Fluorinated Pyrido[2,3-*c*]pyridazines. II.[1] Synthesis and Antibacterial Activity of 1,7-Disubstituted 6-Fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylic Acids

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Chemical modification of pyridonecarboxylic acid antibacterials with a 1,8-naphthyridine ring, such as enoxacin and tosufloxacin, to their 2-aza derivatives was studied. A new series of 1,7-disubstituted 6-fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylic acids (25—27) was prepared by a route involving either alkylation of ethyl 6-fluoro-4(1*H*)-oxo-7-(*p*-tolylthio)pyrido[2,3-*c*]pyridazine-3-carboxylate (7) or intramolecular cyclization of ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-2-[2-(*p*-fluorophenyl)hydrazono]acetate (20), followed by displacement reaction with cyclic amines at C-7; the N-1 substituent in these compounds included of ethyl, 2-fluoroethyl and *p*-fluorophenyl groups, and the C-7 functional group comprised variously-substituted piperazines and pyrrolidines. Antibacterial activities of these compounds were markedly inferior to those of enoxacin and tosufloxacin.

Keywords synthesis; fluorinated pyrido[2,3-*c*]pyridazine; ring construction; alkylation; 1-alkyl-6-fluoro-4-(1*H*)-oxopyrido[2,3-*c*]pyridazine; 1-aryl-6-fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine; ^{13}C-NMR; antibacterial activity

We have previously reported the synthesis of enoxacin (**1a**)[2a] and esafloxacin (**1b**),[2b] which are members of the class of pyridonecarboxylic acid antibacterials with a 1,8-naphthyridine ring; enoxacin is currently used in clinical practice, and esafloxacin is under development as an antibacterial agent for veterinary use. Other members of the 1,8-naphthyridine class antibacterials have appeared recently, as exemplified by A-57132 (**2**)[3b] and tosufloxacin (**3**)[3] bearing a 4-fluorophenyl group and a 2,4-difluorophenyl group, respectively, at the N-1 position. With the aim of finding new antibacterial agents with an improved activity, we planned chemical modifications of the 1,8-naphthyridine derivatives to their 2-aza-analogues **4**, whose structures are characterized by a pyrido[2,3-*c*]pyridazine ring (Chart 1). In the previous study,[1] we developed a convenient synthetic method for 6-fluoro-4(1*H*)-oxo-7-(*p*-tolylthio)pyrido[2,3-*c*]pyridazine-3-carboxylate (**7**), as a precursor for **4**, by the reductive intramolecular cyclization of ethyl 2-diazo-2-[2,5-difluoro-6-(*p*-tolylthio)nicotinoyl]acetate (**5**) (Chart 2).

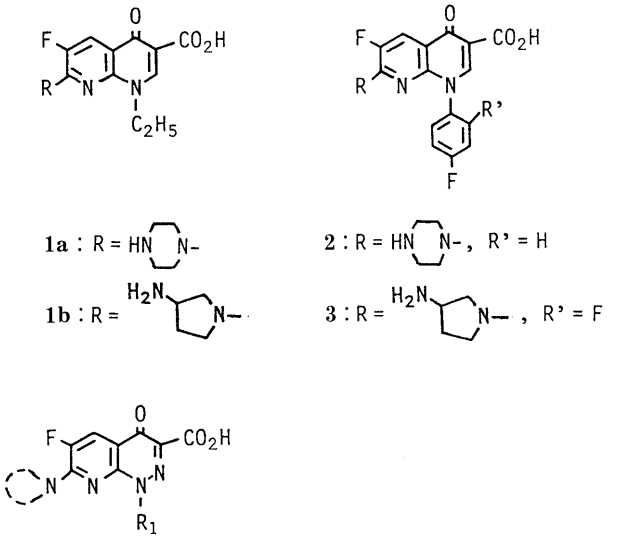
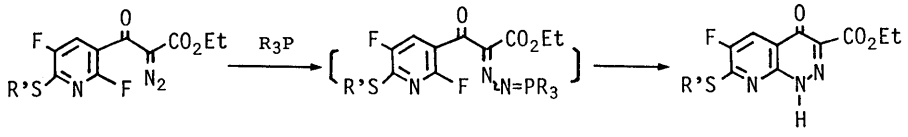


Chart 1

As an extension of that work, the present study was undertaken to prepare a series of 1-substituted 7-(cyclic amino)-6-fluoro-4-(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylic acids of the general structure **4**; the synthesis of these compounds **4**[4] was achieved by a route involving either alkylation of **7** (when R_1 of **4** was ethyl and 2-fluoroethyl groups) or cyclization of ethyl 2-aryl-2-(2-chloro-5-fluoronicotinoyl)hydrazonoacetates (**15** and **20**) (when R_1 of **4** was a *p*-fluorophenyl group), followed by displacement reaction with cyclic amines at the C-7 position.

Chemistry Alkylation of compound **7** might occur either at N-1 or at C-4 OH, because the keto-enol tautomerization of **7** is formally possible. We therefore studied first the alkylation of **7** (Chart 3). Treatment of **7** with ethyl iodide in *N*,*N*-dimethylformamide (DMF) in the presence of anhydrous potassium carbonate gave the monoethyl derivative **8a** in a high yield as a sole product, which was subjected to acid-catalyzed hydrolysis to give the corre-



R' = *p*-$CH_3C_6H_4$; R = *n*-Bu, cyclohexyl

Chart 2

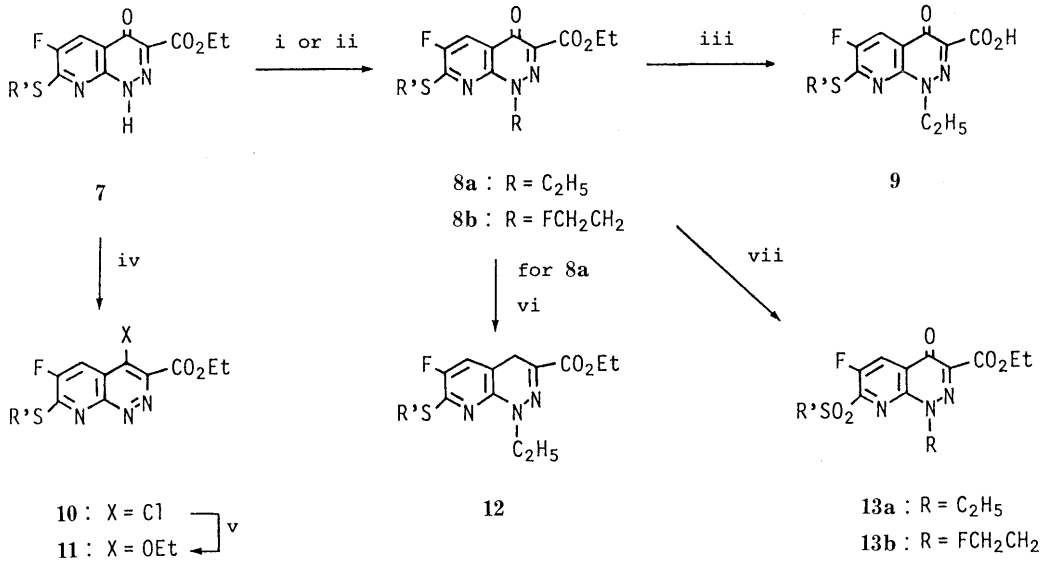


Chart 3

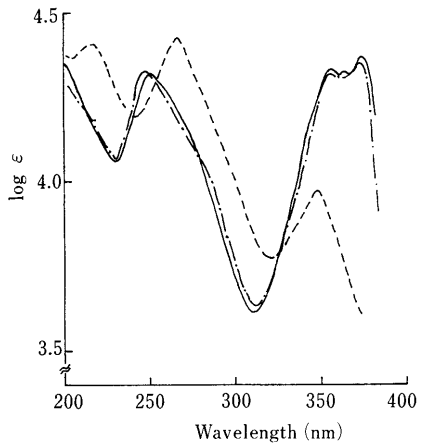


Fig. 1. UV spectra of Pyrido[2,3-*c*]pyridazine Derivatives (**8a**, **8b** and **11**) in EtOH

8a, -·-·-·-; **8b**, ——; **11**, – – –.

sponding carboxylic acid **9**. The location of the ethyl group of **8a** and, in turn, **9** was determined to be at N-1 on the basis of the following chemical evidence. (i) Compound **8a** was clearly different from its regioisomeric 4-ethoxy derivative **11**, which was separately prepared by chlorination of **7** with phosphorus oxychloride, followed by displacement reaction of the resultant 4-chloro derivative **10** with sodium ethoxide. (ii) The reaction of **8a** with a mixture of sodium borohydride and boron trifluoride-etherate produced the 4-deoxo compound **12**. The infrared (IR) spectrum of **12** showed a carbonyl absorption band at ν 1685 cm^{-1} assignable to the ester carbonyl group, and its proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed the presence of new C-4 methylene protons at δ 3.76 as a doublet signal (J=1 Hz) due to coupling with the aromatic C-5 proton; these data supported the assigned structure of **12**.

TABLE I. ^{13}C-NMR Data for 1-Ethyl- and 4-Ethoxypyrido[2,3-*c*]pyridazines (**8a** and **11**)

C-atoms		Compd. **8a**	Compd. **11**
		Chemical shifts[a]	δ ($J_{C,F}$ Hz)
Ring carbons	C(3)	139.87	138.34
	C(4)	168.19 ($J_{C,F}$=2.0)	153.48 ($J_{C,F}$=5.1)
	C(4a)	119.90 ($J_{C,F}$=3.5)	116.04 ($J_{C,F}$=6.2)
	C(5)	117.12 ($J_{C,F}$=19.3)	111.88 ($J_{C,F}$=20.3)
	C(6)	153.43 ($J_{C,F}$=260.8)	155.78 ($J_{C,F}$=269.1)
	C(7)	158.62 ($J_{C,F}$=21.4)	160.33 ($J_{C,F}$=20.2)
	C(8a)	145.57 ($J_{C,F}$=1.7)	155.78 ($J_{C,F}$=1.9)
$\underline{C}O_2CH_2CH_3$		162.97	165.06
$CO_2\underline{C}H_2CH_3$		61.92	62.65
$CO_2CH_2\underline{C}H_3$		14.22	14.16
N_1-$\underline{C}H_2CH_3$		50.17	—
N_1-$CH_2\underline{C}H_3$		13.80	—
C_4-$O\underline{C}H_2CH_3$		—	71.46
C_4-$OCH_2\underline{C}H_3$		—	15.63
p-Tolylthio carbons	C(1′)	122.70 ($J_{C,F}$=2.3)	121.81 ($J_{C,F}$=1.8)
	C(2′, 6′)	130.27	130.51
	C(3′, 5′)	136.16	135.45
	C(4′)	140.66	140.52
	$\underline{C}H_3$(*p*-4′)	21.37	21.46

a) Measured in $CDCl_3$ with tetramethylsilane as an internal standard.

A comparison of the *N*-ethyl compound **8a** with the *O*-ethyl counterpart **11** provided some spectral features permitting the structural assignment of alkylated products in this series. Thus, the IR spectrum of **8a** shows two carbonyl absorption bands at 1730 and 1625 cm^{-1} attributed to the ester carbonyl group and the oxo group, respectively, whereas that of **11** displays only one carbonyl absorption band at 1710 cm^{-1} due to the ester carbonyl group. In the ultraviolet (UV) spectra, as shown in Fig. 1,

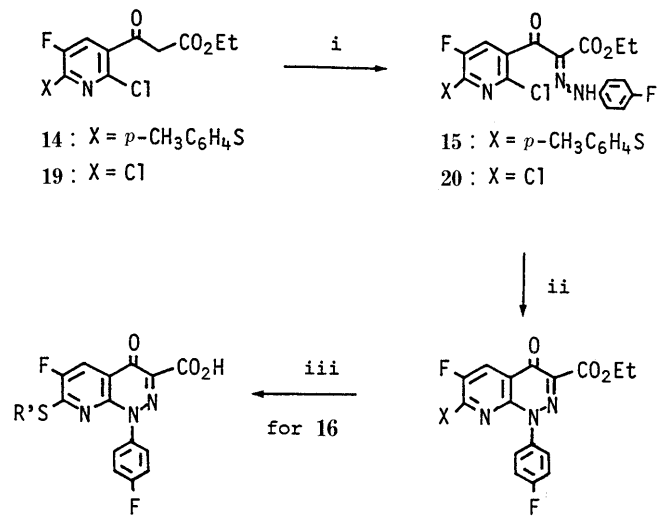
8a differs clearly from **11**. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) data for both compounds, presented in Table I, show that the chemical shifts for the *N*-methylene carbon of **8a** (δ 50.17) and the C-4 *O*-methylene carbon of **11** (δ 71.46) are distinctive.

Taking advantage of the above spectral characteristics, we were able to assign the structure of the *N*-(2-fluoroethyl) derivative **8b** that was derived from the reaction of **7** with 2-fluoroethyltosylate; this alkylation also occurred at N-1 exclusively.

Since the C-7 *p*-tolylthio groups of **8a** and **8b** were, as expected (discussed later), less reactive than a sulfonyl group toward the displacement reaction with an amine, **8a** and **8b** were oxidized with *m*-chloroperbenzoic acid (MCPBA) to the sulfonyl derivatives **13a** and **13b**, respectively.

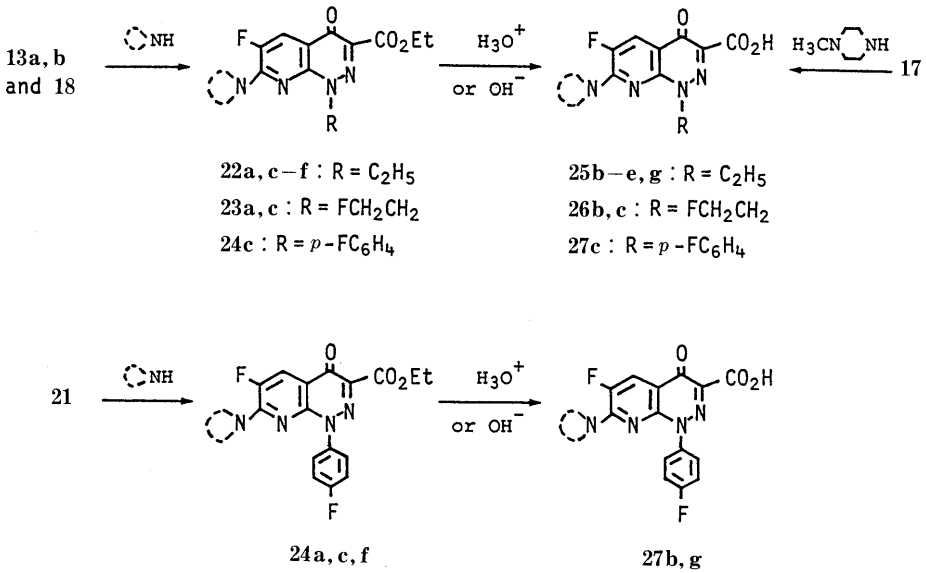
In order to introduce the *p*-fluorophenyl group at N-1 on the 6-fluoropyrido[2,3-*c*]pyridazine ring, a different synthetic route was developed (Chart 4). On the treatment of ethyl 2-chloro-5-fluoro-6-(*p*-tolylthio)nicotinoylacetate (**14**) with *p*-fluorobenzenediazonium chloride, the Japp-Klingemann reaction proceeded smoothly to give the corresponding hydrazone **15**. The hydrazone **15** was then treated with potassium carbonate in refluxing acetonitrile to give the cyclized compound **16**; use of potassium *tert*-butoxide as a base resulted in an effective ring closure of **15** to **16** even at room temperature. A similar coupling reaction of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (**19**) with the same diazonium salt provided the hydrazones **20**, which was treated, this time, with potassium *tert*-butoxide to give compound **21** in an excellent yield. Acid hydrolysis of **16** gave the carboxylic acid **17**. The oxidation of **16** with MCPBA yielded the sulfone **18**.

For the synthesis of the target compounds, we then examined nucleophilic displacement reactions of the esters (**8**, **13**, **16**, **18**, and **21**) and the carboxylic acids (**9** and **17**) with cyclic amines, such as piperazine and 3-aminopyrrolidine, which are believed to be effective substituents for improving the activity of pyridonecarboxylic acid antibacterials[5] (Chart 5). The *p*-tolylthio groups of the esters (**8** and **16**) and the carboxylic acids (**9** and **17**) were less reactive than the sulfonyl (**13** and **18**) and chloro (**21**) groups



reagents : i p-$FC_6H_4N_2^+Cl^-$, aq. NaOAc in $CHCl_3$ - EtOH; ii base; iii H_3O^+, H_2O; iv MCPBA in CH_2Cl_2

Chart 4



a, AcN- ; b, HCl·HN- ; c, H_3CN- ; d, - ; e, HO- ; f, AcNH- ; g, H_2N-

Chart 5

TABLE II. Ethyl 1,7-Disubstituted 6-Fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylates and Their Carboxylic Acids

Compd.	mp (°C) (Recryst. solv.)	Method[a]	Yield[b] (%)	Formula	Analysis (%) Calcd (Found)				
					C	H	F	N	S(Cl)
8a	116.5 (iso-Pr_2O)	—	97	$C_{19}H_{18}FN_3O_3S$	58.90 (58.82	4.68 4.88	4.90 10.80	10.85 8.05	8.28 5.05)
8b	137—138 ($CHCl_3$–iso-Pr_2O)	—	83	$C_{19}H_{17}F_2N_3O_3S$	56.29 (56.15	4.23 4.40	9.37 9.49	10.36 10.16	7.91 8.14)
9	205—206 ($CHCl_3$–EtOH)	—	94	$C_{17}H_{14}FN_3O_3S$	56.82 (56.80	3.93 4.25	5.29 5.29	11.69 11.63	8.92 9.18)
13a	143—144 (EtOH)	—	94	$C_{19}H_{18}FN_3O_5S$	54.41 (54.16	4.33 4.51	4.53 4.77	10.02 9.85	7.64 7.82)
13b	155—156 (AcOEt)	—	95	$C_{19}H_{17}F_2N_3O_5S$	52.17 (52.13	3.92 4.20	8.69 8.70	9.61 9.59	7.33 7.41)
16	154 ($CHCl_3$–EtOH)	—	97	$C_{23}H_{17}F_2N_3O_3S$	60.92 (61.20	3.78 3.89	8.38 8.16	9.27 9.33	7.07 7.26)
17	288—289 (dec.) ($CHCl_3$–EtOH)	—	93	$C_{21}H_{13}F_2N_3O_3S$	59.29 (59.44	3.08 3.26	8.93 8.91	9.88 9.97	7.54 7.65)
18	229—230 ($CHCl_3$–AcOEt)	—	95	$C_{23}H_{17}F_2N_3O_5S$	56.90 (56.77	3.53 3.80	7.83 7.88	8.66 8.55	6.60 6.90)
21	237—238 ($CHCl_3$–EtOH)	—	95	$C_{16}H_{10}ClF_2N_3O_3$	52.55 (52.34	2.76 2.67	10.39 10.29	11.49 11.34	9.69[c] 9.87[c])
22a	219—220 (EtOH)	A	93	$C_{18}H_{22}FN_5O_4$	55.24 (54.99	5.67 5.53	4.85 5.04	17.89 17.64	— —)
22c	117—118 (iso-Pr_2O)	B	77	$C_{17}H_{22}FN_5O_3$	56.19 (56.09	6.10 5.83	5.23 5.43	19.27 18.97	— —)
22d	167—168 (EtOH)	B	94	$C_{16}H_{19}FN_4O_3$	57.48 (57.24	5.73 5.87	5.68 5.77	16.76 16.64	— —)
22e	147—148 (EtOH–iso-Pr_2O)	B	86	$C_{16}H_{19}FN_4O_4$	54.85 (54.65	5.47 5.34	5.42 5.41	15.99 15.95	— —)
22f	206—208 (EtOH)	B	91	$C_{18}H_{22}FN_5O_4$	55.24 (54.88	5.67 5.46	4.85 4.83	17.89 17.64	— —)
23a	214—215 (EtOH)	B	90	$C_{18}H_{21}F_2N_5O_4$	52.81 (52.83	5.17 5.03	9.28 9.39	17.11 17.09	— —)
23c	142—143 (EtOH–iso-Pr_2O)	B	79	$C_{17}H_{21}F_2N_5O_3$	53.54 (53.47	5.55 5.45	9.96 9.90	18.36 18.31	— —)
24a	174—175 (EtOH–iso-Pr_2O)	C	82	$C_{22}H_{21}F_2N_5O_4$	57.77 (57.61	4.63 4.53	8.31 8.58	15.31 15.36	— —)
24c	174—175 (EtOH–iso-Pr_2O)	C C	81[d] 83	$C_{21}H_{21}F_2N_5O_3$	58.74 (58.51	4.93 4.82	8.85 8.68	16.31 16.12	— —)
24f	198—199 ($CHCl_3$–AcOEt)	C	87	$C_{22}H_{21}F_2N_5O_4 \cdot 0.75H_2O$	56.11 (55.94	4.82 4.96	8.07 8.29	14.87 14.85	— —)
25b	279—283 (dec.) (H_2O–EtOH)	D	98	$C_{14}H_{16}FN_5O_3 \cdot HCl \cdot 0.5H_2O$	45.86 (45.75	4.95 4.88	5.16 5.16	19.10 18.69	9.67[c] 10.03[c])
25c	250—252 (dec.) (H_2O–EtOH)	D	90	$C_{15}H_{18}FN_5O_3 \cdot HCl \cdot 0.25H_2O$	47.89 (47.74	5.22 5.12	5.02 5.07	18.62 18.35	9.42[c] 9.29[c])
25d	225 (EtOH)	E	73	$C_{14}H_{15}FN_4O_3$	54.90 (54.94	4.94 4.95	6.20 6.28	18.29 18.39	— —)
25e	214 (EtOH)	E	89	$C_{14}H_{15}FN_4O_4$	52.17 (52.06	4.69 4.75	5.89 5.74	17.38 17.56	— —)
25g	268—270 (dec.) (NH_4OH)	F	77	$C_{14}H_{16}FN_5O_3 \cdot 0.5H_2O$	50.92 (51.22	5.19 5.02	5.72 6.11	21.21 20.95	— —)
26b	268—270 (dec.) (H_2O–EtOH)	D	96	$C_{14}H_{15}F_2N_5O_3 \cdot HCl$	44.75 (45.00	4.29 4.56	10.11 10.40	18.64 18.82	9.43[c] 9.40[c])
26c	>270 (dec.) (H_2O–EtOH)	D	93	$C_{15}H_{17}F_2N_5O_3 \cdot HCl$	46.22 (46.13	4.65 4.47	9.75 10.03	17.97 17.75	9.10[c] 9.02[c])
27b	>290 (dec.) (H_2O)	D	76	$C_{18}H_{15}F_2N_5O_3 \cdot HCl$	51.01 (50.98	3.81 3.83	8.97 9.18	16.53 16.75	8.37[c] 8.09[c])
27c	256—261 (dec.) ($CHCl_3$–EtOH)	E	92	$C_{19}H_{17}F_2N_5O_3 \cdot 2H_2O$	52.20 (52.40	4.84 4.60	8.65 8.54	16.02 15.74	— —)
27g	251—255 (dec.) (H_2O)	D	98	$C_{18}H_{15}F_2N_5O_3 \cdot HCl \cdot 0.4H_2O$	50.16 (50.38	3.93 3.90	8.82 9.06	16.25 16.28	8.22[c] 7.91[c])

a) See Experimental for methods A—E. *b*) Yields are not optimized. *c*) Analysis for Cl is given. *d*) The yield from **18**.

toward the amine nucleophile; for example, treatment of **16** with *N*-methylpiperazine in refluxing acetonitrile for 5 h gave the 7-(4-methyl-1-piperazinyl) analogue **24c** in 49% yield at most, and the reaction of the carboxylic acid **17** with the same amine at 120—130 °C for 3 h in dimethylformamide gave a 35% yield of **25c**. On the contrary, the reaction of the sulfone **18** with the same amine proceeded effectively even at room temperature, giving an 81% yield of **24c**. Compound **24c** was alternatively prepared by the reaction of the 7-chloro derivative **21** with

the same amine in 83% yield. We therefore chose the 7-sulfonyl (**13**) and 7-chloro (**21**) derivatives as superior intermediates for the synthesis of 7-(cyclic amino) analogues **25**—**27**, where the C-7 substituent included (a) 4-acetyl-1-piperazinyl, (b) 1-piperazinyl, (c) 4-methyl-1-piperazinyl, (d) 1-pyrrolidinyl, (e) 3-hydroxy-1-pyrrolidinyl, (f) 3-acetylamino-1-pyrrolidinyl, and (g) 3-amino-1-pyrrolidinyl groups. The displacement reactions of the sulfones **13a** and **13b** with the selected amines gave **22a, c**—**f** and **23a, c**, respectively. A similar treatment of the 7-chloro derivative **21** with the amines produced **24a, f** in excellent yields. Hydrolysis of the esters **22**—**24** produced the carboxylic acids **25**—**27**. The structures of the compounds thus prepared were assigned on the basis of their spectral and elemental analysis data. The poor antibacterial activity, later discussed, of this class led us to abandon a plan to prepare analogues appended with a 2,4-difluorophenyl group at N-1, as in tosufloxacin (**3**).

Antibacterial Activity The series of pyrido[2,3-*c*]pyridazines **25**—**27** prepared in this study was tested for *in vitro* antibacterial activities. Minimum inhibitory concentrations (MICs, μg/ml) of **25b** (equivalent to "2-aza-enoxacin"), **25d**, and **25g** against *Staphylococcus aureus* 209P JC-1 were >100, 25, and 50, respectively, thus showing markedly poor activity, compared with the MICs of 0.78, 0.39, and 0.025 for enoxacin (**1a**), **2** and tosufloxacin (**3**), respectively. Against *Escherichia coli* NIHJ JC-2, all of **25b, 25c**, and **25g** showed an MIC (μg/ml) of 12.5 *versus* those of 0.2, 0.05 and 0.0125 for enoxacin, **2** and tosufloxacin, respectively. Other compounds were virtually inactive against the tested bacteria, including *Pseudomonas aeruginosa* species. Thus, introduction of an additional nitrogen atom at C-2 of the 1,8-naphthyridine antibacterials has a deleterious influence on the activity.

In summary, a new series of 1-substituted 7-(cyclic amino)-6-fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylic acids (**25**—**27**) was prepared. However, there was no compound with a potent antibacterial activity; the insertion of a nitrogen atom at C-2 of the 1,8-naphthyridine antibacterials resulted in a substantial loss of activity.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Jasco A-102 spectrometer for KBr tablets, unless otherwise noted. ^{1}H-NMR spectra were taken at 60, 80, 100, and 200 MHz, with Varian EM-360, FT-80A, HA-100D and GEMINI-200 spectrometers, respectively. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. ^{13}C-NMR spectra were taken at 20 and 75 MHz with Varian FT-80A and XL-300 spectrometers, respectively; SFORD and, in some cases, single resonance (proton-coupled) experiments were performed to assign resonances to individual carbons in molecules, and chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Electron impact mass spectra (EIMS) were recorded on a Hitachi RMU-6 or JEOL JMSD-300 spectrometer. UV spectra were recorded in EtOH on a Shimadzu UV-260 UV-visible recording spectrophotometer. The spectral data for representative compounds are presented. The elemental analysis data for compounds except **11**, **12**, **15**, and **20** are given in Table II. Each extract was dried over anhydrous Na_2SO_4.

Ethyl 1-Ethyl- and 1-(2-Fluoroethyl)-6-fluoro-4(1*H*)-oxo-7-(*p*-tolylthio)-pyrido[2,3-*c*]pyridazine-3-carboxylates (8a and 8b) A stirred mixture of ethyl 6-fluoro-4(1*H*)-oxo-7-(*p*-tolylthio)pyrido[2,3-*c*]pyridazine-3-carboxylate (**7**)[1] (3.0 g, 8.4 mmol) and anhydrous K_2CO_3 (1.74 g, 12.6 mmol) in DMF (25 ml) was heated at 90—100 °C for 15 min, during which time the potassium salt separated out. Ethyl iodide (2.0 g, 12.8 mmol) was added to the mixture at 70—75 °C. The resulting mixture was kept at the same temperature for 1 h and then concentrated to dryness *in vacuo*. After addition of water, the mixture was extracted with $CHCl_3$. The extract was dried, and the solvent was evaporated off *in vacuo*. The residue was crystallized from EtOH–iso-Pr_2O to give **8a** (3.14 g, 97%) as colorless prisms. EIMS *m/z*: 387 (M^+), 342, 315, 287, 286. IR cm^{-1}: 1730, 1625, 1600. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.06 (3H, t, J=7 Hz, $N_1CH_2C\underline{H}_3$), 1.39 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.45 (3H, s, CH_3), 4.13 (2H, q, J=7 Hz, $N_1C\underline{H}_2CH_3$), 4.41 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.28 (2H, d, J=8 Hz, aromatic H), 7.48 (2H, d, J=8 Hz, aromatic H), 8.05 (1H, d, $J_{H,F}$=8 Hz, C_5-H). UV λ_{max} nm (log ε): 201 (4.30), 249 (4.32), 358 (4.31), 376 (4.35). The ^{13}C-NMR spectral analysis data for **8a** are given in Table I.

In a similar manner, the reaction of **7** with 2-fluoroethyltosylate gave **8b** (83%) as pale yellow prisms. EIMS *m/z*: 405 (M^+), 360, 333. IR cm^{-1}: 1720, 1635, 1600. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.40 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.43 (3H, s, CH_3), 3.9—4.3 (2H, m, $N_1CH_2C\underline{H}_2F$), 4.43 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.4—4.8 (2H, m, $N_1C\underline{H}_2CH_2F$), 7.33 (2H, d, J=8 Hz, aromatic H), 7.53 (2H, d, J=8 Hz, aromatic H), 8.10 (1H, d, $J_{H,F}$=8 Hz, C_5-H). UV λ_{max} nm (log ε): 201 (4.36), 250 (4.32), 359 (4.33), 366 (4.32), 376 (4.37).

1-Ethyl- and 1-(*p*-Fluorophenyl)-6-fluoro-4(1*H*)-oxo-7-(*p*-tolythio)pyrido[2,3-*c*]pyridazine-3-carboxylic Acids (9 and 17) A stirred suspension of **8** (1.55 g, 4 mmol) in a mixture of concentrated H_2SO_4 (9 ml), H_2O (15 ml) and EtOH (5 ml) was heated at 100—110 °C for 2 h and then cooled. The mixture was diluted with water, and the resulting crystals were collected by filtration and recrystallized from $CHCl_3$–EtOH to give 1.35 g (94%) of **9** as colorless scales. IR cm^{-1}: 1760, 1610, 1580. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.11 (3H, t, J=7 Hz, $N_1CH_2C\underline{H}_3$), 2.46 (3H, s, CH_3), 4.35 (2H, q, J=7 Hz, $N_1C\underline{H}_2CH_3$), 7.31 (2H, d, J=8 Hz, aromatic H), 7.50 (2H, d, J=8 Hz, aromatic H), 8.10 (1H, d, $J_{H,F}$=8 Hz, C_5-H), 14.20 (1H, s, COOH, exchangeable with D_2O).

A similar treatment of the ester **16** gave **17** (93%) as colorless prisms. EIMS *m/z* 425 (M^+), 381, 353. IR cm^{-1}: 1735, 1610. ^{1}H-NMR (80 MHz, $CDCl_3$): 2.46 (3H, s, CH_3), 6.85—6.95 (2H, m, aromatic H), 7.05—7.25 (6H, m, aromatic H), 8.18 (1H, d, $J_{H,F}$=8 Hz, C_5-H), 14.10 (1H, s, COOH, exchangeable with D_2O).

Ethyl 4-Ethoxy-6-fluoro-7-(*p*-tolylthio)pyrido[2,3-*c*]pyridazine-3-carboxylate (11) A solution of ethyl 4-chloro-6-fluoro-7-(*p*-tolylthio)pyrido[2,3-*c*]pyridazine-3-carboxylate (**10**)[1] (1.13 g, 3.0 mmol) in dry tetrahydrofuran (THF) (5 ml) was added below 0 °C to a stirred solution of sodium ethoxide (224 mg, 3.3 mmol) in absolute EtOH (15 ml). After an additional 15-min period of stirring, the mixture was kept below 10 °C for 1.5 h, then neutralized with 1 N AcOH, and concentrated to dryness *in vacuo*. After addition of $CHCl_3$ and ice-water, the organic layer was separated and dried. The solvent was evaporated off *in vacuo*, and the residue was chromatographed on silica gel with $CHCl_3$–AcOEt as an eluent, followed by recrystallization from AcOEt to give **11** (380 mg, 30%) as colorless prisms, mp 165 °C. *Anal.* Calcd for $C_{19}H_{18}FN_3O_3S$: C, 58.90; H, 4.68; F, 4.90; N, 10.85; S, 8.28. Found: C, 58.80; H, 4.68; F, 4.62; N, 10.75; S, 8.45. EIMS *m/z*: 387 (M^+), 386. IR cm^{-1}: 1710, 1615. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.45 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.50 (3H, t, J=7 Hz, 4-$OCH_2C\underline{H}_3$), 2.42 (3H, s, CH_3), 4.38 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.53 (2H, q, J=7 Hz, 4-$OC\underline{H}_2CH_3$), 7.28 (2H, d, J=8 Hz, aromatic H), 7.55 (2H, d, J=8 Hz, aromatic H), 7.95 (1H, d, $J_{H,F}$=8.5 Hz, C_5-H). UV λ_{max} nm (log ε): 217 (4.41), 268 (4.43), 350 (3.97). The ^{13}C-NMR spectral analysis data for **11** are given in Table I.

Ethyl 1-Ethyl-6-fluoro-1,4-dihydro-7-(*p*-tolylthio)pyrido[2,3-*c*]pyridazine-3-carboxylate (12) Sodium borohydride (83 mg, 2.2 mmol) was added to a stirred mixture of boron trifluoride–ether complex (312 mg, 2.2 mmol) in dry THF (6 ml) under ice-cooling. The whole was stirred for 15 min, then **8a** (380 mg, 0.98 mmol) was added under ice-cooling. The resulting mixture was stirred for 30 min at the same temperature and then heated at 65—70 °C for 15 min. Aqueous AcOH was added portionwise to the solution under ice-cooling. After the generation of hydrogen gas had ceased, the mixture was concentrated to dryness *in vacuo*. After addition of water, the mixture was extracted with $CHCl_3$. The extract was dried, and the solvent was evaporated off *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$ as an eluent, followed by recrystallization from *n*-hexane to give **12** (160 mg, 44%) as pale yellow needles, mp 109.5—110 °C. *Anal.* Calcd for $C_{19}H_{20}FN_3O_2S$: C, 61.11; H, 5.40; F, 5.09; N, 11.25; S, 8.59. Found: C, 61.04; H, 5.40; F, 5.13; H, 11.01; S, 8.68. EIMS *m/z*: 373 (M^+), 344, 299, 270. IR cm^{-1}: 1685, 1605. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.89 (3H, t, J=7 Hz, $N_1CH_2C\underline{H}_3$), 1.33 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.39 (3H, s, CH_3), 3.68 (2H, q, J=7 Hz, $N_2C\underline{H}_2CH_3$), 3.76 (2H, d, $J_{H,H}$=1 Hz, C_4-H_2), 4.32 (2H, q, J=7 Hz,

$C\underline{H}_2CH_3$), 6.98 (1H, dt, $J_{H,F}=8.5$ Hz, $J_{H,H}=1$ Hz, C_5-H), 7.20 (2H, d, $J=8$ Hz, aromatic H), 7.45 (2H, d, $J=8$ Hz, aromatic H).

Ethyl 1-Ethyl-, 1-(2-Fluoroethyl)- and 1-(*p*-Fluorophenyl)-6-fluoro-4(1*H*)-oxo-7-(*p*-toluenesulfonyl)pyrido[2,3-*c*]pyridazine-3-carboxylates (13a, 13b and 18) A stirred mixture of **8a** (3.55 g, 9.2 mmol) and MCPBA (3.17 g, 20.3 mmol) in dichloromethane (50 ml) was heated to reflux for 1 h and then cooled. The mixture was washed with 1 N Na_2CO_3 (30 ml). The organic layer was dried. The solvent was evaporated off to leave a crystalline residue, which was recrystallized from EtOH to give 3.62 g (94%) of **13a** as pale yellow prisms. EIMS *m/z*: 419 (M^+), 374, 347. IR cm^{-1}: 1730, 1640, 1600. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.32 (3H, t, $J=7$ Hz, $N_1CH_2C\underline{H}_3$), 1.40 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.50 (3H, s, CH_3), 4.47 (2H, q, $J=7$ Hz, $N_1C\underline{H}_2CH_3$), 4.50 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.48 (2H, d, $J=8$ Hz, aromatic H), 8.03 (2H, d, $J=8$ Hz, aromatic H), 8.50 (1H, d, $J_{H,F}=9$ Hz, C_5-H).

A similar treatment of **8b** and **16** with MCPBA gave **13b** (95%) and **21** (95%), respectively. Compound **13b**: Colorless prisms. EIMS *m/z*: 437 (M^+). IR cm^{-1}: 1725, 1715 (sh), 1640, 1600. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.40 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.50 (3H, s, CH_3), 4.3—4.7 (2H, m, $N_1CH_2C\underline{H}_2F$), 4.45 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.8—5.1 (2H, m, $N_1C\underline{H}_2CH_2F$), 7.42 (2H, d, $J=8$ Hz, aromatic H), 7.96 (2H, d, $J=8$ Hz, aromatic H), 8.42 (1H, d, $J_{H,F}=8$ Hz, C_5-H). Compound **21**: Colorless needles. IR cm^{-1}: 1730, 1640, 1600. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.39 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.49 (3H, s, CH_3), 4.45 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.0—7.1 (2H, m, aromatic H), 7.2—7.3 (4H, m, aromatic H), 7.72 (2H, d, $J=8$ Hz, aromatic H), 8.15 (1H, d, $J_{H,F}=8$ Hz, C_5-H).

Ethyl 2-[2-Chloro-5-fluoro-6-(*p*-tolylthio)nicotinoyl]- and 2-(2,6-Dichloro-5-fluoronicotinoyl)-2-[2-(*p*-fluorophenyl)hydrazono]acetates (15 and 20) A solution of $NaNO_2$ (560 mg, 8.1 mmol) in H_2O (2 ml) was added portionwise to a stirred suspension of *p*-fluoroaniline (840 mg, 7.5 mmol) in 20% HCl (3.8 ml, 22.5 mmol) below 0 °C. The resultant *p*-fluorobenzenediazonium solution was added at once at below 10 °C to a vigorously stirred mixture containing ethyl 2-[2-chloro-5-fluoro-6-(*p*-tolylthio)nicotinoyl]acetate (**14**)[1] (1.84 g, 5 mmol), NaOAc (2.0 g, 24.4 mmol), EtOH (10 ml), H_2O (10 ml), and $CHCl_3$ (10 ml). The mixture was stirred for 15 min, then kept at room temperature for an additional 30 min. After addition of water, the organic layer was separated and dried. The solvent was evaporated off to leave an oil, which was crystallized from EtOH–*n*-hexane to give **14** (2.2 g, 90%) as pale yellow needles, mp 154—155 °C. *Anal.* Calcd for $C_{23}H_{18}ClF_2N_3O_3S$: C, 56.39; H, 3.70; Cl, 7.24; F, 7.76; N, 8.58; S, 6.54. Found: C, 56.68; H, 3.75; Cl, 6.98; F, 7.53; N, 8.71; S, 6.82. IR cm^{-1}: 3120, 1675 (sh), 1665, 1610. ^{1}H-NMR (80 MHz, $CDCl_3$); a major geometrical isomer: 1.31 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.36 (3H, s, CH_3), 4.36 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 6.79 (2H, d, $J=8$ Hz, aromatic H), 7.20 (4H, d, $J=6$ Hz, aromatic H), 7.50 (2H, d, $J=8$ Hz, aromatic H), 8.03 (1H, d, $J_{H,F}=9$ Hz, C_5-H), 12.45 (1H, br s, NH, exchangeable with D_2O); a minor geometrical isomer: 1.10 (t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.10 (q, $J=7$ Hz, $C\underline{H}_2CH_3$), 8.00 (d, $J_{H,F}=9$ Hz, C_5-H), 14.05 (br s, NH, exchangeable with D_2O). The ratio of the two isomers was estimated to 8 : 1 on the basis of the signal intensity of the methyl protons of the ester groups.

A similar treatment of ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)acetate (**19**)[1] gave the hydrazone **20** (91%) as pale yellow needles, mp 110—111 °C (recrystallized from EtOH–*n*-hexane). *Anal.* Calcd for $C_{16}H_{11}Cl_2F_2N_3O_3$: C, 47.78; H, 2.76; Cl, 17.63; F, 9.45; N, 10.45. Found: C, 48.00; H, 3.02; Cl, 17.75; F, 9.61; N, 10.50. IR cm^{-1}: 3120, 1680, 1660, 1610. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.43 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.42 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.07 (4H, d, $J=6$ Hz, aromatic H), 7.55 (1H, d, $J_{H,F}=7$ Hz, C_4-H), 13.28 (1H, br s, NH, exchangeable with D_2O).

Ethyl 7-(*p*-Tolylthio)- and 7-Chloro-6-fluoro-1-(*p*-fluorophenyl)-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylates (16 and 21) (a) A mixture of **15** (1.64 g, 3.35 mmol), anhydrous K_2CO_3 (500 mg, 3.62 mmol) and CH_3CN (30 ml) was heated to reflux for 30 min and then concentrated to dryness *in vacuo*. After addition of water, the resulting crystals were collected by filtration and recrystallized from $CHCl_3$–EtOH to give 1.48 g (97%) of **16** as colorless needles. IR cm^{-1}: 1715, 1650, 1600. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.40 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.42 (3H, s, CH_3), 4.43 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 6.75—7.25 (8H, m, aromatic H), 8.10 (1H, d, $J_{H,F}=8$ Hz, C_5-H). A similar treatment of **20** gave **21** (92%).

(b) Potassium *tert*-butoxide (590 mg, 5.27 mmol) was added portionwise to a stirred solution of **20** (1.76 g, 4.38 mmol) in dry dioxane below 10 °C. The mixture was stirred at room temperature for an additional 1 h and then neutralized with 2 N AcOH. The solution was concentrated to dryness. After addition of water, the resulting crystals were collected by filtration and recrystallized from $CHCl_3$–EtOH to give 1.51 g (95%) of **21** as colorless needles. IR cm^{-1}: 1720, 1655, 1600. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.41 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.47 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.2—7.3 (2H, m, aromatic H), 7.5—7.6 (2H, m, aromatic H), 8.40 (1H, d, $J_{H,F}=7$ Hz, C_5-H). A similar treatment of **15** gave **16** (94%).

Ethyl 1,7-Disubstituted 6-Fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylates (22—24) Method A: A stirred solution of **13a** (2.10 g, 5 mmol) and anhydrous piperazine (1.72 g, 20 mmol) in $CHCl_3$ (30 ml) was heated to reflux for 15 min and then cooled. Acetic anhydride (6 ml) was added portionwise to the above mixture. The stirring was continued at room temperature for an additional 30 min. After addition of water, the organic layer was separated and dried. The solvent was evaporated off *in vacuo*, and the residue was chromatographed on silica gel with $CHCl_3$ as an eluent, followed by crystallization from EtOH to give **22a** (1.82 g, 93%) as yellow crystals. IR cm^{-1}: 1730, 1650, 1610. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.43 (3H, t, $J=7$ Hz, $N_1CH_2C\underline{H}_3$), 1.48 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.12 (3H, s, CH_3), 3.5—4.0 (8H, m, piperazinyl H), 4.47 (2H, q, $J=7$ Hz, $N_1C\underline{H}_2CH_3$), 4.60 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 8.11 (1H, d, $J_{H,F}=13$ Hz, C_5-H).

Method B: A mixture of **13b** (440 mg, 2 mmol) and *N*-acetylpiperazine (770 mg, 6 mmol) in CH_3CN (20 ml) was stirred at room temperature for 1 h and then concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–EtOH (10 : 1) as an eluent, followed by crystallization from EtOH–iso-Pr_2O to give **23a** (350 mg, 90%) as colorless needles. IR cm^{-1}: 1720, 1640, 1610. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.42 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.15 (3H, s, CH_3), 3.6—4.0 (8H, m, piperazinyl H), 4.45 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.5—4.7 (2H, m, $N_1CH_2C\underline{H}_2F$), 4.8—5.2 (2H, m, $N_1C\underline{H}_2CH_2F$), 8.03 (1H, d, $J_{H,F}=13$ Hz, C_5-H).

Method C: A mixture of **21** (430 mg, 1.17 mmol), *N*-acetylpiperazine (300 mg, 2 mmol) and Et_3N (1 ml) in CH_3CN (10 ml) was stirred at room temperature for 1 h and then concentrated to dryness *in vacuo*. After addition of water, the mixture was extracted with AcOEt. The extract was dried and the solvent was evaporated off. The residue was chromatographed on silica gel with $CHCl_3$ as an eluent, followed by crystallization from EtOH–iso-Pr_2O to give **24a** (440 mg, 82%) as colorless prisms. IR cm^{-1}: 1740, 1630. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.41 (3H, t, $J=7$ Hz, $N_1CH_2C\underline{H}_3$), 2.12 (3H, s, CH_3), 3.65 (8H, s, piperazinyl H), 4.45 (2H, q, $J=7$ Hz, $N_1C\underline{H}_2CH_3$), 7.05—7.60 (4H, m, aromatic H), 8.08 (1H, d, $J_{H,F}=13$ Hz, C_5-H).

1,7-Disubstituted 6-Fluoro-4(1*H*)-oxopyrido[2,3-*c*]pyridazine-3-carboxylic Acids (25—27) Method D: A stirred solution of **22a** (900 mg, 2.3 mmol) in 20% HCl (10 ml) was heated to reflux for 5 h and concentrated to dryness *in vacuo*. After addition of EtOH, the resulting crystals were collected by filtration and recrystallized from H_2O–EtOH to give 810 mg (98%) of **25b** as colorless crystals. IR cm^{-1}: 1730, 1615. ^{1}H-NMR (100 MHz, D_2O at 60 °C): 1.44 (3H, t, $J=7$ Hz, $N_1CH_2C\underline{H}_3$), 3.4—3.6 (4H, m, piperazinyl H), 4.1—4.4 (4H, m, piperazinyl H), 4.64 (2H, q, $J=7$ Hz, $N_1C\underline{H}_2CH_3$), 7.84 (1H, d, $J_{H,F}=13$ Hz, C_5-H).

Method E: A stirred mixture of **22d** (500 mg, 1.53 mmol), 1 N NaOH (3 ml) and water (3 ml) was heated at 70 °C for 15 min. The solution was acidified with 1 N AcOH. The resulting crystals were collected by filtration and recrystallized from EtOH to give 400 mg (73%) of **25d** as pale yellow needles. EIMS *m/z*: 306 (M^+), 262. IR cm^{-1}: 1740, 1625.

Method F: A stirred solution of **22f** (600 mg, 1.53 mmol) in 15% HCl (5 ml) was heated to reflux for 5 h and then concentrated to dryness *in vacuo*. After addition of water, the solution was treated with charcoal and then adjusted to pH 7—8 with 28% NH_4OH. The resulting crystals were collected by filtration and recrystallized from NH_4OH to give 380 mg (77%) of **25g** as yellow crystals. EIMS *m/z*: 321 (M^+), 277. IR cm^{-1}: 3500, 3200, 1660 (sh), 1620, 1590.

Biological Screenings According to the method of Goto *et al.*,[6] the MICs were determined by the twofold dilution method using Mueller-Hinton agar (pH 7.4, Difco); bacterial inocula contained approximately 10^6 colony-forming units and the bacterial growth was observed after a 20-h incubation at 37 °C.

Acknowledgements The authors wish to thank Dr. M. Hashimoto, Director of the Laboratories, for his encouragement throughout this work. Thanks are also due to Dr. S. Nakamura and his co-workers for the biological tests and members of the analytical section of the Laboratories for elemental analysis and spectral measurements.

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