N- and *C*-Glycosylation of 6,7-Difluoro-1,4-dihydro-4-oxo-3-quinoline Carboxylic Acid Ethyl Ester

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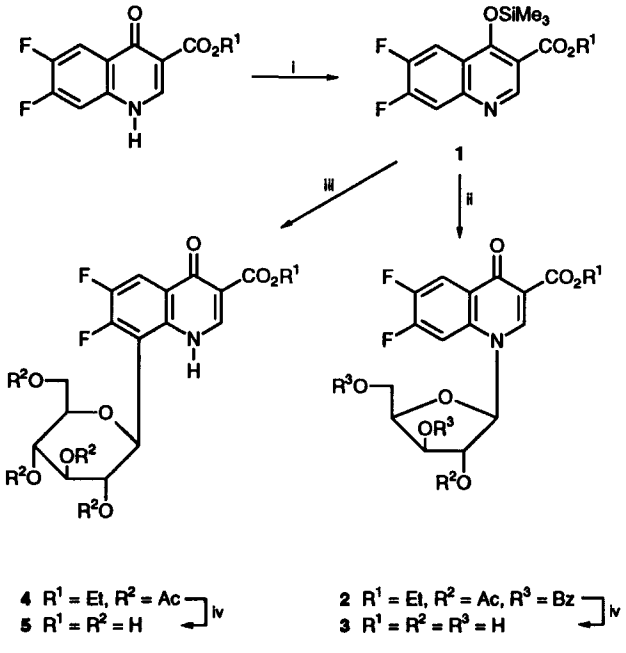
1,2,3,4,6-Penta-*O*-acetyl-α-D-glucopyranose reacts with a silylated ethyl ester of 6,7-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid **1** with *C*-glycosylation to subsequently afford the ethyl ester of 8-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-6,7-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid **4**; on the contrary, condensation of 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-D-xylofuranose with the heterocycle **1** results in an *N*-glycosylation product **2**.

Some derivatives of 6-fluoro-4-quinolone-3-carboxylic acid have proved to be very effective drugs in a new generation of antibiotic preparations.[1] In the search for more compounds in the series with improved transport through biological membranes, we discovered that the direction of reaction of 4-trimethylsilyloxy-6,7-difluoro-3-carboxyethylquinoline **1** with a monosaccharide depended entirely on the structure of the latter. It was also established that the reaction of **1** with 1,2-di-*O*-acetyl-3,5-benzoyl-D-xylofuranose[2] in dichloroethane solution in the presence of $SnCl_4$ led to the expected *N*-nucleoside **2** in 61% yield. Its structure was confirmed by the ^1H NMR spectrum showing double doublets at 7.55 ppm (C_8–H) and 8.21 ppm (C_5-H), and also by a single resonance at 92.82 ppm in the ^{13}C NMR spectrum. The latter signal was assigned to the glycoside carbon in β-xylofuranose.[3–5] In addition, the ^{19}F NMR spectrum exhibited interaction of the fluorine atoms and protons at C_5 and C_8. Hydrolysis of the protecting groups[6] resulted in *N*-(β-D-xylofuranosyl)-6,7-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid **3**. On the contrary, reaction of the siloxy ether **1** with penta-*O*-acetyl-α-D-glucopyranose represented *C*-glycosylation, in which the carbon fragment moved towards C_8, thus substituting for a more acidic proton ($\delta_{C-8} = 106.0$ $^2J_{C-F} = 24$ Hz in C_6H_6.) The structure of the C_8-glycoside **4** was assigned unambiguously by the related resonances in its ^1H, ^{13}C and ^{19}F NMR spectra. Thus, the ^1H NMR spectrum showed a resonance at 8.28 ppm, corresponding to the C_5 proton. The resonance of the fluorine more downfield than that of the *N*-nucleoside **2** was split due to coupling with the C_5 proton. The glycoside was identified by a single series of resonances contributed by the carbons of the sugar fragment described earlier to the substituent's β-orientation.[7] Deacetylation of **4** gave 8-(β-D-glucopyranosyl)-6,7-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid **5**.

Therefore, the reactions of a siloxy ether **1** with carbohydrates show a new synthetic route to two types of hydrophilic derivatives of 6-fluoro-4-quinolone-3-carboxylic acid, Scheme 1.†



Scheme 1 *Reagents and conditions:* i, HMDS, Me_3SiCl, reflux, 6 h; ii, 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-D-xylofuranose, $C_2H_4Cl_2$, $SnCl_4$, 20 °C, 2 h; iii, penta-*O*-acetyl-α-D-glucose, $C_2H_4Cl_2$, $SnCl_4$, 20 °C, 2 h; iv, 0.5 mol dm^{-3} NaOH, MeOH, 20 °C, 2 h.

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† The prepared compounds were purified by GLC on silica gel. ^1H and ^{13}C NMR spectra were registered on a Bruker-300 instrument in $CDCl_3$ ($SiMe_4$ as an internal standard).

Compound **2**: ^1H NMR (δ, ppm) 1.30 (t, 3H, Me, *J* 7.1 Hz), 2.10 (s, 3H, Me), 4.30 (q, 2H, CH_2, *J* 7.1 Hz), 4.84 (1H, 5'–H^a, $J_{5'4'}$ 5.0 Hz, J_{gem} −12.0 Hz), 4.90 (1H, 5'–H^b, $J_{5'4'}$ 6.8 Hz, J_{gem} −12.0 Hz), 5.07 (ddd, 1H, 4'–H, $J_{4,3}$ 3.64 Hz), 5.81 (d, 1H, 3'–H, $J_{3,4}$ 3.64 Hz), 5.53 (s, 1H, 2'–H), 6.05 (s, 1H, 1'–H), 7.55 (dd, 1H, 8–H, $^3J_{8H-7F}$ 11.4 Hz, $^4J_{8H-6F}$ 6.1 Hz), 8.21 (dd, 1H, 5–H, $^3J_{5H-6F}$ 10.4 Hz, $^4J_{5H-7F}$ 8.8 Hz), 9.1 (s, 1H, 2–H), 7.4 (m, 6H, PhH), 7.8 (m, 2H, PhH), 8.09 (m, 2H, PhH). ^{13}C NMR (δ, ppm) 14.25 (Me), 20.57 (Me), 61.15 (CH_2), 60.90 (5'–C), 74.52 (2'–C), 79.50 (3'–C), 81.39 (4'–C), 92.82 (1'–C), 104.64 (d,8–C), 111.09 (3–C), 116.01 (d, 5–C), 127.67 (10–C), 129.20 (9–C), 143.91 (2–C), 148.58 (dd,6–C, $^1J_{6C-6F}$ 252.8 Hz, $^2J_{6C-7F}$ 13.2 Hz), 153.39 (dd,7-C, $^1J_{7C-7F}$ 257.0 Hz, $^2J_{7C-6F}$ 15.1 Hz), 164.47, 165.89, 164.59, 168.95 (C=O), 172.56 (4–C=O), 133.42, 134.20 (Ph). ^{19}F NMR (δ, ppm) 139.92 (6–F, $^3J_{6F-5H}$ 10.4 Hz, $^3J_{6F-7F}$ 22.3 Hz, $^4J_{6F-8H}$ 6.1 Hz), 151.68 (7–F, $^4J_{7F-5H}$ 8.8 Hz, $^3J_{7F-8H}$ 11.4 Hz).

Compound **4**: ^1H NMR (δ, ppm) 1.43 (t, 3H, Me, *J* 7.1 Hz), 1.79 (s, 3H, Me), 2.05 (s, 3H, Me), 2.11 (s, 3H, Me), 2.19 (s, 3H, Me), 4.09 (m, 1H, 5'–H), 4.31 (m, 2H, 6'–H^a, 6'–H^b), 4.40 (q, 2H, CH_2, *J* 7.1 Hz), 5.30–5.60 (m, 4H, 1'–H, 2'–H, 3'–H, 4'–H), 8.28 (dd, 1H, 5–H), 8.52 (s, 1H, 2–H). ^{13}C NMR (δ, ppm) 14.38 (Me), 19.35 (Me), 20.04 (2Me), 20.15 (Me), 61.09 (CH_2), 61.66 (6'–C), 68.28 (4'–C), 69.99 (1'–C), 73.14 (3'–C, 5'–C), 75.39 (2'–C), 106.0 (8–C), 112.40 (3–C), 116.04 (d, 5–C, $^2J_{5C-6F}$ 18.5 Hz), 125.60 (10–C), 135.60 (9–C), 148.50 (dd, 6–C, $^1J_{6C-6F}$ 251.8 Hz, $^2J_{6C-7F}$ 13.4 Hz), 148.60 (2–C), 153.20 (7–C, $^1J_{7C-7F}$ 255.3 Hz, $^2J_{7C-6F}$ 14.9 Hz), 164.75 (C=O), 169.51 (C=O), 169.11 (C=O), 169.74 (C=O), 169.95 (C=O), 172.35 (C=O). ^{19}F NMR (δ, ppm) 143.0 (dd, 6–F, $^3J_{6F-7F}$ 22.0 Hz, $^3J_{6F-5H}$ 11.3 Hz), 154.0 (dd, 7–F, $^3J_{7F-6F}$ 22.0 Hz, $^4J_{7F-FH}$ 9.1 Hz).