Photochemistry of some fluoroquinolones: effect of pH and chloride ion

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A 6-fluoroquinolone (norfloxacin) and the naphthyridine analogue enoxacin give the corresponding 6-hydroxy derivatives by irradiation in water at pH 7.2 and, with lower efficiency, at pH 4.5 and 10. At pH 1 no defluorination takes place and the piperazinyl side chain is degraded. The 6,8-difluoro derivative lomefloxacin is defluorinated selectively from position 8 over the entire pH range considered (pH 1 to 10). The intermediate cation in position 8 does not add water and rather undergoes insertion into the β-CH bond of the neighboring *N*-ethyl group. The cation adds chloride, however. The structure–photoreactivity relationship for fluoroquinolones and the relation with the known phototoxicity of these compounds are commented upon.

Fluorinated organic derivatives are used for applications as varied as new materials or pharmaceuticals due to the fact that fluorine substitution imparts favourable properties while increasing stability, because of the chemical inertness of the carbon–fluorine bond. As an example, several fluoroaromatic or heteroaromatic compounds have been shown to be superior to the non-fluorinated derivatives in their pharmacological activity and are actually used as drugs. A typical case is that of the quinolone antibacterials, where the first generation drugs such as nalidixic acid has been supplanted by fluorine-containing derivatives, nowadays amongst the most heavily prescribed antibacterials. Due to our interest in the photochemistry of heterocycles, we were attracted to this field by the numerous recent reports of the light-related adverse side-effects of such drugs. These have been reported to have phototoxic[1] and photoallergenic effects,[2] as well as, in some cases, photomutagenic and phototumorigenic effects.[3] This is a major limitation on their use in therapy.

The chemical mechanism underlying such effects has not been clarified up to now. A possible mechanism involves oxygen sensitization by these drugs,[4,5] but according to a recent study by Chignell *et al.* this is not the main one.[6,7]

Another possibility is that the drugs react photochemically with some cell component. Evaluation of this path requires that the photochemistry of these drugs is ascertained. Positive evidence about the photoreactions occurring has been scarce up to now. It has been suggested that ciprofloxacin undergoes photodimerization[8] and in the case of (−)-ofloxacin several products arising from the degradation of the alkylamino side-chain have been isolated and characterized.[9] In 1997–1998, several groups reported that defluorination is the main photochemical reaction from some of these drugs. Thus, Chignell *et al.*[10] and Monti *et al.*[11] showed that irradiation of some fluoroquinolones leads to release of fluoride anion, and our group (for the cases of lomefloxacin, enoxacin and norfloxacin)[12] as well as Morimuras one (for orbifloxacin)[13] actually isolated and identified the products of photodefluorination in water.

Fluoroquinolones are amphoteric substrates,[14,15] thus the species present in solution depend on the pH. Thus, the photochemistry is expected to be pH-dependent and there is some literature indication that both the photodecomposition[11,16] and the oxygen photosensitization efficiency[6] of some of these derivatives depend on the pH. However, there is no indication of whether the reaction path may be different at different pH. We now report a product and quantum yield study on the photochemistry of some fluoroquinolones at different pH and in the presence of chloride which allows a better understanding of the mechanism.

Results

Three fluoroquinolones were selected for this study, *viz.* 1-ethyl-6-fluoro-7-piperazinyl-4-oxoquinoline-3-carboxylic acid (**1**, norfloxacin), which may be taken as the simplest example of the commonly used drugs of this group,[17] a naphthyridine analogue, enoxacin (**2**), and lomefloxacin (**3**), which, apart from a methyl group in the chain, differs in having an additional fluorine in position 8. In view of the amphoteric nature of these molecules, conditions were chosen as to have one of the ionic forms predominant.

Two sets of experiments were carried out, in both cases using argon-flushed aqueous solutions of the fluoroquinolones. In the first series, aimed at assessing the relative reactivity of these derivatives, dilute [$(1–2) \times 10^{-4}$ M] solutions were irradiated and the conversion was limited to 30%, in order to minimize secondary photolysis. In the latter series, larger amounts of saturated solutions were irradiated with the aim of separating and identifying the photoproducts.

Effect of pH

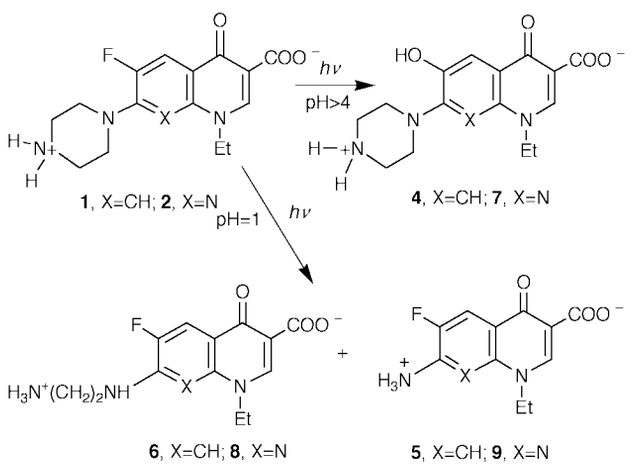
Irradiation of a neutral solution of norfloxacin (**1**) (5×10^{-4} M, $NaHCO_3$ added to bring the pH at 7.2) gave a single major product. We had previously shown in preparative experiments[12c] that this was the hydroxyquinolone **4** through characterization of the corresponding *N*-ethoxycarbonyl derivative (Scheme 1). The effect of pH on the photoreaction was now explored. In every case, the decomposition quantum yield was measured and the fluoride liberated was potentiometrically determined directly from the photolyzed solution. At pH 7.2, Φ_{dec} was 0.06 and the molar amount of fluoride formed was identical (±5%) to that of decomposed **1**. With solutions of **1** at pH 10 (by addition of NaOH) or 4.5 (by addition of either HCl or $HClO_4$) the reaction course remained the same, with the same peak in the HPLC and release of fluoride equivalent to the substrate decomposition, but the quantum yield was lower (Table 1).

On the other hand, when a solution at pH 1 (by addition of either HCl or $HClO_4$) was irradiated, the fluoride liberated was <10% of the substrate decomposed. A preparative experiment under these conditions led to the isolation of two products. These were recognized as the fluorine-containing amino-

Table 1 Photochemical reactions of fluoroquinolones **1** and **2**

		No added salt			0.2 M chloride		
Substrate	pH	Φ_{dec} [a]	F^- (%)	Product	Φ_{dec}	F^- (%)	Product
1	10	0.005 (0.007)	100	**4**	0.007		
1	7.2	0.06 (0.009)	100	**4**	0.06	100	**4**
1	4.5	0.012 (0.01)	100	**4**	0.01	100	**4**
1	1	0.002	<10	**5**	0.002	<10	**5**
3	10	0.065	100	**10**			
3	7.2	0.55 (0.55)	100	**10**	0.5	100	**11**
3	4.5	0.33	93	**10**	0.23	78	**11**
3	1	0.022	74	**10**	0.009	93	**11**

[a] In parentheses is the value in the presence of $NaClO_4$ to make the total anion concentration 0.2 M. The products formed remain the same.

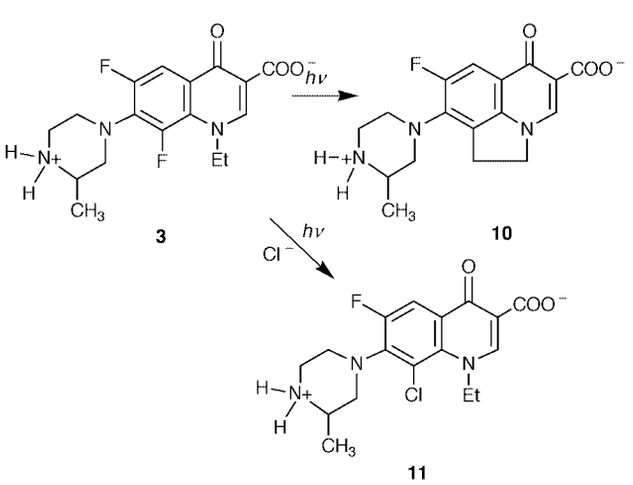


Scheme 1

quinolone **5** (which was obtained by chloroform extraction of the irradiated solution) and **6** (recrystallized from the residue after distillation of the solvent, see Scheme 1).

We extended the preparative experiments to the naphthyridine derivative enoxacin (**2**). This compound under neutral conditions is similarly defluorinated and gives phenol **7**.[12c] When the irradiation was carried out at pH 1, fluorine-containing products were obtained, *viz.* the aminoquinolones **8** and **9** (see Scheme 1).

In the case of the 6,8-difluoroquinolone lomefloxacin (**3**) we had found that irradiation under neutral conditions led to selective defluorination from position 8, and the product resulted not from solvolysis but from cyclization onto the *N*-ethyl chain to give the pyrroloquinolinone **10** (Scheme 2).[12c] The medium dependence of this reaction was now explored. It was found that with this substrate the photoreaction was



Scheme 2

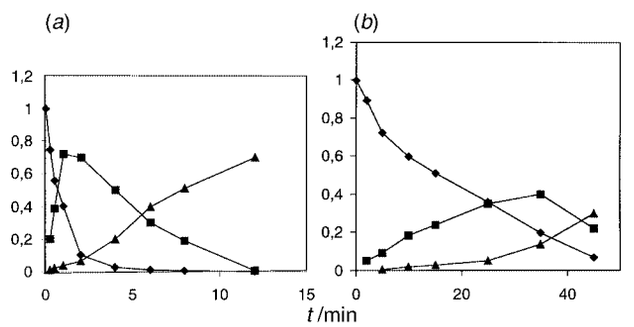


Fig. 1 (*a*) Decomposition of lomefloxacin (**3**) (◆) and formation of products **11** (■) and **1** (●) by irradiation of an aqueous solution 0.2 M in NaCl at pH 7.2. (*b*) The same in 0.1 M HCl.

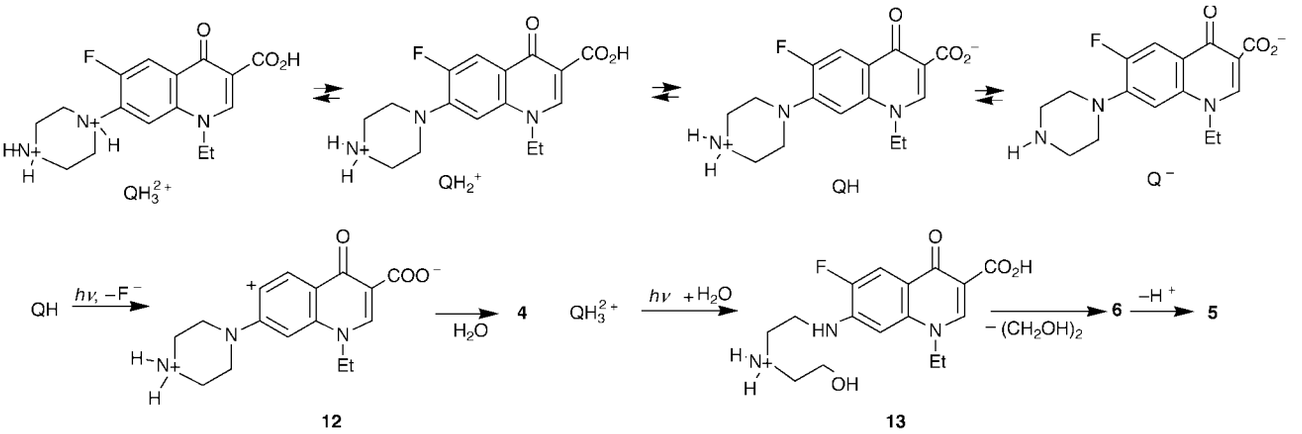
consistently defluorination ($\Phi_{dec} \cong \Phi_{-F^-}$) over the whole range explored (pH 10, 7.2, 4.5 and 1). Compound **10** remained the main product provided that $HClO_4$ was used for acidification (HCl gave a different result, see below). The decomposition quantum yield for **3** was significantly larger than in the case of the monofluoro analogue **1** [Φ_{dec}(**3**) = 0.55 at pH 7.2, see Table 1] and was again reduced both by increasing and decreasing the pH.

Effect of added salts

Carrying out the above reactions at the same pHs as above while maintaining a constant ionic strength by adding sodium perchlorate so as to have a 0.2 M total ion concentration did not change the course of the reactions and caused minor changes in the quantum yield (see Table 1).

Experiments were also carried out in the presence of 0.2 M chloride. In this case, quinolone **1** gave exactly the same results as in the absence of added salt (Table 1), while the chemistry of **3** changed. With this substrate the quantum yield of decomposition decreased somewhat with respect to the perchlorate solution (particularly at low pH, see Table 1) and a new peak was detected by HPLC. Preparative experiments on a neutral solution 0.1 M in NaCl showed in fact that the main product after 35 min irradiation (*ca.* 70% conversion of **3**) was not **10** but the 6-fluoro-8-chloroquinolone **11** (Scheme 2), which was isolated as the *N*-ethoxycarbonyl methyl ester. However, prolonged irradiation up to complete conversion of the starting substrate gave again compound **10** as practically the only product. Likewise, irradiation (7 h) of a solution 0.1 M in HCl gave chlorinated **11**, while longer irradiation gave **10**.

The progress of the reaction could be conveniently monitored by HPLC in small scale experiments, showing that in the presence of chloride compound **11** was practically the only product at the beginning of the irradiation, while the tricyclic derivative **10** increased at the expense of the former at a rate which became significant after most of **3** had been converted [see Fig. 1(*a*) and (*b*) for neutral and acidic solutions respectively].



Scheme 3

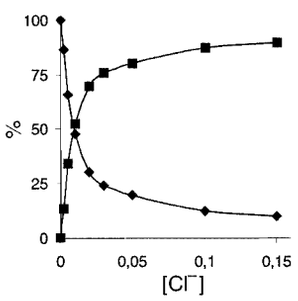


Fig. 2 Proportion of products **10** (◆) and **11** (■) as obtained at *ca.* 25% conversion by irradiation of an aqueous solution of drug **3** at pH 7.2 containing NaCl and $NaClO_4$ (total salt concentration 0.2 M).

In order to have a more precise indication of the effect of chloride concentration on the competition between the two processes from **3**, a further series of experiments with this drug was carried out maintaining a constant ionic strength. Thus irradiations were performed on a neutral solution in the presence of NaCl–$NaClO_4$ in various ratios with a total salt concentration of 0.2 M. The corresponding change in the ratio of products **10** and **11** (measured at *ca.* 25% conversion) is represented in Fig. 2.

Discussion

Reactions of the quinolone excited state: structure and medium dependence

As has been mentioned in the introduction, it has recently become clear that defluorination is the main process upon irradiation of some fluoroquinolones.[12,13] Actually, for the presently considered derivatives **1**–**3** under most conditions, defluorination is the only process ($\Phi_{dec} = \Phi_{-F^-}$, see Table 1).

However, there are important differences in the chemical processes occurring and in the medium dependence among the drugs studied. Thus, substitution of a hydroxy group for the fluorine atom takes place with quinolones **1** and **2**, except at pH 1, where degradation of the alkylamino side-chain is the main process. With compound **3**, on the other hand, defluorination (selectively from position 8) occurs over the whole pH range considered, but leads to intramolecular alkylation rather than substitution by an OH group.

As for the pH dependence, the conditions were chosen in order to explore the behavior of the different ionic forms of these substrates. The dissociation constants for protonation and deprotonation of norfloxacin (**1**) are 6.22 and 8.51 respectively, and the corresponding values for lomefloxacin (**3**) are 5.49 and 8.78.[14] Thus at pH *ca.* 7 these molecules are present essentially as the zwitterions QH (see Scheme 3). On the other hand there is ≥90% of the anion Q^- at pH 10 and of the monocation QH_2^+ (protonation of the piperazine moiety) at pH 4.5. A second protonation has not been characterized for the present quinolones or for the parent 7-amino-4-quinolone. However, taking into account the protonation equilibria of 1-methyl-4-quinolone (pK 2.34)[18] and 7-aminoquinoline (first pK 6.65, second pK −0.03)[19,20] it is reasonable to conclude that the dication QH_3^{2+} is the main species at pH 1 (protonation at the 7-amino group is shown in Scheme 3, other tautomers may be present). As appears in Table 1, the efficiency of the photoreaction changes significantly over the pH range explored.

With substrate **1**, photoinduced solvolysis is the main process in the pH range 4.5–10, though with decreased efficiency under both basic and acidic conditions with respect to neutral conditions. Related photoinduced aromatic substitutions occur either *via* an addition–elimination mechanism [eqn. (1)], as demon-

$$ArX^* + Nu^- \longrightarrow ArXNu^- \longrightarrow ArNu + X^- \quad (1)$$

strated for several nitroanisoles,[21] or *via* a $S_{RN}1$ mechanism, as recently suggested for electron-donating substituted halobenzenes,[22] where the internal charge transfer character of the excited state causes incipient heterolytic labilization on the carbon–halogen bond [eqn. (2)]. The latter mechanism seems

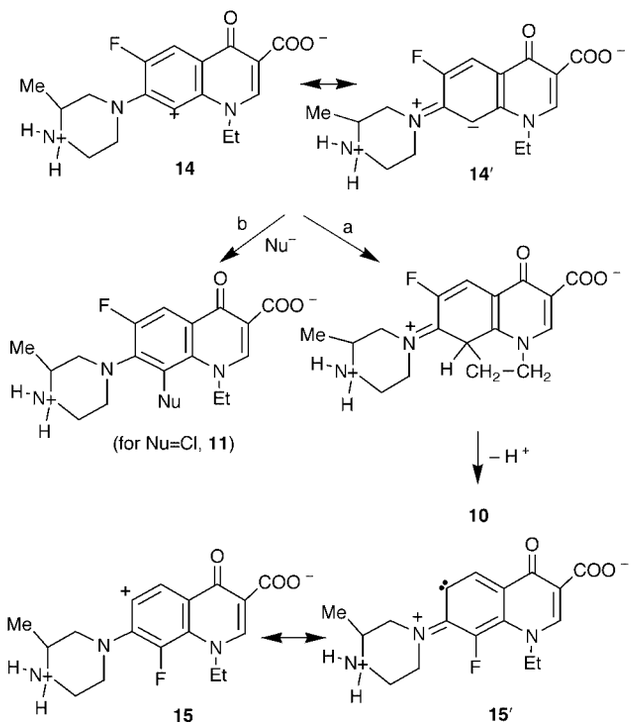
$$ArX^* \equiv Ar^{\delta+}\text{–}X^{\delta-} \longrightarrow Ar^+ + X^- \; Ar^+ + Nu^- \longrightarrow ArNu \quad (2)$$

appropriate for the present substrates, due to the presence of the electron-donating amino group, and better explains some characteristics of the reaction (see below). Cation **12** is then the intermediate in the substitution to give **4** (Scheme 3). The decrease in the quantum yield of reaction by changing the pH is roughly proportional to the decrease in the proportion of zwitterion QH present. A simple hypothesis would thus be that the photonucleophilic substitution is characteristic of this species, rather than of the singly charged ions, *i.e.* that heterolytic C–F bond cleavage is more efficient from the zwitterion QH (where it gives a cation) than from the cation QH^+ (giving a dication) or in the anion Q^- (giving a non-stabilized zwitterion).

At pH 1 the dication QH_3^{2+} is present and since the second protonation—contrary to the first one—involves a nitrogen atom directly linked to the aromatic π system, the degree of internal charge transfer occurring in the excited state is decreased (see Scheme 3). As a result, with quinolones **1** and **2** defluorination becomes a minor path, while the main reaction involves the piperazinyl chain. This is a quite inefficient process and may be envisaged as a hydrolysis of the C–N bond favored by the positive charge on the nitrogen in the dication and giving intermediate **13** (Scheme 3), though there are certainly other possibilities. An inefficient degradation of the *N*-alkyl chain has often been observed with arylalkylamines, *e.g.* in the presence

of excited hydrogen and electron acceptors such as ketones[23] and aromatics[24] under various conditions. It is thus not unexpected that this reaction occurs, with $\Phi \cong 10^{-3}$, when the unimolecular decomposition of the heterocyclic moiety is inhibited. In this way, fluorine-containing aminoquinolones **6** and, by further hydrolysis, **5** are obtained from **1**, and analogously **8** and **9** are obtained from **2**.

With the difluoro derivative **3** defluorination occurs selectively from position 8, is 5 to 10 times more efficient than with **1** or **2** and remains the dominant process over the whole pH range explored (1 to 10), though again the efficiency drops when getting away from neutrality. We previously suggested that the increased photolability introduced by further fluorine substitution in position 8 is due to the increased stability of the aryl cation in this case.[12b] As is shown in Scheme 4, the σ aryl cation



Scheme 4

in position 8 (see structure **14**) is stabilised by the contribution of a mesomeric π cation where the aromaticity of the pyridone moiety is conserved (**14′**),† whereas this is not the case for a cation in position 6, because in that case the π mesomer contributes to a lesser degree, as the pyridone aromaticity is lost in that structure (compare mesomer **15′** in Scheme 4). This explains both the regioselectivity in the photodefluorination of **3** and the lower reactivity of 6-monofluoro derivatives such as **1** and **2**. The extra reactivity of fluorine in position 8 is also in accord with the present finding that reaction at that position in **3** is less pH-dependent than that at position 6 in either **1** or **2**.

Chemistry of the photochemically formed aryl cation

As mentioned above, photoinduced heterolytic C–F bond cleavage leads to a different end result with **1** and **2** on one hand (nucleophilic substitution by water) and with **3** on the other (insertion in a C–H bond). A related case of dual chemistry has been previously observed by Schuster *et al.* with some 4-substituted phenyl cations (resulting from the photodecomposition of the corresponding phenyldiazonium salts) in trifluoroethanol [eqns. (3) and (4)].[26]

† The stabilisation of the pyridone structure *via* neutral and zwitterionic mesomers is well known (ref. 25).

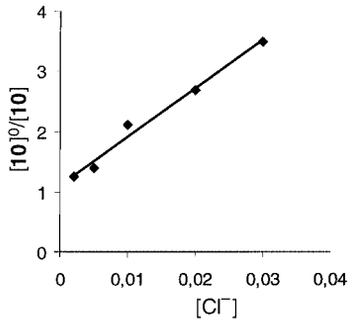


Fig. 3 Ratio of the amount of product **10** formed in the absence ($[\mathbf{10}]^0$) and in the presence of NaCl as obtained by irradiation of an aqueous solution of drug **3** at pH 7.2 containing NaCl and $NaClO_4$ (total concentration 0.2 M).

$$4\text{-}XC_6H_4^+ + CF_3CH_2OH \longrightarrow 4\text{-}XC_6H_4OCH_2CF_3 + H^+ \quad (3)$$

$$4\text{-}XC_6H_4^+ + CF_3CH_2OH \longrightarrow 4\text{-}XC_6H_5^{+\bullet} + CF_3\dot{C}HOH \quad (4)$$

The 4-amino derivatives (X = NEt_2, morpholino) behave as electrophiles and give the trifluoroethyl ethers (as one would expect from the singlet state of the cation) while the 4-benzoyl derivative abstracts hydrogen (as expected from the triplet state).[26] Thus, seemingly strictly related cations may show different reactivity. As suggested before,[12] with the quinolones this is rationalized by the contribution of the π mesomer **14′** to the cation from **3**. In this structure the charge is on the nitrogen and position 8 has a carbene character (possibly a triplet), in line with the observed intramolecular insertion into a C–H bond (presumably a two-step homolytic process) (Scheme 4). On the contrary, cations in position 6, such as those formed from **1** and **2** (see formula **12** in Scheme 3) do not admit such mesomerism and the localized σ cations behave as electrophiles adding water. The present study shows that, while water is unable to trap cation **14**, a charged nucleophile such as chloride ion adds to it, and under these conditions the overall result is again fluorine substitution [to give chlorinated **11**, compare paths (a) and (b) in Scheme 4]. On the other hand, chloride up to 0.2 M does not interfere with the formation of phenol **4** from **1**, consistent with an unselective reaction from the less stabilized cation **12**, which simply adds to the most abundant nucleophile, as happens with the parent phenylium cation.[27,28]

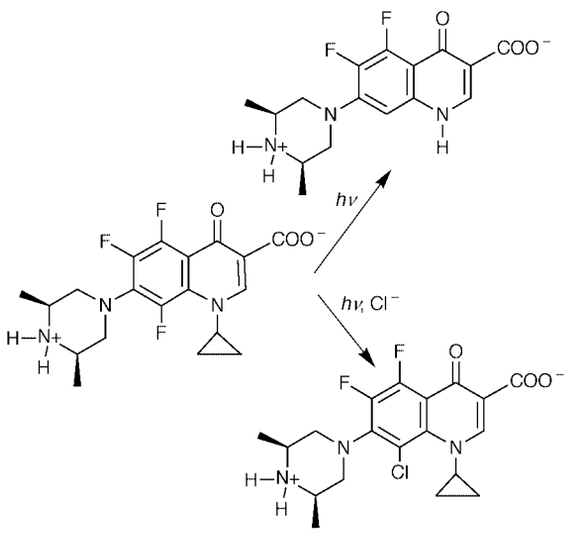
The competition between intermolecular chloride addition and intramolecular insertion has been studied at different chloride concentrations at constant ionic strength (0.2 M total for $NaClO_4$ and NaCl). As Fig. 2 and Table 1 show, path (b) becomes significant at $[Cl^-] = 1 \times 10^{-3}$ M and is >90% at $[Cl^-] = 0.15$ M. Under neutral conditions and constant ionic strength the overall quantum yield changes very little with different ratios of $NaClO_4$: NaCl, while the percentage of **11** changes from 0 to >90%. This supports the above hypothesis that the photochemical process follows an S_N1-type mechanism and the intermediate cation **14**↔**14′** partitions between two paths. If k_a and k_b are the rate constants of the two reactions, the ratio between the amount of compound **10** formed in the absence ($[\mathbf{10}]^0$) and in the presence ($[\mathbf{10}]$) of chloride depends linearly on the anion concentration according to eqn. (5).

$$[\mathbf{10}]^0/[\mathbf{10}] = 1 + k_b/k_a[Cl^-] \quad (5)$$

This expectation is borne out by experiment, as shown in Fig. 3. This gives $k_b/k_a = 80$ M^{-1}. Since the rate constant

of chloride addition obviously cannot overcome the diffusion constant, the cation must have a lifetime $\tau = 1/k_a > 2.5 \times 10^{-7}$ s.‡

The 8-choroquinolone **11** is, as one would expect, itself photoreactive *via* C–Cl fragmentation at position 8 and yields again cation **14**. Therefore, prolonged irradiation of **3** gives the tricyclic derivative **10** also in the presence of chloride through two photochemical steps *via* **11** (see Fig. 1). Efficient defluorination from position 8 and the two-fold electrophile–carbene chemistry of the resulting cation is not exclusive to lomefloxacin. In fact, Murimura found that the 1-cyclopropyl-7-piperidino-5,6,8-trifluoro derivative orbifloxacin likewise undergoes selective monodefluorination.[5,29] The product obtained results from the substitution of a hydrogen for a fluorine atom in position 8 and the loss of the cyclopropyl group from position 1 (Scheme 5). This is probably due to the fact that



Scheme 5

the cation undergoes intramolecular H abstraction from the *N*-cyclopropyl group, analogously to the attack at the *N*-ethyl group observed with **3**, with the difference that the labile cyclopropyl moiety is degraded in this case. However, in the presence of chloride anion, the 8-chloro substituted product conserving the *N*-cyclopropyl chain was obtained also in this case in a growing proportion for $[Cl^-] = 0.05$ to 0.2 M,[29] again analogously to **3**.

Relation with phototoxicity

This chemical evidence should be compared with the results from photobiological research. It has been known for some time that the presence of a halogen (F or Cl) at position 8 strongly enhances the phototoxicity of quinolone drugs.[30] Recently, Chignell showed that 6,8-difluoro derivatives such as lomefloxacin and fleroxacin are 10-fold more efficient in generating single strand DNA breaks after UV-A irradiation than are 6-fluoro derivatives such as norfloxacin.[7b] The fact that the photoinduced defluorination of the species also occurs in the same order, something which is not the case for their ability to activate oxygen,[6,7] coupled with the formation of highly reactive intermediates in the defluorination process, suggests that the biological effect may be due to covalent binding to some cell component *via* such an intermediate. The chemical studies show that an aggressive aryl cation is formed both from 6-fluoro and 6,8-difluoro quinolones, suggesting that the mechanism of phototoxicity remains the same, though the efficiency is different. The photoinduced cleavage appears to be a necessary consequence of the combination of electron donating and accepting substituents which makes the C–F bond labile in the excited state, particularly when in position 8.

The above structure–reactivity relationship is supported by literature data showing that insertion of a further donating group strongly limits photoreactivity and phototoxicity, presumably by affecting the internal charge transfer character of the excited state. Thus, an 8-alkoxy substituent has been consistently found to reduce both the photolability and the phototoxicity as observed with ofloxacin (Φ_{dec} 0.001 at neutral pH)[12b] and other alkoxy derivatives.[31] More generally, all electron-donating groups, independent of their position, have the same effect (*e.g.* a 5-amino-6-fluoro-7-alkylamino-8-methyl derivative has been found to be rather stable).[32] Noteworthy is the case of sparfloxacin, a 5-amino-7-dialkylamino-6,8-difluoroquinolone, where the additional amino group in position 5 *prevents* the photolability that would be expected for the fluoro group in position 8.[33]

Conclusion

Some 6-fluoro- and 6,8-difluoro-7-aminoquinolones have been found to photodecompose, with a higher efficiency in the latter case. The reaction occurring is defluorination, and product analysis and medium dependence suggest that this takes place through an S_N1 mechanism *via* an aryl cation. Although a detailed quantum yield and product analysis has been carried out only in a few cases, the sparse literature data are compatible with the hypothesis that this is a general reaction. The cation in position 6 adds water, while the cation in position 8 instead undergoes a carbene insertion into the neighboring *N*-alkyl chain. Addition is obtained also in position 8 when a charged nucleophile such as choride is present. These drugs absorb in the UV-A region and decompose when exposed to solar or room light. They are known to be phototoxic and the efficiency of photodefluorination correlates with the extent of the photobiological effect. This suggests that the reported phototoxic effect of these drugs may be related to covalent binding of the photochemically generated aryl cation intermediate to some biological substrate. From the point of view of drug design, it should be taken into account that the efficiency of the photodecomposition is related to the internal charge transfer character of the excited state.

Experimental

Norfloxacin (**1**) and enoxacin (**2**) were purchased from Sigma Chemicals Co. (Milan) and used without further purification. Lomefloxacin hydrochloride, from the same supplier, was dissolved in water (0.02 M solution) and 1 M NaOH was added to neutrality. The free base (**3**) was extracted with chloroform (mp 231–234 °C). All other chemicals and solvents were reagent grade or better. The pH was measured by means of a glass electrode.

Small-scale irradiations

Small scale photochemical reactions for quantum yield determination and for the determination of the medium effect were carried out on 10 ml portions of aqueous solution of the drugs (0.1 mM) in serum capped quartz tubes. These were irradiated in a merry-go-round apparatus by means of two 15 W phosphor-coated lamps (center of emission 313 nm). Deoxygenation of the solution was obtained by flushing for 1 h with argon passed through an appropriate furnace for eliminating traces of oxygen.

The light flux was measured by ferrioxalate actinometry.

The substrate decomposition was determined by HPLC (Waters Model 501 apparatus) with optical detection (Waters

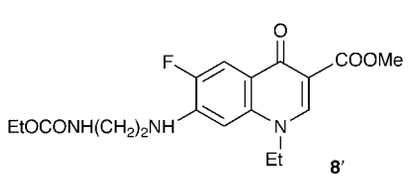
‡ Dr S. Monti (CNR, Bologna, Italy) communicated to us the fact that experiments are under way in her laboratory aimed at establishing the formation of transients.

490E, λ 276 nm). An inverse-phase Merck Purosphere RP-18 e (5 μm) column (3 × 125 mm) was used. The eluant was an 85 : 15 mixture of pH 3 buffer (prepared by adding phosphoric acid to a 0.75% solution of triethylamine until pH 3 was reached) and acetonitrile. A few microlitres of a solution of an appropriate standard (**3** for **1**, ofloxacin for **2** and **3**) were added to the photolyte before analysis.

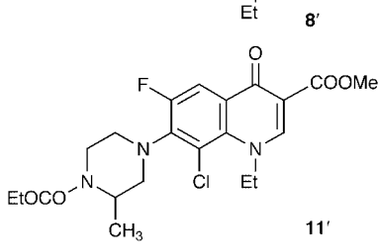
The fluoride concentration was measured by means of an Orion SA520 potentiometer using a selective electrode (Orion F-94-09) after addition of 2 ml of Orion TISAB III buffer (ammonium acetate, ammonium chloride, 1,2-cyclohexylidene-α,δ-dinitrilotetraacetic acid) to the 10 ml photolyte and dilution to 22 ml with distilled water.

Preparative irradiations

A solution of norfloxacin (**1**, 450 mg, 1×10^{-3} M) in 1.4 l of 0.1 M HCl was flushed for 1 h with purified argon and then irradiated in an immersion well apparatus by means of a Pyrex-filtered 500 W medium pressure mercury arc (Helios Italquartz) at 25 °C while maintaining a slow flux of argon. The course of the reaction was monitored by HPLC (see above). After 115 h the acidic solution was extracted with an equal volume of chloroform to give the known amine **5** (50 mg).[34] The aqueous phase was evaporated and the residue recrystallized from ethanol to give 7-(2-aminoethylamino)-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**6**, 70 mg), previously reported[35] but not spectroscopically characterized. ^{1}H NMR [$(CD_3)_2SO$, 80 °C, at room temp., broad lines] δ 1.4 (t, J 7 Hz, 3H), 3.1 (m, 2H), 3.7 (m, 2H), 4.55 (q, J 7 Hz, 2H), 6.7 (br s, exch, 1H), 6.95 (d, J 7 Hz, 1H), 7.71 (d, J 12 Hz, 1H), 8.3 (br s, exch, 2H), 8.3 (s, 1H), 14.0 (br s, exch, 1H). A solution of enoxacin (**2**, 640 mg, 2×10^{-3} M) in 1.1 l of 0.1 M HCl was irradiated under argon as above for 12 h. A precipitate formed during the irradiation and was filtered to give 7-amino-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**9**, 80 mg), previously not spectroscopically characterized.[36] ^{1}H NMR [$(CD_3)_2SO$] δ 1.3 (t, J 7 Hz, 3H), 4.4 (q, J 7 Hz, 2H), 7.8 (br s, exch, 2H), 7.9 (d, J 7 Hz, 1H), 8.3 (s, 1H). ^{13}C NMR [$(CD_3)_2SO$] δ 19.4, 51.5, 112.1, 115.5, 120.9 (d, J 17 Hz), 149.8 (d, J 255 Hz), 150.9, 151.4, 157.1 (d, J 17), 170.8, 180.0. The aqueous solution was neutralized and extracted by 2 × 300 ml 1% ethyl chloroformate in chloroform. The organic layer was washed with aqueous $NaHCO_3$ and water, dried and concentrated. Excess ethereal diazomethane was added and the residue was chromatographed on a silica gel column (eluent, $CHCl_3$–MeOH mixtures) to give, besides functionalized unreacted starting material, 7-(2-ethoxycarbonylaminoethyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid methyl ester (**8′**, 60 mg). Mp 148–150 °C (toluene) (Found: C, 57.1; H, 5.8; N, 11.0. Calc for $C_{18}H_{22}N_3FO_5$: C, 56.99; H, 5.80; N, 11.8%). ^{1}H NMR ($CDCl_3$) δ 1.3 (t, J 7 Hz, 3H), 1.5 (t, J 7 Hz, 3H), 3.5 (m, 2H), 3.7 (m, 2H), 3.9 (s, 3H), 4.1 (q, J 7, 2H), 4.3 (q, J 7 Hz, 2H), 5.85 (br s, exch, 1H), 6.5 (br s, exch, 1H), 7.9 (d, J 12 Hz, 1H), 8.4 (s, 1H). ^{13}C NMR ($CDCl_3$)



8′



11′

δ 14.5, 14.9, 39.9, 41.8, 47.0, 51.9, 60.9, 110.9, 114.6, 117.0 (d, J 17 Hz), 143.8, 146.8 (d, J 255 Hz), 147.2, 150.1 (d, J 15 Hz), 157.3, 166.1, 173.7. Compound **8** has been previously reported but not characterized.[36]

A solution of lomefloxacin (**3**, 70 mg, 1.4×10^{-4} M) in 1.4 l of 0.2 M NaCl solution was irradiated as above for 35 min. The solution was extracted with 3 × 500 ml 1% ethyl choroformate in chloroform and the organic layer was dried, concentrated to 10 ml, treated with excess ethereal diazomethane and evaporated. Chromatography as above gave 8-chloro-1,4-dihydro-7-(4-ethoxycarbonyl-3-methylpiperazinyl)-1-ethyl-6-fluoro-quinoline-3-carboxylic acid methyl ester (**11′**, 11 mg) (Found: C, 55.3; H, 5.7; N, 9.0. Calc for $C_{21}H_{25}N_3FClO_5$: C, 55.57; H, 5.51; N, 9.26%). ^{1}H NMR [$(CD_3)_2CO$] δ 1.3 (t, J 7 Hz, 3H), 1.4 (d, J 7 Hz, 3H), 1.5 (t, J 7 Hz, 3H), 3.15 and 3.55 (two m, 2H), 3.2 and 3.3 (two m, 2H), 3.45 and 4.0 (two m, 2H), 3.75 (s, 3H), 4.15 (m, 2H), 4.75 and 4.82 (two m, 2H), 7.95 (d, J 12 Hz, 1H), 8.55 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.6, 15.6, 15.9, 39.1, 47.4, 51.0, 52.2, 52.6, 55.2, 61.4, 110.6, 113.2 (d, J 22), 128.4, 135.5, 142.5 (d, J 15 Hz), 150.9, 152.4, 155.4, 156.8 (d, J 250 Hz), 165.9, 172.2. m/z 453 (base peak, contains 1 Cl). The non-functionalized product **11** is known.[37]

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