REGIOSELECTIVE NUCLEOPHILIC SUBSTITUTION OF HALOGEN DERIVATIVES OF 1-SUBSTITUTED 4-OXO-1,4-DIHYDROQUINOLINE-3-CARBOXYLIC ACIDS

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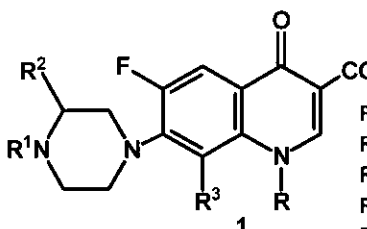
Abstract - The rate of the nucleophilic displacement of the fluoro atom of 7-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate could be enhanced either by the introduction of further fluoro atom(s) into position(s) 6 and/or 8, or by the formation of a boron chelate (e.g. **3**). The regioselectivity of the nucleophilic substitution of the chloro atom in 1-substituted 6-fluoro-7-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids could also be enhanced by the formation of a boron chelate (e.g. **7**).

The discovery[1] of the 3rd generation of quinoline-3-carboxylic acids[2] and the introduction of compounds of this type into human[3] and veterinary[4] therapy (e.g. **1**, "oxacins") were milestones in the treatment of bacterial infections.[5] In the synthesis of these drugs, the regioselective nucleophilic substitution of a halogen atom in position 7 is a key step. When 6,7-difluoro intermediates (**2**, X = 6-F, 7-F) are applied,



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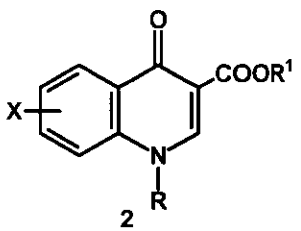
R = Et, R^1 = R^2 = R^3 = H, norfloxacin
R = Et, R^1 = Me, R^2 = R^3 = H, pefloxacin
R = Et, R^1 = H, R^2 = Me, R^3 = F, lomefloxacin
R = cycloPr, R^1 = R^2 = R^3 = H, ciprofloxacin
R = NHMe, R^1 = Me, R^2 = R^3 = H, amifloxacin
R = 4-F-Ph, R^1 = Me, R^2 = R^3 = H, difloxacin



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the nucleophilic displacement of the fluoro atom in position 7 occurs with high regioselectivity.[6] However, in the case of the application of the industrially more economic 6-fluoro-7-chloro intermediates

(**2**, X = 6-F, 7-Cl), the regioselectivity is dramatically lower,[1, 6, 7] as the fluoro atom is a much better leaving group in aromatic nucleophilic substitution than the chloro atom.[8]

We report herein an investigation of the nucleophilic substitution of halogen derivatives of 1-substituted 4-oxo-1,4-dihydroquinoline-3-carboxylic acids and esters (**2**, R^1 = H, Et) with piperazine or its 1- and 2-methyl derivative. The nucleophilic substitution of a halogen atom on the 1,4-dihydroquinolin-4-one skeleton (**2**) with *N*-nucleophiles has not been investigated systematically. 5,6,7,8-Tetrafluoroquinoline[9] underwent nucleophilic displacement solely at position 7 with *N*- and *O*-nucleophiles, while of the 5-, 6-, 7- and 8-fluoroquinoline *N*-oxides[10] only the 7-fluoro derivative reacted with piperazine.

Table 1. Rates[11] of Reaction of Fluoro Derivatives of Ethyl 1-Ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylates (**2**, R = R^1 = Et) with piperazine in DMSO-d_6 at 40 °C

X	*5*-F	6-F	*7*-F	8-F	*5*,6-F_2	6,7-F_2	*7*,8-F_2	6,7,8-F_3
k[a)]	0.19	0.00	0.017	0.00	1.07	0.88	0.11	2.22

a) x 10^{-3} l·mol^{-1}·sec^{-1} Fluoro atom position given in italics denote reactive atoms.

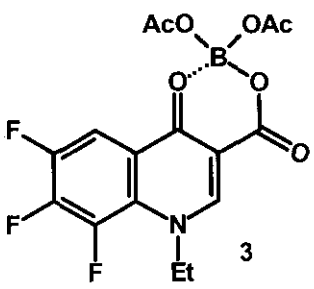
We first investigated[11] the reactivity sequence of a fluoro atom in position 5, 6, 7 or 8 of quinoline-3-carboxylates (**2**, R = R^1 = Et, X = F) on treatment with piperazine in DMSO-d_6 at 40 °C (Table 1). Of the monofluoroquinolones, the 7-fluoro derivative was about 10 times less active than the 5-fluoro compound. No reaction occurred with 6- and 8-fluoro derivatives. When an additional fluoro atom was present in either position 6 or position 8, the reactivity of the 7-fluoro atom increased, and in the case of 6,7-difluoro derivative it was almost as reactive as the 5-fluoro atom in the 5,6-difluoro compound. The reactivity of the 7-fluoro atom was increased further in the 6,7,8-trifluoro derivative. Shibamori *et al.* investigated[12] the reactions of 1-cyclopropyl-4-oxo-5,6,7,8-tetrafluoro-1,4-dihydroquinoline-3carboxylic acid and ester with piperidine (besides other amines) by HPLC. Mixture of 5- and 7-substituted derivatives was obtained, and the amount of the latter was slightly higher in the case of the 3-carboxylic acid. While the 5-substituted compound was the main product (over 87%) in toluene, approximately 1:1 mixture of the 5- and 7-substituted derivatives was formed in acetonitrile and in ethanol.

Table 2. Rates[11] of Reaction of Ethyl 1-Ethyl-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**2**, R = R^1 = Et) with Piperazine or Its 1- or 2-Methyl Derivative in DMSO-d_6 at 40 °C

X = 6,7,8-F_3	Piperazine	1-Methylpiperazine	2-Methylpiperazine
k[a)]	2.22	0.20	0.98[b)]

a) x 10^{-3} l·mol^{-1}·sec^{-1}, b) lomefloxacin ethyl ester

The 6,7,8-trifluoro ester derivative (**2**, R = R^1 = Et, X = 6,7,8-F_3) similarly reacted with 2-methyl- or 1-methylpiperazines (Table 2). 2-Methylpiperazine reacted in position 4 and was about half as reactive as piperazine, while 1-methylpiperazine was *ca.* ten times less reactive. The reaction rate (k = $7.50 \cdot 10^{-3}$ $l \cdot mol^{-1} sec^{-1}$) was higher when 2-methylpiperazine reacted with 6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**2**, R = Et, R^1 = H, X = 6,7,8-F_3) in DMSO-d_6 at 25 °C. The nucleophilic displacement of the 7-fluoro atom was further enhanced when a boron chelate of quinoline-3-carboxylic acid (**3**) was applied. In DMSO-d_6 the reaction rate (k = > $70 \cdot 10^{-3}$ $l \cdot mol^{-1} sec^{-1}$) was at least ten times higher, in the less polar $CDCl_3$ it was lower (k = $2.83 \cdot 10^{-3}$ $l \cdot mol^{-1} sec^{-1}$).



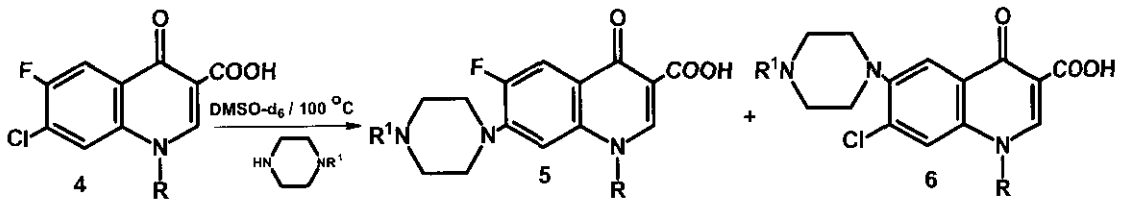


Table 3. Reactions[13] of 1-Substituted 6-Fluoro-7-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acids (**4**) with Piperazine or with 1-Methylpiperazine in DMSO-d_6 at 120-130 °C

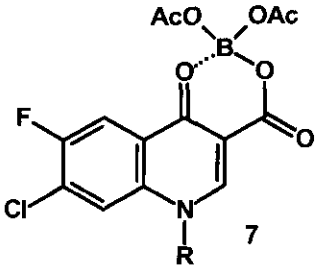
	R	R^1	Ratio of **5** and **6** formed		R	R^1	Ratio of **5** and **6** formed
1	Et	H	80[a]: 20	6	cycloPr	Me	87 : 13
2	Et	Me	82[b]: 18	7	*p*F-Ph	H	83 : 17
3	NHMe	H	84 : 16	8	*p*F-Ph	Me	84[e]: 16
4	NHMe	Me	86[c]: 14	9	2-F-Et	H	89 : 11
5	cycloPr	H	87[d]: 13	10	2-F-Et	Me	89 : 11

a) norfloxacin; b) pefloxacin; c) amifloxacin; d) ciprofloxacin; e) difloxacin

Koga *et al.* reported[1] that, besides norfloxacin (**5**, R = Et, R^1 = H) (66%), the biologically inactive isomeric 7-chloro-6-piperazino derivative (**6**, R = Et, R^1 = H) was isolated in 25% yield from the mixture of reaction products formed from 7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**2**, R = Et, R^1 = H, X = 6-F, 7-Cl) and excess piperazine at 130-140 °C.

The reaction of 7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**2**, R = R^1 = Et, X = 6-F, 7-Cl) with piperazine in DMSO-d_6 at 40 °C was sluggish ($k_{7\text{-}Cl}$ = ~$7 \cdot 10^{-7}$ $l \cdot mol^{-1} sec^{-1}$, $k_{6\text{-}F}$ = ~$3 \cdot 10^{-7}$ $l \cdot mol^{-1} sec^{-1}$), but that of 7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**2**, R = Et,

R^1 = H, X = 6-F, 7-Cl) with piperazine in DMSO-d_6 at 100 °C was faster ($k_{7\text{-Cl}} = 0.75\ 10^{-3}$ l·mol^{-1}·sec^{-1}, $k_{6\text{-F}} = 0.20 \cdot 10^{-3}$ l·mol^{-1}·sec^{-1}). The reaction was not regioselective in either case.



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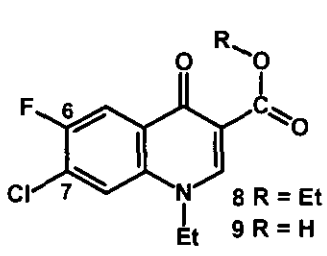
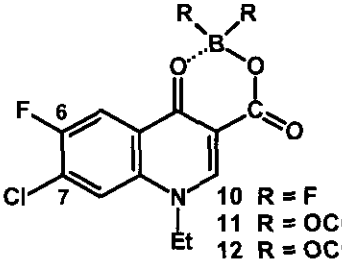
The reactions[13] of 1-substituted 6-fluoro-7-chloro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acids (**4**) with piperazine or with 1-methyl-piperazine in DMSO-d_6 at 120-130 °C led to mixtures of 7- and 6-piperazino derivatives[13] (**5**) and (**6**) in ratios varying between 80:20 and 89:11 (Table 3). Side-product formation could be decreased (to less than 5%) when boron chelates (**7**) were applied instead of the 3-carboxylic acids (**4**).



8 R = Et
9 R = H

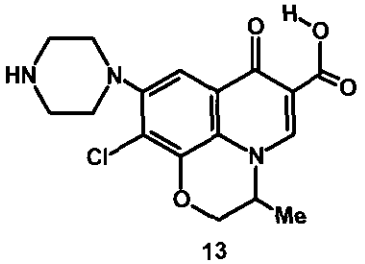


10 R = F
11 R = OCOMe
12 R = OCOEt

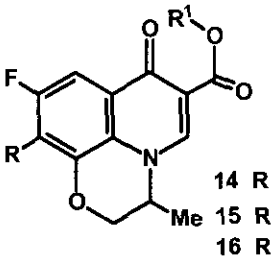
	R	Et	H		F	OCOMe	OCOEt
C-6		154.4	154.6	Δδ = ~ 1.5 ppm	156.0	156.2	156.0
C-7		125.6	126.6	Δδ = ~ 3.7-4.7 ppm	130.3	130.4	130.2

Scheme 1. Some selected ^{13}C NMR data in DMSO-d_6

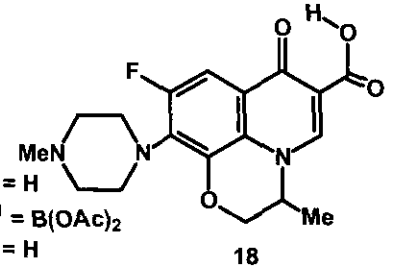
Boron chelate formation (e.g. **7** or **10-12**) decreases the electron density on C-7 more than on C-6 (see ^{13}C NMR data in Scheme 1). Accordingly, besides an enhancement of the reaction rate, the regioselectivity of the nucleophilic displacement of the 7-chloro atom is increased. Industrially, the application of acetyl derivatives[14] (e.g. **7**) is more favorable than that of fluoro derivatives (e.g. **10**), whose formation involves use of the corrosive boron trifluoride etherate or 42% tetrafluoroboric acid.



13



14 R =Cl, R^1 = H
15 R = Cl, R^1 = $B(OAc)_2$
16 R = F, R^1 = H
17 R = F, R^1 = BF_2



18

When an electron-donating atom or group was present at position 8 of the quinolone moiety, the regioselectivity could not be influenced by boron complex formation. Only the 9-piperazino derivative

(**13**) was formed from 9-fluoro-10-chloro-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid[15] (**14**) and from its boron derivative[16] (**15**), whereas both the 9,10-difluoro derivative[15] (**16**) and its difluoro boron derivative[17] (**17**) reacted with 1-methylpiperazine to give ofloxacin (**18**).

For some further examples of the applications of boron complexes to enhance the reactivity of the fluoro atom at position 7 of the quinolone moiety, see under Ref. 18.

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11. 1-Substituted 4-oxo-1,4-dihydroquinoline-3-carboxylate (**2**, R = Et) (0.02 $mol \cdot l^{-1}$) reacted with a cyclic amine (0.06 $mol \cdot l^{-1}$) in DMSO-d_6 at 40 °C in an NMR tube, and the reaction was monitored by ^1H NMR. The rate constant of the second-order reaction was calculated on the basis of the signal of 2-H, using the equation $dA/dt = -k[A]_*[B]$ with the MATLAB and MicroMath programs, where [A] denotes to the concentration of the starting quinoline, and [B] the concentration of the secondary amine.
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13. Reactions were carried out in NMR tubes in DMSO-d_6 at 120-130 °C, and the ratios of **5** and **6** were calculated from the ^{1}H NMR spectra by comparing the integrals of the doublet signals of 5-H (~7.9 ppm, $^3J_{5\text{-H},6\text{-F}}$ = ~16.4 Hz) in **5** and that of the singlet signal of 5-H (~8.3 ppm) in **6**.

14. The appropriate 1-substituted 6-fluoro-7-chloro-4-oxo-1,4-dihydro-4*H*-quinoline-6-carboxylate-(O^3,O^4)-bis(acetate-O)-boron **7** (2 mmol) and secondary amine (6 mmol) (piperazine and 1-methylpiperazine) in DMSO (10 mL) was stirred at 110 °C for 2 h. A solution of 3% aqueous sodium hydroxide (20 mL) was added to the brownish-red solution and the reaction mixture was boiled under reflux for 1 h. The hot pale-yellow solution was filtered and the pH value was adjusted to 7 by adding 96% acetic acid (*ca* 1.8 mL). The reaction mixture was left to crystallize in a refrigerator overnight. The white crystals were filtered off, washed with water and methanol, dried to give the appropriate **5**. Yield: norfloxacin (R = Et, R^1 = H) 93%, pefloxacin (R = Et, R^1 = Me) 96%, amifloxacin (R = NHMe, R^1 = Me) 92%, ciprofloxacin (R = cycloPr, R^1 = H) 95%, difloxacin (R = *p*F-Ph, R^1 = Me), which contains 3.5%, 2.9%, 2.3%, 2.2%, and 4.3% of isomeric **6**, respectively, according to ^{1}H NMR investigations.

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17. The 9-fluoro-10-chloro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxacine-6-carboxylate-(O^6,O^7)-bis(acetate-O)-boron (425 mg) and piperazine (258 mg) in DMSO (5 mL) was stirred at 110 °C for 1 h. The excess of piperazine was removed in *vacuo*, and the residue was treated with 6% aqueous sodium hydroxide (2 mL) and acetone (5 mL). The reaction mixture was refluxed for 1 h, and the pH of the solution was then adjusted to 7. The crystals of **13** were filtered off, washed with water, dried and recrystallized from methanol. mp >270 °C, yield 62% (225 mg), ^{1}H NMR (DMSO-d_6) δ: 7.46 ppm (s, 8-H).

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