Me). Anal. ($C_{21}H_{25}N\cdot HCl$) C, H, N, Cl.

Compound **8c**: NMR identical with **2c** except for δ 6.05 (dt, J = 10 and 2 × 6.5 Hz, (Z)-CH_2CH=CH), 5.67 (dt, J = 10 and 2 × 1.5 Hz, (Z)-CH=CHC≡), 3.4 (dd, J = 6.5 and 1.5 Hz, NCH_2CH=); MS, *m/e* 291.

(E,E)-N-Methyl-N-2,4-nonadienyl-1-naphthalenemethanamine (2). A solution of (E,E)-2,4-nonadienal (20 g, 127 mmol) and 1-naphthalenemethanamine (20.4 g, 127 mmol) in benzene was boiled in a Dean-Stark apparatus until the calculated amount of water had separated. After removal of solvent, the Schiff base was taken up in methanol, treated with solid $NaBH_4$ (4,8 g, 127 mmol) in several portions at 40 °C, and stirred for 1 h at this temperature. This reaction mixture was used directly for reductive methylation[17] following the procedure of Sondengam.[18] Aqueous 35% formaldehyde solution (57 mL, 636 mmol) was added and the reaction mixture refluxed for 1 h. The mixture was then treated under ice cooling with solid $NaBH_4$ (24 g, 636 mmol) in several portions and stirred at room temperature overnight. After concentration, the residue was partitioned between aqueous $NaHCO_3$ solution and ethyl acetate and the organic phase dried and concentrated. The crude **7** (37.2 g, quant) thus obtained was shown by TLC and NMR to be of about 80% purity. Chromatography (toluene/ethyl acetate = 9/1) over silica furnished pure **2** (25 g, 67%) as a colorless oil: NMR for NCH_2-(E)-CH_α=CH_β-(E)-CH_γ=$CH_\delta CH_2$, 6.18 (H_β), 6.08 (H_γ), 5.72 (H_α), 5.65 (H_δ); $J_{H_\alpha CH_2N}$ = 6.75 Hz, $J_{H_\alpha H_\beta}$ = 14.5 Hz, $J_{H_\beta CH_2N}$ = 1.2 Hz, $J_{H_\beta H_\gamma}$ = 10.3 Hz, $J_{H_\gamma H_\delta}$ = 14.5 Hz, $J_{H_\gamma CH_2}$ = 1.35 Hz, $J_{H_\delta CH_2}$ = 6.9 Hz; 3.87 (s, Ar CH_2N), 3.13 (dd, NCH_2CH=), 1.9-2.2 (m, =CCH_2). Anal. ($C_{21}H_{27}N$) C, H, N.

(E)-N-Methyl-N-4-nonen-2-ynyl-1-naphthalenemethanamine (9a) and Its Z Isomer 9b. 3-Octen-1-yne[19] (3.2 g, 15.8 mmol, E/Z = 1:2), N-methyl-1-naphthalenemethanamine (2.7 g, 15.8 mmol), paraformaldehyde (0.47 g, 15.8 mmol), and CuCl (0.16 g, 1.58 mmol) were reacted as described for the preparation of **3a** by Mannich condensation. By chromatography (hexane/butyl acetate = 10/1) of the crude reaction mixture the stereoisomers could be separated. Z isomer **9b** (1.58 g, 34%, DC R_f 0.46, oil) was isolated first, followed by a 1:1 mixture of **9a** and **9b** (1.72 g, 37%) and a pure sample of **9a** (0.19 g, 4%, DC R_f 0.42, oil).

Compound **9a**: NMR δ 6.22 (dt, J = 16 and 2 × 7 Hz, (E)-CH=CHCH_2), 5.58 (dm, J = 16 Hz, ≡C-(E)-CH=CH), 4.0 (s, Ar CH_2N), 3.44 (d, J = 1.5 Hz, NCH_2C≡), 2.38 (s, NCH_3), 2.0-2.3 (m, =CCH_2); mp (hydrochloride) 103-106 °C. Anal. ($C_{21}H_{25}N\cdot HCl$) C, H, N, Cl.

Compound **9b**: NMR identical with **8a** except for δ 5.95 (dt, J = 11 and 7 Hz, (Z)-CH=CHCH_2), 5.55 (dm, J = 11 Hz, ≡C-(Z)-CH=CH), 3.49 (d, J = 1.5 Hz, NCH_2C≡), 2.2-2.5 (m, =CCH_2).

Registry No. 2, 92525-78-5; **3a**, 92525-79-6; **3a**·HCl, 92525-80-9; **3b**, 78628-65-6; **4a**, 91161-71-6; **4b**, 78628-64-5; **4b**·HCl, 78628-66-7; **4c**, 92525-81-0; **5a**, 92525-82-1; **5b**, 92525-83-2; **6a**, 78629-20-6; **6b**, 67978-48-7; **6c**, 78629-22-8; (E)-**7a**, 78629-21-7; (Z)-**7a**, 78629-19-3; (E)-**7b**, 67978-51-2; (Z)-**7b**, 67978-52-3; (E)-**7c**, 78629-28-4; (Z)-**7c**, 78629-29-5; **8a**, 78628-81-6; **8b**, 78628-73-6; **8c**, 78628-85-0; **9a**, 92525-84-3; **9b**, 92525-85-4; R_1NHCH_3, 14489-75-9; $R_1N(CH_3)$-CH_2C≡CH, 2321-99-5; R_1NH_2, 118-31-0; *t*-BuC≡CC≡CH, 4911-56-2; *n*-BuC≡CBr, 1119-64-8; *t*-BuC≡CH, 917-92-0; C-H_2=CHCHO, 107-02-8; *n*-BuC≡CH, 693-02-7; *sec*-BuC≡CH, 922-59-8; (E,E)-*n*-BuCH=CHCH=CHCHO, 5910-87-2; (E)-*n*-BuCH=CHC≡CH, 42104-42-7; (Z)-*n*-BuCH=CHC≡CH, 42091-89-4.

(17) For a new modification of reductive methylation using salts of phosphorus acid as reducing agent, see: Loibner, H.; Pruckner, A., Stütz, A. *Tetrahedron Lett.* **1984**, 2535.

(18) Sondengam, B. L.; Hentchoya Hémo, J.; Charles, G. *Tetrahedron Lett.* **1973**, *3*, 261.

(19) Pages 109, 125 in ref 16.

Pyridonecarboxylic Acids as Antibacterial Agents. 4.[1] Synthesis and Antibacterial Activity of 7-(3-Amino-1-pyrrolidinyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid and Its Analogues

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The title compounds (**28-56**) with an amino- and/or hydroxy-substituted cyclic amino group at C-7 were prepared with 1-substituted 7-chloro-, 7-(ethylsulfonyl)-, and 7-(tosyloxy)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids and their ethyl esters (**3-7**) with cyclic amines such as 3-aminopyrrolidine. The N-1 substituent includes ethyl, vinyl, and 2-fluoroethyl groups. As a result of in vitro and in vivo antibacterial screenings, three compounds, 1-ethyl- and 1-vinyl-7-(3-amino-1-pyrrolidinyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids (**33a** and **33b**) and 1-vinyl-7-[3-(methylamino)-1-pyrrolidinyl] analogue **34b**, were found to be more active than enoxacin (**2**) and to be worthy of further biological study. Structure-activity relationships are discussed.

As exemplified by pipemidic acid (**1**),[2] we showed first that a piperazinyl group was of much importance for the improvement of antibacterial activity and pharmacokinetic properties of a class of pyridonecarboxylic acid antibacterial agents. During the last few years, several analo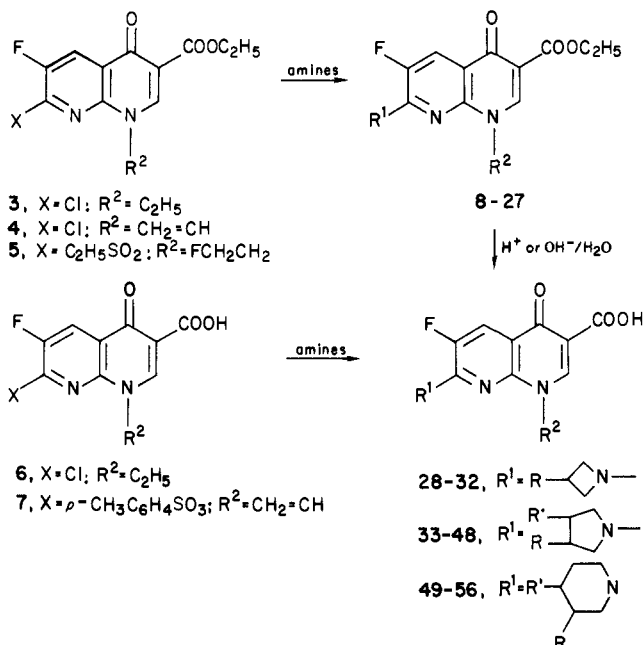gues having both fluoro and piperazinyl groups in their molecules were reported successively;[3,4] their antibacterial activities are noticeably much more potent and broader than

(1) Paper 3: Matsumoto, J.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H.; Nishimura, H. *J. Heterocycl. Chem.*, **1984**, *21*, 673.

(2) Matsumoto, J.; Minami, S. *J. Med. Chem.* **1975**, *18*, 74.

(3) Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. *J. Med. Chem.* **1980**, *23*, 1358. Goueffon, Y.; Montay, G.; Roquet, F.; Pesson, M. *C. R. Hebd. Seances Acad. Sci.* **1981**, 37. Grohe, K.; Zieiler, H.; Metzger, K. G. German Offen. 3 033 157, **1982**; *Chem. Abstr.* **1982**, *97*, 55790u. Hayakawa, I.; Hiramitsu, T. European Patent Appl. 47 005, **1982**; *Chem. Abstr.* **1982**, *97*, 55821b.

(4) Matsumoto, J.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H.; Nishimura, H. *J. Med. Chem.* **1984**, *27*, 292.

Scheme I[a]

3, X=Cl; R[2]= C_2H_5
4, X=Cl; R[2]= $CH_2=CH$
5, X= $C_2H_5SO_2$; R[2]= FCH_2CH_2

8-27

6, X=Cl; R[2]= C_2H_5
7, X= p-$CH_3C_6H_4SO_3$; R[2]= $CH_2=CH$

28-32, R[1]=R—⟨N—

33-48, R[1]= R'/R ⟩N—

49-56, R[1]=R'—⟨N⟩

[a] For 28-56: a, R[2] = C_2H_5; b, R[2] = $CH_2=CH$; c, R[2] = FCH_2CH_2; see Table II for R and R'.

those of the precedents[5] in this class. One of them, enoxacin (2, originally called AT-2266), was described in

1, pipemidic acid

2, enoxacin
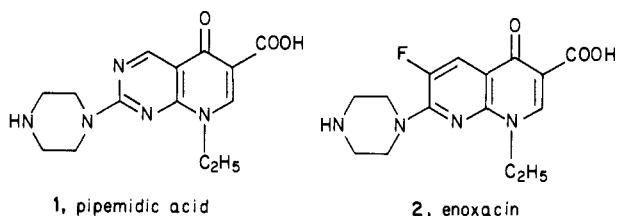
previous papers.[1,4] Our next effort in this area was mainly directed at a search for analogues with a substituent that might cause a greater enhancement in activity than the piperazinyl group. Amino-substituted alicyclic amino groups such as 3-aminopyrrolidinyl or 3-aminoazetidinyl may be expected to offer such an enhancement of activity since the physicochemical properties of these groups seem to be generally similar to those of the piperazinyl group. The present paper deals with a synthesis of 1-substituted 6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids (28-56) with an amino- and/or hydroxy-substituted alicyclic amino group at C-7 and includes a discussion of structure–activity relationships of these compounds.

Chemistry. The main routes utilized for the preparation of the carboxylic acids 28-56 are shown in Scheme I. Upon treatment of ethyl 1,7-disubstituted 6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates 3, 4, and 5 with an appropriate amine (method A), the displacement reaction proceeded regioselectively at C-7 to give the corresponding esters 8-27. The esters were then hydrolyzed under either acidic (method B) or alkaline (method C) conditions, giving the corresponding carboxylic acids. Displacement of the 7-chloro and 7-tosyloxy groups of 6 and 7, respectively, by an amine (method D) gave the carboxylic acids 31a, 32a, 38a,b, 40a, 42a, 44a, 46a, 52a, 54a, and 56a.

Acylation of 33a,b,c, 34b,c, 46a, and 52a with acetic anhydride, trifluoroacetic anhydride, or a formic acid–

(5) For example, see: Albrecht, R. *Prog. Drug Res.* 1977, *21*, 9.

Scheme II

57

58 → 4 + 7

59

60 → 5
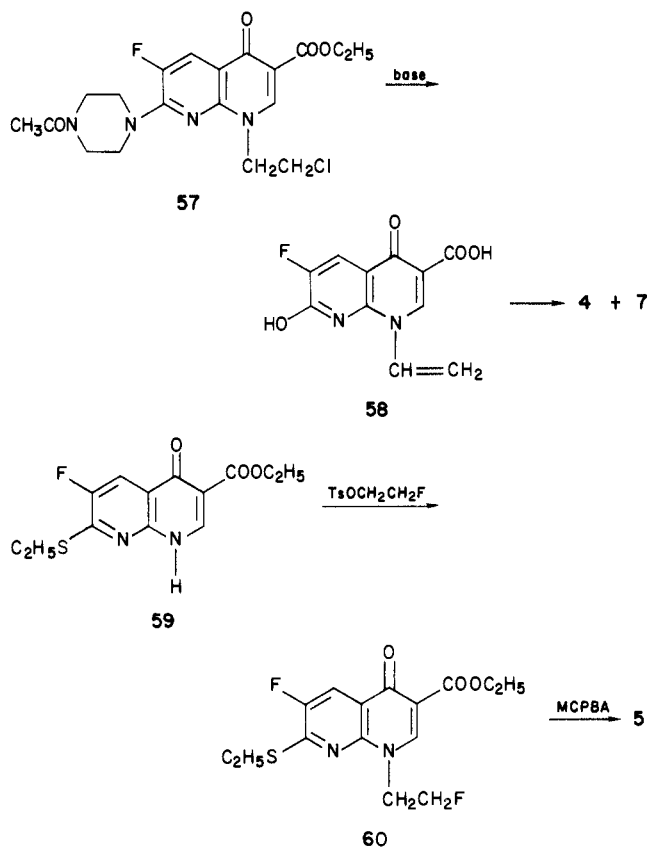
formamide mixture (method E) gave the corresponding acyl compounds 39a,b, 40b,c, 41a, 42b,c, 47a, and 53a. Alkaline hydrolysis of 42a gave 34a (method F). Reductive N-methylation of 34c with a mixture of formic acid and 37% formalin (method G) afforded 7-[3-(dimethylamino)-1-pyrrolidinyl] derivative 38c. The compounds prepared thus by the methods A–G are summarized in Table II.

Among the starting compounds (3-5 and 7), 3 was prepared by esterification of the carboxylic acid 6, which had previously been reported,[4] and 4, 5, and 7 were derived as shown in Scheme II. Thus, alkaline treatment of the 1-(2-chloroethyl) derivative 57,[4] followed by chlorination of the 7-hydroxy-1-vinyl derivative 58 and successive treatment with ethanol, afforded the 7-chloro-1-vinyl compound 4. Tosylation of 58 gave 7-(tosyloxy)-1-vinyl analogue 7. Compound 5 was derived from 59[1] by treatment with 2-fluoroethyl tosylate, followed by oxidation of the resultant 1-(2-fluoroethyl) derivative 60 with *m*-chloroperbenzoic acid; the site of alkylation in this case was assigned on the basis of ^{13}C NMR spectral analysis.
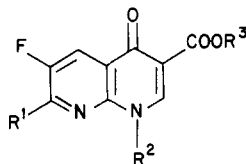
Biological Results and Discussion

The results of the in vitro antibacterial activity for compounds prepared in the present study against Gram-positive (*Staphylococcus aureus* 209P JC-1) and Gram-negative bacteria (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* Tsuchijima) are summarized in Table II. The data for enoxacin (2) are included for comparison.

It is noteworthy that the replacement of the piperazinyl group at C-7 of 2 by the 3-aminopyrrolidinyl group (33a) causes an enhancement in activity against all the bacteria tested. The replacement of the 3-aminopyrrolidinyl ring by a larger membered ring, such as 3- and 4-aminopiperidine (49a and 50a), results in a retention or increase in activity against *S. aureus*, whereas it causes a decrease in activity against *P. aeruginosa*. On the contrary, the

Table I. 1,7-Disubstituted 6-Fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids

no.	R^1	R^2	R^3	mp, °C	recrystn solvent	yield,[a] %	formula[b]
3	Cl	C$_2$H$_5$	C$_2$H$_5$	191–194	AcOEt	96	C$_{13}$H$_{12}$ClFN$_2$O$_3$
4	Cl	CH$_2$=CH	C$_2$H$_5$	150–151	AcOEt	77	C$_{13}$H$_{10}$ClFN$_2$O$_3$
5	C$_2$H$_5$SO$_2$	FCH$_2$CH$_2$	C$_2$H$_5$	176–178	EtOH	74	C$_{15}$H$_{16}$F$_2$N$_2$O$_5$S
7	*p*-CH$_3$C$_6$H$_4$SO$_3$	CH$_2$=CH	H	190–192	EtOH-CHCl$_3$	62	C$_{18}$H$_{13}$FN$_2$O$_6$S
8	3-CH$_3$CONH-1-azet[c]	C$_2$H$_5$	C$_2$H$_5$	229–230	EtOH	63	C$_{18}$H$_{21}$FN$_4$O$_4$
9	3-CF$_3$CONH-1-azet	CH$_2$=CH	C$_2$H$_5$	251–253	EtOH-CHCl$_3$	75	C$_{18}$H$_{16}$F$_4$N$_4$O$_4$
10	3-morpholino-1-azet	C$_2$H$_5$	C$_2$H$_5$	195–196	MeCN	90	C$_{20}$H$_{25}$FN$_4$O$_4$
11	3-HO-1-azet	C$_2$H$_5$	C$_2$H$_5$	265–268	EtOH-CHCl$_3$	97	C$_{16}$H$_{18}$FN$_3$O$_4$
12	3-CH$_3$CONH-1-pyr[d]	C$_2$H$_5$	C$_2$H$_5$	267–270	EtOH-CHCl$_3$	90	C$_{19}$H$_{23}$FN$_4$O$_4$
13	3-CF$_3$CONH-1-pyr	CH$_2$=CH	C$_2$H$_5$	280–282	EtOH-CHCl$_3$	92	C$_{19}$H$_{18}$F$_4$N$_4$O$_4$
14	3-CH$_3$CONH-1-pyr	FCH$_2$CH$_2$	C$_2$H$_5$	269–270	EtOH-CHCl$_3$	73	C$_{19}$H$_{22}$F$_2$N$_4$O$_4$
15	3-CF$_3$CON(CH$_3$)-1-pyr	CH$_2$=CH	C$_2$H$_5$	160–161	AcOEt-(*i*-Pr)$_2$O	73	C$_{20}$H$_{20}$F$_4$N$_4$O$_4$
16	3-CH$_3$CON(CH$_3$)-1-pyr	FCH$_2$CH$_2$	C$_2$H$_5$	227–229	EtOH-CHCl$_3$	80	C$_{20}$H$_{24}$F$_2$N$_4$O$_4$
17	3-CH$_3$CON(C$_2$H$_5$)-1-pyr	C$_2$H$_5$	C$_2$H$_5$	205–206	EtOH	92	C$_{21}$H$_{27}$FN$_4$O$_4$
18	3-CH$_3$CON(CH$_2$CF$_3$)-1-pyr	C$_2$H$_5$	C$_2$H$_5$	226–228	EtOH	81	C$_{21}$H$_{24}$F$_4$N$_4$O$_4$
19	3-CF$_3$CON(CH$_2$CF$_3$)-1-pyr	CH$_2$=CH	C$_2$H$_5$	138–140	AcOEt-Et$_2$O	89	C$_{19}$H$_{19}$F$_7$N$_4$O$_3$
20	3-CH$_3$CON(C$_3$H$_7$)-1-pyr	C$_2$H$_5$	C$_2$H$_5$	180–181	EtOH-AcOEt	76	C$_{22}$H$_{29}$FN$_4$O$_4$
21	3-CH$_3$CONHN(COCH$_3$)-1-pyr	C$_2$H$_5$	C$_2$H$_5$	277–279	EtOH-CHCl$_3$	82	C$_{21}$H$_{26}$FN$_5$O$_5$
22	3-CH$_3$CONH-4-CH$_3$COO-1-pyr	C$_2$H$_5$	C$_2$H$_5$	254–255	EtOH	77	C$_{21}$H$_{25}$FN$_4$O$_6$
23	3-Cl-1-pyr	C$_2$H$_5$	C$_2$H$_5$	207–208	EtOH	90	C$_{17}$H$_{19}$ClFN$_3$O$_3$
24	3-CH$_3$CONH-piper[e]	C$_2$H$_5$	C$_2$H$_5$	202–203	EtOH	90	C$_{20}$H$_{25}$FN$_4$O$_4$·$^1/_2$H$_2$O
25	4-CH$_3$CONH-piper	C$_2$H$_5$	C$_2$H$_5$	195–196	EtOH-MeCN	90	C$_{20}$H$_{25}$FN$_4$O$_4$
26	4-C$_6$H$_5$CONH-piper	C$_2$H$_5$	C$_2$H$_5$	246–247	EtOH-CHCl$_3$	86	C$_{25}$H$_{27}$FN$_4$O$_4$
27	3-HO-piper	C$_2$H$_5$	C$_2$H$_5$	189–190	EtOH	81	C$_{18}$H$_{22}$FN$_3$O$_4$·$^1/_5$H$_2$O

[a] Yields are of purified products by method A except for **3–5** and **7** and are not maximal. [b] All compounds were analyzed for C, H, N and where present Cl, F, and S; analytical results were within ±0.4% of theoretical values. [c] Azetidinyl = azet. [d] Pyrrolidinyl = pyr. [e] Piperidinyl = piper.

replacement by a smaller ring such as 3-aminoazetidine (**28a**) shows the same level of activity as that of **2** against all the organisms.

The replacement of the amino group of **28a**, **33a**, **49a**, and **50a** by a hydroxyl group (giving **30a**, **46a**, **55a**, and **56a**, respectively) causes a significant decrease in Gram-negative activity compared with the corresponding amino-substituted compounds. Alkylation or formylation of the hydroxyl group (giving **31a**, **32a**, and **47a**) reduces furthermore the activity against Gram-negative bacteria.

Compounds **52a** and **53a**, which have a methylene group between the amino group and the piperadinyl ring, are less active than **50a**. Compound **54a** with a carbamoyl group is also inferior to **49a**.

Introduction of an alkyl group such as a methyl, ethyl, 2,2,2-trifluoroethyl, or propyl group to the amino nitrogen atom on the pyrrolidinyl ring of **33a** (giving **34a–37a**) reduces generally the activity against the organisms in this order. The dimethylamino compound **38a** shows activity similar to that of the ethylamino congener **35a**.

Acylation of the amino group on the pyrrolidinyl ring, giving **39a–42a** (see Table II), results in a decrease in activity. The decrease is greater with Gram-negative activity than with Gram-positive activity.

Compounds **43a** and **48a** with a hydrazino and chloro group, respectively, on the pyrrolidinyl ring are comparable to **33a** in activity against Gram-positive bacteria, whereas they are much less active against Gram-negative organisms, particularly *P. aeruginosa*.

When the N-1 substituent is varied while the C-7 substituent is kept constant as the most active 3-aminopyrrolidinyl group, introduction of a vinyl group (**33b**) influences markedly the antibacterial activity. Thus, the vinyl group significantly enhances Gram-negative activity without a decrease of Gram-positive activity. On the other

hand, introduction of a fluoroethyl group (**33c**) reduces Gram-positive activity, whereas Gram-negative activity remains unchanged. Either alkylation or acylation of compounds **33b,c** (giving **34b,c–42b,c**) causes a decrease in activity. This is consistent with the case of the same modification of the 1-ethyl compound **33a** as discussed above.

In each comparison between the ethyl compounds (series **a**) and their vinyl analogues (series **b**) of **28**, **33**, **34**, **36**, **38–40**, and **42**, the vinyl group enhances Gram-negative activity, whereas it reduces Gram-positive activity; this relationship is in agreement with that observed in our previous works.[2,4] The fluoroethyl group shows a tendency to enhance Gram-negative activity and to reduce Gram-positive activity (compare **33a**, **34a**, **38a**, **40a**, and **42a** with **33c**, **34c**, **38c**, **40c**, and **42c**, respectively).

Thus, the 10 compounds **28a,b**, **33a–c**, **34a–c**, **46a**, and **50a**, being equal or superior to **2** in the in vitro antibacterial activity, were tested with oral administration upon systemic infections due to *S. aureus* 50774, *E. coli* P-5101, and *P. aeruginosa* 12 in mice. The results are listed in Table III, which includes, for reference, the minimal inhibitory concentration (MIC) against the organisms employed.

The therapeutic efficacies of **28a**, **34a**, **46a**, and **50a** are obviously inferior to those of **2**. Compounds **28b**, **33a–c**, and **34a,b** compare very favorably with **2**. Of much interest are **33a,b** and **34b**, which are much more efficient than **2**, particularly against staphylococcal and pseudomonal infections. In conclusion, the 3-aminopyrrolidinyl group proved to be equivalent to or more efficient than the piperazinyl group. In variation of the N-1 substituent of **28a**, **33a**, and **34a**, the vinyl group causes an outstanding increase in efficacy on all the infections tested, whereas the 2-fluoroethyl group tends to reduce the efficacy in general.

Table II. 1,7-Disubstituted 6-Fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids and Their in Vitro Antibacterial Activity

no.	R	R'	R²	mp, °C	recrystn solvent	method^a (starting material)	yield,^b %	formula^c	S. aureus 209P JC-1	E. coli NIHJ JC-2	P. aeruginosa Tsuchijima
2^e									0.78	0.2	0.78
28a	H_2N		C_2H_5	266-269 dec	NaOH-AcONH$_4$^f	C (8)	38	$C_{14}H_{15}FN_4O_3$	0.78	0.1	0.78
28b	H_2N		CH_2=CH	250-255 dec	NaOH-AcOH^f	C (9)	63	$C_{14}H_{13}FN_4O_3$	1.56	0.1	0.39
29a	$O(CH_2CH_2)_2N$		C_2H_5	260-262	MeCN-CHCl$_3$	C (10)	86	$C_{18}H_{21}FN_4O_4$	1.56	6.25	50
30a	HO		C_2H_5	284-286	DMF	C (11)	91	$C_{14}H_{14}FN_3O_4$	0.78	0.78	3.13
31a	CH_3O		C_2H_5	233-235	MeCN	D (6)	48	$C_{15}H_{16}FN_3O_4$	0.78	3.13	6.25
32a	C_2H_2O		C_2H_5	201-203	MeCN	D (6)	77	$C_{16}H_{18}FN_3O_4$	0.78	3.13	25
33a	H_2N	H	C_2H_5	272-290 dec	EtOH-H$_2$O	B (12)	84	$C_{15}H_{17}FN_4O_3$·HCl	0.2	0.1	0.39
33b	H_2N	H	CH_2=CH	253-257	NaOH-AcOH^f	C (13)	83	$C_{15}H_{15}FN_4O_3$	0.2	0.025	0.2
33c	H_2N	H	FCH_2CH_2	251-255	HCl-NH$_4$OH^f	B (14)	73	$C_{15}H_{16}F_2N_4O_3$	0.39	0.1	0.39
34a	CH_3NH	H	C_2H_5	242-245	NaOH-AcONH$_4$^f	F (42a)	71	$C_{16}H_{19}FN_4O_3$	0.39	0.2	1.56
34b	CH_3NH	H	CH_2=CH	265-267 dec	NaOH-AcOH^f	C (15)	87	$C_{16}H_{17}FN_4O_3$	0.78	0.1	0.78
34c	CH_3NH	H	FCH_2CH_2	243-245	HCl-NH$_4$OH^f	B (16)	65	$C_{16}H_{18}F_2N_4O_3$	0.78	0.2	0.78
35a	C_2H_5NH	H	C_2H_5	>290 dec	EtOH-H$_2$O	B (17)	82	$C_{17}H_{21}FN_4O_3$·HCl	0.78	0.78	3.13
36a	CF_3CH_2NH	H	C_2H_5	203-204	EtOH	B (18)	67	$C_{17}H_{18}F_4N_4O_3$	0.78	1.56	50
36b	CF_3CH_2NH	H	CH_2=CH	183-185	MeCN	C (19)	87	$C_{17}H_{16}F_4N_4O_3$	1.56	6.25	100
37a	C_3H_7NH	H	C_2H_5	268-269 dec	H$_2$O	B (20)	91	$C_{18}H_{23}FN_4O_3$·HCl·$3/2$H$_2$O	25	6.25	>100
38a	$(CH_3)_2N$	H	C_2H_5	234-236	MeCN-CHCl$_3$	D (6)	84	$C_{17}H_{21}FN_4O_3$	1.56	0.78	6.25
38b	$(CH_3)_2N$	H	CH_2=CH	199-201	EtOH-CHCl$_3$	D (7)	86	$C_{17}H_{19}FN_4O_3$	3.13	0.39	3.13
38c	$(CH_3)_2N$	H	FCH_2CH_2	247-249	EtOH-CHCl$_3$	G (34c)	45	$C_{17}H_{20}F_2N_4O_3$	0.78	0.2	6.25
39a	OHCNH	H	C_2H_5	285-286	HCOOH-Me$_2$CO	E (33a)	81	$C_{16}H_{17}FN_4O_4$	0.78	0.78	3.13
39b	OHCNH	H	CH_2=CH	287-289	DMF	E (33b)	78	$C_{16}H_{15}FN_4O_4$	0.78	0.39	3.13
40a	CH_3CONH	H	C_2H_5	283-284	DMF-EtOH	D (6)	97	$C_{17}H_{19}FN_4O_4$	0.78	6.25	6.25
40b	CH_3CONH	H	CH_2=CH	287-289 dec	DMF	E (33b)	88	$C_{17}H_{17}FN_4O_4$	1.56	0.78	12.5
40c	CH_3CONH	H	FCH_2CH_2	294-297	DMF-EtOH	E (33c)	74	$C_{17}H_{18}F_2N_4O_4$	1.56	1.56	25
41a	CF_3CONH	H	C_2H_5	290-292	CF$_3$COOH-H$_2$O	E (33a)	79	$C_{17}H_{16}F_4N_4O_4$	0.78	1.56	6.25
42a	$CH_3CON(CH_3)$	H	C_2H_5	287-289	DMF	D (6)	98	$C_{18}H_{21}FN_4O_4$	0.78	6.25	25
42b	$CH_3CON(CH_3)$	H	CH_2=CH	274-275	DMF-EtOH	E (34b)	89	$C_{18}H_{19}FN_4O_4$	1.56	3.13	25
42c	$CH_3CON(CH_3)$	H	FCH_2CH_2	291-294	DMF	E (34c)	42	$C_{18}H_{20}F_2N_4O_4$	0.39	1.56	25
43a	H_2NNH	H	C_2H_5	249-250	EtOH-H$_2$O	B (21)	84	$C_{15}H_{18}FN_5O_3$·HCl·$1/5$H$_2$O	0.39	1.56	12.5
44a	H_2NCONH	H	C_2H_5	266-267	DMF-EtOH	D (6)	91	$C_{16}H_{18}FN_5O_4$	6.25	3.13	25
45a	H_2N	HO	C_2H_5	280-285 dec	EtOH-H$_2$O	B (22)	96	$C_{15}H_{17}FN_4O_4$·HCl	1.56	1.56	3.13
46a	HO	H	C_2H_5	291-293	DMF-EtOH	D (6)	79	$C_{15}H_{16}FN_3O_4$	0.39	0.78	0.78
47a	OHCO	H	C_2H_5	234-236	EtOH-CHCl$_3$	E (46a)	74	$C_{16}H_{16}FN_3O_5$	0.39	1.56	3.13
48a	Cl	H	C_2H_5	274-275	EtOH-CHCl$_3$	C (23)	87	$C_{15}H_{15}ClFN_3O_3$	0.2	0.39	12.5

no.			R		mp	method	yield (%)	formula			
49a	H_2N	H	C_2H_5	EtOH	169-170	B (24)	61	$C_{16}H_{19}FN_4O_3\cdot 1/2H_2O$	0.78	0.78	6.25
50a	H	H_2N	C_2H_5	HCl-AcONa[f]	268-272	B (25)	74	$C_{16}H_{19}FN_4O_3$	0.2	0.2	1.56
51a	H	C_6H_5CONH	C_2H_5	AcOH	287-288	B (26)	89	$C_{23}H_{23}FN_4O_3$	12.5	1.56	>100
52a	H	H_2NCH_2	C_2H_5	EtOH-CHCl₃	213-214	D (6)	88	$C_{17}H_{21}FN_4O_3\cdot H_2O$	1.56	0.39	12.5
53a	H	$CH_3CONHCH_2$	C_2H_5	EtOH-CHCl₃	267-268	E (52a)	73	$C_{19}H_{23}FN_4O_4$	1.56	0.78	25
54a	H_2NCO	H	C_2H_5	DMF	>300	D (6)	96	$C_{17}H_{19}FN_4O_4$	12.5	6.25	50
55a	HO	HO	C_2H_5	EtOH	208-209	C (27)	33	$C_{16}H_{18}FN_3O_4$	3.13	1.56	25
56a	H	HO	C_2H_5	EtOH-CHCl₃	217-218	D (6)	89	$C_{16}H_{18}FN_3O_4$	3.13	0.78	6.25

ᵃCapital letters refer to the method described in the Experimental Section. ᵇ,ᶜSee footnotes in Table I. ᵈSee the Experimental Section. ᵉEnoxacin; see ref 4. ᶠPurified by reprecipitation on treatment with the acid and subsequently with the base or vice versa.

Table III. Oral Efficacy on Systemic Infections[a]

| no. | ED_{50}:[b] min inhibitory concn[c] | | |
	S. aureus 50774	*E. coli* P-5101	*P. aeruginosa* 12
2	10.0 (0.78)	1.8 (0.1)	9.0 (0.78)
28a	8.8 (0.78)	4.1 (0.1)	12.5 (0.78)
25b	5.3 (0.78)	1.3 (0.05)	4.4 (0.78)
33a	3.0 (0.39)	1.7 (0.1)	3.7 (0.78)
33b	1.6 (0.39)	0.72 (0.05)	1.6 (0.2)
33c	4.6 (0.39)	2.8 (0.1)	6.3 (0.39)
34a	4.8 (0.78)	1.4 (0.2)	6.5 (0.78)
34b	1.6 (0.78)	2.0 (0.2)	3.7 (0.78)
34c	15 (0.78)	2.8 (0.1)	19.3 (0.78)
46a	5.5 (0.39)	6.8 (0.39)	42 (3.13)
50a	>25 (0.78)	6.3 (0.39)	16.2 (1.56)

ᵃFor experimental details, see ref 4. Challenge dose (cells per mouse); 5×10^8 for *S. aureus*, 9×10^6 for *E. coli*, and 4×10^3 for *P. aeruginosa*. ᵇIn milligram per kilogram. ᶜIn microgram per milliliter.

Compounds **28b**, **33a–c**, and **34a–c** exhibit weak oral acute toxicity in mice, all being >2000 mg/kg of the median lethal dose (LD_{50}).

These findings indicate that 1-ethyl- and 1-vinyl-7-(3-amino-1-pyrrolidinyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids (**33a** and **33b**) and 1-vinyl-7-[3-(methylamino)-1-pyrrolidinyl] analogue **34b** are worth further biological evaluation as possible potent antibacterial agents.

Experimental Section

Chemistry. All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi Model 215 spectrophotometer. ¹H NMR spectra were taken at 60 or 100 MHz on either a Varian EM-360A or HA-100 spectrometer and ¹³C NMR spectra were obtained with a Varian FT-80A spectrometer with Me₄Si as an internal standard. Mass spectra were recorded on a Hitachi RMU-6L spectrometer. IR, NMR, and mass spectra were obtained on all compounds and were consistent with assigned structures. Elemental analyses are indicated only by symbols of the elements; analytical results were within ±0.4% of theoretical values.

Ethyl 7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (3). To a stirred suspension containing 24.9 g (0.092 mol) of 7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**6**),[4] 19 mL of NEt₃, and 200 mL of CHCl₃ was added portionwise 11 mL of ethyl chlorocarbonate, while the temperature was maintained at 5–10 °C under ice-cooling. After the mixture was stirred for 30 min at the same temperature, 50 mL of EtOH was added. The reaction mixture was allowed to stir for 4 h at room temperature and concentrated to dryness in vacuo. After addition of 50 mL of EtOH, the precipitate was collected by filtration and recrystallized from AcOEt to give 26.6 g (96%) of 3.

Ethyl 7-Chloro-6-fluoro-1,4-dihydro-4-oxo-1-vinyl-1,8-naphthyridine-3-carboxylate (4). A mixture containing 20.0 g (0.08 mol) of 6-fluoro-1,4-dihydro-7-hydroxy-4-oxo-1-vinyl-1,8-naphthyridine-3-carboxylic acid (**58**) and 60 mL of POCl₃ was heated at 115 °C for 6 min. The excess of POCl₃ was evaporated in vacuo and 150 mL of CHCl₃ was added to the residue. After addition of 30 mL of EtOH, the mixture was allowed to stir at 40 °C for 30 min and cooled and then 100 mL of water was added. The organic phase was separated, dried over Na₂SO₄, and evaporated in vacuo. The residue was crystallized from a mixture of AcOEt and Et₂O to give 18.2 g (77%) of 4.

Ethyl 7-(Ethylsulfonyl)-6-fluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (5). To a mixture containing 24.0 g (0.07 mol) of ethyl 7-(ethylthio)-6-fluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**60**) and 200 mL of CHCl₃ was added 24.1 g (0.14 mol) of *m*-chloroperbenzoic acid under ice-cooling. The mixture was allowed to stir at room temperature for 2 h. After addition of 10% Na₂CO₃, the organic phase was separated and dried over K₂CO₃, and the solvent was evaporated in vacuo. The residue

was crystallized from EtOH to give 19.4 g (74%) of 5.

6-Fluoro-1,4-dihydro-4-oxo-7-(tosyloxy)-1-vinyl-1,8-naphthyridine-3-carboxylic Acid (7). A mixture containing 2.5 g (0.01 mol) of 58, 3.8 g (0.02 mol) of tosyl chloride, 1.4 g (0.01 mol) of K_2CO_3, and 20 mL of MeCN was heated to reflux for 4 h. After filtration, the filtrate was concentrated to dryness in vacuo. The residue was chromatographed on silica gel with $CHCl_3$. The solid resulting from the main fraction was crystallized from a mixture of EtOH and $CHCl_3$ to give 2.5 g (62%) of 7.

Ethyl 1,7-Disubstituted 6-Fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates (8–27) (Table I). Method A. A mixture containing 0.01 mol of an ester (3–5), 0.015 mol of an appropriate amine, 1.5 mL of NEt_3, and 40 mL of EtOH was heated to reflux for 0.5–4 h and concentrated to dryness in vacuo. After addition of 80 mL of water, the residue was filtered off or extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated in vacuo. The resulting solid was crystallized from an appropriate solvent to give 8–27.

1,7-Disubstituted 6-Fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids (28–56) (Table II). Method B. A mixture containing 0.01 mol of an ester (12, 14, 16–18, 20–22, or 24–26), and 20% HCl was heated to reflux for 3–10 h and then concentrated to dryness in vacuo. The resulting solid was filtered off and washed with EtOH. Recrystallization from the solvent given in Table II gave the corresponding compound (33a, 35a–37a, 43a, 45a, or 51a). Neutralization of the filtrate with aqueous ammonia afforded 33c, 34c, 49a, or 50a.

Method C. A stirred suspension containing 0.01 mol of an ester (8–11, 13, 15, 19, 23, or 27), 40 mL of 5–10% NaOH, and 5–10 mL of EtOH was heated at 60–100 °C for 0.5–2 h, allowed to cool, and adjusted to pH 6–7 with 30% AcOH. The resulting solid was filtered off, washed with water, and recrystallized from an appropriate solvent to give the corresponding carboxylic acid (28a,b, 29a, 30a, 33b, 34b, 36b, 48a, or 55a).

Method D. A stirred suspension containing 0.01 mol of 6 or 7, 0.015 mol of an amine, 3 mL of NEt_3, and 50 mL of a solvent (EtOH, MeCN, or DMF) was heated at 100–110 °C for 1–4 h. The reaction mixture was concentrated to dryness in vacuo. The residue was taken up in 3% AcOH, and the solution was adjusted to pH 6–7. The resulting solid was filtered off, washed with water, and recrystallized from an appropriate solvent to give 31a, 32a, 38a,b, 40a, 42a, 44a, 46a, 52a, 54a, or 56a.

Method E. A mixture containing 0.01 mol of 33a–c, 34b,c, 46a, or 52a and an acylating agent [formic acid (30 mL)–formamide (10 mL), acetic anhydride (10 mL)–acetic acid (30 mL), or trifluoroacetic anhydride (30 mL)] was heated at 100–110 °C for 1–3 h with stirring. The reaction mixture was concentrated to dryness in vacuo. The residue was triturated with water or EtOH. The resulting solid was filtered off and recrystallized from an appropriate solvent to give the corresponding acyl compound (39a,b, 40b,c, 41a, 42b,c, 47a, or 53a).

Method F. A solution of 7-[3-(*N*-methylacetamido)-1-pyrrolidinyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (42a) (3.0 g, 0.08 mol) in 75 mL of 10% NaOH was heated to reflux for 4 h, allowed to cool, and adjusted to pH 6–7 with AcOH. The resulting solid was filtered off, washed with water, and taken up in 25 mL of 2% NaOH. The solution was neutralized with 10% AcOH to give 1.9 g (71%) of 34a.

Method G. A mixture containing 1.9 g (0.0054 mol) of 6-fluoro-1-(2-fluoroethyl)-1,4-dihydro-7-[3-(methylamino)-1-pyrrolidinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (34c), 4 mL of 37% formalin, and 6 mL of formic acid was heated at 100–110 °C for 8 h with stirring. The reaction mixture was concentrated to dryness in vacuo. The residue was taken up in 10 mL of water. The mixture was adjusted to pH 8–9 with an

aqueous ammonia. The resulting solid was filtered off, washed with water, and recrystallized from a mixture of $CHCl_3$ and EtOH to give 0.9 g (45%) of 38c.

6-Fluoro-1,4-dihydro-7-hydroxy-4-oxo-1-vinyl-1,8-naphthyridine-3-carboxylic Acid (58). To a stirred mixture containing 42.5 g (0.10 mol) of ethyl 7-(4-acetyl-1-piperazinyl)-1-(2-chloroethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (57)[4] and 300 mL of EtOH was added a solution of KOH (16.8 g, 0.30 mol) in 300 mL of EtOH. The mixture was heated to reflux for 2 h. After addition of 500 mL of 20% NaOH, the mixture was heated at 120 °C for 18 h, during which period the EtOH was removed gradually by distillation. The resulting precipitate was filtered off, washed with 10% NaOH, and dissolved in a mixture of water (250 mL) and AcOH (25 mL). The solution was treated with charcoal and acidified with concentrated HCl to give 21.2 g (85%) of 58. Recrystallization from a mixture of EtOH and $CHCl_3$ gave an analytical sample, mp 256–259 °C. Anal. ($C_{11}H_7FN_2O_4$) C, H, F, N.

Ethyl 7-(Ethylthio)-6-fluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (60). A mixture containing 25.0 g (0.085 mol) of ethyl 7-(ethylthio)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (59),[1] 15.2 g (0.11 mol) of K_2CO_3, and 250 mL of DMF was heated at 65 °C for 1 h with stirring. To this mixture was added 24.0 g (0.11 mol) of 2-fluoroethyl tosylate. The resulting mixture was heated at 100–105 °C for 1.5 h with stirring and then filtered to remove insoluble materials. The filtrate was concentrated to dryness in vacuo. The residue was taken up in a mixture of water (150 mL) and $CHCl_3$ (250 mL). The organic phase was separated, washed with water, and dried over Na_2SO_4. The $CHCl_3$ was evaporated in vacuo and the residue was crystallized from AcOEt to give 27.8 g (96%) of 60. Recrystallization from a mixture of AcOEt and CH_2Cl_2 gave an analytical sample, mp 174–175 °C. Anal. ($C_{15}H_{16}F_2N_2O_3S$) C, H, N, S.

Biological Screenings. The in vitro antibacterial activity, in vivo efficacy on systemic infections, and acute toxicity were tested by the same methods reported in a previous paper.[4] Acute toxicity tests for 28a, 46a, and 50a were not performed.