The photochemistry of lomefloxacin. An aromatic carbene as the key intermediate in photodecomposition

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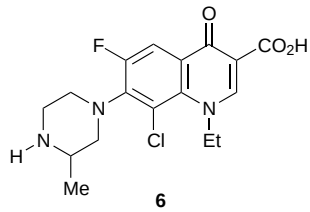
Irradiation of the 6,8-difluoroquinolone antibiotic lomefloxacin causes selective heterolytic defluorination from position 8 and leads to products rationalized as arising from the cation either *via* nucleophile addition or intramolecular carbene C–H insertion and hydrogen transfer.

The strong antibacterial activity of fluoroquinoles (FQ) has led to their large-scale use in medicine.[1] A major drawback of this relatively new class of antibiotics is their phototoxic effects.[2–8] There are indications that reactive oxygen species, such as singlet oxygen, superoxide anion or hydroxyl radical, play a role in some cases.[9–14] However, this is not necessarily the main mechanism underlying such an effect. As an example, it has recently been reported that in the case of lomefloxacin **1**, which is not only more phototoxic than other FQs but also more photomutagenic and carcinogenic,[15,16] the phototoxic effect is not related to singlet oxygen and superoxide anion generation[17] and furthermore photoinduced single strand breaks in plasmid DNA are actually *decreased* in the presence of oxygen.[18] This suggests that oxygen activation is not involved, and that a different mechanism operates; it has also been noted that fluoride ion is liberated during the photolysis of **1**.[18] An investigation of the photochemistry of **1** was thus warranted. As is shown in the following, a detailed product study demonstrates the unusual photochemical behaviour of this molecule and suggests a mechanism for the toxic and particularly the carcinogenic/mutagenic activity.

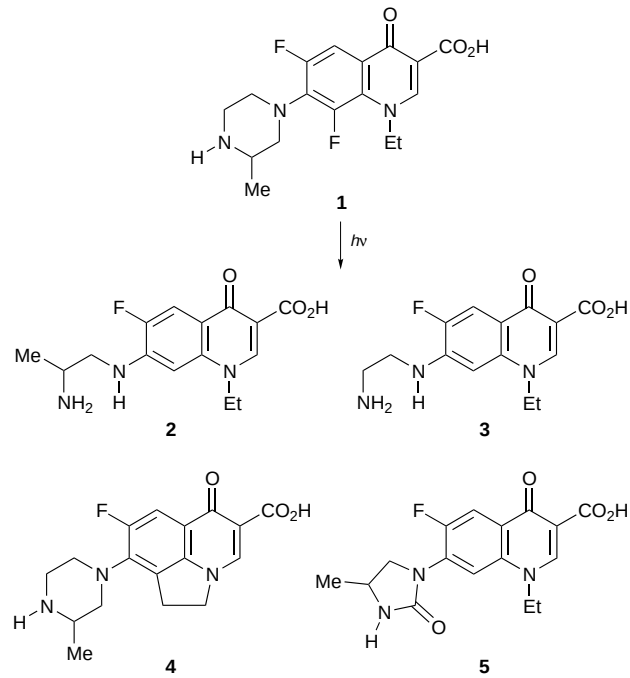
Irradiation (λ > 310 nm) of lomefloxacin **1** (10^{-4} M) in argon-flushed phosphate buffer (pH 7.4) up to 90% conversion gave several products. These were transformed into the corresponding *N*′-ethylcarbamates by treatment with ethyl chloroformate, extracted with chloroform, esterified by treatment with diazomethane and chromatographically separated. In this way, the main photolysis products were recognised as the two diamines **2** and **3**, accompanied by minor amounts of the tricyclic derivative **4** and a trace of the imidazolonyl derivative **5** (Scheme 1). Irradiation of the hydrochloride of **1** in argon-flushed water (pH 4.3) gave the 8-chloro derivative **6** as one of the main products.†



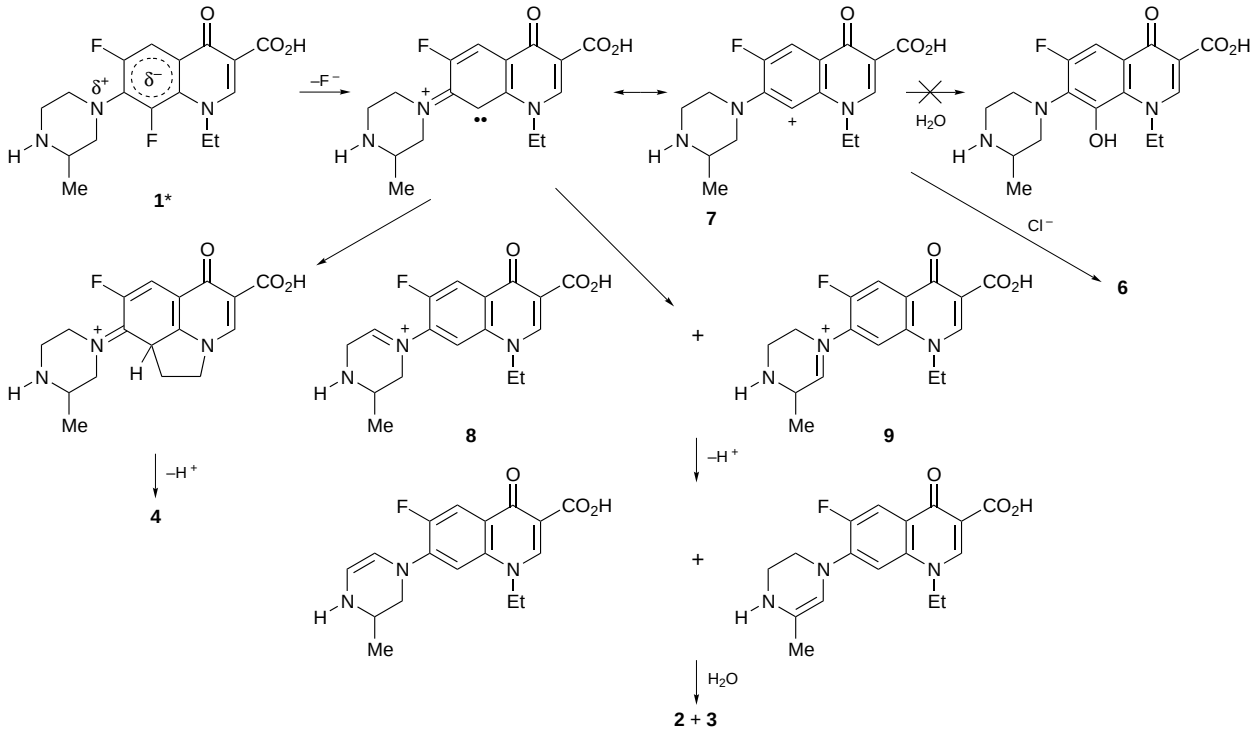
6

Inspection of **2**–**5** shows that two processes occurred in all cases, *viz* (i) reductive defluorination selectively at position 8, and (ii) modification of an *N*-alkyl chain, either the piperazinyl group (products **2**, **3** and **5**) or the 1-ethyl group (product **4**). Since the photoproducts are themselves FQs, competitive light-absorption by the products and the starting material occurred. However, when the irradiation was limited to a lower conversion (35%) the ratio of products was essentially the same. Furthermore, we found that **1** (Φ_{dec} 0.65) was far more sensitive to irradiation than all the monofluoro FQs we examined under these conditions (Φ_{dec} < 0.03) and also than compounds **2**–**5**, which are monofluoro derivatives. Thus, these products arose from a monophotonic reaction, and both processes (i) and (ii) occurred in a single reaction rather than *via* two sequential photoinitiated steps. Furthermore the product distribution was again similar in air-equilibrated solution. On the other hand, irradiation of the monohydrochloride omitting the buffer gave product **6**, conserving the piperazine ring intact and with substitution of a chloro group for the 8-fluoro atom.

The mechanism we propose is indicated in Scheme 2. The reaction proceeds from the short-lived singlet excited state and is by far the main decay path ($\Phi_{react} \approx 0.65$, τ_{fluo} < 1 ns, little influence of dissolved oxygen, thus Φ_{isc} is low and the triplet has little role in the reaction). Homolysis of the C–F bond is obviously out of question (bond dissociation energy C–F = 125 kcal mol^{-1}, energy of signlet excited **1** = 81 kcal mol^{-1}). Thus heterolytic loss of F^- is involved, and the mechanism proposed must explain also the other modification occurring concurrently. The singlet state has an internal charge transfer character (strong Stokes shift, 6000 cm^{-1}) and the zwitterionic form is important in **1***. Loss of fluoride leads to cation **7**, for which mesomeric carbocationic and carbene forms can be considered. In phosphate buffer we isolated no product arising from the carbocation (such as phenols), but that product **6** formed when the nucleophile is chloride substantiates this path. On the other hand a striking indication for carbene reactivity comes from the structure of product **4**, obviously resulting from well precedented carbene C–H insertion[19] into the conforma-



Scheme 1



Scheme 2

tionally suitable δ position. Products **2** and **3** also arise from the carbene *via* intramolecular hydrogen transfer to give the rearranged cations **8** and **9**. These deprotonate to enediamines, which in turn are hydrolysed, whether in solution or during work up, to the observed diamines. Compound **5** also results from demolition of the piperazinyl chain coupled with defluorination.

There are only a few precedents for photoinduced defluorination in aromatic or heterocyclic chemistry, *viz* those of *N*-formyl-4-fluorotryptophan methyl ester[20] and of some dimethoxyfluorobenzenes,[21] both involving related activation by electron-donating groups. The peculiarly high photoreactivity of lomefloxacin with respect to other FQs (see above) is certainly due to the selective defluorination from position 8, apparently due to activation by both the adjacent amino groups, which increase the zwitterionic character of the singlet excited state and facilitate the fragmentation indicated in Scheme 2. Studies in progress in this laboratory show however that this type of reactivity is rather general, and defluorination accompanied by alkylamino chain degradation also takes place in FQs containing only the 6-fluoro group, although with a lower efficiency.‡

The fact that cation **7** exhibits carbene chemistry dominated by *intramolecular* C–H insertion and hydrogen transfer strongly suggests that the cause of the observed carcinogenic/mutagenic effect of this drug is formation of a covalent bond by direct reaction of excited **1** with DNA through a related *intermolecular* process.

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Footnotes

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† All products have been fully characterised by elemental analysis and spectroscopic means as the corresponding *N*′-ethylcarbamate methyl esters.

‡ Release of fluoride by irradiation of enoxacin has been detected (ref. 22).

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