A New Synthetic Route to 7-Halo-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid, an Intermediate for the Synthesis of Quinolone Antibacterial Agents [1]

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Starting from *m*-fluorotoluene, 7-chloro-6-fluoro- and 6,7-difluoro-1-cyclopropyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids, **3** and **16** were synthesized. Compounds **3** and **16** are useful intermediates for the synthesis of a class of quinolone antibacterial agents. The synthetic route involves two processes; i) construction of the quinoline ring by an intramolecular cyclization accompanied by the elimination of a nitro group and ii) introduction of fluorine atom by replacement of a nitro group with potassium fluoride. 7-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**18**) was prepared from **3** or **16**. The antibacterial activity of **18** compares favorably with that of ciprofloxacin (**2**).

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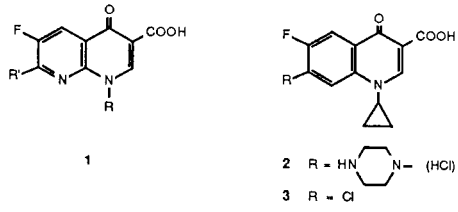
In a previous paper [2], a synthesis of the 6-fluoro-1,8-naphthyridine derivatives **1** with excellent antibacterial activity was reported. An interest in finding more potent antibacterial agents led us to synthetic study of the 1-cyclopropyl-6-fluoroquinoline derivatives such as ciprofloxacin (**2**) [3].

Chart I



1-Cyclopropyl-7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**3**) is known to be a key intermediate for the preparation of quinolone antibacterials with a cyclic amino group at C-7 [4]. The known method [4] for the synthesis of **3** seemed undesirable to us because hydrogen fluoride had to be used at the fluorination process. On these grounds our first efforts were focussed on an alternative and efficient method for the synthesis of **3** starting from commercially available *m*-fluorotoluene (**4a**). The present synthetic route involves construction of the quinoline ring by the intramolecular cyclization of the enaminoketoester **11a** accompanied by the elimination of the nitro group as shown in Scheme I.

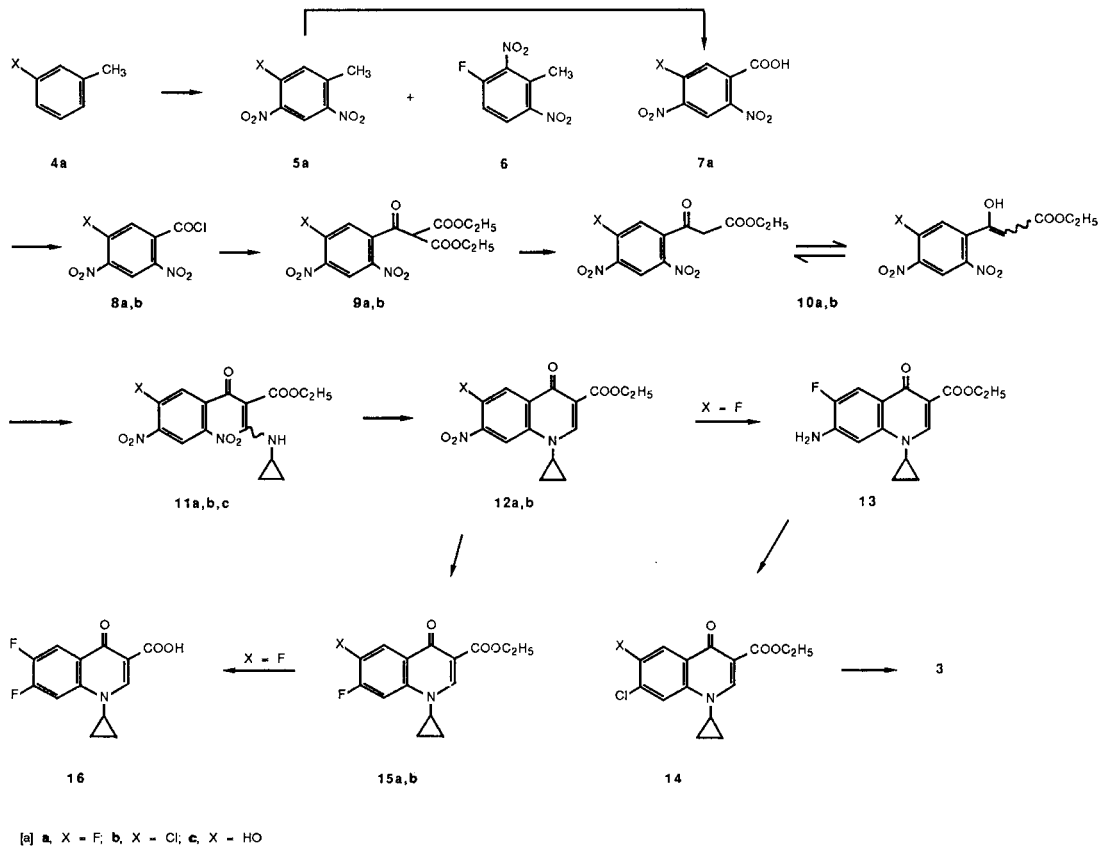
Nitration of **4a** with a mixed acid (nitric acid and sulfuric acid) gave a mixture of 5-fluoro-2,4-dinitrotoluene (**5a**) and 3-fluoro-2,6-dinitrotoluene (**6**). The desired dinitro compound **5a** was isolated in 81% yield from the mixture by fractional crystallization from isopropyl ether. Oxidation of **5a** with chromic acid in concentrated sulfuric acid gave the benzoic acid derivative **7a**, which was treated with thionyl chloride to yield **8a**. Condensation of **8a** with diethyl ethoxymagnesium malonate in tetrahydrofuran yielded the benzoylmalonate derivative **9a**. Heating of **9a** with *p*-toluenesulfonic acid in water gave the β-ketoester **10a**. The ^{1}H nmr spectrum (in deuteriochloroform) of **10a** shows signals at δ 3.90 for the methylene protons and at δ 5.45 for the enol olefinic proton, and suggests that **9a** equilibrates in an approximately 6:1 ratio of the keto and enol forms in the solution.

Compound **10a** was allowed to react with ethyl orthoformate in acetic anhydride followed by treatment with an equimolar amount of cyclopropylamine gave predominantly the enaminoketoester **11a**, which was found to be a mixture of geometrical isomers by its ^{1}H nmr spectrum. In these processes, the fluorine atom of **10a**, being activated by the *o*- and *p*-nitro groups, was not replaced by cyclopropylamine. Cyclization of **11a** proceeded smoothly on treatment with sodium hydride in a mixture of tetrahydrofuran and toluene to give the quinoline **12a** in good yield. However, treatment of **11a** with potassium carbonate in acetonitrile resulted in a formation of the phenol derivative **11c**.

The 7-nitroquinoline **12a** was hydrogenated in acetic acid with palladium-on-charcoal to give the corresponding 7-amino compound **13**. Diazotization of **13** with sodium nitrite in concentrated hydrochloric acid, followed by successive treatment with cuprous chloride gave the 7-chloroquinoline **14** in 58% yield on the basis of **12a**. Finally, acidic hydrolysis of the ester **14** afforded the desired compound **3**.

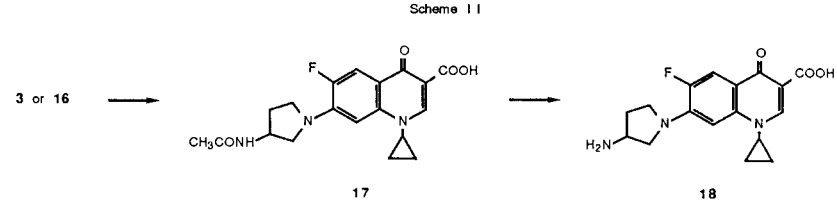
Compound **12b** was prepared from *m*-chlorotoluene by a route similar to that for **12a** from *m*-fluorotoluene (**4a**). In order to convert **12b** to **12a**, we attempted to replace

Scheme I [a]



[a] a, X = F; b, X = Cl; c, X = HO

Scheme II



the 6-chloro group of **12b** with a fluorine atom. However, the reaction of **12b** with potassium fluoride in dimethylsulfoxide failed to produce **12a**, but giving **15b** which resulted from replacement of the nitro group at C-7 by fluorine atom. This finding led us to apply the reaction under the same conditions to the 6-fluoro-7-nitro compound **12a**, and the 6,7-difluoroquinoline **15a** was obtained in 31% yield. The ester **15a** was then hydrolyzed to the corresponding acid **16**.

The 3-aminopyrrolidinyl group, which had been reported by the present authors to be promising for improving antibacterial activity [2], was introduced at the C-7 position **3** or **16**. Thus, heating of 7-chloro compound **3** with 3-acetylaminopyrrolidine in dimethylsulfoxide at *ca.* 140° gave **17** in 63% yield. With 7-fluoro compound **16** instead of **3**, the replacement reaction under reflux in pyridine proceeded more smoothly to give **17** in 93% yield; **16** was more satisfactory than **3** as an intermediate for the preparation of **17** and its analogues. The acetyl group in **17** was removed by alkaline hydrolysis to give the desired compound **18**. Also prepared was ciprofloxacin (**2**) by the reaction of **16** with piperazine in an excellent yield.

The *in vitro* antibacterial activity of the prepared compounds **2** and **18** was tested against representative organisms. Activity of compound **18** compares very favorably with that of ciprofloxacin (**2**), as given in Table I. The 3-aminopyrrolidinyl group, as well as piperazinyl group, proved an efficient C-7 substituent for improvement of activity in a class of quinolone and azaquinolone antibacterial agents.

Table I

In Vitro Antibacterial Activity

Organisms	MIC ug/ml	
	18	Ciprofloxacin (**2**)
S. aureus 209P JC-1	0.025	0.1
S. pyogenes A65	0.2	0.2
S. faecalis 2473	0.39	0.78
E. coli NIH JC-2	0.125	0.0063
P. mirabilis IFO 3849-4	0.1	0.1
K. pneumoniae P5709	0.025	0.025
S. marcescens S-9	0.05	0.05
P. aeruginosa 12	0.1	0.1

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Jasco A-102 spectrometer. ^{1}H nmr spectra were taken at 60 or 80 MHz on a Varian EM-360A or FT-80A spectrometer with tetramethylsilane, except for **18** which was measured with sodium 2,2-dimethyl-2-silapentane-5-sulfonate, as an internal standard.

5-Fluoro-2,4-dinitrotoluene (**5a**) and 3-Fluoro-2,6-dinitrotoluene (**6**).

To a stirred mixture of nitric acid (d = 1.42, 125 ml) and concentrated sulfuric acid (180 ml) was added dropwise **4a** (50 g, 455 mmoles) under ice-cooling at such a rate that the temperature did not rise over 35°. The mixture was allowed to stir for 30 minutes at room temperature and poured onto ice-water (*ca.* 1 *l*). The resulting precipitate was collected by filtration and dissolved in ethyl acetate. The solution was washed successively with saturated sodium bicarbonate and saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated to dryness. The resulting solid was recrystallized from isopropyl ether to give 5-fluoro-2,4-dinitrotoluene (**5a**) (74 g, 81%), mp 79-80° (recrystallized from a mixture of ether and isopropyl ether); ir (potassium bromide): 1530, 1340 cm^{-1}; ^{1}H nmr (60 MHz, deuteriochloroform): δ 2.75 (3H, s), 7.40 (1H, d, J = 10 Hz), 8.90 (1H, d, J = 7 Hz).

Anal. Calcd. for $C_7H_5FN_2O_4$: C, 42.01; H, 2.52; F, 9.49; N, 14.00. Found: C, 42.03; H, 2.46; F, 9.82; N, 13.98.

The mother liquor of recrystallization was concentrated to dryness, and the residue was chromatographed on silica gel with a mixture of hexane and isopropyl ether (2:3, v/v) as an eluent. The first eluate afforded 3-fluoro-2,6-dinitrotoluene (**6**), mp 54-55° (recrystallized from a mixture of isopropyl ether and hexane); ir (potassium bromide): 1530, 1350 cm^{-1}; ^{1}H nmr (60 MHz, deuteriochloroform): δ 2.57 (3H, s), 7.37 (1H, d d, J = 8, 7 Hz), 8.20 (1H, d d, J = 7, 5 Hz).

Anal. Calcd. for $C_7H_5FN_2O_4$: C, 42.01; H, 2.52; F, 9.49; N, 14.00. Found: C, 42.06; H, 2.73; F, 9.48; N, 14.13.

5-Fluoro-2,4-dinitrobenzoic Acid (**7a**).

To a stirred suspension of **5a** (28.0 g, 140 mmoles) in concentrated sulfuric acid (280 ml) was gradually added a solution of anhydrous chromic acid (33.6, 336 mmoles) in water (25 ml) under cooling over a period of 20 minutes while the temperature was maintained at −6° to 0°. The mixture was allowed to stir vigorously for 3.5 hours at room temperature, poured onto ice-water, and extracted with ethyl acetate. After addition of saturated sodium bicarbonate, the aqueous layer was separated, acidified with 20% hydrochloric acid, extracted with ethyl acetate. The extract was dried over magnesium sulfate and treated with charcoal. After evaporation of ethyl acetate, hexane was added. The resulting solid was collected by filtration and recrystallized from a mixture of ether and hexane to give **7a** (17.3 g, 53%), mp 164-166°; ir (potassium bromide): 1725, 1530, 1340 cm^{-1}; ^{1}H nmr (80 MHz, deuteriochloroform): δ 5.0-7.5 (1H, b), 8.17 (1H, d, J = 10 Hz), 8.84 (1H, d, J = 6.5 Hz).

Anal. Calcd. for $C_7H_3FN_2O_6$: C, 36.54; H, 1.31; F, 8.26; N, 12.17. Found: C, 36.59; H, 1.26; F, 8.10; N, 11.91.

5-Fluoro-2,4-dinitrobenzoyl Chloride (**8a**).

A mixture of **7a** (100 g, 435 mmoles) and thionyl chloride (400 ml) was heated to reflux for 2.5 hours. The excess of thionyl cholide was evaporated *in vacuo*, and a mixture of ether (200 ml) and isopropyl ether (200 ml) was added. The resulting precipitate was collected by filtration and recrystallized from a mixture of ethyl acetate and ether gave **8a** (81 g, 75%), mp 73°; ir (potassium bromide): 1770, 1535, 1340 cm^{-1}; ^{1}H nmr (80 MHz, deuteriochloroform): δ 7.60 (1H, d, J = 9 Hz), 8.92 (1H, d, J = 7 Hz).

Anal. Calcd. for $C_7H_2ClFN_2O_5$: C, 33.83; H, 0.81; Cl, 14.26; F, 7.64; N, 11.27. Found: C, 34.02; H, 1.01; Cl, 13.86; F, 7.46; N, 11.48.

Diethyl 5-Fluoro-2,4-dinitrobenzoylmalonate (**9a**).

Diethyl malonate (31 ml, 202 mmoles) was treated with magnesium (4.9 g, 204 mmoles) in a mixture of ethanol (35 ml), ether (50 ml) and carbon tetrachloride (2 ml) by the conventional method, and the resulting solution was diluted with dry tetrahydrofuran (200 ml). To the stirred mixture was added dropwise a solution of **8a** (50 g, 0.201 mole) in dry tetrahydrofuran (100 ml) under ice-cooling over a period of 20 minutes while the temperature was maintained at 4° to 18°. The reaction mixture was allowed to stir for 1 hour at room temperature, and the solvent was evaporated *in vacuo* at 60°. After addition of chloroform, 1*N* hydrochloric acid (100 ml) was gradually added under ice-cooling. The organic layer was separated, washed with 2% sodium bicarbonate (75 ml) and dried over anhydrous sodium sulfate. After treatment of charcoal, the resulting solution was concentrated under reduced pressure to give an oil **9a**, which was used in the next step without purification.

Ethyl 5-Fluoro-2,4-dinitrobenzoylacetate (**10a**).

A mixture containing the oil **9a** obtained above, *p*-toluenesulfonic acid (250 mg) and water (250 ml) was heated at 125° for 1 hour with vigorous stirring. The reaction mixture was extracted with ethyl acetate and dried over anhydrous sodium sulfate. After evaporation of ethyl acetate, isopropyl ether was added. The resulting precipitate was collected by filtration and washed with isopropyl ether to give **10a** (43 g, 71%), which was recrystallized from a mixture of ether and isopropyl ether, mp 60-61°; ir (potassium bromide): 1725, 1700, 1525, 1345 cm^{-1}; ^{1}H nmr (80 MHz, deuteriochloroform): δ 1.25 and 1.35 (3H, each t, J = 7 Hz), 3.90 (2H × 6/7, s), 4.16 and 4.32 (2H, each q, J = 7 Hz), 5.45 (1H × 1/7, s), 7.52 and 7.54 (1H, each d, J = 9 Hz), 8.63 and 8.90 (1H, each d, J = 6.5 Hz).

Anal. Calcd. for $C_{11}H_9FN_2O_7$: C, 44.01; H, 3.02; F, 6.33; N, 9.33. Found: C, 44.01; H, 3.07; F, 6.58; N, 9.27.

Ethyl 5-Chloro-2,4-dinitrobenzoylacetate (**10b**).

According to the method as in the preparation of **9a** and **10a**, 5-chloro-2,4-dinitrobenzoyl chloride [5] (23.0 g, 85 mmoles) was treated to give **10b** (21.0 g, 77%), which was recrystallized from a mixture of chloroform and hexane, mp 120° (lit [6], mp 105-110°); ir (potassium bromide): 1720, 1705, 1540, 1335 cm^{-1}; ^{1}H nmr (80 MHz, deuteriochloroform): δ 1.28 and 1.37 (3H, each t, J = 7 Hz), 3.92 (2H × 7/10, s), 4.18 and 4.32 (2H, each q, J = 7 Hz), 5.47 (1H × 3/10, s), 7.75 and 7.80 (1H, each s), 8.45 and 8.71 (1H, each s), 11.9-12.5 (1H × 3/10, br).

Anal. Calcd. for $C_{11}H_9ClN_2O_7$: C, 41.72; H, 2.86; Cl, 11.20; N, 8.85. Found: C, 41.93; H, 2.86; Cl, 11.30; N, 9.05.

Ethyl 3-Cyclopropylamino-2-(5-fluoro-2,4-dinitrobenzoyl)acrylate (**11a**).

A stirred mixture containing **10a** (20.0 g, 67 mmoles), ethyl orthoformate (14.8 g, 100 mmoles) and acetic anhydride (17.0 g, 167 mmoles) was heated at 120° for 1 hour during which period the resulting ethyl acetate was removed. The mixture was concentrated to dryness under reduced pressure. After addition of ethanol (100 ml) and ether (20 ml), a solution of cyclopropylamine (3.9 g, 68 mmoles) in ethanol (20 ml) was add-

ed over a period of 3 minutes while the temperature was maintained at 4° to 8° under ice-cooling. The reaction mixture was allowed to stir for 10 minutes at room temperature, and cooled. The resulting precipitate was collected by filtration and washed successively with ethanol and ether to give **11a** (19.0 g, 78%), which was recrystallized from ethanol. The product was an approximate 1:9 (or 9:1) mixture of the *cis* and *trans* isomers, mp 106-107°; ir (potassium bromide): 1680, 1620, 1535, 1345 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform): (the major isomer) δ 0.7-1.1 (4H, m), 1.13 (3H, t, J = 7 Hz), 2.8-3.2 (1H, m), 4.03 (2H, q, J = 7 Hz), 7.16 (1H, d, J = 10 Hz), 8.25 (1H, d, J = 14 Hz), 8.89 (1H, d, J = 6.5 Hz), 10.5-11.4 (1H, br).

Anal. Calcd. for $C_{15}H_{14}FN_3O_7$: C, 49.05; H, 3.84; F, 5.17; N, 11.44. Found: C, 48.79; H, 3.99; F, 5.32; N, 11.35.

Ethyl 2-(5-Chloro-2,4-dinitrobenzoyl)-3-cyclopropylaminoacryrate (**11b**).

According to the method as in the preparation of **11a**, **10b** (10.0 g, 31.6 mmoles) was treated to give **11b** (11.0 g, 91%), which was recrystallized from ethanol. The product was an approximate 1:9 (or 9:1) mixture of the *cis* and *trans* isomers, mp 141-142° (lit [6], mp 130-132°); ir (potassium bromide): 1675, 1630, 1530, 1350 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform): (the major isomer) δ 0.7-1.2 (4H, m), 1.10 (3H, t, J = 7 Hz), 2.8-3.2 (1H, m), 3.98 (2H, q, J = 7 Hz), 7.40 (1H, s), 8.25 (1H, d, J = 14 Hz), 8.70 (1H, s), 10.5-11.1 (1H, br).

Anal. Calcd. for $C_{15}H_{14}ClN_3O_7$: C, 46.95; H, 3.68; Cl, 9.24; N, 10.95. Found: C, 47.07; H, 3.57; Cl, 9.31; N, 10.85.

Ethyl 3-Cyclopropylamino-2-(5-hydroxy-2,4-dinitrobenzoyl)acrylate (**11c**).

A mixture containing **10a** (2.3 g, 6.27 mmoles), potassium carbonate (1.0 g, 7.25 mmoles) and acetonitrile (46 ml) was heated to reflux for 2 hours and concentrated to dryness under reduced pressure. After addition of dilute hydrochloric acid, the mixture was extracted with ethyl acetate. The extract was taken up with 2*N* sodium carbonate. The aqueous phase was separated, acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and concentrated to dryness. After addition of ether, the resulting solid was collected by filtration and recrystallized from ethanol to give **11c** (0.7 g, 31%), which was an approximate 1:19 (or 19:1) mixture of the *cis* and *trans* isomers, mp 153-154°; ir (potassium bromide): 3270, 1680, 1630, 1520 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform): (the major isomer) δ 0.7-1.1 (4H, m), 1.06 (3H, t, J = 7 Hz), 2.8-3.2 (1H, m), 4.00 (2H, q, J = 7 Hz), 6.95 (1H, s), 8.19 (1H, d, J = 14 Hz), 8.97 (1H, s), 10.7-11.0 (1H, m), 10.92 (1H, s).

Anal. Calcd. for $C_{15}H_{15}N_3O_8 \cdot 0.25\ H_2O$: C, 48.72; H, 4.22; N, 11.36. Found; C, 48.85; H, 4.22; N, 11.22.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-nitro-4-oxoquinoline-3-carboxylate (**12a**).

To a solution of **11a** (34.0 g, 93 mmoles) in dry tetrahydrofuran (340 ml) was slowly added 60% sodium hydride (4.0 g, 102 mmoles) under ice-cooling. After addition of toluene (680 ml), the stirred mixture was heated at 110° to 135° for 30 minutes during which period tetrahydrofuran was removed, and concentrated to dryness under reduced pressure. After addition of a small amount of water under ice-cooling, the residue was taken up in dilute acetic acid and extracted with chloroform. The extract was dried over magnesium sulfate and concentrated to dryness. After addition of isopropyl ether, the resulting solid was collected by filtration and washed with isopropyl ether to give **12a** (26.5 g, 89%), which was recrystallized from ethanol, mp 205-206°; ir (potassium bromide): 1725, 1610, 1565, 1345 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform): δ 1.0-1.4 (4H, m), 1.43 (3H, t, J = 7 Hz), 3.3-3.6 (1H, m), 4.41 (2H, q, J = 7 Hz), 8.36 (1H, d, J = 10 Hz), 8.65 (1H, d, J = 6 Hz), 8.68 (1H, S).

Anal. Calcd. for $C_{15}H_{13}FN_2O_5$: C, 56.25; H, 4.09; F, 5.93; N, 8.75. Found: C, 56.12; H, 4.25; F, 6.09; N, 8.82.

Ethyl 6-Chloro-1-cyclopropyl-1,4-dihydro-7-nitro-4-oxoquinoline-3-carboxylate (**12b**).

To a stirred solution of **11b** (5.0 g, 13 mmoles) in dry dioxane (50 ml) was gradually added 60% sodium hydride (0.52 g, 13 mmoles) under ice-cooling. The mixture was heated at 80° for 50 minutes with stirring. After evaporation of dioxane, 10% acetic acid (50 ml) was added. The resulting mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate and concentrated to dryness. After addition of ether, the resulting solid was collected by filtration to give **12b** (4.0 g, 91%), which was recrystallized from ethyl acetate, mp 219-220° (lit [6], mp 208-210°); ir (potassium bromide): 1720, 1630, 1550, 1330 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform): δ 1.0-1.7 (4H, m), 1.43 (3H, t, J = 7 Hz), 3.3-3.7 (1H, m), 4.40 (2H, q, J = 7 Hz), 8.38 (1H, s), 8.58 (1H, s), 8.63 (1H, s).

Anal. Calcd. for $C_{15}H_{13}ClN_2O_5$: C, 53.50; H, 3.89; Cl, 10.53; N, 8.32. Found: C, 53.70; H, 3.84; Cl, 10.53; N, 8.45.

Ethyl 7-Amino-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**13**).

In the presence of 5% palladium-on-charcoal, **12a** (3.6 g, 11.2 mmoles) was hydrogenated in ethanol (70 ml) at room temperature until the required volume of hydrogen (*ca.* 750 ml) had been taken up. The catalyst was removed by filtration and washed with chloroform. The filtrate was concentrated to dryness. After addition of ethanol, the product was collected by filtration and washed successively with ethanol and ether to give **13** (2.6 g, 80%), which was recrystallized from ethanol mp 237-240°; ir (potassium bromide): 3250, 3200, 1670, 1630 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform): δ 0.8-1.3 (4H, m), 1.26 (3H, t, J = 7 Hz), 3.2-3.7 (1H, m), 4.20 (2H, q, J = 7 Hz), 7.58 (1H, d, J = 6 Hz), 7.67 (1H, d, J = 12 Hz), 8.38 (1H, S), 8.96 (1H, S), 9.28 (1H, S).

Anal. Calcd. for $C_{15}H_{15}FN_2O_3 \cdot 0.75\ H_2O$: C, 59.30; H, 5.47; F, 6.25; N, 9.22. Found: C, 59.30; H, 5.34; F, 6.23; N, 9.15.

Ethyl 7-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**14**).

To a stirred solution of **13** (6.8 g, 19.4 mmoles) in concentrated hydrochloric acid (90 ml) was added dropwise a solution of sodium nitrite (1.8 g, 25.2 mmoles) in water (18 ml) over a period of 10 minutes while the temperature was maintained at −6° to 7°. The reaction mixture was added dropwise to a solution of cuprous chloride (3.8 g, 38.8 mmoles) in concentrated hydrochloric acid (30 ml) over a period of 30 minutes and was stirred at room temperature for 1 hour. After addition of water, the mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate and concentrated to dryness. The resulting solid was recrystallized from ethyl acetate to give **14** (4.4 g, 73%), mp 224-225°; ir (potassium bromide): 1720, 1610 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform): δ 1.0-1.6 (4H, m), 1.40 (3H, t, J = 7 Hz), 3.2-3.6 (1H, m), 3.38 (2H, q, J = 7 Hz), 7.97 (1H, d, J = 6.5 Hz), 8.18 (1H, d, J = 9 Hz), 8.54 (1H, s).

Anal. Calcd. for $C_{15}H_{13}ClFNO_3$: C, 58.17; H, 4.23; Cl, 11.45; F, 6.13; N, 4.52. Found: C, 58.37; H, 4.40; Cl, 11.35; F, 6.40; N, 4.63.

7-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate Acid (**3**).

A suspension of **14** (4.4 g, 14.2 mmoles) in a mixture of 10% hydrochloric acid (100 ml) and ethanol (10 ml) was heated at 120° to 130° for 3 hours with stirring and allowed to cool. The resulting precipitate was collected by filtration and washed with water to give **3** (4.0 g, quantitative), which was recrystallized from a mixture of chloroform and ethanol, mp 246-247° (lit [4], mp 234-237°); ir (potassium bromide): 1730, 1610 cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6): δ 1.1-1.5 (4H, m), 3.6-4.1 (1H, m), 8.20 (1H, d, J = 9 Hz), 8.52 (1H, d, J = 6.5 Hz), 8.75 (1H, s).

Anal. Calcd. for $C_{13}H_9ClFNO_3$: C, 55.43; H, 3.22; Cl, 12.59; F, 6.74; N, 4.97. Found: C, 55.69; H, 3.42; Cl, 12.40; F, 6.93; N, 5.13.

Ethyl 1-Cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**15a**).

A mixture containing **12a** (9.5 g, 29.7 mmoles), spray-dried potassium fluoride [7] (4.5 g, 77.6 mmoles) and dry dimethylsulfoxide (30 ml) was heated at 165° for 1 hour and concentrated to dryness under reduced

pressure. The residue was taken up in a mixture of water and chloroform. The organic layer was separate, washed with water, dried over anhydrous sodium sulfate, and concentrated to dryness. The residue was chromatographed on silica gel with a mixture of chloroform and ethanol (50:1, v/v) as an eluent to give **15a** (2.7 g, 31%), which was recrystallized from ethyl acetate, mp 229-230° (lit [8], mp 231-233°); ir (potassium bromide): 1725, 1620 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform): δ 1.0-1.6 (4H, m), 1.42 (3H, t, J = 7 Hz), 3.2-3.6 (1H, m), 4.40 (2H, q, J = 7 Hz), 7.72 (1H, d d, J = 10, 6 Hz), 8.26 (1H, d d, J = 9, 8.5 Hz), 8.56 (1H, s).

Anal. Calcd. for $C_{15}H_{13}F_2NO_3$: C, 61.43; H, 4.47; F, 12.96; N, 4.78. Found: C, 61.66; H, 4.41; F, 12.89; N, 4.83.

Ethyl 6-Chloro-1-cyclopropyl-7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**15b**).

A mixture containing **12b** (1.0 g, 2.97 mmoles), spray-dried potassium fluoride (0.53 g, 9.14 mmoles) and dry dimethylsulfoxide (3 ml) was heated at 128° to 138° for 1.5 hours with stirring and concentrated to dryness under reduced pressure. The residue was taken up in a mixture of water and chloroform. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, and concentrated to dryness. After addition of ethanol, the resulting precipitate was collected by filtration and recrystallized from ethyl acetate to give **15b** (0.30 g, 33%), mp 225°; ir (potassium bromide): 1720, 1630 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform): δ 1.0-1.6 (4H, m), 1.42 (3H, t, J = 7 Hz), 3.2-3.6 (1H, m), 4.38 (2H, d, J = 7 Hz), 7.65 (1H, d, J = 10 Hz), 8.48 (1H, d, J = 7 Hz), 8.55 (1H, s).

Anal. Calcd. for $C_{15}H_{13}ClFNO_3$: C, 58.17; H, 4.23; Cl, 11.45; F, 6.13; N, 4.52. Found: C, 58.26; H, 4.30; Cl, 11.18; F, 6.08; N, 4.67.

1-Cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**16**).

A suspension of **15a** (2.7 g, 9.2 mmoles) in a mixture of 10% hydrochloric acid (70 ml) and ethanol (5 ml) was heated at 120° for 3 hours with stirring. After addition of water, the resulting precipitate was collected by filtration and washed with water to give **16** (2.4 g, 95%), which was recrystallized from a mixture of chloroform and ethanol, mp 287-289° (lit [8], mp 234-236°); ir (potassium bromide); 1725, 1615 cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6): δ 1.0-1.5 (4H, m), 3.6-4.0 (1H, m), 8.26 (1H, d d, J = 11, 9 Hz), 8.38 (1H, d d, J = 11, 7.5 Hz), 8.75 (1H, s).

Anal. Calcd. for $C_{13}H_9F_2NO_3$: C, 58.87; H, 3.42; F, 14.33; N, 5.28. Found: C, 59.03; H, 3.40; F, 14.32; N, 5.39.

Ethyl 7-(3-Acetylamino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**17**).

i) A mixture containing **3** (0.30 g, 1.07 mmoles), 3-acetylaminopyrrolidine (0.68 g, 5.33 mmoles) and dimethylsulfoxide (1.5 ml) was heated at 137° to 144° for 1 hour with stirring, and concentrated to dryness under reduced pressure. After addition of water (15 ml), the precipitate was collected by filtration and washed successively with water and ethanol to give **17** (0.25 g, 63%), which was recrystallized from a mixture of chloroform and ethanol, mp >300°; ir (potassim bromide): 3340, 1700, 1675, 1630 cm^{-1}; ^1H nmr (80 MHz, DMSO-d_6): δ 1.0-1.4 (4H, m), 1.8-2.3 (2H, m), 1.81 (3H, S), 3.4-4.0 (5H, m), 4.1-4.6 (1H, m), 7.30 (1H, d, J = 8 Hz), 7.78 (1H, d, J = 14 Hz), 8.0-8.6 (1H, br), 8.53 (1H, S), 15.45 (1H, s).

Anal. Calcd. for $C_{19}H_{20}FN_3O_4$: C, 61.12; H, 5.40; F, 5.09; N, 11.25. Found: C, 61.24; H, 5.50; F, 5.12; N, 11.20.

ii) A mixture containing **16** (1.0 g, 3.77 mmoles), 3-acetylaminopyrrolidine (0.72 g, 5.62 mmoles) and pyridine (1.5 ml) was heated at 90° to 115° for 1.5 hours with stirring and concentrated to dryness under reduced pressure. The mixture was acidified with dilute hydrochloric acid, and the precipitate was collected by filtration and washed with water to give **17** (1.3 g, 92%).

7-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**18**).

A mixture of **17** (1.08 g, 2.90 mmoles) and 2*N* sodium hydroxide (20 ml) was heated at 110° to 120° for 12.5 hours with stirring and cooled. After treatment with charcoal, the solution was adjusted to *p*H 6-7 with 30% acetic acid. The resulting precipitate was collected by filtration and dissolved in dilute acetic acid. The solution was treated with charcoal and neutralized with aqueous ammonia to give **18** (0.58 g, 60%), mp 277-279° dec; ir (potassium bromide): 3430, 1620, cm^{-1}; ^1H nmr (80 MHz, sodium deuteroxide-deuterium oxide): δ 0.8-1.4 (4H, m), 1.4-2.5 (2H, m), 2.6-3.7 (5H, m), 4.6-5.0 (1H, m), 6.67 (1H, d, J = 8 Hz), 7.62 (1H, d, J = 14 Hz), 8.34 (1H, s).

Anal. Calcd. for $C_{17}H_{18}FN_3O_3 \cdot 0.75\ H_2O$: C, 59.21; H, 5.70; F, 5.51; N, 12.19. Found: C, 59.34; H, 5.93; F, 5.35; N, 12.12.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic Acid Hydrochloride (**2**).

A mixture containing **16** (7.0 g, 26.4 mmoles), piperazine (9.1 g, 106 mmoles) and pyridine (70 ml) was heated at 105° to 113° for 1 hour with stirring, and concentrated to dryness under reduced pressure. After addition of water (150 ml), the mixture was adjusted to *p*H 7 by 10% hydrochloric acid, and cooled. The resulting precipitate was collected by filtration, washed with water, and dissolved in 4% hydrochloric acid (50 ml) at 85°. After treatment with charcoal, the solution was cooled. The resulting crystal was collected by filtration and washed with ethanol to give **2** (8.0 g, 78%), mp >300° (lit [4], mp 308-310°).

Antibacterial Activity.

According to the method of Goto *et al.* [9], the MIC was determined by the twofold agar dilution method using Mueller-Hinton agar (*p*H 7.4, Difco); bacterial inocula contained approximately 10^6 colony-forming units and the bacterial growth was observed after 20 hours incubation at 37° (Table I).

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REFERENCES AND NOTES

[1] This is part **7** in a series of "Pyridone-Carboxylic Acid Antibacterial Agents". Part **6**: H. Egawa, T. Miyamoto and J. Matsumoto, *Chem. Pharm. Bull.*, **34**, 4098 (1986). During the course of this work a related patent appeared, ref [6].

[2] H. Egawa, T. Miyamoto, A. Minamida, Y. Nishimura, H. Okada, H. Uno and J. Matsumoto, *J. Med. Chem.*, **27**, 1543 (1984).

[3] R. Wise, J. M. Andrews and L. J. Edwards, *Antimicrob. Agents Chemother.*, **23**, 559 (1983).

[4] K. Grohe, U. Petersen and K. H. Kuck, German Offen. DE patent 3248507 (1984); *Chem. Abstr.*, **101**, 211165z (1984).

[5] H. Goldstein and R. Stamm, *Helv. Chim. Acta*, **35**, 1330 (1952).

[6] K. Grohe, European Patent 168733A_2 (1986).

[7] N. Ishikawa, T. Kitazume, T. Yamazaki, Y. Mochida and T. Tatsuno, *Chem. Letters*, 761 (1981).

[8] Daiichi Seiyaku Co. Ltd., Japanes Patent Kokai 60-72885 (1985); *Chem. Abstr.*, **103**, 141855q (1985).

[9] S. Goto, K. Jo, T. Kawakita, N. Kosaki, S. Mitsuhasi, T. Nisino, N. Ohsawa and H. Tanami, *Chemotherapy*, **29**, 76 (1981).