Synthesis and Reactions of 7-Substituted 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids as an Antibacterial Agent [1]

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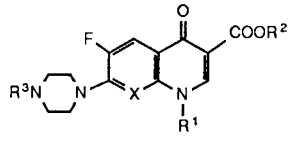
Received April 10, 1987

1-Cyclopropyl- and 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives having a sulfinyl or sulfonyl group at C-7 were synthesized from 2,6-dichloro-5-fluoronicotinic acid derivatives by the route involving the Dieckmann-type cyclization. The displacement reactions of these compounds with pyrrolidine and piperidine gave mainly the 7-(1-pyrrolidinyl)- and 7-(1-piperidinyl)-1,8-naphthyridine derivatives **24-27**, respectively. Enoxacin, a potent antibacterial agent, was also synthesized with the analogous route.

J. Heterocyclic Chem., **24**, 1333 (1987).

Enoxacin (**1**) [2], a pyridonecarboxylic acid antibacterial agent, was developed by the present authors and introduced recently into practice in the antibacterial chemotherapy. It has C-6 fluorine and C-7 piperazinyl groups on the 1,8-naphthyridine ring. A continuing study of structure-activity relationships on the amine moiety in this series led us to finding a new C-7 substituent, 3-aminopyrrolidinyl group, which was effective for improving antibacterial activity [3], Ciprofloxacin (**2**) [4], which is characterized chemically by having a cyclopropyl group at N-1 on the quinoline ring, possesses better activity compared with the parent compound, norfloxacin (**3**) [5], This fact prompted us to introduce a cyclopropyl group to N-1 of the 1,8-naphthyridine bearing piperazinyl or 3-aminopyrrolidinyl group at C-7.

Scheme I



1 X = N, R^1 = C_2H_5, R^2 and R^3 = H

2 X = CH, R^1 = cyclopropyl, R^2 and R^3 = H

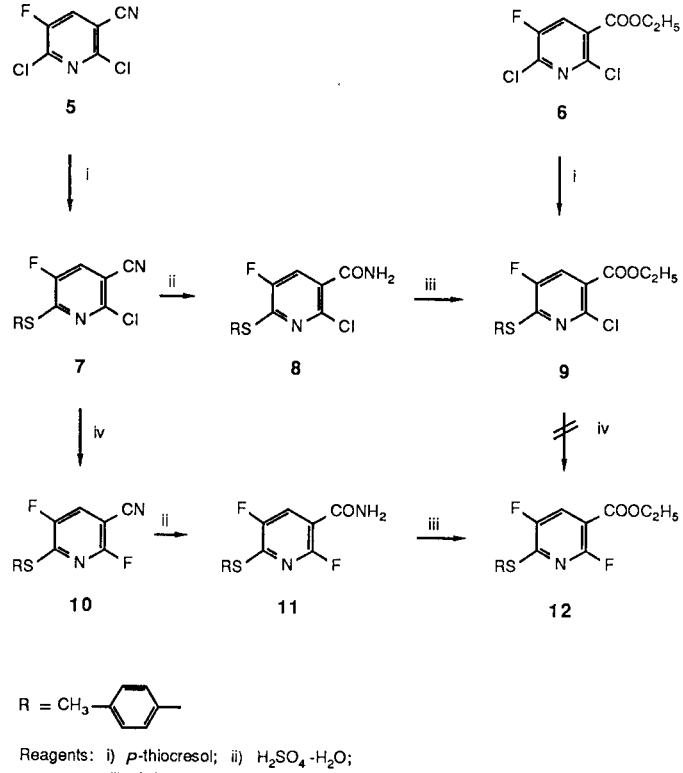
3 X = CH, R^1 = C_2H_5, R^2 and R^3 = H

4 X = N, R^1 = H, R^2 = C_2H_5, R^3 = $COCH_3$

Direct alkylation at N-1 of the 1,8-naphthyridine **4** [2] with a cyclopropyl halide is practically not applicable to the introduction of a cyclopropyl group because of the inertness of this halide. In our recent paper [6], an alternative synthesis of enoxacin by the route involving the Dieckmann-type cyclization [7] was reported. We planned to prepare, by a similar route, 1-cyclopropyl-1,8-naphthyridine derivatives, using ethyl 3-(cyclopropylamino)propionate (**13a**). This paper deals with a synthesis of 1-cyclopropyl- and 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives having a sulfinyl or sulfonyl group at C-7, and with reactivities of the C-7 leaving group with cyclic amines.

2,6-Dichloro-5-fluoronicotinonitrile **5** and -nicotinic acid ester **6** were used as starting materials. In order to prepare an appropriate intermediate for the Dieckmann-type cyclization, it is necessary to replace the C-2 chloro groups of **5** and **6** with the *N*-alkyl-*N*-(2-ethoxycarbonylethyl)amino group derived from **13**. However, the displacement reactions of **5** and **6** with **13** were expected to proceed not at

Scheme II



Reagents: i) *p*-thiocresol; ii) H_2SO_4-H_2O; iii) BF_3-C_2H_5OH; iv) KF

C-2 but predominantly at C-6 because the reaction with 1-acetylpiperazine had regioselectively occurred at C-6 as reported previously [6]. Therefore, the regioselectivity of *p*-thiocresol as a nucleophile other than amines was examined; if the selective displacement at C-6 is realized, the resulting *p*-tolylthio group may be converted, after the construction of the 1,8-naphthyridine ring, to a good leaving group such as sulfinyl and sulfonyl groups for the following substitution with cyclic amines.

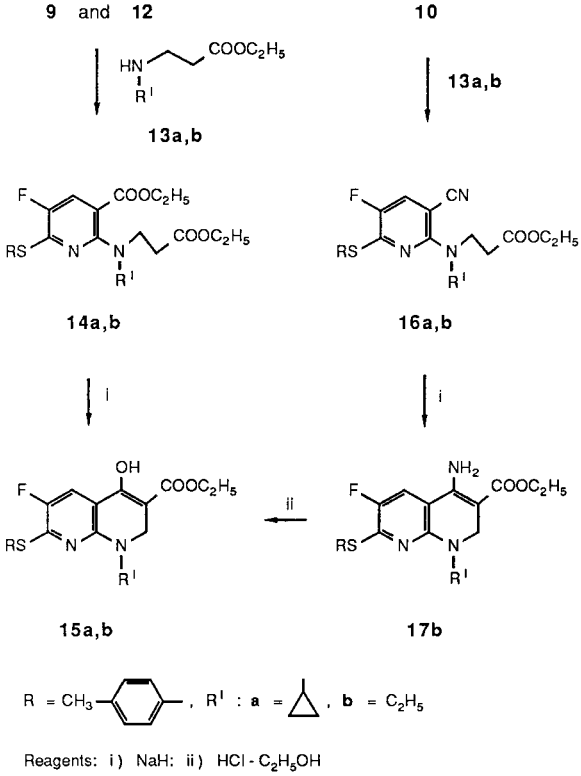
Thus the reactions of **5** and **6** with potassium salt of *p*-thiocresol proceeded regioselectively to give the sulfides **7** and **9**, respectively, as a sole product (Scheme II). Hydrolysis of the cyano group of **7** gave the amide **8**, which was converted to the ester **9** on treatment with boron trifluoride etherate in ethanol. In order to make the introduction of **13** to C-2 of **9** easy, we intended to replace the chloro group by a fluoro group. However, an attempted reaction of **9** with potassium fluoride failed to give the difluoronitinate **12**. The requisite compound **12** therefore was prepared from **7** as follows; on heating of **7** with potassium fluoride in dimethyl sulfoxide, the chloro group of **7** was easily replaced by a fluoro group to give the difluoronicotinonitrile **10**, which was converted to the ester **12** *via* the amide **11**.

When **9** was heated at 120° to 130° with **13a** in dimethylformamide in the presence of sodium bicarbonate, the desired diester **14a** was produced in 23% yield along with a 60% recovery of **9** (Scheme III). The reaction of **12** with **13a** under similar conditions proceeded smoothly to afford **14a** in 96% yield. Compound **14b** was similarly prepared from the reaction of **12** with ethyl 3-(ethylamino)propionate (**13b**). Furthermore, the reactions of **10** with **13a** and **13b** under the same conditions gave the nicotinonitriles **16a** and **16b**, respectively.

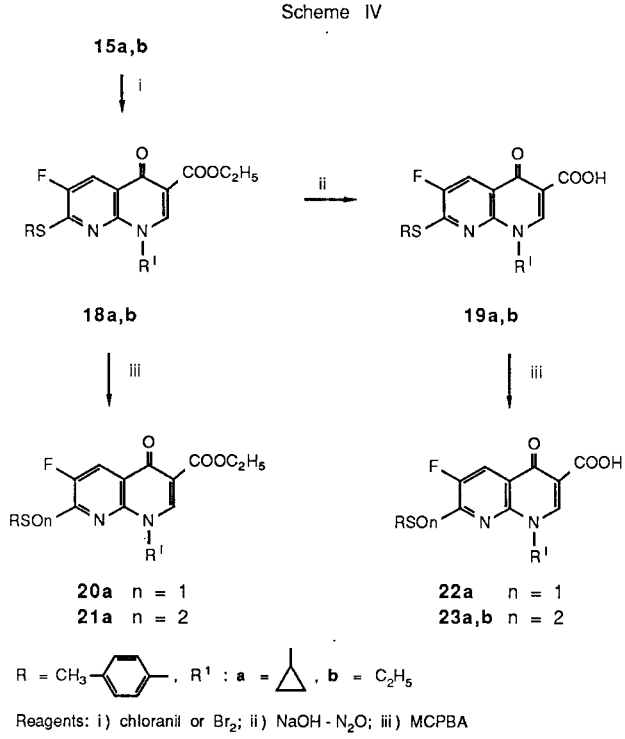
The Dieckmann-type cyclization of **14a** and **14b** was carried out on treatment with sodium hydride in toluene to afford ethyl 1-cyclopropyl- and 1-ethyl-6-fluoro-1,2-dihydro-4-hydroxy-7-(*p*-tolylthio)-1,8-naphthyridine-3-carboxylates **15a** and **15b**, respectively. The proton nuclear magnetic resonance (pmr) spectra of **15a** and **15b** show singlet signals at δ 4.10 and 4.22 for the C-2 methylene protons, and at δ 12.00 and 12.10 for the C-4 enol proton, respectively. These data suggest that **15a** and **15b** exist in the enol form in deuteriochloroform. Intramolecular cyclization of **16** was then examined. Thus, the treatment of **16b** with sodium hydride in toluene gave the 4-amino-1,2-dihydro-1,8-naphthyridine **17b**, whereas the same treatment of **16a** did not afford the expected compound. Partial acidic hydrolysis of **17b** led to **15b**.

Dehydrogenation of **15** was carried out on treatment with chloranil in toluene to give the corresponding 1,4-dihydro-4-oxo-1,8-naphthyridine derivative **18** (Scheme IV). Treatment of **15a** with bromine in chloroform, without base, also afforded **18a**, which would arise from the spontaneous elimination of hydrogen bromide from the probable intermediate ethyl 3-bromo-4-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine derivative. Alkaline hydrolysis of the

Scheme III



Scheme IV



ester **18** gave the carboxylic acid **19**. On treatment with an equimolar *m*-chloroperbenzoic acid (MCPBA), the sulfenyl groups of **18a** and **19a** were easily oxidized to afford the sulfoxides **20a** and **22a**, respectively. With use of 2-fold molar MCPBA, oxidation of **18a**, **19a** and **19b** gave the sulfones **21a**, **23a** and **23b**, respectively.

The scope of displacement reactions of **20a-23a** was examined with use of pyrrolidine and piperidine as a nucleophile (Scheme V). Thus, compounds **20a-23a** were heated under reflux for 30 minutes with pyrrolidine or piperidine in acetonitrile in the presence of triethylamine, the results from which were given in Table I. In the reactions with pyrrolidine, the sulfones **21a** and **23a** gave exclusively the 7-(1-pyrrolidinyl) derivatives **24** and **25**, respectively, while the sulfoxides **20a** and **22a** afforded **24** and **25** together with a considerable amount of the 7-hydroxy derivatives **28** and **29**, respectively, though a mechanism of the formation of **28** and **29** remains unclear. In the reactions of the sulfoxides **20a** and **22a** with piperidine, the concomitant formation of **28** and **29**, as well as the desired products **26** and **27**, were observed. The reaction of the ester **21a** with piperidine gave the 6-substituted compound **30** in 21% yield accompanied by a 66% yield of the main product **26**. The formation of **30** would be due to the steric and electron-withdrawing effect of the sulfonyl group. However, such displacement reaction at C-6 was not observed in the reaction of the carboxylic acid **23a** with piperidine. These displacement reactions are summarized as follows; i) the sulfonyl groups of **21a** and **23a** are more favorable as a leaving group than the sulfinyl groups of **20a** and **22a**, ii) the carboxylic acids **22a** and **23a** react more regioselectively than the esters **20a** and **21a**, and iii) regioselectively for the ester **21a** seems to depend on the nucleophilicity of the amines used (pyrrolidine is well known to be more nucleophilic than piperidine), although the examples are limited.

Table I

Displacement Reactions of Sulfoxides and Sulfones with Amines

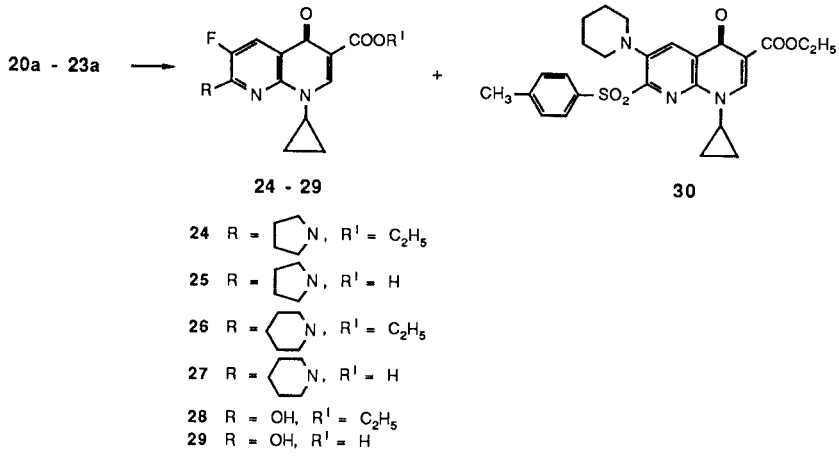
Starting Compd.	Reagent	Method [a]	Product (Yield, %) [b]
Sulfoxides			
20a	pyrrolidine	A	**24** (62), **28** (19)
	piperidine	A	**26** (54), **28** (25)
22a	pyrrolidine	D	**25** (74), **29** (23)
	piperidine	E	a 2:1 mixture of **27** and **29** (89)
Sulfones			
21a	pyrrolidine	B	**24** (91)
	piperidine	C	**26** (66), **30** (21)
23a	pyrrolidine	F	**25** (97)
	piperidine	F	**27**(86)

[a] See the Experimental for Methods A-F. [b] Yields are of the isolated products.

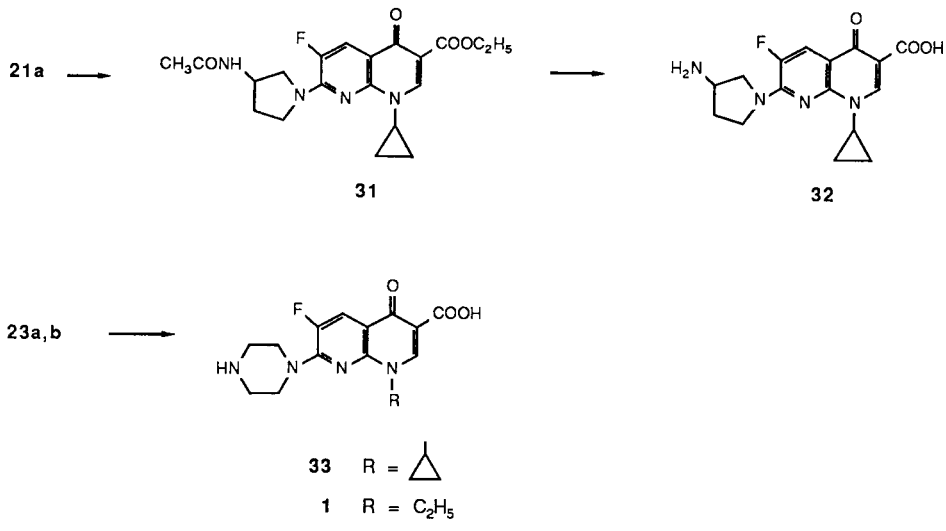
On these grounds, the desired 3-aminopyrrolidinyl and piperazinyl analogs, **32** and **33**, were synthesized as shown in Scheme VI. The reaction of 3-acetylaminopyrrolidine with the ester **21a** produced exclusively the 7-substituted derivative **31**, which was deprotected by hydrochloric acid to give **32**. The carboxylic acid **23a** reacted with piperazine, giving **33** as a sole product. Similarly, enoxacin (**1**) was synthesized by the reaction of **23b** with piperazine.

The present method would be of much use for a synthesis of the 1,8-naphthyridine derivatives bearing the different N-1 substituent of which introduction is difficult or impossible with direct alkylation by the conventional method. Antibacterial activity of **32**, **33** and their related compounds thus prepared will be reported elsewhere.

Scheme V



Scheme VI



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. The ^{1}H nmr (pmr) spectra were taken at 60 MHz on a Varian EM-360A or at 80 MHz on a Varian FT-80A spectrometer with tetramethylsilane, except for **32** and **33** which were measured on a Varian HA-100D spectrometer with sodium 2,2-dimethyl-2-silapentane-5-sulfonate, as an internal standard. Mass spectra were recorded on a JEOL JMS D-300.

2-Chloro-5-fluoro-6-(*p*-tolylthio)nicotinonitrile (**7**).

To a stirred solution of *p*-thiocresol (23.2 g, 187 mmoles) and 85% potassium hydroxide (12.2 g, 185 mmoles) in ethanol (200 ml) was added a solution of **5** [6] (32.5 g, 170 mmoles) in ethanol (200 ml). The mixture was stirred for 2 hours at room temperature. After addition of water (400 ml), the resulting crystals were collected by filtration, and washed successively with water and ethanol to give **7** (42.4 g, 90%), which was recrystallized from ethanol, mp 124-125°; ir (potassium bromide): 2230 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 2.44 (3H, s), 7.1-7.7 (5H, m).

Anal. Calcd. for $C_{13}H_8ClFN_2S$: C, 56.02; H, 2.89; Cl, 12.72, F, 6.82, N, 10.05, S, 11.50. Found: C, 56.32; H, 2.95; Cl, 12.67; F, 6.71; N, 10.09; S, 11.59.

2-Chloro-5-fluoro- and 2,5-Difluoro-6-(*p*-tolylthio)nicotinamides **8** and **11**.

A stirred mixture of **7** (13.0 g, 46.7 mmoles) and concentrated sulfuric acid (65 ml) was heated at 50° to 55° for 1 hour, and poured into ice-water. The mixture was extracted with chloroform. The extract was dried over sodium sulfate, and concentrated to dryness. The resulting solid was recrystallized from a mixture of dichloromethane and *n*-hexane to give **8** (10.7 g, 77%), mp 150-151°; ir (potassium bromide): 3450, 1690 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 2.40 (3H, s), 6.2-7.1 (2H, br), 7.24 and 7.42 (each 2H, d, J = 8 Hz), 7.90 (1H, d, J = 9 Hz).

Anal. Calcd. for $C_{13}H_{10}ClFN_2OS$: C, 52.62; H, 3.40; Cl, 11.95; F, 6.40; N, 9.44; S, 10.81. Found: C, 52.74; H, 3.48; Cl, 12.08; F, 6.19; N, 9.31; S, 10.73.

Also prepared according to this procedure was **11** (32.8 g, 84%) from **10** (36.5 g), **11**, mp 143-144° (recrystallized from a mixture of ether and *n*-hexane); ir (potassium bromide): 3500, 3450, 1680 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 2.40 (3H, s), 6.1-6.9 (2H, br), 7.24 and 7.46 (each 2H, d, J = 8 Hz), 8.10 (1H, dd, J = 8, 8.5 Hz).

Anal. Calcd. for $C_{13}H_{10}F_2N_2OS$: C, 55.71; H, 3.60; F, 13.56; N, 9.99; S, 11.44. Found: C, 55.70; H, 3.20; F, 13.59; N, 10.01; S, 11.68.

Ethyl 2-Chloro-5-fluoro- and 2,5-Difluoro-6-(*p*-tolylthio)nicotinates **9** and **12**.

i) To a stirred solution of **8** (10.5 g, 35.4 mmoles) in absolute ethanol (150 ml) was added boron trifluoride etherate (40 ml) under ice-cooling. The mixture was stirred at 50° to 60° for 30 minutes during which period the resulting ether was removed, and heated under reflux for an additional 23 hours. After removal of the solvent, water was added. The mixture was extracted with chloroform. The extract was washed with saturated sodium bisulfate, dried over sodium sulfate, and concentrated to dryness. The resulting solid was recrystallized from a mixture of ether and *n*-hexane to give **9** (10.5 g, 91%), mp 69-70°; ir (potassium bromide): 1735 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 1.36 (3H, t, J = 7 Hz), 2.38 (3H, s), 4.38 (2H, q, J = 7 Hz), 7.26 and 7.50 (each 2H, d, J = 8 Hz), 7.82 (1H, d, J = 9 Hz).

Anal. Calcd. for $C_{15}H_{13}ClFNO_2S$: C, 55.30; H, 4.02; Cl, 10.88; F, 5.83; N, 4.30; S, 9.84. Found: C, 55.33; H, 3.86; Cl, 10.94; F, 5.89; N, 4.22; S, 9.69.

Also prepared according to this procedure was **12** (5.4 g, 98%) from **11** (5.0 g); **12**, mp 68-70° (recrystallized from *n*-hexane); ir (potassium bromide): 1710 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 1.36 (3H, t, J = 7 Hz), 2.40 (3H, s), 4.36 (2H, q, J = 7 Hz), 7.24 and 7.48 (each 2H, d, J = 8 Hz), 7.92 (1H, dd, J = 7, 8 Hz).

Anal. Calcd. for $C_{15}H_{13}F_2NO_2S$: C, 58.24; H, 4.24; F, 12.28; N, 4.53; S, 10.37. Found: C, 57.93; H, 4.28; F, 12.50; N, 4.75; S, 10.60.

ii) According to the method described for the preparation of **7**, **6** [6] (3.2 g, 13.5 mmoles) was treated with *p*-thiocresol (1.8 g, 14.5 mmoles) to give **9** (4.0 g, 91%).

2,5-Difluoro-6-(*p*-tolylthio)nicotinonitrile (**10**).

A mixture of **7** (36.0 g, 129 mmoles), spray-dried potassium fluoride [8] (22.2 g, 338 mmoles) and dimethyl sulfoxide (180 ml) was heated at 130° to 135° for 1 hour with vigorous stirring. After removal of the solvent under reduced pressure, water (180 ml) was added. The resulting solid was collected by filtration, washed with water, and recrystallized from ethanol to give **10** (30.0 g, 89%), mp 120-121°; ir (potassium bromide): 2240 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 2.40 (3H, s), 7.2-7.8 (5H, m).

Anal. Calcd. for $C_{13}H_8F_2N_2S$: C, 59.53; H, 3.07; F, 14.49; N, 10.68; S, 12.23. Found: C, 59.70; H, 3.27; F, 14.31; N, 10.62; S, 12.04.

Ethyl 3-(Cyclopropylamino)propionate (**13a**).

According to the literature method [9] described for the preparation of ethyl 3-(ethylamino)propionate (**13b**), ethyl acrylate (122 g, 1.22 mole)

was treated with cyclopropylamine (75 g, 1.32 mole) to give **13a** (129 g, 64%), bp 101-102° (17-18 mm Hg); ir (neat): 3300, 1730 cm^{-1}; pmr (80 MHz, deuteriochloroform): 0.2-0.5 (4H, m), 1.26 (3H, t, J = 7 Hz), 1.7-2.3 (2H, m), 2.48 and 2.96 (each 2H, t, J = 7 Hz), 4.14 (2H, q, J = 7 Hz); ms: 157 (M^+).

Ethyl 2-[*N*-Cyclopropyl- and *N*-Ethyl-*N*-(2-ethoxycarbonyl)ethyl]amino-5-fluoro-6-(*p*-tolylthio)nicotinates **14a,b**.

i) A mixture of **12** (3.9 g, 12.6 mmoles), **13a** (4.0 g, 25.5 mmoles), sodium bicarbonate (2.1 g, 25.0 mmoles) and dimethylformamide (60 ml) was heated at 110° to 120° for 8 hours with vigorous stirring. The insoluble material was filtered off, and the filtrate was concentrated to dryness under reduced pressure. The residue was taken up in a mixture of water and toluene. The toluene layer was separated, washed successively with dilute hydrochloric acid and water, and dried over sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with a mixture of chloroform and *n*-hexane (3:2, v/v) as an eluent to give the oil **14a** (5.4 g, 96%); ir (neat): 1730, 1710 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 0.2-0.9 (4H, m), 1.24 and 1.34 (each 3H, t, J = 7 Hz), 2.28 (2H, t, J = 7 Hz), 2.38 (3H, s), 2.5-3.0 (1H, m), 3.50 (2H, t, J = 7 Hz), 4.14 and 4.28 (each 2H, q, J = 7 Hz), 7.18 and 7.48 (each 2H, d, J = 8 Hz), 7.54 (1H, d, J = 9 Hz); ms: 446 (M^+), 431, 417, 401, 373, 359, 345, 331.

Also prepared according to this procedure was the oil **14b** (2.7 g, 96%) from **12** (2.0 g); **14b**, ir (neat): 1730, 1710 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 0.90, 1.22 and 1.30 (each 3H, t, J = 7 Hz), 2.24 (2H, t, J = 7 Hz), 2.38 (3H, s), 3.00 (2H, t, J = 7 Hz), 3.22, 4.06 and 4.30 (each 2H, q, J = 7 Hz), 7.0-7.7 (5H), m); ms: 434 (M^+), 419, 405, 389, 361, 347, 333, 319, 287.

ii) According to the method described above, **9** (2.0 g, 6.1 mmoles) was heated with **13a** (2.1 g, 13.4 mmoles) at 120° to 130° to give **14a** (0.63 g, 23%) with a recovery of **9** (1.2 g, 60%), respectively.

Ethyl 1-Cyclopropyl- and 1-Ethyl-6-fluoro-1,2-dihydro-4-hydroxy-7-(*p*-tolylthio)-1,8-naphthyridine-3-carboxylates **15a,b**.

i) To a stirred solution of **14a** (3.2 g, 7.2 mmoles) in toluene (50 ml) was added 65% sodium hydride (0.32 g, 8.7 mmoles). After addition of ethanol (0.2 ml), the mixture was stirred for 2 hours at room temperature, and acidified with 10% acetic acid. The toluene layer was separated, and dried over sodium sulfate. After removal of the solvent, the resulting solid was triturated with *n*-hexane, and collected by filtration to give **15a** (2.5 g, 87%), which was recrystallized from a mixture of isopropyl ether and *n*-hexane, mp 124-125°; ir (potassium bromide): 1655, 1620 cm^{-1}; pmr (60 MHz, deuteriochlorform): δ 0.1-0.6 (4H, m), 1.32 (3H, t, J = 7 Hz), 1.7-2.2 (1H, m), 2.38 (3H, s), 4.10 (2H, s), 4.24 (2H, q, J = 7 Hz), 7.18 and 7.50 (each 2H, d, J = 8 Hz), 7.34 (1H, d, J = 9 Hz), 12.00 (1H, s).

Anal. Calcd. for $C_{21}H_{21}FN_2O_3S$: C, 62.98; H, 5.29; F, 4.74; N, 7.00; S, 8.01. Found: C, 62.75; H, 5.22; F, 4.77; N, 6.80; S, 8.28.

Also prepared according to this procedure was **15b** (0.76 g, 85%) from **14b** (1.0 g); **15b**, mp 107-110° (recrystallized from a mixture of ether and *n*-hexane); ir (potassium bromide): 1660, 1625 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 0.72 and 1.30 (each 3H, t, J = 7 Hz), 2.40 (3H, s), 3.02 and 4.24 (each 2H, q, J = 7 Hz), 4.22 (2H, s), 7.1-7.7 (5H, m), 12.10 (1H, s).

Anal. Calcd. for $C_{20}H_{21}FN_2O_3S$: C, 61.84; H, 5.45; F, 4.89; N, 7.21; S, 8.25. Found: C, 61.91; H, 5.44; F, 5.00; N, 7.17; S, 8.47.

ii) A mixture of **17b** (1.0 g, 2.6 mmoles), concentrated hydrochloric acid (1 ml) and ethanol (20 ml) was stirred for 1 hour at 80°, and concentrated to dryness under reduced pressure. After addition of water, the resulting solid was collected by filtration, and recrystallized from a mixture of ether and *n*-hexane to give **15b** (0.9 g, 90%).

2-[*N*-Cyclopropyl- and *N*-Ethyl-*N*-(2-ethoxycarbonyl)ethyl]amino-5-fluoro-6-(*p*-tolylthio)nicotinonitriles **16a,b**.

According to the method described for the preparation of **14a**, **10** (1.0 g, 3.8 mmoles) was treated with **13a** (1.2 g, 7.6 mmoles) to give the oil **16a** (1.1 g, 72%), ir (neat): 2220, 1725 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 0.5-1.2 (4H, m), 1.26 (3H, t, J = 7 Hz), 2.14 (2H, t, J = 7 Hz), 2.38 (3H, s), 2.7-3.2 (1H, m), 3.42 (2H, t, J = 7 Hz), 4.12 (2H, q, J = 7 Hz), 7.0-7.6 (5H, m); ms: 399 (M^+), 384, 370, 354, 326, 312, 298, 284, 258.

Similarly prepared was **16b** (1.1 g, 75%) from **10** (1.1 g); **16b**, mp 52-53° (recrystallized from *n*-hexane); ir (potassium bromide): 2220, 1725 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 1.06 and 1.24 (each 3H, t, J = 7 Hz), 2.16 (2H, t, J = 7 Hz), 2.38 (3H, s), 3.42 (2H, t, J = 7 Hz), 3.46 and 4.10 (each 2H, q, J = 7 Hz), 7.1-7.7 (5H, m); ms: 387 (M^+), 372, 358, 342, 314, 300, 286, 272.

Anal. Calcd. for $C_{20}H_{22}FN_3O_2S$: C, 62.00; H, 5.72; F, 4.90; N, 10.84; S, 8.28. Found: C, 62.04; H, 5.55; F, 5.07; N, 10.75; S, 8.30.

Ethyl 4-Amino-1-ethyl-6-fluoro-1,2-dihydro-7-(*p*-tolylthio)-1,8-naphthyridine-3-carboxylate (**17b**).

To a stirred solution of **16b** (2.3 g, 5.9 mmoles) in toluene (23 ml) was added 65% sodium hydride (0.26 g, 7.1 mmoles). After addition of ethanol (0.4 ml), the mixture was stirred for 2 hours at room temperature, and acidified with acetic acid. The mixture was extracted with ethyl acetate, and dried over sodium sulfate. After removal of the solvent, the resulting solid was triturated with *n*-hexane, and collected by filtration to give **17b** (2.1 g, 91%), which was recrystallized from a mixture of ether and *n*-hexane, mp 111-114°; ir (potassium bromide): 3440, 3320, 1655, 1630 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 0.74 and 1.30 (each 3H, t, J = 7 Hz), 2.38 (3H, s), 3.08 and 4.18 (each 2H, q, J = 7 Hz), 4.10 (2H, s), 6.0-6.5 (2H, m), 6.9-7.7 (5H, m).

Anal. Calcd. for $C_{20}H_{22}FN_3O_2S$: C, 62.00; H, 5.72; F, 4.90; N, 10.84; S, 8.28. Found: C, 61.99; H, 5.82; F, 5.02; N, 10.66; S, 8.47.

Ethyl 1-Cyclopropyl- and 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(*p*-tolylthio)-1,8-naphthyridine-3-carboxylates **18a,b**.

i) A mixture of **15a** (2.9 g, 7.3 mmoles), chloranil (1.8 g, 7.3 mmoles) and toluene (60 ml) was heated under reflux for 1.5 hours, and cooled. The resulting precipitate was collected by filtration, and dissolved in chloroform. The solution was washed successively with 1*N* sodium hydroxide (40 ml) and water, and dried over sodium sulfate. After removal of the solvent, the resulting solid was triturated with isopropyl ether, and collected by filtration to give **18a** (2.4 g, 83%), which was recrystallized from a mixture of ethanol and isopropyl ether, mp 186-187°; ir (potassium bromide): 1690, 1640 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 0.5-0.9 (4H, m), 1.40 (3H, t, J = 7 Hz), 2.44 (3H, s), 2.8-3.3 (1H, m), 4.38 (2H, q, J = 7 Hz), 7.30 and 7.58 (each 2H, d, J = 8 Hz), 8.24 (1H, d, J = 9 Hz), 8.54 (1H, s).

Anal. Calcd. for $C_{21}H_{19}FN_2O_3S$: C, 63.30; H, 4.81; F, 4.77; N, 7.03; S, 8.05. Found: C, 63.18; H, 4.78; F, 4.99; N, 7.01; S, 8.31.

Also prepared according to this procedure was **18b** (1.4 g, 94%) from **15b** (1.5 g); **18b**, mp 168-170° (recrystallized from ethyl acetate); ir (potassium bromide): 1690, 1620 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 1.02 and 1.40 (each 3H, t, J = 7 Hz), 2.44 (3H, s), 3.86 and 4.36 (each 2H, q, J = 7 Hz), 7.24 and 7.46 (each 2H, d, J = 8 Hz), 8.20 (1H, d, J = 9 Hz), 8.36 (1H, s).

Anal. Calcd. for $C_{20}H_{19}FN_2O_3S$: C, 62.16: H, 4.96; F, 4.92; N, 7.25; S, 8.30. Found: C, 62.31; H, 4.93; F, 4.98; N, 7.23; S, 8.50.

ii) To a stirred solution of **15a** (13.0 g, 32.5 mmoles) in chloroform (100 ml) was added dropwise a solution of bromine (1.8 ml) in chloroform (18 ml) over a period of 30 minutes. The mixture was stirred for 1 hour at room temperature, and washed with a solution of sodium thiosulfate (5.0 g) in water (50 ml). The chloroform layer was separated, and dried over sodium sulfate. After removal of the solvent, the resulting solid was triturated with isopropyl ether, and collected by filtration to give **18a** (10.5 g, 81%).

1-Cyclopropyl- and 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(*p*-tolylthio)-1,8-naphthyridine-3-carboxylic Acids **19a,b**.

To a solution of **18a** (25.0 g, 62.8 mmoles) in dioxane (200 ml) was added 1*N* sodium hydroxide (70 ml). The mixture was heated under reflux for 1 hour and acidified with 0.5*N* hydrochloric acid (200 ml). The resulting crystals were collected by filtration and washed successively with water, ethanol and ether to give **19a** (22.5 g, 97%), which was recrystal-

lized from a mixture of chloroform and ethanol, mp 224-226°; ir (potassium bromide): 1720, 1620 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 0.6-0.9 (4H, m), 2.44 (3H, s), 3.0-3.5 (1H, m), 7.30 and 7.54 (each 2H, d, J = 8 Hz), 8.18 (1H, d, J = 9 Hz), 8.74 (1H, s), 14.44 (1H, s).

Anal. Calcd. for $C_{19}H_{15}FN_2O_3S$: C, 61.61; H, 4.08; F, 5.13; N, 7.56; S, 8.66. Found: C, 61.58; H, 4.11; F, 5.23; N, 7.56; S, 8.88.

Also prepared according to this procedure was **19b** (2.8 g, 89%) from **18b** (3.4 g); **19b**, mp 239-241° (recrystallized from a mixture of chloroform and ethanol); ir (potassium bromide): 1710, 1615 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 1.04 (3H, t, J = 7 Hz), 2.46 (3H, s), 4.06 (2H, q, J = 7 Hz), 7.34 and 7.56 (each 2H, d, J = 8 Hz), 8.24 (1H, d, J = 9 Hz), 8.84 (1H, s), 14.70 (1H, s).

Anal. Calcd. for $C_{18}H_{15}FN_2O_3S$: C, 60.32; H, 4.22; F, 5.30. N, 7.82; S, 8.95. Found: C, 60.19; H, 3.98; F, 5.55; N, 7.57; S, 9.16.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(*p*-tolylsulfinyl)-1,8-naphthyridine-3-carboxylate (**20a**).

To a stirred solution of **18a** (5.0 g, 12.6 mmoles) in chloroform (25 ml) was added 80% MCPBA (2.8 g, 13.0 mmoles) under ice-cooling. The mixture was stirred for 1.5 hours at room temperature, washed with 1*N* sodium hydroxide (15 ml), and dried over sodium sulfate. After removal of the solvent, the resulting solid was triturated with ethyl acetate, and collected by filtration to give **20a** (4.7 g, 90%), which was recrystallized from a mixture of chloroform and ethanol, mp 194-195°; ir (potassium bromide): 1685, 1640 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 0.8-1.2 (4H, m), 1.38 (3H, t, J = 7 Hz), 2.36 (3H, s), 3.5-3.9 (1H, m), 4.36 (2H, q, J = 7 Hz), 7.26 and 7.72 (each 2H, d, J = 8 Hz), 8.34 (1H, d, J = 9 Hz), 8.66 (1H, s).

Anal. Calcd. for $C_{21}H_{19}FN_2O_4S$: C, 60.86; H, 4.62; F, 4.58; N, 6.76; S, 7.74. Found: C, 60.82; H, 4.38; F, 4.58; N, 6.68; S, 7.87.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(*p*-tolylsulfonyl)-1,8-naphthyridine-3-carboxylate (**21a**).

According to the method described for the preparation of **20a**, **18a** (5.0 g, 12.6 mmoles) was treated successively with 80% MCPBA (6.0 g, 27.8 mmoles) and 1*N* sodium hydroxide (30 ml) to give **21a** (4.8 g, 89%), which was recrystallized from a mixture of chloroform and ethanol, mp 218-220°; ir (potassium bromide): 1685, 1640 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 0.8-1.3 (4H, m), 1.40 (3H, t, J = 7 Hz), 2.50 (3H, s), 3.2-3.7 (1H, m), 4.40 (2H, q, J = 7 Hz), 7.44 and 8.04 (each 2H, d, J = 8 Hz), 8.56 (1H, d, J = 9 Hz), 8.72 (1H, s).

Anal. Calcd. for $C_{21}H_{19}FN_2O_5S$: C, 58.60; H, 4.45; F,4.41; N, 6.51; S, 7.45. Found: C, 58.73; H, 3.34; F, 4.45; N, 6.51; S, 7.48.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(*p*-tolylsulfinyl)-1,8-naphthyridine-3-carboxylic Acid (**22a**).

To a stirred solution of **19a** (5.0 g, 13.5 mmoles) in chloroform (25 ml) was added 80% MCPBA (3.0 g, 13.9 mmoles) under ice-cooling. The mixture was stirred for 1 hour at room temperature. After addition of ethanol (50 ml), the resulting crystals were collected by filtration, and washed successively with ethanol and ether to give **22a** (4.6 g, 88%), which was recrystallized from a mixture of chloroform and ethanol, mp 222-223°; ir (potassium bromide): 1720, 1610 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 0.8-1.3 (4H, m), 2.34 (3H, s), 3.6-4.0 (1H, m), 7.40 and 7.74 (each 2H, d, J = 8 Hz), 8.56 (1H, d, J = 9 Hz), 8.84 (1H, s), 15.00 (1H, s).

Anal. Calcd. for $C_{19}H_{15}FN_2O_4S$: C, 59.06; H, 3.91; F, 4.92; N, 7.25; S, 8.30. Found: C, 58.90; H, 3.66; F, 4.83; N, 7.07; S, 8.11.

1-Cyclopropyl- and 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(*p*-tolylsulfonyl-1,8-naphthyridine-3-carboxylic Acids **23a,b**.

According to the method described for the preparation of **22a**, **19a** (5.0 g, 13.5 mmoles) was treated with 80% MCPBA (6.0 g, 27.8 mmoles) to give **23a** (4.8 g, 88%), which was recrystallized from a mixture of chloroform and ethanol, mp 236-239°; ir (potassium bromide): 1730, 1610 cm^{-1}; pmr (60 MHz, deuteriochloroform): δ 0.8-1.4 (4H, m), 2.50 (3H, s), 3.4-3.8 (1H, m), 7.46 and 8.02 (each 2H, d, J = 8 Hz), 8.62 (1H, d, J = 9 Hz), 9.00 (1H, s), 13.82 (1H, s).

Anal. Calcd. for $C_{19}H_{15}FN_2O_5S$: C, 56.71; H, 3.76; F, 4.72; N, 6.96; S, 7.97. Found: C, 56.51; H, 3.81; F, 4.96; N, 6.92; S, 8.18.

Similarly prepared was **23b** (2.8 g, 92%) from **19b** (2.8 g); **23b**, mp 240-242° (recrystallized from a mixture of chloroform and ethanol); ir (potassium bromide): 1710, 1600 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 1.32 (3H, t, J = 7 Hz), 2.48 (3H, s), 4.36 (2H, q, J = 7 Hz), 7.42 and 7.96 (each 2H, d, J = 8 Hz), 8.60 (1H, d, J = 9 Hz), 8.96 (1H, s), 13.74 (1H, s).

Anal. Calcd. for $C_{18}H_{15}FN_2O_5S$: C, 55.38; H, 3.87; F, 4.87; N, 7.18; S, 8.21. Found: C, 55.20; H, 3.75; F, 4.86; N, 7.20; S, 8.49.

Displacement Reactions of **20a-23a** (Table I).

Method A. A mixture of **20a** (1.0 g), pyrrolidine or piperidine (0.3 ml), triethylamine (0.4 ml) and acetonitrile (10 ml) was heated under reflux for 30 minutes. After removal of the solvent, the residue was taken up in a mixture of chloroform and water. The chloroform layer was separated, washed with 0.5*N* sodium hydroxide (20 ml), and dried over sodium sulfate. After removal of the solvent, the resulting solid was triturated with ether, and collected by filtration to give **24** or **26**.

Compound **24** had mp 200-201° (recrystallized from a mixture of chloroform and ethanol); ir (potassium bromide): 1680, 1620 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 0.9-1.4 (4H, m), 1.50 (3H, t, J = 7 Hz), 1.7-2.4 (4H, m), 3.3-4.2 (5H, m), 4.36 (2H, q, J = 7 Hz), 8.02 (1H, d, J = 13 Hz), 8.42 (1H, s).

Anal. Calcd. for $C_{18}H_{20}FN_3O_3$: C, 62.60; H, 5.84; F, 5.50; N, 12.17. Found: C, 62.47; H, 5.98; F, 5.57; N, 12.15.

Compound **26** had mp 158-161° (recrystallized from ethanol); ir (potassium bromide): 1725, 1625 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 0.8-1.3 (4H, m), 1.40 (3H, t, J = 7 Hz), 1.5-1.8 (6H, m), 3.3-3.6 (1H, m), 3.6-3.9 (4H, m), 4.34 (2H, q, J = 7 Hz), 8.06 (1H, d, J = 14 Hz), 8.46 (1H, s).

Anal. Calcd. for $C_{19}H_{22}FN_3O_3$: C, 63.50; H, 6.17; F, 5.29; N, 11.69. Found: C, 63.86; H, 5.96; F, 5.15; N, 11.84.

The sodium hydroxide solution was acidified with hydrochloric acid. The resulting crystals were collected by filtration, and was washed with ethanol to give **28**, mp 257-259° (recrystallized from a mixture of chloroform and ethanol); ir (potassium bromide): 1730, 1690, 1655 cm^{-1}; pmr (60 MHz, DMSO-d_6): δ 0.9-1.4 (4H, m), 1.26 (3H, t, J = 7 Hz), 3.3-3.7 (1H, m), 4.16 (2H, q, J = 7 Hz), 7.90 (1H, d, J = 11 Hz), 8.36 (1H, s), 12.5-13.3 (1H, br).

Anal. Calcd. for $C_{14}H_{13}FN_2O_4$: C, 57.53; H, 4.48; F, 6.50; N, 9.59. Found: C, 57.20; H, 4.61; F, 6.40; N, 9.63.

Method B. According to the Method A, **21a** was treated with pyrrolidine to give **24**. Compound **28** was not obtained.

Method C. According to Method A, **21a** was treated with piperidine to give a mixture of **26** and **30**, both of which were isolated by silica gel column chromatography with chloroform.

Compound **30** had mp 205-206° (recrystallized from ethyl acetate); ir (potassium bromide): 1690, 1645 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 0.7-1.0 (4H, m), 1.36 (3H, t, J = 7 Hz), 1.5-2.0 (6H, m), 2.44 (3H, s), 3.0-3.3 (4H, m), 3.4-3.9 (1H, m), 4.36 (2H, q, J = 7 Hz), 7.32 and 7.90 (each 2H, d, J = 7 Hz), 8.52 and 8.56 (each 1H, s).

Anal. Calcd. for $C_{26}H_{29}N_3O_5S$: C, 63.01; H, 5.90; N, 8.48; S, 6.47. Found: C, 63.00; H, 5.95; N, 8.61; S, 6.22.

Method D. A mixture of **22a** (1.0 g), pyrrolidine (0.3 ml), triethylamine (0.8 ml) and acetonitrile (10 ml) was heated under reflux for 30 minutes. The resulting crystals were collected by filtration to give **25**, mp >300° (recrystallized from a mixture of chloroform and ethanol); ir (potassium bromide): 1720, 1630 cm^{-1}; pmr (80 MHz, DMSO-d_6): δ 0.8-1.3 (4H, m), 1.6-2.1 (4H, m), 3.4-4.0 (5H, m), 7.94 (1H, d, J = 12 Hz), 8.54 (1H, s), 15.36 (1H, s).

Anal. Calcd. for $C_{16}H_{16}FN_3O_3$: C, 60.56: H, 5.08; F, 5.99; N, 13.24. Found: C, 60.37; H, 5.16; F, 6.18; N, 13.33.

The mother liquor was concentrated, and diluted with 1*N* hydrochloric acid. The resulting crystals were collected by filtration, and washed with ethanol to give **29**, mp >300° (recrystallized from dimethylformamide, lit [10], mp 325-327°); ir (potassium bromide): 1730, 1680, 1640 cm^{-1}; pmr

(80 MHz, DMSO-d_6): δ 1.0-1.4 (4H, m), 3.5-3.9 (1H, m), 8.12 (1H, d, J = 10 Hz), 8.58 (1H, s), 10-15 (2H, br).

Anal. Calcd. for $C_{12}H_9FN_2O_4$: C, 54.55; H, 3.43; F, 7.19; N, 10.60. Found: C, 54.54; H, 3.59; F, 7.41; N, 10.77.

Method E. According to Method D, **22a** was treated with piperidine to give a 2:1 mixture of **27** and **29**. The ratio was confirmed by pmr measurements.

Method F. According to Method D, **23a** was treated with pyrrolidine or piperidine to give **25** or **27**. Compound **29** was not obtained.

Compound **27** had mp 260-261° (recrystallized from a mixture of chloroform and ethanol); ir (potassium bromide): 1720, 1630 cm^{-1}; pmr (80 MHz, DMSO-d_6): δ 1.0-1.3 (4H, m), 1.6-1.9 (6H, m), 3.6-4.0 (5H, m), 8.00 (1H, d, J = 14 Hz), 8.58 (1H, s), 15.20 (1H, s).

Anal. Calcd. for $C_{17}H_{18}FN_3O_3$: C, 61.62; H, 5.48; F, 5.73; N, 12.68. Found: C, 61.92; H, 5.24; F, 7.77; N, 12.90.

Ethyl 7-(3-Acetylamino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**31**).

A mixture of **21a** (7.0 g, 16.3 mmoles), 3-acetylaminopyrrolidine (3.0 g, 23.4 mmoles), triethylamine (2.5 ml) and acetonitrile (100 ml) was heated under reflux for 1 hour. After removal of the solvent, the residue was taken up in a mixture of 1*N* hydrochloric acid and chloroform. The chloroform layer was separated, dried over sodium sulfate, and concentrated to dryness. The resulting solid was triturated with ethyl acetate, and collected by filtration to give **31** (5.2 g, 79%), which was recrystllized from a mixture of ethanol and isopropyl ether, mp 246-248°; ir (potassium bromide): 3280, 1675, 1625 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 0.9-1.3 (4H, m), 1.36 (3H, t, J = 7 Hz), 1.9-2.3 (2H, m), 2.16 (3H, s), 3.3-3.6 (1H, m), 3.6-3.9 (4H, m), 4.34 (2H, q, J = 7 Hz), 4.5-4.9 (1H, br), 7.5-7.7 (1H, br), 7.58 (1H, d, J = 13 Hz), 8.36 (1H, s).

Anal. Calcd. for $C_{20}H_{23}FN_4O_4$: C, 59.69; H, 5.76; F, 4.72; N, 13.92. Found: C, 59.51; H, 5.73; F, 4.72; N, 13.83.

7-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**32**).

A mixture of **31** (4.8 g, 11.9 mmoles) and 20% hydrochloric acid (70 ml) was heated under reflux for 10 hours, and concentrated to dryness under reduced pressure. The resulting solid was recrystallized from a mixture of water and ethanol to give the hydrochloride of **32** (3.9 g, 88%), mp 275-280° dec; ir (potassium bromide): 3400, 1700, 1630 cm^{-1}; pmr (100 MHz, deuterioxide): δ 0.8-1.4 (4H, m), 2.1-2.7 (2H, m), 3.4-3.7 (1H, m), 3.7-4.3 (4H, m), 4.7-5.0 (1H, m), 7.40 (1H, d, J = 12 Hz), 8.34 (1H, s).

Anal. Calcd. for $C_{16}H_{18}ClFN_4O_3$: C, 52.11; H, 4.92; Cl, 9.61; F, 5.15; N, 15.19. Found: C, 52.20; H, 5.08; Cl, 9.40: F, 4.90; N, 15.24.

The hydrochloride of **32** (4.3 g) was dissolved in water (100 ml) at 80°. The solution was neutralized with 0.1*N* sodium hydroxide at 80° to 90°, and cooled. The resulting crystals were collected by filtration, and washed successively with water and ethanol to give **32** (4.0 g), mp 266-267° dec; ir (potassium bromide): 3400, 1720, 1635 cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}FN_4O_3$: C, 57.83; H, 5.16; F, 5.72; N, 16.86. Found: C, 57.82; H, 5.32; F, 5.88; N, 16.81.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic Acid (**33**).

A mixture of **23a** (1.0 g, 2.5 mmoles), piperazine (0.5 g, 5.8 mmoles), triethylamine (0.8 ml) and acetonitrile (10 ml) was heated under reflux for 30 minutes. After addition of water (20 ml), the solution was treated with charcoal, and neutralized with 10% acetic acid. The resulting crystals were collected by filtration, and washed successively with water and ethanol to give **33** (0.64 g, 77%), mp 264-266°; ir (potassium bromide): 1720, 1630 cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}FN_4O_3$: C, 57.83; H, 5.16; F, 5.72; N, 16.86. Found: C, 57.66; H, 5.27; F, 5.72; N, 16.57.

The hydrochloride of **33** had mp 280-294° dec, recrystallized from a mixture of water and ethanol; ir (potassium bromide): 1720, 1625 cm^{-1}; pmr (deuterium oxide): 100 MHz, δ 0.8-1.4 (4H, m), 3.4-3.6 (4H, m), 3.5-3.8 (1H, m), 4.2-4.4 (4H, m), 7.70 (1H, d, J = 13 Hz), 8.56 (1H, s).

Anal. Calcd. for $C_{16}H_{18}ClFN_4O_3$: C, 52.11; H, 4.92; Cl, 9.61; F, 5.15; N, 15.19. Found: C, 52.07; H, 4.68; Cl, 9.61; F, 4.85; N, 15.16.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic Acid (**1**).

According to the method described for the preparation of **33**, **23b** (1.0 g, 2.6 mmoles) was treated with piperazine (0.5 g, 5.8 mmoles) to give **1** (0.56 g, 68%), which was identical with an authentic specimen prepared by the reported method [2].

Acknowledgements.

The authors wish to thank members of the analytical section of the Laboratories for elemental analyses and spectral measurements.

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