The Synthesis and Biological Activity of 8-Fluoro-9-(4-methyl-1-piperazinyl)-6-oxo-6*H*-benzo[*c*]quinolizine-5-carboxylic Acid

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A one-pot synthesis of ethyl 8,9-difluoro-6-oxo-6*H*-benzo[*c*]quinolizine-5-carboxylate **11** has been developed. The condensation of ethyl 2-pyridylacetate and 2,4,5-trifluorobenzoyl chloride followed by intramolecular nucleophilic aromatic substitution gave the desired ring system. This intermediate was converted to the title compound and its *in vitro* biological activity is reported.

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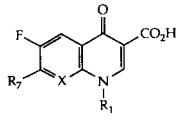
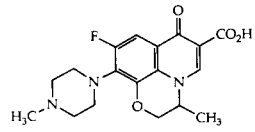
The importance of the quinolone [1] class of antibacterials has been demonstrated in the last ten years. Compounds such as ciprofloxacin **1** [2], enoxacin **2** [3], CL 305,668 **3** [4] and olfloxacin **4** [5] are exemplary of those introduced. Each one represents a distinct structural variation wherein antibacterial efficacy is preserved. Few syntheses have been directed towards the preparation of con-





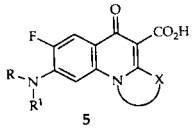
1 R_1 = cyclopropyl, R_7 = piperazinyl, X = CH

2 R_1 = ethyl, R_7 = piperazinyl, X = N

3 R_1 = cyclopropyl, R_7 = 3-fluoromethyl-1-piperazinyl, X = CH

4

geners with general structure **5**. Recently, however, 5-oxo-1,2-dihydro-5*H*-thiazole[3,2-*a*]quinoline-4-carboxylic acid derivatives such as **6** have appeared and show good antibacterial activity [6].



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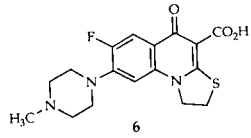

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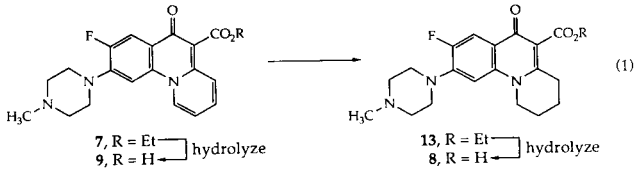
We are interested in developing viable synthetic routes to fused heterocycles similar to **5** for biological evaluation and herein we report an expedient synthesis of **7** and its conversion to **13** (equation 1). The antibacterial activity of their free acids **8** and **9** is also presented.



7, R = Et → hydrolyze → **9**, R = H

13, R = Et → hydrolyze → **8**, R = H (1)

A recent report describes the synthesis of **8** *via* a two-step process involving a β-ketoester enolate condensation with 2-methoxy-3,4,5,6-tetrahydropyridine followed by nucleophilic aromatic substitution [7].

Chemistry.

Key to our method is an intramolecular nucleophilic aromatic substitution of the pyridyl ketoester intermediate **10** to form **11** as shown in equation (2).

10 **11** (2)

Our synthetic sequence is outlined in Scheme 1. Preparation of ethyl lithio 2-pyridylacetate at −5° in THF followed by condensation with 2,4,5-trifluorobenzoyl chloride

Scheme 1

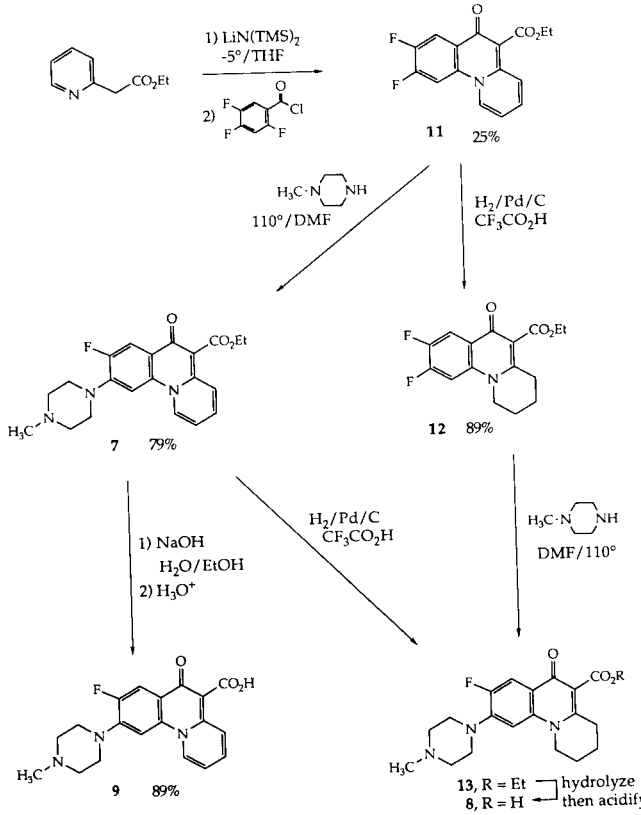


Table I

In Vitro Antibacterial Activity of 8 and 9

Organism MIC, μg/ml [a]

Compound	Sa (A) [b]	Sa (S) [c]	S (f) [d]	S (C) [e]	E (A) [f]	Sm [g]	Et(C) VGH [h]	Pa VGH [i]
8	128	128	128	128	32	32	64	128
9	128	128	128	128	8	8	64	128
ciprofloxacin	1	0.12	1	1	0.01	0.06	0.01	0.1

[a] Minimum inhibitory concentration (MIC) is the lowest concentration of the quinolone that inhibits visible growth of the organism after 48 hours at 37°. [b] *Staphylococcus aureus* VGH 84-47. [c] *Staphylococcus aureus* Smith. [d] *Streptococcus faecalis* VGH 84-65. [e] *Staphylococcus aureus* ATCC 29213. [f] *Escherichia coli* ATCC 25922. [g] *Serratia marcescens* MOR 84-41. [h] *Enterobacter cloacae* VGH 84-39. [i] *Pseudomonas aeruginosa* VGH 84-4.

led directly to **11** in 25% yield. The presumed intermediate **10** in all cases neither was detected nor isolated.

The fused tricycle **11** proved to be a valuable intermediate for the completion of our synthesis. Catalytic hydrogenation of **11** in trifluoroacetic acid gave **12** in 89% yield. Nucleophilic aromatic substitution of **12** with *N*-methylpiperazine formed **13** (66%).

Alternatively, ester **11** underwent nucleophilic substitution with *N*-methylpiperazine to give **7** (79%), which, on base hydrolysis produced the acid **9** in 89% yield. Ester **7**, on the other hand, was converted to **8** in 24% yield *via* the two-step sequence shown.

Biology.

Table I contains a summary of the *in vitro* antibacterial data for acids **8** and **9** against four gram-positive and four gram-negative organisms. For comparison, the activity of ciprofloxacin **1** is shown. Some gram-negative activity is seen for **9** but it is devoid of any gram-positive antibacterial behavior. Even less activity is realized for **8**.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. The following were used for spectral characterizations: mass spectra, Varian CH-7 spectrometer, ir spectra, FT Nicolet 7199 spectrometer. The ^1H (80 MHz) and ^{13}C (75 MHz) nmr spectra were recorded either on a Varian FT80 or Nicolet NT-300 WB spectrometer. Analtech silica gel GF plates (250 mm) were used for thin layer chromatography. Silica gel (300-400 mesh) Merck Kieselgel 60 was employed for flash column chromatography. Solvents used were from freshly opened bottles of spectroscopy grade quality with no special drying procedure observed.

The nmr peaks were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; dd, doublet of doublets. The ir nmr and ms data of all compounds were consistent with assigned structure.

Ethyl 8,9-Difluoro-6-oxo-6*H*-benzo[*c*]quinolizine-5-carboxylate (**11**).

To a solution of ethyl 2-pyridylacetate (3.3 g, 0.02 mole) tetrahydrofuran (50 ml) at −5°, under argon was added lithium bis(trimethylsilyl)amide (25 ml as a 1*M* THF solution) dropwise over 30 minutes. Stirring was continued for an additional 2 hours at −5°. This mixture was added dropwise, under argon to a −5° solution of 2,4,5-trifluorobenzoyl chloride (3.9 g, 18.9 mmoles) in tetrahydrofuran (50 ml) over one hour. Following an additional hour of stirring the mixture was allowed to slowly reach room temperature. Water was added, the resulting solids collected, washed with cold water and dried giving 1.5 g (25%) of the desired compound **11**, mp 200-203°; ^1H nmr (deuteriochloroform): δ 1.4 (t, 3H, CH_3), 4.4 (q, 2H, CH_2), 6.8 (t, 1H), 7.3 (m, 1H), 7.65 (d, 1H, J = 12 Hz), 7.9 (dd, 1H, J = 15 and 7 Hz), 8.35 (m, 2H).

Anal. Calcd. for $C_{16}H_{11}F_2NO_3$: C, 63.37; H, 3.66; N, 4.62; F, 12.53. Found: C, 63.46; H, 3.80; N, 4.45; F, 12.71.

Ethyl 8-Fluoro-9-(4-methyl-1-piperazinyl)-6-oxo-6*H*-benzo[*c*]quinolizine-5-carboxylate (**7**).

A mixture of ethyl 8,9-difluoro-6-oxo-6*H*-benzo[*c*]quinolizine-5-carboxylate **11** (2.0 g, 6.6 mmoles), *N*-methylpiperazine (3.3 g, 33 mmoles) was heated at 110° for 2 hours in DMF (50 ml). The solvent was evaporated and the residue partitioned between water and dichloromethane. The organic layer was dried and the solvent removed giving 2.0 g of **7** (79%), mp 167-170°. A sample was recrystallized from acetone-hexane to give a yellow solid, mp 173-174°; ^1H nmr (deuteriochloroform): δ 1.4 (t, 3H, CH_3), 1.6 (H_2O), 2.4 (s, 3H, CH_3), 2.65 (t, 4H, $2CH_2$ of piperazine), 3.3 (t, 4H, $2CH_2$ of piperazine), 4.5 (q, 2H, CH_2), 6.75 (t, 1H, 7.5 Hz), 7.25 (m, 2H), 7.7 (d, 1H, J = 11 Hz), 8.2 (d, 1H, 15 Hz), 8.35 (d, 1H, 7.5 Hz).

Anal. Calcd. for $C_{21}H_{22}FN_3O_3$: C, 65.78; H, 5.78; F, 4.96; N, 10.96. Found: C, 65.72; H, 5.86; F, 5.28; N, 10.62.

8-Fluoro-9-(4-methyl-1-piperazinyl)-6-oxo-6*H*-benzo[*c*]quinolizine-5-carboxylic Acid (**9**).

A mixture of ethyl ester **7** (0.38 g, 1.0 mmoles), 0.1*N* sodium hydroxide (25 ml) and ethyl alcohol (5 ml) was refluxed for 18 hours. The mixture was cooled to room temperature and the *p*H adjusted to 6 with acetic acid. Most of the volatiles were removed under vacuum to give after filtration 0.31 g of **9** (89%) mp 264-266°; ^{1}H nmr (DMSO-d_6-trifluoroacetic acid): δ 2.95 (s, 3H, CH_3), 3.35 (m, 4H, $2CH_2$ of piperazine), 3.65 (t, 2H, CH_2 of piperazine), 3.95 (t, 2H, CH_2 of piperazine), 7.2 (t, 1H, J = 7 Hz), 8.0 (m, 2H), 9.6 (d, 1H, 7 Hz), 9.7 (d, 1H, 9 Hz).

Anal. Calcd. for $C_{19}H_{18}FN_3O_3$: C, 64.22; H, 5.11; F, 5.35; N, 11.82. Found: C, 64.06; H, 5.20; F, 5.49; N, 11.68.

8-Fluoro-2,3,4,6-tetrahydro-9-(4-methyl-1-piperazinyl)-6-oxo-1*H*-benzo[*c*]quinolizine-5-carboxylic Acid (**8**) from **7**.

A mixture of ethyl 8-fluoro-9-(4-methyl-1-piperazinyl)-6-oxo-6*H*-benzo[*c*]quinolizine-5-carboxylate **7** (0.35 g, 0.91 mmole), 10% palladium-on-carbon (0.47 g) in trifluoroacetic acid (50 ml) was shaken under 40 lb of hydrogen pressure in a Parr apparatus for 18 hours. The mixture was filtered and the solvent evaporated. The concentrate was partitioned between aqueous potassium carbonate and dichloromethane. The organic layer was dried and the solvent removed giving 0.32 g (91%) of ethyl 8-fluoro-2,3,4,6-tetrahydro-9-(4-methyl-1-piperazinyl)-6-oxo-1*H*-benzo[*c*]quinolizine-5-carboxylate **13**, mp 163-165°.

Anal. Calcd. for $C_{21}H_{26}FN_3O_3$: C, 65.50; H, 6.76; N, 10.85; F, 4.90. Found: C, 64.89; H, 6.93; N, 10.63; F, 4.97.

A mixture containing ethyl 8-fluoro-2,3,4,6-tetrahydro-9-(4-methyl-1-piperazinyl)-6-oxo-1*H*-benzo[*c*]quinolizine-5-carboxylate **13** (75 mg, 0.19 mmole), 0.1*N* sodium hydroxide (7 ml, 0.7 mmole) and ethanol (1 ml) was stirred at 100° for 18 hours. On cooling to room temperature the *p*H was adjusted to *ca.* 5 with acetic acid. The solvent was removed and the remaining solid was triturated with hot water then filtered to give the acid **8** (20 mg, 27%) mp 258-259°; ^{1}H nmr (DMSO-d_6): δ 1.8 (pentet, 4H, $2CH_2$), 2.0 (pentet, 4H, $2CH_2$), 2.2 (s, 3H, CH_3), 3.6 (t, 4H, $2CH_2$ of piperazine), 4.4 (t, 4H, $2CH_2$ of piperazine), 7.3 (d, 1H, 7 Hz, H_{10}), 7.9 (d, 1H, J = 13 Hz, H_7).

Anal. Calcd. for $C_{19}H_{22}FN_3O_3$: C, 63.49; H, 6.17; F, 5.29; N, 11.69. Found: C, 63.38; H, 6.11; F, 5.23; N, 11.64.

Ethyl 8,9-Difluoro-1,2,3,4-tetrahydro-6-oxo-6*H*-benzo[*c*]quinolizine-5-carboxylate (**12**).

A mixture of ethyl 8,9-difluoro-6-oxo-6*H*-benzo[*c*]quinolizine-5-carboxylate **11** (0.5 g, 1.65 mmoles) and 10% palladium-on-carbon (0.5 g) in trifluoroacetic acid (50 ml) was shaken under 40 lb of hydrogen pressure in a Parr apparatus for 2 hours. The mixture was filtered and the solvent evaporated. The concentrate was partitioned between aqueous sodium bicarbonate and dichloromethane. The organic layer was dried with magnesium sulfate followed by addition of hexane to precipitate the desired product, **12** (0.45 g, 89%), mp 166-168°; ^{1}H nmr (deuteriochloroform): δ 1.4 (t, 3H, CH_3), 1.9 (pentet, 2H, CH_2), 2.15 (pentet, 2H, CH_2), 3.0 (t, 2H, CH_2), 4.0 (t, 2H, CH_2), 4.4 (q, 2H, CH_2), 7.33 (dd, 1H, J = 15 and 7 Hz), 8.2 (t, 1H, 7 Hz).

Anal. Calcd. for $C_{16}H_{15}F_2NO_3$: C, 62.53; H, 4.92; F, 12.73; N, 4.56. Found: C, 62.52; H, 4.77; F, 12.43; N, 4.46.

Ethyl 8-Fluoro-2,3,4,6-tetrahydro-9-(4-methyl-1-piperazinyl)-6-oxo-1*H*-benzo[*c*]quinolizine-5-carboxylate (**13**) from **12**.

A mixture of **12** (0.31 g, 1 mmole), 4-methylpiperazine (0.3 g, 3 mmoles) and pyridine (10 ml) was heated at 120° for 96 hours. The solvent was removed under vacuum and the residue was dissolved in methylene chloride and this solution was dried (sodium sulfate). The methylene chloride solution was passed through a plug of magnesol. The filtrate was reduced in volume followed by the addition of hexane to precipitate the product, ethyl 8-fluoro-2,3,4,6-tetrahydro-9-(4-methyl-1-piperazinyl)-6-oxo-1*H*-benzo[*c*]-quinolizine-5-carboxylate, weighing 0.25 g (66%) after drying, mp 167-168°; ^{1}H nmr (deuteriochloroform): δ 1.4 (t, 3H, CH_3), 1.8 (m, 2H, CH_2), 2.1 (m, 2H, CH_2), 2.4 (s, 3H, CH_3), 2.6 (t, 4H, $2CH_2$ of piperazine), 3.0 (t, 2H, CH_2), 3.25 (t, 4H, $2CH_2$ of piperazine), 4.05 (t, 2H, CH_2), 4.4 (q, 2H, CH_2), 6.8 (d, 1H, 7 Hz, H_{10}), 8.0 (d, 1H, J = 9 Hz, H_8).

Anal. Calcd. for $C_{21}H_{26}FN_3O_3$: C, 65.10; H, 6.76; F, 4.90; N, 10.85. Found: C, 64.89; H, 6.93; F, 4.97; N, 10.63.

Acknowledgments.

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REFERENCES AND NOTES

[1] The term quinolone is used collectively for a compound class that generally possesses the moiety 1-(substituted)-1,4-dihydro-4-oxopyridine-3-carboxylic acid.

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