SYNTHESIS OF ETHYL 1-ETHYL-6-FLUORO-1,4-DIHYDRO-8-HYDROXY-4-OXOQUINOLINE-3-CARBOXYLATE

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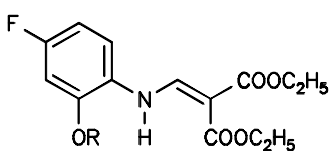
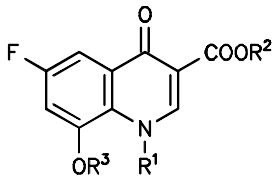
In connection with our research into antibacterial fluoroquinolones[1,2] we required ethyl 1-ethyl-6-fluoro-1,4-dihydro-8-hydroxy-4-oxoquinoline-3-carboxylate (*IIc*) as an intermediate. This paper describes synthesis of this compound and the corresponding carboxylic acid.

Starting 5-fluoro-2-nitrophenol was hydrogenated over palladium on carbon to provide the corresponding amino derivative, which, without purification, was treated with diethyl ethoxymethylene malonate under the usual conditions to provide *N*-(2-hydroxy-4-fluorophenyl)aminomethylene malonate (*Ia*). Benzylation of *Ia* provided the *O*-benzyl derivative *Ib* in good yield. Unfortunately the yield of the cyclization step was not improved by this protection and we obtained *IIa* in about 50% yield. *N*-Alkylation of this compound with iodoethane provided *IIb*, which was hydrogenolytically debenzylated over palladium on carbon to yield the required compound *IIc*. For antimicrobial testing also corresponding carboxylic acid *IId* was prepared by alkaline saponification of *IIc*. Compound *IIc* can be easily *O*-alkylated at the position 8, as demonstrated by preparation of the *O*-propargyl derivative *IIe*.





Ia, R = H
Ib, R = $C_6H_5CH_2$

	R^1	R^2	R^3
IIa	H	C_2H_5	$C_6H_5CH_2$
IIb	C_2H_5	C_2H_5	$C_6H_5CH_2$
IIc	C_2H_5	C_2H_5	H
IId	C_2H_5	H	H
IIe	C_2H_5	C_2H_5	$HC \equiv CCH_2$

Elemental analyses and spectral data (^{1}H NMR, IR, UV, MS) of all the prepared compounds are in accordance with the proposed structures. Compounds *IIa – IIe* were virtually inactive as antibacterials when tested in vitro against a variety of organisms.

EXPERIMENTAL

Melting points were measured on a Thomas Hoover capillary apparatus and are uncorrected. IR spectra were taken on a Digilab FTS 15E spectrophotometer in chloroform, wavenumbers are given in cm^{-1}. UV spectra were taken on a Cary 17D spectrometer in ethanol, molar absorption coefficients (ε) are given in $m^2\ mol^{-1}$, wavelengths (λ) in nm. ^{1}H NMR spectra were recorded on a Varian XL-200 instrument (200 MHz) in deuteriochloroform, unless otherwise stated, chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Mass spectra were obtained on a VG 7070 E-HF spectrometer.

Diethyl *N*-(2-Hydroxy-4-fluorophenyl)aminomethylenemalonate (*Ia*)

A mixture of 5-fluoro-2-nitrophenol (15.7 g, 0.1 mol), ethanol (150 ml) and 10% Pd on carbon (1.4 g) was hydrogenated in the Paar apparatus, then the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in ethanol (50 ml), diethyl ethoxymethylenemalonate was added (21.6 g, 0.1 mol) and the mixture was refluxed under nitrogen for 1 h. The reaction mixture was cooled and the separated crystals were filtered off and recrystallized from ethanol yielding 28 g (94%) of yellow crystals, m.p. 180 – 181 °C. For $C_{14}H_{16}FNO_5$ (297.3) calculated: 56.56% C, 5.43% H, 6.39% F, 4.71% N; found: 56.50% C, 5.44% H, 6.27% F, 4.64% N. IR spectrum: 3 231 (OH, NH); 1 671 (COO). UV spectrum, λ_{max}(log ε): 336 (3.38), 286 (2.93), 278 (2.83), 227 (3.23). Mass spectrum, *m*/*z*: 297. ^{1}H NMR spectrum: 1.24 t, 6 H, J = 7 (2 × CH_3); 4.20 q, 4 H, J = 7 (2 × CH_2); 6.52 m, 2 H (C-3, C-5); 7.05 m, 1 H (C-2); 8.32 s, 0.5 H (CH); 8.46 s, 0.5 H (CH).

Diethyl *N*-(2-Benzyloxy-4-fluorophenyl)aminomethylenemalonate (*Ib*)

Benzyl bromide (17.1 g, 0.1 mol) was added dropwise to a stirred mixture of *Ia* (29.7 g, 0.1 mol) and anhydrous potassium carbonate (27.6 g, 0.2 mol) in acetone (1 l) and then the mixture was stirred at room temperature for 12 h. Solid portion was filtered off and washed with acetone. Acetone solutions were combined, evaporated under reduced pressure and the residue was crystallized twice from ethanol yielding 36.9 g (95%) of white crystals, m.p. 112 – 113 °C. For $C_{21}H_{22}FNO_5$ (387.4) calculated: 65.11% C, 5.72% H, 4.90% F, 3.62% N; found: 65.02% C, 5.72% H, 4.97% F, 3.74% N. IR spectrum: 1 698 (COO). UV spectrum, λ_{max} (log ε): 333 (3.37), 287 (2.97), 280 (2.85), 227 (3.27). Mass spectrum, *m*/*z*: 387. ^{1}H NMR spectrum: 1.20 t, 6 H, J = 7 (2 × CH_3); 4.10 q, 4 H, J = 7 (2 × CH_2); 5.02 s, 2 H (CH_2 of benzyl); 6.60 m, 2 H (C-3, C-5); 7.05 m, 1 H (C-2); 7.20 – 7.40 m, 5 H (arom. H of benzyl); 8.32 s, 0.5 H (CH); 8.46 s, 0.5 H (CH).

Ethyl 8-Benzyloxy-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (*IIa*)

Compound *Ib* (2.5 g, 6.5 mmol) was added to diphenyl ether (25 ml) at 250 °C and the mixture was stirred at reflux for 15 min. Then the mixture was allowed to cool to about 30 °C, the cool mixture was poured into hexane (250 ml) and stirred for 2 h. Insoluble portion was filtered off and washed with acetone to yield 1.15 g (52%) of yellow precipitate, which was used for further reaction without purification. An analytical sample was purified by crystallization from acetone, m.p. 245 – 247 °C. For $C_{19}H_{16}FNO_4$ (341.3) calculated: 66.86% C, 4.72% H, 5.57% F, 4.10% N; found: 66.76% C,

4.50% H, 5.75% F, 4.09% N. IR spectrum: 1 712 (COO). UV spectrum, λ_{max} (log ε): 320 (3.15), 307 (3.17), 227 (2.96), 220 (3.45). Mass spectrum, *m/z*: 341. ^{1}H NMR spectrum: 1.42 t, 3 H, *J* = 7 (CH_3); 4.42 q, 2 H, *J* = 7 (CH_2); 5.28 s, 2 H (CH_2 of benzyl); 6.96 dd, 1 H, *J*(H,H) = 3, *J*(H,F) = 8 (C-7); 7.25 – 7.50 m, 5 H (arom. H of benzyl); 7.58 dd, 1 H, *J*(H,H) = 3, *J*(H,F) = 8 (C-5); 8.80 s, 1 H (CH).

Ethyl 8-Benzyloxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (*IIb*)

Sodium hydride (80% suspension in mineral oil, 0.25 g, 8 mmol)) was added portionwise to a stirred solution of *IIa* (1.7 g, 5 mmol) in dry *N*,*N*-dimethylformamide (40 ml) and the mixture was stirred at room temperature for 1 h. Then iodoethane (1.56 g, 10 mmol) was added and the mixture was stirred at room temperature for 6 h, another portion of iodoethane was added (1.56 g, 10 mmol) and stirring continued for additional 14 h. The mixture was evaporated to dryness under reduced pressure, the residue was triturated with water, filtered off and washed with water. Crystallization from ethanol provided 1.3 g (70%) of white crystals, m.p. 160 – 161 °C. For $C_{21}H_{20}FNO_4$ (369.4) calculated: 68.28% C, 5.46% H, 5.14% F, 3.79% N; found: 68.16% C, 5.48% H, 5.18% F, 3.78% N. IR spectrum: 1 722 (COO), 1 688 (C=O). UV spectrum, λ_{max} (log ε): 322 (3.22), 314 (3.22), 257 (2.87), 230 (3.49), 225 (3.51). Mass spectrum, *m/z*: 369. ^{1}H NMR spectrum: 1.25 t, 3 H, *J* = 7 (CH_3); 1.44 t, 3 H, *J* = 7 (CH_3); 4.35 – 4.45 m, 4 H (CH_2); 5.16 s, 2 H (CH_2 of benzyl); 7.02 dd, 1 H, *J*(H,H) = 3, *J*(H,F) = 8 (C-7); 7.35 – 7.45 m, 5 H (arom. H of benzyl); 7.84 dd, 1 H, *J*(H,H) = 3, *J*(H,F) = 8 (C-5); 8.45 s, 1 H (CH).

Ethyl 1-Ethyl-6-fluoro-1,4-dihydro-8-hydroxy-4-oxoquinoline-3-carboxylate (*IIc*)

A mixture of *IIb* (1.0 g, 2.7 mmol), ethanol (200 ml) and 10% Pd on carbon (0.25 g) was hydrogenated in the Paar apparatus. Then the mixture was heated to reflux under nitrogen and the catalyst was filtered off and washed with boiling ethanol. The filtrate was evaporated and the residue was crystallized from ethanol, yield 0.64 g (85%); m.p. 284 – 287 °C (decomp.). For $C_{14}H_{14}FNO_4$ (279.3) calculated: 60.21% C, 5.05% H, 6.80% F, 5.02% N; found: 59.99% C, 4.90% H, 6.81% F, 5.22% N. IR spectrum: 1 720 (COO); 1 620 (C=O). UV spectrum, λ_{max} (log ε): 325 (3.16), 317 (3.15), 233 (3.36), 223 (3.37); $\lambda_{infl.}$ (log ε): 343 (2.95), 271 (2.60), 258 (2.88). Mass spectrum, *m/z*: 279. ^{1}H NMR spectrum: 1.25 – 1.45 m, 6 H (2 × CH_3); 4.20 q, 2 H, *J* = 7 (CH_2); 4.62 q, 2 H, *J* = 7 (CH_2); 7.00 dd, 1 H, *J*(H,H) = 3, *J*(H,F) = 8 (C-7); 7.42 dd, 1 H, *J*(H,H) = 3, *J*(H,F) = 8 (C-5); 8.52 s, 1 H (CH).

1-Ethyl-6-fluoro-1,4-dihydro-8-hydroxy-4-oxoquinoline-3-carboxylic Acid (*IId*)

A mixture of *IIc* (0.5 g, 1.8 mmol), sodium hydroxide (0.5 g, 12.5 mmol), and water (5 ml) was refluxed for 4 h, diluted with water (20 ml) and acidified with concentrated hydrochloric acid. The formed precipitate was filtered off, washed with water, dried and crystallized from *N*,*N*-dimethylformamide; yield 0.32 g (71%), not melting up to 300 °C. For $C_{12}H_{10}FNO_4$ (251.2) calculated: 57.37% C, 4.01% H, 7.56% F, 5.58% N; found: 56.99% C, 3.84% H, 7.36% F, 5.56% N. IR spectrum: 1 691 (COO), 1 624 (C=O). UV spectrum, λ_{max} (log ε): 238 (3.08), 238 (3.43), 223 (3.37); $\lambda_{infl.}$ (log ε): 345 (2.91), 320 (3.07), 265 (2.81). Mass spectrum, *m/z*: 251. ^{1}H NMR spectrum (CD_3SOCD_3): 1.40 t, 3 H, *J* = 7 (CH_3); 4.84 q, 2 H, *J* = 7 (CH_2); 7.15 dd, 1 H, *J*(H,H) = 3, *J*(H,F) = 8 (C-7); 7.52 dd, 1 H, *J*(H,H) = 3, *J*(H,F) = 8 (C-5); 8.85 s, 1 H (CH).

Ethyl 1-Ethyl-6-fluoro-1,4-dihydro-8-(2-propinyloxy)-4-oxoquinoline-3-carboxylate (*IIe*)

Sodium hydride (80% suspension in mineral oil, 0.06 g, 2 mmol) was added to a stirred suspension of *IIc* (0.56 g, 2 mmol) in *N*,*N*-dimethylformamide (10 ml) and the mixture was stirred at room temperature for 1 h. Then propargyl bromide (0.35 g, 3 mmol) was added dropwise via syringe and the mixture was stirred at room temperature under nitrogen for 2 days. The mixture was evaporated under reduced pressure, triturated with water and insoluble portion was filtered off, washed with water and dried. The crude product was dissolved in methylene chloride and purified by flash chromatography (silica gel Merck 60, chloroform–methanol 95 : 5). Crystallization from ethanol provided 0.57 g (90%) of white crystals; m.p. 186 – 187 °C. For $C_{17}H_{16}FNO_4$ (317.4) calculated: 64.35% C, 5.08% H, 5.99% F, 4.41% N; found: 63.98% C, 5.00% H, 6.03% F, 4.22% N. IR spectrum: 3 306 (C≡C–H); 1 724 (COO); 1 680 (C=O). UV spectrum, λ_{max} (log ε): 322 (3.18), 313 (3.18), 223 (3.45); $\lambda_{infl.}$ (log ε): 340 (2.96). Mass spectrum, *m*/*z*: 317. ^{1}H NMR spectrum: 1.35 – 1.55 m, 6 H (2 × CH_3); 2.65 t, 1 H, *J* = 1.5 (≡CH); 4.35 q, 2 H, *J* = 7 (CH_2); 4.52 q, 2 H, *J* = 7 (CH_2); 4.78 d, 2 H, *J* = 2 (O–CH_2); 7.00 dd, 1 H, *J*(H,H) = 3, *J*(H,F) = 8 (C-7); 7.92 dd, 1 H, *J*(H,H) = 3, *J* (H,F) = 8 (C-5); 8.38 s, 1 H (CH).

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