An Intramolecular Cyclization of 7-Substituted 6-Fluoro-1,8-naphthyridine and -quinoline Derivatives [1] [2]

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A synthesis of 1,4-oxazine and pyrazine ring systems by an intramolecular cyclization of 7-substituted 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine and -quinoline derivatives having a nitrogen or oxygen nucleophilic site in the C-7 appendage was studied. The *in vitro* antibacterial activities of compounds prepared by this method were tested.

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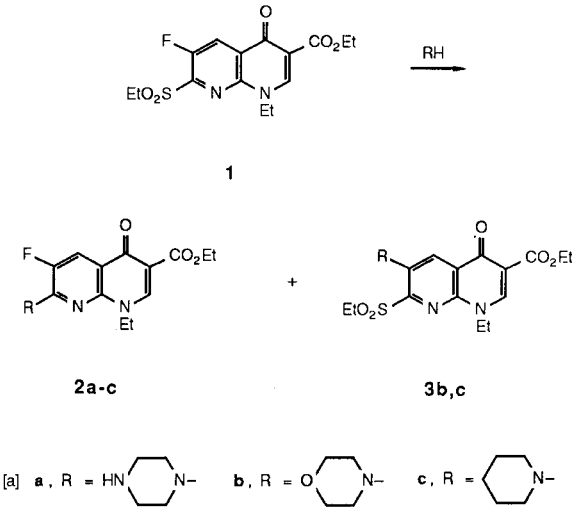
In the previous paper [3] of this series, it was reported that the reaction of ethyl 1-ethyl-7-ethylsulfonyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**1**) with piperazine yielded the 7-(1-piperazinyl) derivative **2a** in good yield. In our continuing studies, it was found that, on treatment of **1** with morpholine and piperidine, the 6-fluoro group of **1** as well as the 7-ethylsulfonyl group was replaced with morpholine and piperidine to give the corresponding 6-substituted derivatives **3b** and **3c**, besides the desired 7-substituted analogues **2b** and **2c**.

Scheme I [a]

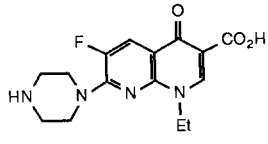


These findings led us to study the nucleophilic displacement of the C-6 fluorine on the 1,8-naphthyridine and the related quinoline ring systems.

We began with a study of the reactivity at the C-6 position of the 7-substituted 6-fluoro-1,8-naphthyridine derivatives.

Treatment of 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid (**4**) with morpholine, however, merely gave back the starting material.

Chart I



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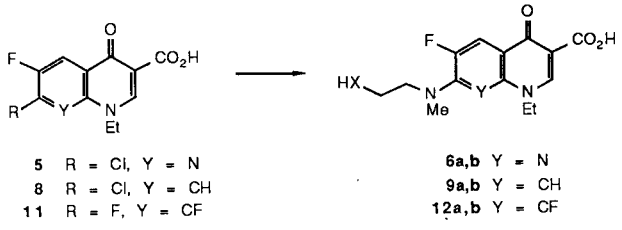
An attempted reaction of **4** with sodium methoxide was unsuccessful as well, resulting in decomposition.

Since the difficulty of the intermolecular displacement of the C-6 fluorine was suggested, we examined an intramolecular displacement, which would be expected to take place more easily. Thus 6-fluoro-7-[[*N*-methyl-*N*-[2-(methylamino)ethyl]]amino]- and 7-[[*N*-(2-hydroxymethyl)-*N*-methyl]amino]-1,8-naphthyridine derivatives **6a** and **6b** having a nucleophilic site in the C-7 appendages were prepared. Treatment of 7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**5**) with *N*,*N*'-dimethylethylenediamine in acetonitrile gave the [*N*-methyl-*N*-[2-(methylamino)ethyl]]amino derivative **6a**. On heating **6a** in dimethylformamide at 100°, an intramolecular cyclization proceeded with ease to give 6-ethyl-1,2,3,4,-6,9-hexahydro-1,4-dimethyl-9-oxopyrazino[2,3-*b*] [1,8]-naphthyridine-8-carboxylic acid (**7a**) in 64% isolated yield. The structure of **7a** was assigned on the basis of disappearence of a coupling signal for the C-10 proton (the proton corresponding to the C-5 proton in **6a**) due to the absence of fluorine in its proton nuclear magnetic resonance (^{1}H-nmr) spectrum, and supported by mass spectrum and elemental analysis. The same type of reaction proceeded with the [*N*-(2-hydroxyethyl)-*N*-methyl]amino derivative **6b**, which was derived from the reaction of **5** with *N*-methylethanolamine. Thus treatment of **6b** with sodium hydride in dimethylformamide caused an intramolecular cyclization, giving 6-ethyl-3,4,6,9-tetrahydro-4-methyl-9-oxo-2*H*-[1,4]oxazino[3,2-*b*] [1,8]naphthyridine-8-carboxylic acid (**7b**) in 44% yield.

6-Fluoroquinoline analogues were then examined to determine whether the same type of cyclization would

occur. It was found that they reacted similarly to the 1,8-naphthyridine derivatives. Thus when 7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**8**) and *N,N'*-dimethylethylenediamine were heated to reflux in pyridine, the displacement reaction at C-7, accompanied by a concomitant intramolecular cyclization at C-6, occurred to give directly (63%) 6-ethyl-1,2,3,4,6,9-hexahydro-9-oxopyrido[2,3-*g*]quinoxaline-8-carboxylic acid (**10a**). The 7-[[*N*-(2-hydroxyethyl)-*N*-methyl]amino]-6-fluoroquinoline derivative **9b**, derived from the reaction of **8** with *N*-methylethanolamine in pyridine, was treated with sodium hydride in dimethylformamide to yield 6-ethyl-3,4,6,9-tetrahydro-4-methyl-9-oxo-2*H*-pyrido[2,3-*g*] [1,4]benzoxazine-8-carboxylic acid (**10b**) in 60% yield.

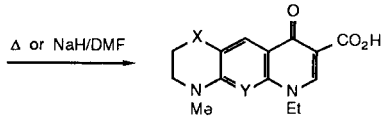
Scheme II [a]



5 R = Cl, Y = N
8 R = Cl, Y = CH
11 R = F, Y = CF

6a,b Y = N
9a,b Y = CH
12a,b Y = CF

[a] **a**, X = NMe, **b**, X = O

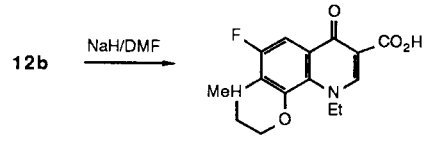


7a,b Y = N
10a,b Y = CH
13a,b Y = CF

Recently the 6,8-difluoroquinoline nucleus has attracted attention as a quinoline ring system because of increases in potency and spectrum of activity seen with these analogues [4].

It was of much interest for us to know the relative reactivities of the C-6 and C-8 fluorine atoms toward cyclization involving the C-7 nucleophiles. Hence, we tried to extend the foregoing reactions to the several 6,8-difluoroquinoline derivatives. Treatment of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**11**) with *N,N'*-dimethylethylenediamine in acetonitrile led to displacement at C-7 accompanied by intramolecular cyclization at C-6, giving directly 6-ethyl-5-fluoro-1,2,3,4,6,9-hexahydro-1,4-dimethyl-9-oxopyrido[2,3-*g*]quinoxaline-8-carboxylic acid (**13a**). The ^{1}H-nmr spectrum of **13a** showed the appearence of a doublet signal (J = 2 Hz) for the C-10 proton (δ = 8.07) due to *para*-coupling with the C-5 fluorine, in agreement with the assigned structure. On the other hand, 7-[[*N*-(2-hydroxyethyl)-*N*-methyl]amino]-6,8-quinoline derivative **12b**, derived from the reaction of **11** with *N*-methylethanolamine, when treated with sodium hydride in dimethylformamide yielded not **13b**, but 10-ethyl-5-fluoro-3,4,7,10-tetrahydro-4-methyl-7-oxo-2*H*-pyrido[3,2-*h*] [1,4]benzoxazine-8-carboxylic acid (**14**), arising from cyclization at the C-8 position of **12b**. The structure of **14** was assigned on the basis of its ^{1}H-nmr spectrum showing the *ortho*-coupling (J = 13 Hz) between the C-6 proton and the C-5 fluorine. The result from this reaction is consistent with that reported independently by Itoh *et al.* [5].

Scheme III



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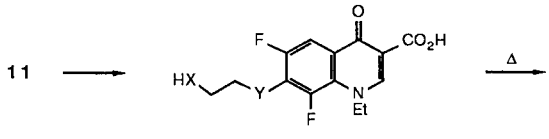
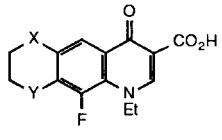
Such differences in reactivity between the C-7 substituents prompted us to examine further the intramolecular cyclization of 6,8-difluoroquinoline derivatives having other C-7 substituents. The [2-(methylamino)ethyl]amino, (2-aminoethyl)amino, (2-hydroxyethyl)amino and 2-aminoethoxy groups were selected as representative C-7 substituents. The reaction of **11** with *N*-methylenediamine, ethylenediamine and monoethanolamine in acetonitrile gave 7-[[2-(methylamino)ethyl]amino], 7-[2-(aminoethyl)-amino] and 7-[(2-hydroxyethyl)amino] derivatives **15a**, **15b** and **15c**, respectively. Heating **15a** or **15b** in dimethylformamide resulted in cyclization, at the C-6 position to yield 6-ethyl-5-fluoro-1,2,3,4,6,9-hexahydro-1-methyl-9-oxopyrido[2,3-*g*]quinoxaline-8-carboxylic acid derivatives **16a** or **16b**, respectively. Attempted cyclization of **15c** on treatment with sodium hydride in dimethylformamide was unsuccessful, leading to decomposition. 7-(2-Aminoethoxy) derivative **15d**, derived from the route

Scheme IV



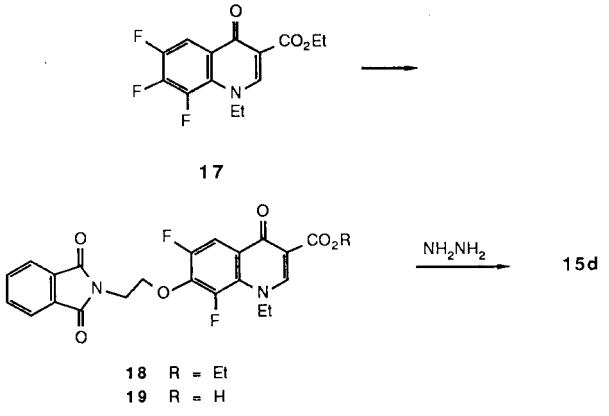
15a X = NMe, Y = NH
15b X = NH, Y = NH
15c X = O, Y = NH
15d X = NH, Y = O



16a X = NMe, Y = NH
16b X = NH, Y = NH

shown in Scheme V, also failed to cyclize on heating in dimethylformamide or pyridine, resulting in the recovery of unchanged **15d**.

Scheme V



As a result, it was observed that the nitrogen atom of the C-7 substituent in the 6,8-difluoroquinoline derivatives attacked at the C-6 position, whereas the oxygen atom did so at the C-8 position, though being supported by limited examples. This may be due to a difference in nucleophilicity between nitrogen and oxygen at the C-7 substituent; a more rational mechanism remains to be elucidated.

The presence of a cyclic amino group such as pyrrolidinyl and piperazinyl groups at C-7 of the pyridonecarboxylic acid derivatives is known to enhance their antibacterial activities [6]. Therefore, intramolecular cyclization reactions were applied to 7-(2-hydroxymethyl- and 2-aminomethyl-1-pyrrolidinyl)-6,8-difluoroquinoline derivatives **23** and **25** which were available from the reactions shown in Scheme VI. When **23** was treated with sodium hydride in dimethylformamide, the cyclization occurred at C-8 to give 10-ethyl-5-fluoro-2,3,7,10,12,12a-hexahydro-7-oxo-1*H*-pyrrolo[2,1-*c*]pyrido[3,2-*h*][1,4]benzoxazine-8-carboxylic acid (**26**) in 80% yield. Heating **25** in dimethylformamide (even without base) gave, as expected, 10-ethyl-11-fluoro-1,2,3,3a,4,5,7,10-octahydro-7-oxopyrrolo[1,2-*a*]pyrido[3,2-*g*]quinoxaline-8-carboxylic acid (**27**) in 78% isolated yield. Thus the regioselective ring closure developed in the acyclic C-7 substituted 6,8-difluoroquinolines also applied in cyclic C-7 substituted examples as well.

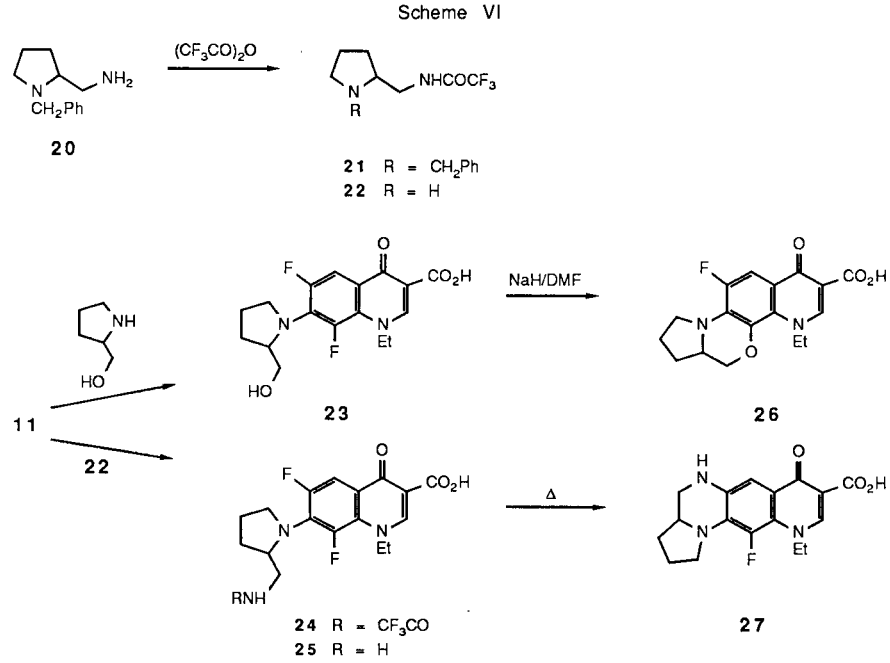
In vitro anitbacterial activities of compounds **7**, **10**, **13a**, **14**, **16**, **26** and **27** prepared by the foregoing intramolecular cyclization reactions were tested; however, there was found no compound with potent activity. Thus the minimal inhibitory concentrations (MICs) (μg/ml) of **7b**, **10a**, **14**, **26** and **27** for *S. aureus 209P JC-1* were 25, 12.5, 6.25, 3.13 and 25, respectively, and those of **7b**, **10a** and **14** for *E. coli NIHJ JC-2* were 25, 25 and 6.25, respectively. As for *P. aeruginosa 12*, compound **14** only inhibited at a concentration of 25 μg/ml.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus, and are uncorrected. Infrared (ir) spectra were recorded on a Jasco A-102 or a Hitachi 215 spectrometer. The ^{1}H-nmr (pmr) spectra were taken at 60 MHz with a Varian EM-360A, at 80 MHz with a Varian FT-80A or at 100 MHz with a Varian HA-100D spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS D-300 or on a Hitachi RMU-6L spectrometer.

Ethyl 1-Ethyl-6-fluoro-1,4-dihydro-7-morpholino-4-oxo-1,8-naphthyridine-3-carboxylate (**2b**) and Ethyl 1-Ethyl-7-ethylsulfonyl-1,4-dihydro-6-morpholino-4-oxo-1,8-naphthyridine-3-carboxylate (**3b**).

Scheme VI



A mixture containing ethyl 1-ethyl-7-ethylsulfonyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**1**) [3] (1.5 g, 4.2 mmoles), morpholine (1.0 g, 11.5 mmoles) and acetonitrile (30 ml) was heated to reflux for 3 hours. The reaction mixture was concentrated to dryness *in vacuo*. The residue was triturated with ethyl acetate. The solid was collected and recrystallized from ethyl acetate to give ethyl 1-ethyl-6-fluoro-1,4-dihydro-7-morpholino-4-oxo-1,8-naphthyridine-3-carboxylate (**2b**) (680 mg, 46%), mp 169.5-171.5°; ir (potassium bromide): 2950, 1680, 1635 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 1.31-1.73 (6H, m), 3.85 (8H, s), 4.18-4.80 (4H, m), 8.24 (1H, d, J = 13 Hz), 8.58 (1H, s).

Anal. Calcd. for $C_{17}H_{20}FN_3O_4$: C, 57.55; H, 5.85; F, 5.36; N, 11.85. Found: C, 57.53; H, 5.83; F, 5.65; N, 11.56.

The filtrate was concentrated to dryness *in vacuo* and the residue was recrystallized from ether to give ethyl 1-ethyl-7-ethylsulfonyl-1,4-dihydro-6-morpholino-4-oxo-1,8-naphthyridine-3-carboxylate (**3b**) (320 mg, 18%), mp 169.5-172.0°; ir (potassium bromide): 2950, 1680, 1650 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 1.31-1.83 (9H, m), 3.11-3.42 (4H, m), 3.72 (2H, q, J = 7 Hz), 3.75-4.20 (4H, m), 4.23-4.72 (4H, m), 8.80 (2H, s).

Anal. Calcd. for $C_{19}H_{25}N_3O_6S$: C, 53.88; H, 5.95; N, 9.92; S, 7.57. Found: C, 54.16; H, 6.05; N, 9.88; S, 7.30.

Ethyl 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperidino-1,8-naphthyridine-3-carboxylate (**2c**) and Ethyl 1-Ethyl-7-ethylsulfonyl-1,4-dihydro-4-oxo-6-piperidino-1,8-naphthyridine-3-carboxylate (**3c**).

According to the procedure as in the preparation of **2b** and **3b**, **2c** and **3c** were prepared by the reaction of **1** with piperidine. Ethyl 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperidino-1,8-naphthyridine-3-carboxylate (**2c**), mp 174.5-176.0° (recrystallized from ethyl acetate, 38%); ir (potassium bromide): 2910, 1680, 1630 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 1.25-2.02 (12H, m), 3.57-4.03 (4H, m), 4.20-4.78 (4H, m), 8.15 (1H, d, J = 13 Hz), 8.54 (1H, s).

Anal. Calcd. for $C_{18}H_{22}FN_3O_3 \cdot 3/10H_2O$: C, 61.27; H, 6.45; F, 5.38; N, 11.91. Found: C, 61.11; H, 6.60; F, 5.68; N, 12.01.

Ethyl 7-ethylsulfonyl-1-ethyl-1,4-dihydro-4-oxo-6-piperidino-1,8-naphthyridine-3-carboxylate (**3c**), mp 95.5-98.0° (recrystallized from ethyl acetate-hexane 49%); ir (potasssium bromide): 2930, 1690, 1640 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 1.22-2.07 (15H, m), 3.00-3.38 (4H, m), 3.69 (2H, q, J = 6 Hz), 4.10-4.78 (4H, m), 8.74 (2H, s).

Anal. Calcd. for $C_{20}H_{27}N_3O_5S \cdot 1/5H_2O$: C, 56.56; H, 6.50; N, 9.89; S, 7.54. Found: C, 56.21; H, 6.61; N, 9.97; S, 7.61.

1-Ethyl-6-fluoro-1,4-dihydro-7-[[*N*-methyl-*N*-[2-(methylamino)ethyl]]-amino]-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**6a**).

A mixture containing 1.0 g (3.7 mmoles) of 1-ethyl-7-chloro-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**5**) [7], *N*,*N*'-dimethylethylenediamine (650 mg, 7.4 mmoles), triethylamine (750 mg, 7.4 mmoles) and acetonitrile (30 ml) was heated to reflux for 1 hour. The reaction mixture was cooled and the resulting solid was collected. The solid was dissolved in 1 *N* sodium hydroxide and the solution was neutralized with acetic acid. The precipitate was filtered off and washed with water to give **6a** (800 mg, 67%), mp 296-298° dec; ir (potassium bromide): 3400, 1620 cm^{-1}; pmr (60 MHz, deuteriotrifluoroacetic acid): δ 1.72 (3H, t, J = 7 Hz), 3.12 (3H, s), 3.57 (3H, d, J = 3 Hz), 3.51-4.00 (2H, m), 4.20-4.65 (2H, m), 4.73 (2H, q, J = 7 Hz), 8.28 (1H, d, J = 13 Hz), 9.28 (1H, s).

Anal. Calcd. for $C_{15}H_{19}FN_4O_3 \cdot 1/3H_2O$: C, 54.87; H, 6.04; F, 5.76; N, 17.06. Found: C, 54.69; H, 6.08; F, 5.87; N, 17.34.

1-Ethyl-6-fluoro-1,4-dihydro-7-[[*N*-(2-hydroxyethyl)-*N*-methyl]amino]-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**6b**).

According to the procedure as in the preparation of **6a**, **6b** was prepared in 82% yield, mp 240-241°; ir (potassium bromide): 3250, 1690, 1620 cm^{-1}; pmr (80 MHz, acetic acid-d_4): δ 1.51 (3H, t, J = 7 Hz), 3.43 (3H, d, J = 3.5 Hz), 3.95 (4H, br), 4.48 (2H, q, J = 7 Hz), 8.02 (1H, d, J = 13 Hz), 8.92 (1H, s).

Anal. Calcd. for $C_{14}H_{16}FN_3O_4$: C, 54.37; H, 5.21; F, 6.14; N, 13.59. Found: C, 54.67; H, 5.00; F, 6.11; N, 13.72.

6-Ethyl-1,2,3,4,6,9-hexahydro-1,4-dimethyl-9-oxopyrazino[2,3-*b*][1,8]-naphthyridine-8-carboxylic Acid (**7a**).

A stirred suspension of **6a** (500 mg, 1.6 mmoles) in dimethylformamide (10 ml) was heated at 100° for 8 hours. The reaction mixture was cooled. The resulting solid was collected, washed with water and recrystallized from chloroform-ethanol to give **7a** (300 mg, 64%), mp 297-300° dec; ir (potassium bromide): 3400, 1700, 1615 cm^{-1}; pmr (100 MHz, deuteriochloroform): δ 1.48 (3H, t, J = 7 Hz), 2.98 and 3.28 (each 3H, s), 3.27-3.40 and 3.64-3.80 (each 2H, m), 4.40 (2H, q, J = 7 Hz), 7.20 (1H, s), 8.43 (1H, s), 16.10 (1H, s); ms: m/e 302 (M^+).

Anal. Calcd. for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.34; H, 5.88; N, 18.47.

6-Ethyl-3,4,6,9-tetrahydro-4-methyl-9-oxo-2*H*-[1,4]oxazino[3,2-*b*][1,8]-naphthyridine-8-carboxylic Acid (**7b**).

To a suspension of **6b** (350 mg, 1.1 mmoles) in dimethylformamide (15 ml) was added 130 mg (3.3 mmoles) of 60% sodium hydride (in mineral oil). The mixture was heated at 90° for 13 hours with stirring and then cooled. The resulting solid was collected and chromatographed on silica gel with chloroform-methanol to give **7b** (150 mg, 44%), which was recrystallized from chloroform-ethanol, mp >300°; ir (potassium bromide): 3400, 1700, 1625 cm^{-1}; pmr (80 MHz, DMSO-d_6): δ 1.41 (3H, t, J = 7 Hz), 3.25 (3H, s), 3.68 (2H, t, J = 5 Hz), 4.30 (2H, t, J = 5 Hz), 4.50 (2H, q, J = 7 Hz), 7.47 (1H, s), 8.83 (1H, s), 15.78 (1H, s); ms: m/e 289 (M^+).

Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.18; H, 5.33; N, 14.52.

1-Ethyl-6-fluoro-1,4-dihydro-7-[[*N*-(2-hydroxyethyl)-*N*-methyl]amino]-4-oxoquinoline-3-carboxylic Acid (**9b**).

A mixture containing 1.5 g (5.6 mmoles) of 7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**8**) [8], *N*-methylethanolamine (1.25 g, 16.7 mmoles) and pyridine (30 ml) was heated to reflux for 24 hours. The reaction mixture was cooled. The resulting solid was collected, and dissolved in 1 *N* sodium hydroxide. The solution was neutralized with acetic acid and the precipitate was filtered off and recrystallized from ethanol to give **9b** (1.15 g, 67%), mp 224-226°; ir potassium bromide): 3350, 1710, 1625 cm^{-1}; pmr (80 MHz, DMSO-d_6): δ 1.41 (3H, t, J = 7 Hz), 3.13 (3H, d, J = 1.5 Hz), 3.58 (4H, br), 6.92 (1H, d, J = 8 Hz), 7.80 (1H, d, J = 15 Hz), 8.85 (1H, s), 15.5 (1H, s).

Anal. Calcd. for $C_{15}H_{17}FN_2O_4$: C, 58.44; H, 5.56; F, 6.16; N, 9.09. Found: C, 58.21; H, 5.67; F, 6.02; N, 9.13.

6-Ethyl-1,2,3,4,6,9-hexahydro-1,4-dimethyl-9-oxopyrido[2,3-*g*]quinoxaline-8-carboxylic Acid (**10a**).

A mixture containing **8** (600 mg, 2.2 mmoles), *N*,*N*'-dimethylethylenediamine (600 mg, 6.8 mmoles) and pyridine (30 ml) was heated to reflux for 13 hours. The reaction mixture was concentrated to dryness *in vacuo*. The residue was dissolved in 1 *N* sodium hydroxide and the solution was neutralized with acetic acid. The precipitate was filtered off and recrystallized from ethanol to give **10a** (420 mg, 63%), mp 272-274° dec; ir (potassium bromide): 3400, 1700, 1620 cm^{-1}; pmr (80 MHz, DMSO-d_6): δ 1.40 (3H, t, J = 7 Hz), 2.92 and 3.07 (each 3H, s), 3.21-3.69 (4H, m), 4.45 (2H, q, J = 7 Hz), 6.52 (1H, s), 7.05 (1H, s), 8.13 (1H, s), 16.50 (1H, s); ms: m/e 301 (M^+).

Anal. Calcd. for $C_{16}H_{19}N_3O_3$: C, 62.83; H, 6.43; N, 13.74. Found: C, 62.90; H, 6.43; N, 13.65.

6-Ethyl-3,4,6,9-tetrahydro-4-methyl-9-oxo-2*H*-pyrido[2,3-*g*][1,4]benzoxazine-8-carboxylic Acid (**10b**).

To a suspension of **9b** (500 mg, 1.6 mmoles) in dimethylformamide (20 ml) was added 190 mg (4.8 mmoles) of 60% sodium hydride (in mineral oil). The mixture was heated at 60° for 5 hours with stirring and concentrated to dryness *in vacuo*. The residue was dissolved in water and the solution was neutralized with acetic acid. The resulting mixture was extracted with chloroform. The extract was concentrated to dryness *in*

vacuo and the residue was triturated with ethyl acetate. The resulting solid was recrystallized from chloroform-ethanol to give **10b** (280 mg, 60%), mp >300°; ir (potassium bromide): 3400, 1700, 1620 cm^{-1}; pmr (80 MHz, DMSO-d_6): δ 1.38 (3H, t, J = 7 Hz), 3.10 (3H, s), 3.49 (2H, t, J = 5 Hz), 4.28 (2H, t, J = 5 Hz), 4.48 (2H, q, J = 7 Hz), 6.72 (1H, s), 7.42 (1H, s), 8.72 (1H, s); ms: m/e 288 (M^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.21; H, 5.87; N, 9.55.

1-Ethyl-6,8-difluoro-1,4-dihydro-7-[[*N*-(2-hydroxyethyl)-*N*-methyl]amino]-4-oxoquinoline-3-carboxylic Acid (**12b**).

A mixture containing 1.0 g (3.7 mmoles) of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**11**) [4], *N*-methylethanolamine (820 mg, 11.1 mmoles) and acetonitrile (20 ml) was heated to reflux for 4.5 hours. The reaction mixture was concentrated to dryness *in vacuo*. The residue was dissolved in water and the solution was neutralized with acetic acid. The precipitate was filtered off, washed with water and recrystallized from ethanol to give **12b** (950 mg, 79%), mp 181-182°; ir (potassium bromide): 3550, 3450, 1700, 1620 cm^{-1}; pmr (60 MHz, DMSO-d_6): δ 1.45 (3H, t, J = 7 Hz), 3.09 (3H, t, J = 3.5 Hz), 3.21-3.92 (4H, m), 4.42-4.87 (2H, m), 7.81 (1H, d d, J = 13, 2 Hz), 8.95 (1H, s).

Anal. Calcd. for $C_{15}H_{16}F_2N_2O_4 \cdot 1/4H_2O$: C, 54.49; H, 5.03; F, 11.44; N, 8.47. Found: C, 54.63; H, 4.89; F, 11.62; N, 8.39.

6-Ethyl-5-fluoro-1,2,3,4,6,9-hexahydro-1,4-dimethyl-9-oxopyrido[2,3-*g*]-quinoxaline-8-carboxylic Acid (**13a**).

A mixture containing **11** (1.0 g, 3.7 mmoles), *N,N'*-dimethylethylenediamine (980 mg, 11.1 mmoles) and acetonitrile (20 ml) was heated to reflux for 3 hours. The reaction mixture was cooled and the resulting solid was collected. The solid was dissolved in 1 *N* sodium hydroxide and the solution was neutralized with acetic acid. The precipitate was filtered off and recrystallized from ethanol to give **13a** (1.15 g, 98%), mp 277-280°; ir (potassium bromide): 3400, 1720, 1620 cm^{-1}; pmr (60 MHz, deuteriotrifluoroacetic acid): δ 1.73 (3H, t, J = 7 Hz), 3.47 and 3.60 (each 3H, s), 4.67 (4H, s), 4.72-5.32 (2H, m), 8.07 (1H, d, J = 2 Hz), 9.25 (1H, s); ms: m/e 319 (M^+).

Anal. Calcd. for $C_{16}H_{18}FN_3O_3$: C, 60.18; H, 5.68; F, 5.95; N, 13.16. Found: C, 60.05; H, 5.83; F, 6.00; N, 13.05.

10-Ethyl-5-fluoro-3,4,7,10-tetrahydro-4-methyl-7-oxo-2*H*-pyrido[3,2-*h*]-[1,4]benzoxazine-8-carboxylic Acid (**14**).

To a suspension of **12b** (500 mg, 1.5 mmoles) in dimethylformamide (15 ml) was added 180 mg (4.5 mmoles) of 60% sodium hydride (in mineral oil). The mixture was heated at 60° for 7 hours with stirring and concentrated to dryness *in vacuo*. The residue was dissolved in water and the solution was neutralized with acetic acid. The resulting mixture was extracted with chloroform. The extract was concentrated to dryness *in vacuo* and the residue was recrystallized from ethanol to give **14** (250 mg, 53%), mp 259-260°; ir (potassium bromide): 3400, 1720, 1620 cm^{-1}; pmr (60 MHz, DMSO-d_6): δ 1.42 (3H, t, J = 7 Hz), 3.17 (3H, d, J = 3.5 Hz), 3.30-3.61 (2H, m), 4.21-4.62 (2H, m), 4.75 (2H, q, J = 7 Hz), 7.63 (1H, d, J = 13 Hz), 8.80 (1H, s); ms: m/e 306 (M^+).

Anal. Calcd. for $C_{15}H_{15}FN_2O_4$: C, 58.82; H, 4.94; F, 6.20; N, 9.15. Found: C, 58.82; H, 5.13; F, 6.22; N, 9.07.

1-Ethyl-6,8-difluoro-1,4-dihydro-7-[[2-(methylamino)ethyl]amino]-4-oxoquinoline-3-carboxylic Acid (**15a**).

A mixture containing **11** (1.0 g, 3.7 mmoles), *N*-methylethylenediamine (820 mg, 11 mmoles) and acetonitrile (30 ml) was heated to reflux for 4 hours. The resulting mixture was concentrated to dryness *in vacuo*. The residue was mixed with 20% acetic acid and the resulting mixture was filtered to remove the insoluble materials. The filtrate was neutralized with ammonia. The precipitate was filtered off to give **15a** (830 mg, 69%), mp 216-218°; ir (potassium bromide): 3400, 1620 cm^{-1}; pmr (80 MHz, deuteriotrifluoroacetic acid): δ 1.54 (3H, t, J = 7 Hz), 2.87 (3H, s), 3.28-3.65 and 3.90-4.10 (each 2H, m), 7.78 (1H, d d, J = 12, 1.5 Hz), 8.73 (1H, s).

Anal. Calcd. for $C_{15}H_{17}N_3O_3F_2 \cdot 2H_2O$: C, 49.88; H, 5.86; F, 10.47; N, 11.63. Found: C, 50.01; H, 6.00; F, 10.47; N, 11.72.

7-[2-(Aminoethyl)amino]-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**15b**).

According to the procedure as in the preparation of **15a**, **15b** was isolated in 97% yield, mp 230-231°; ir (potassium bromide): 3350, 1620 cm^{-1}; pmr (60 MHz, deuteriotrifluoroacetic acid): δ 1.79 (3H, t, J = 7 Hz), 3.58-4.50 (4H, m), 4.68-5.31 (2H, m), 8.28 (1H, d d, J = 12.5, 2 Hz), 9.31 (1H, s).

Anal. Calcd. for $C_{14}H_{15}N_3O_3F_2 \cdot 1/2H_2O$: C, 52.20; H, 5.04; F, 11.86; N, 13.12. Found: C, 52.36; H, 5.21; F, 11.93; N, 13.40.

1-Ethyl-6,8-difluoro-1,4-dihydro-7-[2-(hydroxyethyl)amino]-4-oxoquinoline-3-carboxylic Acid (**15c**).

According to the above procedure, **15c** was prepared in 91% yield, mp 217-219°; ir (potassium bromide): 3250, 1690, 1620 cm^{-1}; pmr (60 MHz, deuteriotrifluoroacetic acid): δ 1.80 (3H, t, J = 7 Hz), 4.21 (4H, s), 4.68-5.22 (2H, m), 8.18 (1H, d d, J = 13, 2 Hz), 9.19 (1H, s).

Anal. Calcd. for $C_{14}H_{14}F_2N_2O_4 \cdot 1/4H_2O$: C, 53.08; H, 4.61; F, 11.99; N, 8.84. Found: C, 53.03; H, 4.73; F, 11.68; N, 8.73.

7-(2-Aminoethoxy)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**15d**).

A mixture containing **19** (1.75 g, 4.0 mmoles), hydrazine monohydrate (1.0 g, 10 mmoles) and methanol (150 ml) was heated to reflux for 72 hours. The reaction mixture was concentrated to dryness *in vacuo*. The residue was dissolved in water and the solution was neutralized with acetic acid. The precipitate was filtered off to give **15d** (700 mg, 57%), mp 217-219°; ir (potassium bromide): 3280, 1690, 1630 cm^{-1}; pmr (80 MHz, DMSO-d_6): δ 1.39 (3H, t, J = 7 Hz), 3.53 (4H, s), 4.38-4.63 (2H, m), 4.48-4.96 (1H, m), 5.30 (1H, br), 7.72 (1H, d, J = 12 Hz), 8.78 (1H, s), 15.13 (1H, s).

Anal. Calcd. for $C_{14}H_{14}F_2N_2O_4$: C, 53.85; H, 4.52; F, 12.17; N, 8.97. Found: C, 54.02; H, 4.54; F, 12.30; N, 9.09.

6-Ethyl-5-fluoro-1,2,3,4,6,9-hexahydro-1-methyl-9-oxopyrido[2,3-*g*]-quinoxaline-8-carboxylic Acid (**16a**).

A suspension of **15a** (350 mg, 10.8 mmoles) in dimethylformamide (10 ml) was heated to reflux for 1 hour. The reaction mixture was concentrated to dryness *in vacuo*. Water was added to the residue and the mixture was neutralized with ammonia and extracted with chloroform. The extract was concentrated to dryness *in vacuo*, and the residue was recrystallized from chloroform-ethanol to give **6a** (210 mg, 64%), mp 242-245°; ir (potassium bromide): 3400, 1710, 1610 cm^{-1}; pmr (80 MHz, acetic acid-d_6): δ 1.55 (3H, t, J = 6 Hz), 3.28 (3H, s), 3.23-3.77 (4H, m), 4.35-4.78 (2H, m), 7.20 (1H, d, J = 1.5 Hz), 8.49 (1H, s); ms: m/e 305 (M^+).

Anal. Calcd. for $C_{15}H_{16}FN_3O_3 \cdot 1/4H_2O$: C, 58.17; H, 5.37; F, 6.10; N, 13.57. Found: C, 58.37; H, 5.61; F, 6.34; N, 13.60.

6-Ethyl-5-fluoro-1,2,3,4,6,9-hexahydro-9-oxopyrido[2,3-*g*]quinoxaline-8-carboxylic Acid (**16b**).

A suspension of **15b** (500 mg, 1.6 mmoles) in dimethylformamide (10 ml) was heated to reflux for 2 hours. The reaction mixture was concentrated to dryness *in vacuo*. Water was added to the residue and the mixture was neutralized with ammonia. The resulting solid was collected and chromatographed on silica gel with chloroform-methanol to give **16b** (180 mg, 39%), which was recrystallized from ethanol, mp 288-292°; ir (potassium bromide): 3350, 1620 cm^{-1}; pmr (60 MHz, deuteriotrifluoroacetic acid): δ 1.78 (3H, t, J = 7 Hz), 4.13 (4H, s), 4.75-5.28 (2H, m), 8.71 (1H, d, J = 2 Hz), 9.29 (1H, s); ms: m/e 291 (M^+).

Anal. Calcd. for $C_{14}H_{14}FN_3O_3 \cdot 1.0H_2O$: C, 54.37; H, 5.21; F, 6.14; N, 13.59. Found: C, 54.56; H, 5.10; F, 6.04; N, 13.41.

Ethyl 1-Ethyl-6,8-difluoro-1,4-dihydro-4-oxo-7-[(2-phthalimido)ethoxy]-quinoline-3-carboxylate (**18**).

A stirred suspension of 2-(hydroxyethyl)phthalimide (3.8 g, 19.9 mmoles) and 1 g (25 mmoles) of 60% sodium hydride (in mineral oil) in

toluene (100 ml) was heated at 60° for 15 minutes. To the mixture was added 5 g (16.7 mmoles) of ethyl 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**17**) [8]. The resulting mixture was heated at the same temperature for 2.5 hours and then cooled. Water was added to the resulting mixture. The organic layer was separated, and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with chloroform-methanol followed by recrystallization from ethyl acetate to give **18** (3.3 g, 42%), mp 149-150°; ir (potassium bromide): 1770, 1710, 1685, 1640, 1620 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 1.37 (3H, t, J = 7 Hz), 1.38 (3H, d t, J = 7, 1 Hz), 4.00-4.67 (8H, m), 7.58-7.92 (4H, m), 7.97 (1H, d d, J = 11, 2 Hz), 8.30 (1H, s).

Anal. Calcd. for $C_{24}H_{20}F_2N_2O_6$: C, 61.28; H, 4.29; F, 8.08; N, 5.96. Found: C, 61.35; H, 4.32; F, 7.93; N, 5.99.

1-Ethyl-6,8-difluoro-1,4-dihydro-4-oxo-7-[(2-phthalimido)ethoxy]quinoline-3-carboxylic Acid (**19**).

A mixture containing **18** (2.9 g, 6.2 mmoles), 1 *N* sodium hydroxide (40 ml) and ethanol (2 ml) was heated at 90-100° for 5 minutes. The mixture was neutralized with acetic acid. The precipitate was filtered off and recrystallized from chloroform-ethanol to give **19** (2.0 g, 73%), mp 248-252°; ir (potassium bromide): 1720, 1620 cm^{-1}; pmr (80 MHz, sodium deuteroxide-deuterium oxide): δ 1.37 (3H, d t, J = 7, 1 Hz), 3.75 (2H, t), 4.26-4.59 (4H, m), 7.15-7.62 (5H, m), 8.35 (1H, s).

Anal. Calcd. for $C_{22}H_{16}F_2N_2O_6 \cdot 3/2H_2O$: C, 56.29; H, 4.08; F, 8.09; N, 5.97. Found: C, 56.20; H, 3.92; F, 7.92; N, 6.01.

1-Benzyl-2-[(trifluoroacetylamino)methyl]pyrrolidine (**21**).

Trifluoroacetic anhydride (2.2 g, 10.6 mmoles) was added to a solution of 1.0 g (5.3 mmoles) of 2-aminomethyl-1-benzylpyrrolidine (**20**) [9] in chloroform (20 ml) with ice-cooling. The reaction mixture was stirred at the room temperature for 1 hour. Water and 10% sodium hydroxide was added successively to the mixture. The organic layer was separated and concentrated to dryness *in vacuo*. The residue was crystallized from hexane to give **21** (1.3 g, 88%), mp 55-56°; ir (potassium bromide): 3300, 2800, 1700 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 1.33-3.55 (9H, m), 3.65 (2H, d d, J = 34, 14 Hz), 7.28 (5H, s).

Anal. Calcd. for $C_{14}H_{17}F_3N_2O$: C, 58.63; H, 5.99; F, 19.91; N, 9.78. Found: C, 58.46; H, 6.26; F, 19.88; N, 9.77.

1-Ethyl-6,8-difluoro-1,4-dihydro-7-(2-hydroxymethyl-1-pyrrolidinyl)-4-oxoquinoline-3-carboxylic Acid (**23**).

A mixture containing **11** (1.0 g, 3.7 mmoles), pyrrolidinemethanol (1.5 g, 14.9 mmoles) and dimethylsulfoxide (5 ml) was heated at 80° for 3 hours with stirring. The resulting mixture was concentrated to dryness *in vacuo*. The residue was dissolved in a mixture of water and acetic acid, and the mixture was extracted with chloroform. The extract was concentrated to dryness *in vacuo*. The residue was triturated with ether, and the solid was recrystallized from acetonitrile to give **23** (1.2 g, 92%), mp 212-213°; ir (potassium bromide): 3450, 1710, 1620 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 1.55 (3H, t, J = 7 Hz), 1.76-2.43 (4H, m), 2.82 (1H, br), 3.27-4.77 (7H, m), 7.78 (1H, d d, J = 13, 2 Hz), 8.37 (1H, s).

Anal. Calcd. for $C_{17}H_{18}F_2N_2O_4$: C, 57.95; H, 5.15; F, 10.78; N, 7.95. Found: C, 57.69; H, 5.16; F, 10.56; N, 8.00.

1-Ethyl-6,8-difluoro-1,4-dihydro-4-oxo-7-[2-[[(trifluoroacetyl)amino]-methyl]-1-pyrrolidinyl]quinoline-3-carboxylic Acid (**24**).

A mixture containing **21** (1.5 g, 5.2 mmoles), 5% palladium-carbon (100 mg) and acetic acid (30 ml) was shaken under hydrogen gas until the required volume of hydrogen was absorbed. The mixture was filtered to remove the catalyst and the filtrate was concentrated to dryness *in vacuo*. The residue was combined with a mixture of **11** (1.0 g, 3.7 mmoles), triethylamine (2.6 g, 26.0 mmoles) and acetonitrile (30 ml). After heating to reflux for 13 hours, the mixture was concentrated to dryness *in vacuo*. The residue was taken up in chloroform and the solution was washed with water and concentrated to dryness *in vacuo*. The residue was recrystallized from ethyl acetate to give **24** (1.0 g, 61%), mp 194-195°; ir (potassium bromide): 1720, 1620 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 1.55 (3H, t, J = 7 Hz), 1.67-2.40 (4H, m), 3.26-4.06 (4H, m), 4.23-4.71 (3H, m), 7.19 (1H, br), 7.84 (1H, d d, J = 13, 2 Hz), 8.32 (1H, s), 14.75 (1H, s).

Anal. Calcd. for $C_{19}H_{18}F_5N_3O_4$: C, 51.01; H, 4.06; F, 21.23; N, 9.39. Found: C, 51.17; H, 3.98; F, 20.97; N, 9.50.

7-(2-Aminomethyl-1-pyrrolidinyl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**25**).

A suspension of **24** (350 mg, 0.8 mmoles) in 1 *N* sodium hydroxide (5 ml) was heated at 90° for 5 minutes. The reaction mixture was neutralized with acetic acid. The resulting solid was collected by filtration and recrystallized from chloroform-ethanol to give **25** (150 mg, 55%), mp 225-230° dec; ir (potassium bromide): 3400, 1620 cm^{-1}; pmr (80 MHz, acetic acid-d_4): δ 1.56 (3H, q, J = 7 Hz), 1.80-2.72 (4H, m), 3.01-3.58 (3H, m), 3.67-4.21 (1H, m), 4.60-4.86 (3H, m).

Anal. Calcd. for $C_{17}H_{19}F_2N_3O_3 \cdot 1/2H_2O$: C, 56.66; H, 5.59; F, 10.54; N, 11.66. Found: C, 56.89; H, 5.31; F, 10.40; N, 11.71.

10-Ethyl-5-fluoro-2,3,7,10,12,12a-hexahydro-7-oxo-1*H*-pyrrolo[2,1-*c*]-pyrido[3,2-*h*][1,4]benzoxazine-8-carboxylic Acid (**26**).

To a suspension of **23** (900 mg, 2.55 mmoles) in dimethylformamide (10 ml) was added 310 mg (7.65 mmoles) of 60% sodium hydride (in mineral oil). The mixture was heated at 110° for 3 hours with stirring and concentrated to dryness *in vacuo*. The residue was dissolved in water, and the solution was neutralized with acetic acid, and then extracted with chloroform. The extract was concentrated to dryness *in vacuo*. The residue was triturated with ether, and the resulting solid was recrystallized from chloroform-ethanol to give **26** (680 mg, 80%), mp >300°; ir (potassium bromide): 3400, 1715, 1620 cm^{-1}; pmr (60 MHz, deuteriotrifluoroacetic acid): δ 1.69 (3H, t, J = 6.5 Hz), 1.90-2.13 (4H, m), 3.45-5.32 (7H), 7.98 (1H, d, J = 13 Hz), 9.05 (1H, s); ms: m/e 332 (M^+).

Anal. Calcd. for $C_{17}H_{17}FN_2O_4 \cdot 1/4H_2O$: C, 60.62; H, 5.24; F, 5.64; N, 8.32. Found: C, 60.55; H, 5.18; F, 5.63; N, 8.12.

10-Ethyl-11-fluoro-1,2,3,3a,4,5,7,10-octahydro-7-oxopyrrolo[1,2-*a*]pyrido-[3,2-*g*]quinoxaline-8-carboxylic Acid (**27**).

A solution of **25** (150 mg, 0.4 mmoles) in dimethylformamide (10 ml) was heated at 70° for 3 hours. The reaction mixture was concentrated to dryness *in vacuo*. The residue was taken up in water and the solution was neutralized with 10% ammonia. The resulting solid was collected by filtration and recrystallized from chloroform-ethanol to give **27** (110 mg, 78%), mp >300°; ir (potassium bromide): 3350, 1700, 1620, 1600 cm^{-1}; pmr (80 MHz, DMSO-d_6): δ 1.40 (3H, t, J = 7 Hz), 1.48-2.36 (4H, m), 2.61-4.95 (5H, m), 4.28-4.62 (2H, m), 6.68 (1H, br), 7.20 (1H, d, J = 1 Hz), 8.53 (1H, s), 15.94 (1H, s); ms: m/e 331 (M^+).

Anal. Calcd. for $C_{17}H_{18}FN_3O_3$: C, 61.62; H, 5.48; F, 5.73; N, 12.68. Found: C, 61.55; H, 5.49; F, 5.73; N, 12.69.

Antibacterial Activity.

According to the method of Goto *et al.* [10], 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°.

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