching frequencies of phenolic hydroxy groups typically can be found in the range of 3600–3590 cm^{-1} and those of secondary amides or vinylogous analogs thereof in the range of 3450–3390 cm^{-1}.[38,40,72] How-

ever, the majority of our compounds were found to exist as hydrogen-bonded dimers as revealed by a broad and structured band in the region between 3200 and 2400 cm^{-1} (Figure 4). In contrast, 8-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone (Figure 5) and other quinolinones carrying a bulky substituent at the 8-position, are monomeric and hence give rise to slim NH frequencies in the range of 3430 to 3350 cm^{-1} typical for an ordinary secondary carboxamide.

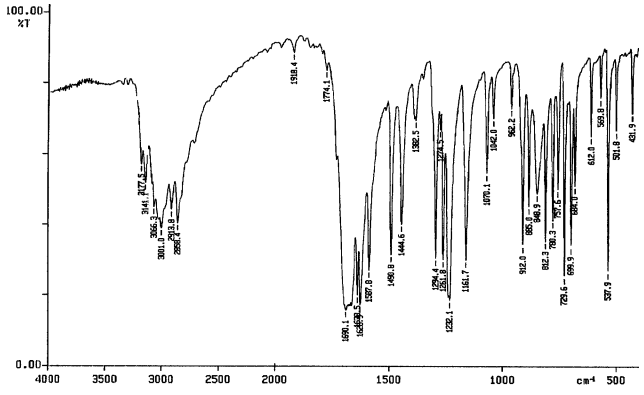


Figure 4. Infrared spectrum of solid 3,8-difluoro-2(1*H*)-quinolinone, a dimer.

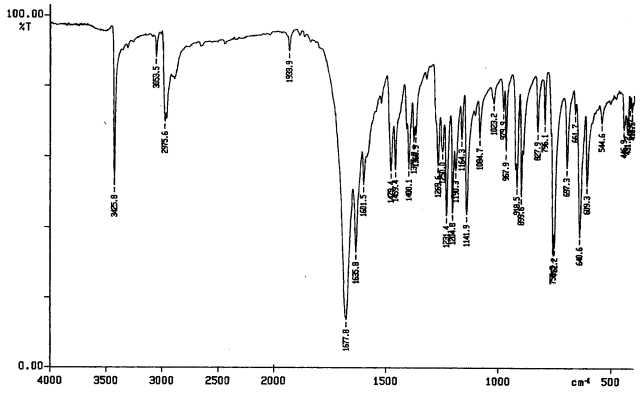


Figure 5. Infrared spectrum of solid 8-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone, a monomer.

Discussion and Conclusion

On the basis of pK_a, UV, IR and NMR evidence, the structure of 2,3,5,6-tetrafluoro-4-hydroxypyridine rather than that of 2,3,5,6-tetrafluoro-4-(1*H*)-pyridinone was assigned to the product formed by the reaction of pentafluoropyridine with sodium hydroxide.[73] Whereas 2(1*H*)- and 4(1*H*)-pyridinone and even 3,5-dichloro-4(1*H*)-pyridinone[74] exist mainly, if not exclusively, in the lactam form, 6-chloro-2(1*H*)- and 2-chloro-4(1*H*)-pyridinone contain appreciable proportions of the hydroxy tautomer if dissolved in moderately polar media (ethanol as opposed to water).[74] The hydroxy forms of 2,6-dichloro- and 2,3,5,6-tetrachloro-4-(1*H*)-pyridinone and 3,4,5,6-tetrachloro-2(1*H*)-pyridinone prevail whatever the solvent.[74]

Viewed against this background there was little reason to expect the yet unknown 3-fluoro-2(1*H*)-pyridinone or regioisomers thereof (e.g., the 6-fluoro analog[75]) not to favor the lactam form. As the driving force for switching into the aromatic hydroxyimine structures is in the quinoline series even smaller than in the pyridine series,[17,76–78] we did not really believe 3-fluoro-2(1*H*)-quinolinones, assisted or not by a bulky 8-substituent, to populate the lactim tautomer to a significant extent. This sceptical expectation having been confirmed by the present investigation, we are happy to follow Katritzky's advice to "call a spade a spade"[79] and to call a 3-fluoro-substituted 2(1*H*)-quinolinone also in the future a quinolinone.

Experimental Section

General: Working practices and abbreviations have been specified in previous articles from this laboratory.[80–83] Elementary analyses were performed by the laboratories of I. Beetz (96301 Kronach, Germany) or Solvias (4002 Basel, Switzerland). The expected percentages were calculated using the atomic weight numbers listed in the 1999 IUPAC recommendations.

^1H, ^{13}C and ^{19}F NMR spectra were recorded at 400, 101 and 376 MHz, respectively, relative to the internal standards (δ = 0.00 ppm) tetramethylsilane and trichlorofluoromethane. The samples were dissolved in $CDCl_3$ or, if marked by an asterisk, in [D_6]-DMSO. UV spectra were recorded using a Varian Carry 50 spectrophotometer. A Perkin–Elmer 1420 was used to register the infrared spectra of 3-fluoro-2(1*H*)-quinolinone powders incorporated in potassium bromide pellets.

The p*K*a values of 2(1*H*)-quinolinone, of the 3-fluoro-2(1*H*)-quinolinones **1a**–**1h** and the **1h**-precursor **10** have been determined by potentiometric titration[84] using a GlpK_a instrument.[85] The 0.5–5.0 mM aqueous solutions of the samples contained also a 0.10 M concentration of potassium nitrate as an ionic strength adjuster. The solutions were acidified to pH 1.8 by adding 0.5 M hydrochloric acid before being titrated with 0.5 M aqueous potassium hydroxide at 22 °C to pH 12.2. Typically, more than 25 readings were collected for each run. Furthermore, spectrophotometrically monitored titrations[86] were performed using a D-PAS module[85] in conjunction with the GlpK_a instrument providing a series of pH-variable spectra in the pH range from 12 to 2. The pK_a values were calculated by means of the target factor analysis method[87] using the absorption data of 15–20 wavelength channels.

1. 3-Fluoro-2(1*H*)-quinolinones

The preparation of 3-fluoro-2(1*H*)-quinolinone[61] (**1a**), 3,8-difluoro-2(1*H*)-quinolinone[62] (**1b**) and 3-fluoro-8-methyl-2(1*H*)-quinolinone[62] (**1e**) has already been reported. The other compounds were made accordingly.[61–63]

General Procedure:[61–63] Butyllithium (40 mmol) in hexanes (25 mL) and methyl 2-fluoro-3-methoxy-2-propenoate[61] (2.7 g, 20 mmol) were consecutively added to a solution of the aniline (40 mmol) in tetrahydrofuran (50 mL), kept in an ice bath. After 2 h at 25 °C, the mixture was poured into 2.0 M hydrochloric acid (0.10 L). The organic layer was decanted and the aqueous one extracted with diethyl ether (3 × 0.10 L). The combined organic phases were washed with brine (2 × 25 mL) and the solvents evaporated. The residue was dissolved in 70% (approx. 12 M) aqueous sulfuric acid (50 mL). After 5 h at 60 °C, the mixture was poured

into ice/water (0.5 L) and the precipitate collected by filtration. The raw material was adsorbed on silica gel (15 mL) and eluted with a 3:7 (v/v) mixture of ethyl acetate and hexanes from a column filled with more silica gel (0.15 L).

3-Fluoro-2(1*H*)-quinolinone (1a):[61] ^{19}F NMR: δ = –132.0 (d, J = 9.7 Hz) ppm. ^{13}C NMR: δ = 158.0 (d, J = 26.4 Hz, 1 C), 150.8 (d, J = 253 Hz, 1 C), 135.2 (s, 1 C), 129.8 (s, 1 C), 127.4 (d, J = 6.0 Hz, 1 C), 123.6 (s, 1 C), 120.3 (d, J = 16.4 Hz, 1 C), 118.8 (d, J = 7.9 Hz, 1 C), 116.2 (s, 1 C) ppm.

3,8-Difluoro-2(1*H*)-quinolinone (1b):[62] ^{19}F NMR: δ = –128.6 (dd, J = 9.2, 2.3 Hz), –134.3 (m) ppm. ^{13}C NMR: δ = 155.9 (d, J = 27.8 Hz, 1 C), 151.8 (d, J = 257 Hz, 1 C), 149.2 (d, J = 246 Hz, 1 C), 147.9 (s, 1 C), 124.1 (d, J = 13.2 Hz, 1 C), 123.3 (d, J = 6.6 Hz, 1 C), 123.0 (dd, J = 5.9, 3.7 Hz, 1 C), 120.4 (dd, J = 6.6, 2.9 Hz, 1 C), 119.3 (dd, J = 16.8, 2.9 Hz, 1 C), 114.7 (dd, J = 16.8, 2.9 Hz, 1 C) ppm.

8-Chloro-3-fluoro-2(1*H*)-quinolinone (1c): From 2-chloroaniline (4.2 mL, 5.1 g, 40 mmol); colorless needles (from ethanol); m.p. 192–194 °C; yield 2.3 g (58%). ^{1}H NMR: δ = 9.37 (s, broadened, 1 H), 7.56 (d, J = 7.8 Hz, 1 H), 7.48 (d, J = 9.4 Hz, 2 H), 7.22 (t, J = 7.8 Hz, 1 H) ppm. ^{19}F NMR: δ = –129.4 (d, J = 9.5 Hz) ppm. C_9H_5ClFNO (197.60): calcd. C 54.71, H 2.55; found C 54.68, H 2.63.

8-Bromo-3-fluoro-2(1*H*)-quinolinone (1d): From 2-bromoaniline (6.9 g, 40 mmol); colorless stars; m.p. 201–202 °C (from ethanol); yield 2.9 g (59%). ^{1}H NMR: δ = 9.35 (s, broadened, 1 H), 7.71 (dd, J = 7.8, 1.1 Hz, 1 H), 7.51 (d, J = 7.8 Hz, 1 H), 7.46 (d, J = 9.5 Hz, 1 H), 7.15 (t, J = 7.8 Hz, 1 H) ppm. ^{19}F NMR: δ = –129.5 (d, J = 9.5 Hz) ppm. C_9H_5BrFNO (242.05): calcd. C 44.66, H 2.08; found C 45.19, H 2.37.

8-Ethyl-3-fluoro-2(1*H*)-quinolinone (1f): From 2-ethylaniline (5.0 mL, 4.9 g, 40 mmol); colorless needles; m.p. 149–151 °C; yield 2.8 g (73%). ^{1}H NMR: δ = 10.05 (s, broadened, 1 H), 7.49 (d, J = 10.0 Hz, 1 H), 7.49 (d, J = 9.8 Hz, 1 H), 7.40 (d, J = 7.7 Hz, 1 H), 7.36 (d, J = 7.9 Hz, 1 H), 7.20 (t, J = 7.7 Hz, 1 H), 2.90 (q, J = 7.5 Hz, 2 H), 1.35 (t, J = 7.5 Hz, 3 H) ppm. ^{19}F NMR: δ = –132.9 (dd, J = 10.0, 4.5 Hz) ppm. $C_{11}H_{10}FNO$ (191.20): calcd. C 69.10, H 5.27; found C 69.23, H 5.29.

3-Fluoro-8-isopropyl-2(1*H*)-quinolinone (1g): From 2-isopropylaniline (5.6 mL, 5.4 g, 40 mmol); colorless needles; m.p. 156–158 °C; yield 2.9 g (71%). ^{1}H NMR: δ = 9.89 (s, broadened, 1 H), 7.49 (d, J = 9.9 Hz, 1 H), 7.45 (d, J = 7.6 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 7.26 (t, J = 7.8 Hz, 1 H), 3.33 (sept, J = 6.8 Hz, 1 H), 1.36 (d, J = 6.8 Hz, 6 H) ppm. ^{19}F NMR: δ = –133.1 (dd, J = 10.0, 5.0 Hz) ppm. $C_{12}H_{12}FNO$ (205.23): calcd. C 70.23, H 5.89; found C 70.16, H 5.75.

8-*tert*-Butyl-3-fluoro-2(1*H*)-quinolinone (1h): From 2-*tert*-butylaniline (6.2 mL, 6.0 g, 40 mmol); colorless platelets; m.p. 136–138 °C; yield 2.9 g (66%). ^{1}H NMR: δ = 9.17 (s, broadened, 1 H), 7.52 (d, $J \approx 8$ Hz, 1 H), 7.49 (d, J = 10.1 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 1 H), 7.21 (t, J = 7.7 Hz, 1 H), 1.54 (s, 9 H) ppm. ^{19}F NMR: δ = –132.9 (dd, J = 10.0, 5.5 Hz) ppm. ^{13}C NMR: δ = 155.6 (d, J = 27.8 Hz, 1 C), 150.0 (d, J = 253 Hz, 1 C), 134.3 (d, J = 1.5 Hz, 1 C), 133.2 (d, J = 1.5 Hz, 1 C), 127.3 (d, J = 2.2 Hz, 1 C), 126.7 (d, J = 5.9 Hz, 1 C), 123.1 (s, 1 C), 120.9 (d, J = 16.1 Hz, 1 C), 119.7 (d, J = 6.6 Hz, 1 C), 34.1 (s, 1 C), 30.4 (s, 3 C) ppm. $C_{13}H_{14}FNO$ (219.26): calcd. C 71.21, H 6.44; found C 71.09, H 6.66.

6-*tert*-Butyl-3-fluoro-2(1*H*)-quinolinone (2): From 4-*tert*-butylaniline (6.3 mL, 6.0 g, 40 mmol); colorless needles; m.p. 216–218 °C; yield 2.4 g (55%). ^{1}H NMR: δ = 7.6 (m, 2 H), 7.5 (m, 2 H), 1.37 (s, 9 H) ppm. ^{19}F NMR: δ = –132.8 (d, J = 10.0 Hz) ppm. $C_{13}H_{14}FNO$ (219.26): calcd. C 71.21, H 6.44; found C 70.88, H 6.72.

5,7-Di-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone (5): From 3,5-di-*tert*-butylaniline[88] (8.2 g, 40 mmol); colorless needles; m.p. 232–233 °C; yield 2.8 g (51%). ^{1}H NMR: δ = 8.18 (d, J = 13.0 Hz, 1 H), 7.36 (s, 1 H), 7.31 (d, J = 1.5 Hz), 1.54 (s, 9 H), 1.38 (s, 9 H) ppm. ^{19}F NMR: δ = –133.5 (d, J = 13.0 Hz) ppm. $C_{17}H_{22}FNO$ (275.36): calcd. C 74.15, H 8.05; found C 74.14, H 7.91.

5,8-Di-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone (6): From 2,5-di-*tert*-butylaniline (8.2 g, 40 mmol); colorless needles; m.p. 198–199 °C; yield 4.5 g (82%). ^{1}H NMR: δ = 9.25 (s, broadened, 1 H), 8.23 (d, J = 13.4 Hz, 1 H), 7.43 (d, J = 8.4 Hz, 1 H), 7.24 (d, J = 8.4 Hz, 1 H), 1.55 (s, 9 H), 1.53 (s, 9 H) ppm. ^{19}F NMR: δ = –132.7 (dd, J = 13.2, 5.9 Hz) ppm. $C_{17}H_{22}FNO$ (275.36): calcd. C 74.15, H 8.05; found C 74.13, H 8.02.

6,8-Di-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone (7): From 2,4-di-*tert*-butylaniline[88–89] (8.2 g, 40 mmol); colorless needles; m.p. 134–135 °C; yield 3.9 g (71%). ^{1}H NMR: δ = 9.13 (s, broad, 1 H), 7.57 (d, J = 1.9 Hz, 1 H), 7.48 (d, J = 10.2 Hz, 1 H), 7.37 (d, J = 2.1 Hz), 1.55 (s, 9 H), 1.36 (9 H) ppm. ^{19}F NMR: δ = –133.5 (dd, J = 10.0, 5.5 Hz) ppm. $C_{17}H_{22}FNO$ (275.36): calcd. C 74.15, H 8.05; found C 74.12, H 8.04.

5-*tert*-Butyl-3-fluoro-2(1*H*)-quinolinone (3): Concentrated (98%) sulfuric acid (10 mL) was added to 5,8-di-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone (**6**; 5.6 g, 20 mmol) in heptanes (0.20 L). After having been heated for 24 h under reflux, the mixture was poured on ice. The organic layer was decanted and the aqueous one was extracted with ethyl acetate (3 × 0.10 L). The combined organic phases were dried and the solvents evaporated. The residue was absorbed on silica gel (25 mL) and eluted with a 3:7 (v/v) mixture of ethyl acetate and hexanes from a column filled with more silica gel (0.25 L). The by-product 8-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone (**1h**, see above; yield 0.50 g, 11%) had a considerably shorter retention time than the main component, isomer **3**; colorless needles; m.p. 219–221 °C; yield 3.6 g (82%). ^{1}H NMR: δ = 8 26 (d, J = 13.2 Hz, 1 H), 7.46 (dd, J = 8.4, 1.0 Hz, 1 H), 7.43 (t, J = 7.9 Hz, 1 H), 7.31 (dd, J = 7.7, 1.0 Hz, 1 H), 1.54 (s, 9 H) ppm. ^{19}F NMR: δ = –132.1 (d, J = 13.0 Hz) ppm. $C_{13}H_{14}FNO$ (219.26): calcd. C 71.21, H 6.44; found C 71.33, H 6.70.

7-*tert*-Butyl-3-fluoro-2(1*H*)-quinolinone (4): 5,7-Di-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone (**5**; 2.2 g, 8.0 mmol) were stirred in concentrated (98%) sulfuric acid (40 mL) for 5 h at 60 °C. When the mixture was worked up as described in the preceding paragraph, most of the starting material (1.7 g, 77%) was recovered and a small amount of compound **4** was obtained; colorless needles; m.p. 199–201 °C; yield 0.24 g (14%). ^{1}H NMR: δ = 7.50 (d, J = 9.6 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.40 (s, broad, 1 H), 7.34 (ddd, J = 8.2, 1.8, 0.6 Hz, 1 H), 1.38 (s, 9 H) ppm. ^{19}F NMR: δ = –133.3 (d, J = 10.0 Hz) ppm. $C_{13}H_{14}FNO$ (219.26): calcd. C 71.21, H 6.44; found C 71.16, H 6.68.

2. *O*-Methyl and *N*-Methyl 3-fluoro-2(1*H*)-quinolinones

3-Fluoro-2-methoxyquinoline (8a) and 3-Fluoro-1-methyl-2(1*H*)-quinolinone (9a): Under vigorous stirring, potassium hydride (0.80 g, 20 mmol) and, 30 min later, dimethyl sulfate (1.9 mL, 2.5 g, 20 mmol) were added to 3-fluoro-2(1*H*)-quinolinone (**1a**) in dimethylformamide (40 mL). After having been left for 1 h at 25 °C, the mixture was evaporated to dryness and the residue absorbed on silica gel (25 mL). Products **8a** and **9a** were successively eluted from a column filled with more silica gel (0.25 L) using a 1:9 (v/v) mixture of ethyl acetate and hexanes. **Quinoline 8a:** Colorless prisms; m.p. 47–48 °C; yield 0.29 g (8%). ^{1}H NMR: δ = 7.85 (d, J

= 8.3 Hz, 1 H), 7.67 (d, *J* = 8.1 Hz, 1 H), 7.64 (d, *J* = 10.3 Hz, 1 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 4.16 (s, 3 H) ppm. ^{19}F NMR: δ = –138.6 (d, *J* = 10.4 Hz). ^{13}C NMR: δ = 153.1 (d, *J* = 13.8 Hz, 1 C), 147.7 (d, *J* = 263 Hz, 1 C), 142.7 (s, 1 C), 128.5 (s, 1 C), 127.0 (s, 1 C), 126.9 (d, *J* = 4.8 Hz, 1 C), 125.4 (d, *J* = 3.5 Hz, 1 C), 124.9 (s, 1 C), 119.3 (d, *J* = 14.8 Hz, 1 C), 53.9 (s, 1 C) ppm. $C_{10}H_8FNO$ (177.18): calcd. C 67.79, H 4.55; found C 67.85, H 4.66. **Quinolinone 9a:** Colorless needles; m.p. 111–112 °C; yield 2.2 g (62%). ^{1}H NMR: δ = 7.58 (ddd, *J* ≈ 8.5, 1.6, 0.6 Hz, 1 H), 7.55 (d, *J* = 7.6 Hz, 1 H), 7.42 (d, *J* = 9.1 Hz, 1 H), 7.39 (d, *J* = 8.3 Hz, 1 H), 7.29 (t, *J* = 7.7 Hz, 1 H), 3.79 (s, 3 H) ppm. ^{19}F NMR: δ = –128.9 (d, *J* = 9.0 Hz) ppm. ^{13}C NMR: δ = 156.4 (d, *J* = 26.4 Hz, 1 C), 150.6 (d, *J* = 252 Hz, 1 C), 137.0 (s, 1 C), 129.7 (d, *J* = 2.9 Hz, 1 C), 128.4 (d, *J* = 5.9 Hz, 1 C), 123.1 (s, 1 C), 118.8 (d, *J* = 8.1 Hz, 1 C), 118.0 (d, *J* = 16.8 Hz, 1 C), 114.3 (d, *J* = 1.5 Hz, 1 C), 29.9 (s, 1 C) ppm. $C_{10}H_8FNO$ (177.18): calcd. C 67.79, H 4.55; found C 67.85, H 4.63.

3,8-Difluoro-2-methoxyquinoline (8b) and 3,8-Difluoro-l-methyl-2(1*H*)-quinolinone (9b): An analogous reaction with 3,8-difluoro-2(1*H*)-quinolinone (**1b**; 4.0 g, 20 mmol) also afforded a mixture of regioisomers which were separated again by chromatography. **Quinoline 8b:** Colorless prisms; m.p. 89–91 °C; yield 0.60 g (15%). ^{1}H NMR: δ = 7.67 (dd, *J* = 10.3, 1.7 Hz, 1 H), 7.47 (dd, *J* ≈ 8.5, 2.0 Hz, 1 H), 7.3 (m, 2 H), 4.21 (s, 3 H) ppm. ^{19}F NMR: –126.5 (m), –136.8 (dd, *J* = 10.3, 3.4 Hz). ^{13}C NMR: δ = 156.8 (d, *J* = 255 Hz, 1 C), 153.3 (d, *J* = 14.4 Hz, 1 C), 147.7 (d, *J* = 264 Hz, 1 C), 132.4 (dd, *J* = 11.9, 3.1 Hz, 1 C), 127.4 (dd, *J* = 4.1, 2.2 Hz, 1 C), 124.9 (d, *J* = 8.2 Hz, 1 C), 122.4 (t, *J* = 4.7 Hz, 1 C), 119.2 (dd, *J* = 15.1, 2.5 Hz, 1 C), 113.3 (dd, *J* = 19.5, 2.5 Hz, 1 C), 54.2 (s, 1 C) ppm. $C_{10}H_7F_2NO$ (195.17): calcd. C 61.54, H 3.61; found C 61.76, H 4.05. **Quinolinone 9b:** Colorless needles; m.p. 144–145 °C; yield 3.0 g (77%). ^{1}H NMR: δ = 7.38 (dd, *J* = 8.7, 1.2 Hz, 1 H), 7.15–7.35 (m, 3 H), 3.84 (d, *J* = 8.4 Hz, 3 H) ppm. ^{19}F NMR: δ = –121.6 (m), –127.0 (dd, *J* = 8.6, 2.4 Hz) ppm. ^{13}C NMR: δ = 156.6 (d, *J* = 26.4 Hz, 1 C), 150.7 (d, *J* = 254 Hz, 1 C), 150.1 (d, *J* = 247 Hz, 1 C), 126.1 (d, *J* = 7.5 Hz, 1 C), 124.3 (dd, *J* = 6.3, 3.8 Hz, 1 C), 123.4 (d, *J* = 8.8 Hz, 1 C), 121.3 (dd, *J* = 7.5, 3.1 Hz, 1 C), 117.7 (dd, *J* = 17.6, 3.1 Hz, 1 C), 117.0 (dd, *J* = 23.9, 3.1 Hz, 1 C), 33.6 (dd, *J* = 15.7, 1.3 Hz, 1 C) ppm. $C_{10}H_7F_2NO$ (195.17): calcd. C 61.54, H 3.61; found C 61.73, H 3.92.

8-*tert*-Butyl-3-fluoromethoxyquinolinone (8h): The consecutive treatment of 8-*tert*-butyl-3-fluoro-2(1*H*)-quinolinone (**1h**; 4.4 g, 20 mmol) with potassium hydride and dimethyl sulfate, analogously as described in the two preceding paragraphs, gave a single product; colorless prisms; m.p. 86–87 °C; yield 4.2 g (90%). ^{1}H NMR: δ = 7.62 (d, *J* = 10.5 Hz, 1 H), 7.58 (d, *J* = 7.8 Hz, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 4.17 (s, 3 H), 1.65 (s, 9 H) ppm. ^{19}F NMR: δ = –140.4 (d, *J* = 10.5 Hz) ppm. ^{13}C NMR: δ = 150.2 (d, *J* = 13.2 Hz, 1 C), 146.1 (d, *J* = 263 Hz, 1 C), 145.9 (s, 1 C), 141.1 (d, *J* = 3.7 Hz, 1 C), 126.9 (d, *J* = 2.9 Hz, 1 C), 125.7 (d, *J* = 4.4 Hz, 1 C), 125.6 (d, *J* = 2.2 Hz, 1 C), 124.7 (s, 1 C), 120.1 (d, *J* = 13.9 Hz, 1 C), 54.3 (s, 1 C), 36.1 (s, 1 C), 30.4 (s, 3 C) ppm. $C_{14}H_{16}FNO$ (233.28): calcd. C 72.08, H 6.91; found C 71.96, H 6.98.

8-*tert*-Butyl-3-fluoro-1-methyl-2(1*H*)-quinolinone (9h): At 0 °C, potassium hydride (1.2 g, 30 mmol), followed 30 min later by 2-fluoro-3-methoxyacryloyl chloride[63] (4.1 g, 30 mmol) was added to a vigorously stirred solution of 2-*tert*-butyl-*N*-methylaniline[90] (2.1 g, 30 mmol) in tetrahydrofuran (60 mL). The intermediate *N*-2-*tert*-butylphenyl-2-fluoro-3-methoxy-*N*-methyl-2-propenamide was isolated by distillation under reduced pressure [yellowish oil; b.p. 130–131 °C/0.1 Torr; yield 6.7 g (84%). ^{1}H NMR: δ = 7.50 (d, *J* = 8.3 Hz, 1 H), 7.28 (t, *J* = 8.3 Hz, 1 H), 7.17 (t, *J* = 7.7 Hz, 1 H), 6.95 (d, *J* = 7.7 Hz, 1 H), 6.88 (d, *J* = 17.9 Hz, 1 H), 3.75 (s, 3 H), 3.20 (s, 3 H), 1.38 (s, 9 H) ppm. ^{19}F NMR: δ = –147.3 (d, *J* = 17.9 Hz) ppm. $C_{15}H_{20}FNO_2$ (265.33): calcd. C 67.90, H 7.60; found C 67.64, H 7.86]. The viscous liquid (6.6 g, 25 mmol) was heated with 70% (approx. 12 M) aqueous sulfuric acid (50 mL) for 5 h to 60 °C. The mixture was poured into ice/water, neutralized with solid sodium hydrogen carbonate and extracted with ethyl acetate (3 × 0.25 L). The combined organic layers were dried and the solvents evaporated. The residue was purified by chromatography on silica gel (0.25 L) using a 1:9 (v/v) mixture of ethyl acetate and hexanes as the eluent; colorless needles; m.p. 126–127 °C (after sublimation); yield 2.6 g (37%; 45% with respect to the amide intermediate). ^{1}H NMR: δ = 7.67 (dm, *J* = 7.5 Hz, 1 H), 7.3 (m, 2 H), 7.19 (t, *J* = 7.5 Hz, 1 H), 3.72 (s, 3 H), 1.50 (s, 9 H) ppm. ^{19}F NMR: δ = –132.2 (d, *J* = 8.8 Hz) ppm. ^{13}C NMR: δ = 159.6 (d, *J* = 26.4 Hz, 1 C), 149.7 (d, *J* = 255 Hz, 1 C), 139.8 (s, 1 C), 139.2 (s, 1 C), 131.5 (d, *J* = 2.9 Hz, 1 C), 125.8 (d, *J* = 5.9 Hz, 1 C), 123.1 (s, 1 C), 121.9 (d, *J* = 5.9 Hz, 1 C), 118.9 (d, *J* = 16.8 Hz, 1 C), 43.8 (d, *J* = 1.5 Hz, 1 C), 36.9 (s, 1 C), 32.6 (s, 3 C) ppm. $C_{14}H_{16}FNO$ (233.28): calcd. C 72.08, H 6.91; found C 72.20, H 6.91.

Acknowledgments

This work was supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (grants 20-49′307-96, 20-55′303-98 and 20-100′336-00). The authors are obliged to Mr. Björn Wagner, Dr. Manfred Kansy and Prof. Klaus Müller, all from Hoffmann-La Roche (Basel, Switzerland) for the reported pK_a measurements.

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Received: February 1, 2008
Published Online: March 27, 2008

