Fluorocinnoline Derivatives. II.[1] Synthesis and Antibacterial Activity of Fluorinated 1-Alkyl-1,4-dihydro-4-oxocinnoline-3-carboxylic Acids

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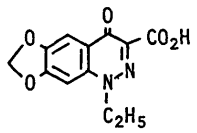
Chemical modification of cinoxacin was studied with the aim of improving its antibacterial activity and spectrum. Alkylation of ethyl 6,7,8-trifluoro- and 6,7-difluoro-4-hydroxycinnoline-3-carboxylates (1 and 7) with alkyl iodide or dialkyl sulfate gave ethyl 1-alkyl-6,7,8-trifluoro- and 6,7-difluoro-1,4-dihydro-4-oxocinnoline-3-carboxylates (2 and 8), together with the isomeric anhydro-bases 3 and 9 of 2-alkyl-3-ethoxycarbonyl-6,7,8-trifluoro- and 6,7-difluoro-4-hydroxycinnolinium hydroxides, respectively. Acid-catalyzed hydrolysis of the 1-alkyl derivatives 2 and 8 gave the corresponding carboxylic acids 4 and 10. The same treatment of 3 and 9, accompanied with decarboxylation of the inner salts 5 and 11, afforded the anhydro-bases 6 and 12 of 2-alkyl-4-hydroxycinnolinium hydroxides, respectively. Displacement reactions of 4 and 10 with nucleophiles such as amine, alkoxide and thiolate gave 7-substituted 1-alkyl-6,8-difluoro- and 6-fluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic acids (13 and 17—35). Antibacterial activities of these compounds were evaluated and compared with those of cinoxacin and norfloxacin. Some compounds showed a broader spectrum and more potent activity than cinoxacin, but were considerably inferior in activity to norfloxacin.

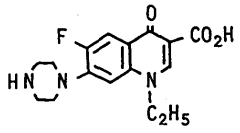
Keywords fluorinated 4-oxocinnoline-3-carboxylate; alkylation; 7-amino-4-oxocinnoline-3-carboxylic acid; cinoxacin; norfloxacin; antibacterial agent

Cinoxacin (I),[2] whose chemical structure is characterized by a 4-oxocinnoline-3-carboxylic acid moiety, shows good antibacterial activity mainly against gram-negative bacteria. Its activity, however, is considerably lower than that of a new class of quinolone antibacterials such as norfloxacin (II).[3] Probably for this reason, little attention has been paid to chemical modifications of cinoxacin aimed at improving its activity,[4] although almost two decades have passed since cinoxacin was discovered. An interest in finding more potent antibacterial agents in this class led us to examine the synthesis of 7-substituted 1-alkyl-6,8-difluoro- and 6-fluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic acids (III).

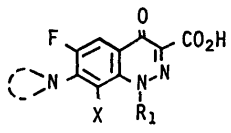
In the previous paper,[1] we reported a new method for the cinnoline ring construction permitting the synthesis of ethyl 6,7,8-trifluoro- and 6,7-difluoro-4-hydroxycinnoline-3-carboxylates (**1** and **7**). As an extension of that study, the alkylation of **1** and **7** was first examined; this might occur at either N-1 or N-2, or both. Several studies on the alkylation of 4-hydroxycinnolines have appeared thus far. 4-Hydroxycinnolines are alkylated partly at N-1, but mainly at N-2 in a protic solvent under basic conditions, whereas ethyl 4-hydroxycinnoline-3-carboxylates undergo the alkylation exclusively at N-1, probably owing to the steric factor of the C-3 carboxyl group.[5-7] Brundage and Lesher[8] reported that 6-bromo-1,4-dihydro-4-oxocinnoline-3-carboxylic acid, under basic conditions, was alkylated at both N-1 and N-2 to an almost equal extent and the resulting inner salt of the N-2 alkyl compound was readily decarboxylated to give the anhydro-base of 2-alkyl-6-bromo-4-hydroxycinnolinium hydroxide.



I: cinoxacin



II: norfloxacin



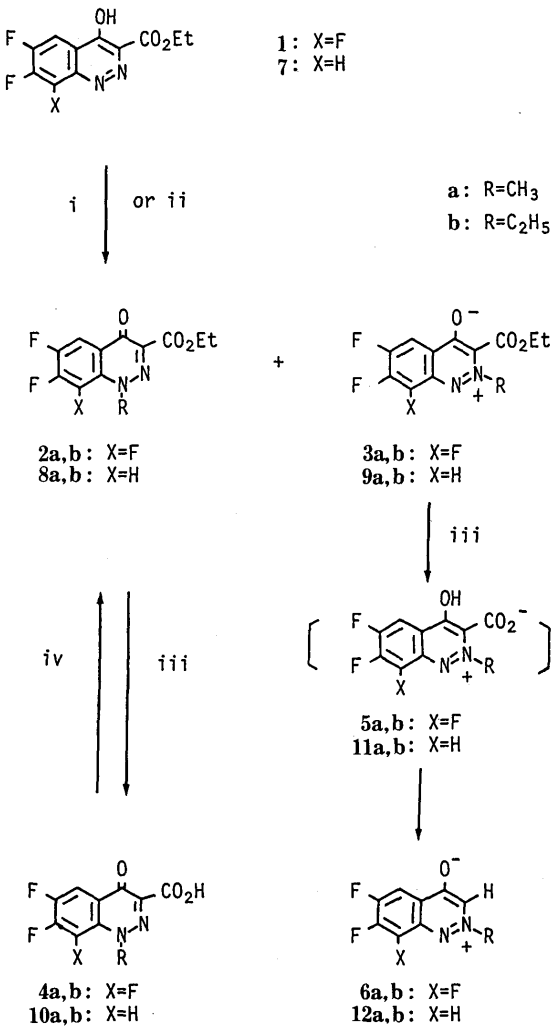
III: X = F, H

R_1 = alkyl

Chart 1

In our case, the alkylation of the esters **1** and **7** actually occurred at N-2 as well as at N-1. The alkylation of **1** and **7** with alkyl iodide (methyl and ethyl iodides) or dialkyl sulfate (dimethyl and diethyl sulfates) in the presence of anhydrous potassium carbonate in dimethylformamide gave a mixture of ethyl 1-alkyl-1,4-dihydro-4-oxocinnoline-carboxylates (**2** and **8**) and the anhydro-bases (**3** and **9**) of 2-alkyl-3-ethoxycarbonyl-4-hydroxycinnolinium hydroxides in good to excellent yields; in the reaction of **1** with methyl iodide, the ratio of the N-1 methyl compound **2a** and the isomeric anhydro-base **3a** was estimated to be approximately 3:1 on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) analysis. In a similar treatment with ethyl iodide, the ratio of **2b** and **3b** was approximately 1:1. An attempt to isolate each isomer, **2** and **3**, was unsuccessful. On the other hand, the mixture of **8** and **9** was separated by silica gel column chromatography into the N-1 alkyl compounds (**8a**, 62% and **8b**, 44% yields) and the isomeric anhydro-bases (**9a**, 9% and **9b**, 25% yields).

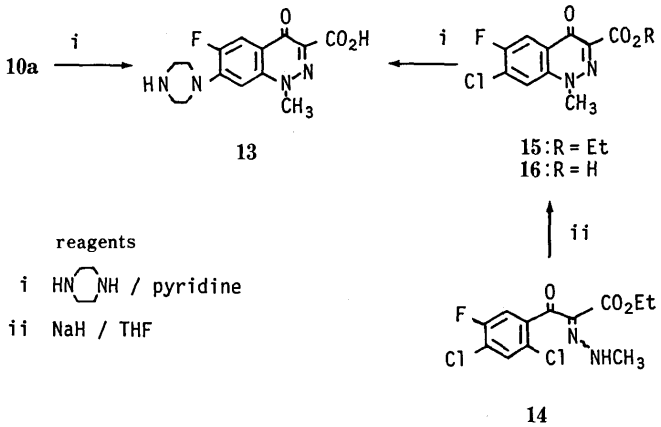
Acid-treatment of the mixture of **2** and **3** gave 1-alkyl-6,7-8-trifluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic acids (**4a**, 60% and **4b**, 45% yields) and the anhydro-bases (**6a**, 26% and **6b**, 34% yields) of 2-alkyl-6,7,8-trifluoro-4-hydroxycinnolinium hydroxides. Esterification of the carboxylic acids **4a** and **4b** regenerated **2a** and **2b**, respectively. A similar hydrolysis of **8** and **9** gave 1-alkyl-6,7-difluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic acid (**10**) and the anhydro-base (**12**) of 2-alkyl-6,7-difluoro-4-hydroxycin-



reagents

i MeI or EtI, K_2CO_3 / DMF
ii Me_2SO_4 or Et_2SO_4, K_2CO_3 / DMF
iii AcOH, H_2O, concd. H_2SO_4 (8:6:1, v/v)
iv $ClCO_2Et$, Et_3N / abs. EtOH

Chart 2



reagents

i HN⌒NH / pyridine
ii NaH / THF

Chart 3

nolinium hydroxide, respectively. The formation of the anhydro-bases **6** and **12** can be rationalized in terms of the hydrolysis of each ester group followed by decarboxylation

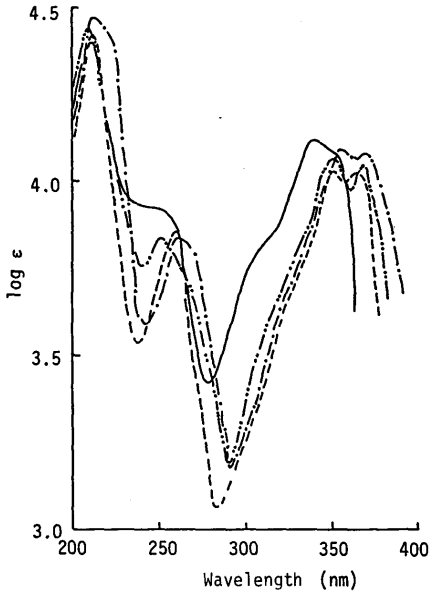


Fig. 1. Fluorocinnoline Derivatives (**6a**, **8a**, **9a** and **12a**)
6a, -·-·-·-; **8a**, ——; **9a**-·-·-; **12a**, - - - -.

of the intermediate inner salts **5** and **11**, respectively.

The structural assignments of **2** and **4** were based on the ^{1}H-NMR analysis (Table I); long-range couplings ($J_{H,F}$ = 8 Hz) of the methyl protons of **2a** and **4a** with the C-8 fluorine atom were observed. Similarly, in the ethyl protons of **2b** and **4b** the coupling constants ($J_{H,F}$) were observed as 3.5 Hz for methylene protons and 1.5 Hz for methyl protons. The structures of **8** and **10** were also assigned on the basis of their spectral data compared with those of **2** and **4**, respectively. The site of the alkyl groups of **10a** and, hence, of **8a** was confirmed by the conversion to the piperazinyl analogue **13**, which was alternatively derived from 7-chloro-6-fluoro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylic acid (**16**); compound **16** was prepared by an unambiguous route[1] starting from ethyl 3-(2,4-dichloro-5-fluorophenyl)-2-(2-methylhydrazono)-3-oxopropionate (**14**) *via* the cinnoline derivative **15** (Chart 3).

The structural assignment of the anhydro-bases **6** and **12** was based on their spectral data. Their ^{1}H-NMR spectra (Table I) showed loss of the ethyl proton signals of the ester groups with a concomitant appearance of a singlet signal assignable to the C-3 aromatic proton. No coupling of the alkyl protons of **6** with the C-8 fluorine atom was observed; this suggests that the site of the alkyl group of **6** is not at N-1, but is either at N-2 or at the C-4 hydroxy group. In order to solve this problem, we examined the ultraviolet (UV) spectrum of **6** (Table II). The spectrum shows four absorption maxima at about 209, 254 (with inflections at longer wavelengths of about 265 and 278, respectively), 352 and 368 nm along with a minimum at about 290 nm; this closely resembles the reported data[5d] for the anhydro-base of 2-alkyl-4-hydroxycinnolinium hydroxide, and differs clearly from the data for 4-alkoxycinnoline described by Ames *et al.*,[5d] who have extensively studied the tautomerism and the alkylation of various 4-hydroxycinnolines. Analogously, the UV spectrum of **12** closely resembles that of **6**. Therefore, we concluded that the alkyl groups of **6** and **12**, and hence their esters **3** and **9**, were located at N-2. The UV

TABLE I. ^{1}H-NMR Data for the Cinnoline Derivatives

Compd.	Chemical shifts in $CDCl_3$ δ (J=Hz)					
	3-H	5-H	8-H	NCH_3 or NCH_2CH_3	NCH_2CH_3	OCH_2CH_3
2a	—	8.03 (m, $J_{H,F}$=10, 8, 2)	—	4.38 (d, $J_{H,F}$=8)	—	1.45 4.48
2b	—	8.02 (m, $J_{H,F}$=9, 8, 2)	—	4.63 (dq, $J_{H,H}$=7, $J_{H,F}$=3.5)	1.55 (dt, $J_{H,H}$=7, $J_{H,F}$=1.5)	1.43 4.46
3a	—	7.88 (m, $J_{H,F}$=10, 8, 2)	—	4.40 s	—	1.47 4.55
3b	—	7.87 (m, $J_{H,F}$=9, 8, 2)	—	4.60 (q, $J_{H,H}$=7)	1.70 (t, $J_{H,H}$=7)	1.45 4.53
4a	—	8.10 (m, $J_{H,F}$=9, 8, 2)	—	4.57 (d, $J_{H,F}$=8)	—	13.75[a] brs
4b	—	8.25 (m, $J_{H,F}$=9, 8, 2)	—	4.90 (dq, $J_{H,H}$=7, $J_{H,F}$=3.5)	1.65 (dt, $J_{H,H}$=7, $J_{H,F}$=1.5)	14.80[a] brs
6a	7.83 s	7.85 (dd, $J_{H,F}$=10, 8, 2)	—	4.36 s	—	—
6b	7.85 s	7.88 (m, $J_{H,F}$=10, 8, 2)	—	4.50 (q, $J_{H,H}$=7)	1.73 (t, $J_{H,H}$=7)	—
8a	—	8.18 (dd, $J_{H,F}$=10, 9)	7.30 (dd, $J_{H,F}$=10, 6)	4.13 s	—	1.43 4.45
8b	—	8.20 (dd, $J_{H,F}$=10, 9)	7.33 (dd, $J_{H,F}$=11, 6)	4.47 (q, $J_{H,H}$=7)	1.57 (t, $J_{H,H}$=7)	1.43 4.47
9a	—	8.06 (dd, $J_{H,F}$=10, 8)	7.57 (dd, $J_{H,F}$=10, 7)	4.38 s	—	1.48 4.54
9b	—	8.06 (dd, $J_{H,F}$=10, 8)	7.61 (dd, $J_{H,F}$=10, 7)	4.55 (q, $J_{H,H}$=7)	1.67 (t, $J_{H,H}$=7)	1.45 4.53
10a	—	8.30 (dd, $J_{H,F}$=9, 8)	7.63 (dd, $J_{H,F}$=10, 6)	4.37 s	—	*ca.* 13.0[a] brs
10b	—	8.25 (dd, $J_{H,F}$=9, 8)	7.55 (dd, $J_{H,F}$=10, 6)	4.70 (q, $J_{H,H}$=7)	1.65 (t, $J_{H,H}$=7)	14.1[a] brs
12a	7.80 s	8.05 (dd, $J_{H,F}$=10, 8)	7.55 (dd, $J_{H,F}$=10, 7)	4.30 s	—	—
12b	7.83 s	8.05 (dd, $J_{H,F}$=10, 9)	7.57 (dd, $J_{H,F}$=11, 7)	4.44 (q, $J_{H,H}$=7)	1.70 (t, $J_{H,H}$=7)	—
16	—	8.20 (d, $J_{H,F}$=8)	7.85 (d, $J_{H,F}$=6)	4.40 s	—	14.0[a] brs

a) Chemical shifts of the carboxylic acid group are shown (exchangeable with D_2O).

TABLE II. UV Spectral Data (in Ethanol) for the Cinnoline Derivatives

Compd.	λ_{max} nm (log ε)	Compd.	λ_{max} nm (log ε)
1	208 (4.35) 253 (3.87) 333 (4.09)	**8a**	209 (4.40) 252 (3.93) 341 (4.13)
2a	211 (4.33) 240 (3.96) 340 (4.10)	**8b**	210 (4.40) 252 (3.94) 342 (4.13)
2b	211 (4.29) 240 (3.89) 341 (4.07)	**9a**	213 (4.47) 265 (3.83) 357 (4.10) 372 (4.08)
6a	209 (4.44) 254 (3.85) 352 (4.06) 368 (4.04)	**9b**	213 (4.48) 265 (3.83) 357 (4.08) 372 (4.07)
6b	209 (4.45) 253 (3.87) 351 (4.05) 368 (4.03)	**12a**	211 (4.42) 260 (3.86) 351 (4.03) 365 (4.01)
7	208 (4.39) 251 (3.94) 334 (4.10)	**12b**	211 (4.47) 260 (3.91) 351 (4.08) 365 (4.06)

spectra of **9a** and **12a** are shown in Fig. 1 as compared to those of **6a** and **8a**; there was a close resemblance in the UV spectrum between **9** and **12**, except for a slight bathochromic shift for the former, probably due to the ethoxycarbonyl group.

The cyclic amines, such as 3-aminopyrrolidine and piperazine, which have been widely accepted as effective substituents for improving the activity of quinolone antibacterials, were employed in the following displacement reaction of the acids **4** and **10**.

Regioselective nucleophilic displacement with the selected amine gave the desired 7-substituted 1-alkyl-6,8-difluoro- (**17**—**25**) and 6-fluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic acids (**29b**—**34b**) in high yields. The displacement position of these compounds was confirmed to be at C-7 by ^{1}H-NMR spectral analysis; the C-8 fluorine of **18b**, for example, couples to the protons of the N-1 ethyl group ($J_{H,F}$=1.5 and 4 Hz) and the C-5 proton shows a double-doublet signal ($J_{H,F}$=13.5 and 2 Hz) due to coupling to the C-6 and C-8 fluorines. The higher reactivity at C-7 is probably owing to an electron-drawing effect of the C-4 carbonyl group. Treatment of **4b** with sodium methoxide and sodium methylthiolate gave the 7-methoxy (**27b**) and 7-methylthio (**28b**) derivatives, respectively. The reaction of the C-7 chlorine of **16** with piperazine under reflux for 15 h in pyridine gave the 7-piperazinyl derivative **13**, but in unsatisfactory yield (39%); moreover, this was accompanied with the 6-piperazinyl derivative, the structure of which was confirmed by mass spectral analysis. The reaction of the C-7 fluorine of **10a**, however, proceeded smoothly and regioselectively under mild conditions to give **13** in 91% yield; this fact indicates that fluorine is superior to chlorine as a leaving group. All compounds gave satisfactory analytical and spectral data.

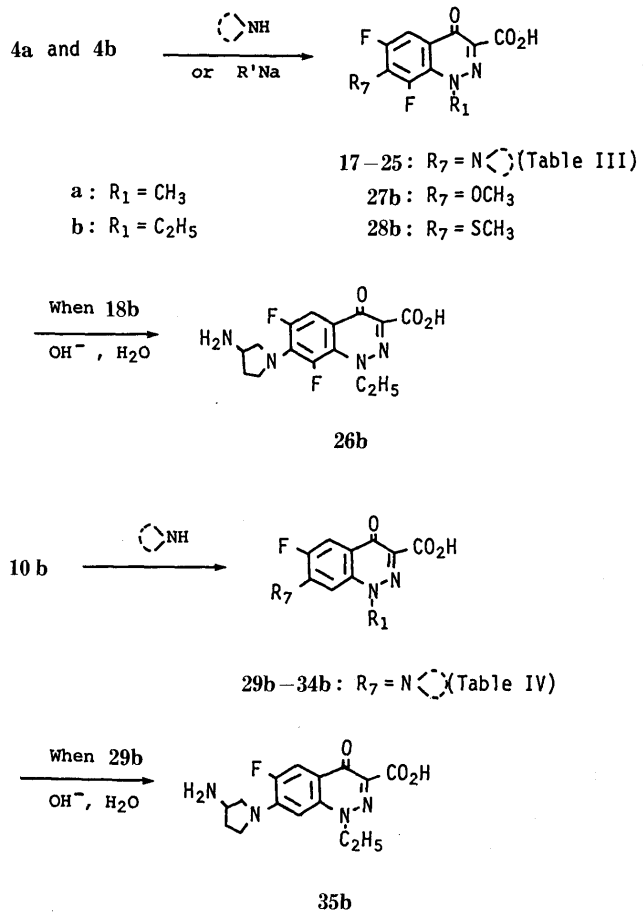


Chart 4

Biological Results and Discussion

In vitro antibacterial activity of the 6,8-difluoro- (**20b**—**26b**) and 6-fluoro-1-ethylcinnolone derivatives (**30b**—**35b**) against representative gram-positive (*Staphylococcus aureus* 209P JC-1, *Staphylococcus aureus* SMITH and *Streptococcus pyogenes* COOK) and gram-negative (*Escherichia coli* NIHJ JC-2, *Klebsiella pneumoniae* PCI 602, *Serratia marcescens* IFO 3736 and *Pseudomonas aeruginosa* IFO 3445) bacteria is given in Table V, which includes data for cinoxacin and norfloxacin for comparison.

There is no striking difference in antibacterial activity between the 6-fluoro and 6,8-difluoro analogues. In general, those compounds are more highly active than cinoxacin against gram-positive *S. aureus*, whereas the piperazine-substituted analogues **23b**, **24b**, **33b** and **34b** have the same level of activity as cinoxacin against gram-negative *E. coli* and *K. pneumoniae*; no noticeable enhancement of activity against *P. aeruginosa* was found.

Comparison of the activity between norfloxacin and its aza-analogue **33b** indicates that introduction of an additional nitrogen atom at position 2 of the quinolone ring causes a considerable decrease in activity. Among the cinnolone derivatives tested, no compound superior to norfloxacin in activity was found.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco A-102 spectrometers (KBr tablet). ^{1}H-NMR spectra were taken at 80 MHz with a Varian FT-80A spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet,

TABLE III. 7-Substituted 1-Alkyl-6,8-difluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic Acids (**17**—**28**)

Compd.	R_1	R_7	mp (°C) (Recryst. solv.)	Method[a]	Yield[b] (%)	Formula	Analysis (%) Calcd (Found)			
							C	H	F	N
17b	Et	Me_2N–	190—191 (EtOH–iso-Pr_2O)	A	90.8	$C_{13}H_{13}F_2N_3O_3$	52.53 (52.57)	4.41 4.36	12.78 13.05	14.14 14.27)
18b	Et	AcHN–	215—216 ($CHCl_3$–EtOH)	B	75.9	$C_{17}H_{18}F_2N_4O_4$	53.68 (53.43)	4.77 4.81	9.99 10.02	14.73 14.62)
19b	Et	AcN–	231—232 (EtOH)	B	72.1	$C_{17}H_{18}F_2N_4O_4$	53.68 (53.78)	4.77 4.87	9.99 10.00	14.73 14.57)
20a	Me		234—235 (EtOH)	C	81.2	$C_{14}H_{13}F_2N_3O_3$	54.37 (54.29)	4.24 4.16	12.29 11.99	13.59 13.34)
20b	Et		209—210 (EtOH–iso-Pr_2O)	C	75.6	$C_{15}H_{15}F_2N_3O_3$	55.53 (55.43)	4.68 4.88	11.75 12.01	13.00 12.80)
21b	Et	HO–	225—226 ($CHCl_3$–EtOH)	D	75.5	$C_{15}H_{15}F_2N_3O_4$	53.10 (52.79)	4.46 4.63	11.20 11.38	12.38 12.33)
22b	Et	H_2N–	250—251 (dec.) (NH_4OH)	E	81.4	$C_{16}H_{18}F_2N_4O_3$	54.54 (54.25)	5.15 5.22	10.78 10.56	15.90 15.63)
23b	Et	HN–	276—277 (dec.) (NH_4OH)	E	76.8	$C_{15}H_{16}F_2N_4O_3 \cdot 1/2\,H_2O$	51.90 (51.66)	4.94 4.86	10.89 11.05	16.14 16.18)
24b	Et	CH_3N–	198—199	E	57.9	$C_{16}H_{18}F_2N_4O_3 \cdot H_2O$	51.91 (51.89)	5.45 5.23	10.21 10.21	15.14 15.07)
25b	Et	O–	201—202 (EtOH)	C	64.9	$C_{15}H_{15}F_2N_3O_4$	53.18 (53.27)	4.46 4.41	11.20 11.28	12.38 12.41)
26b	Et	H_2N–	267—268 (dec.)	F	85.1	$C_{15}H_{16}F_2N_4O_3 \cdot 1/4\,H_2O$	52.58 (52.62)	4.85 4.93	11.03 10.86	16.35 16.21)
27b	Et	CH_3O–	156—157 (MeOH–iso-Pr_2O)	G	95.8	$C_{12}H_{10}F_2N_2O_4$	50.71 (51.00)	3.55 3.59	13.37 13.36	9.86 9.96)
28b	Et	CH_3S–	161—162 (EtOH–iso-Pr_2O)	H	84.8	$C_{12}H_{10}F_2N_2SO_3 \cdot 6/5\,H_2O$[c]	44.80 (44.96)	3.89 3.61	11.75 11.73	8.71 8.59)

a) See Experimental. *b*) The yield was not optimized. *c*) Hygroscopic crystals. Calcd (Found) %: S, 9.97 (10.06).

TABLE IV. 7-Substituted 1-Alkyl-6-fluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic Acids (**29b**—**35b**)

Compd.	R_1	R_7	mp (°C) (Recryst. solv.)	Method[a]	Yield[b] (%)	Formula	Analysis (%) Calcd (Found) C	H	F	N
29b	Et	AcHN-piperazinyl	279—280 (dec.) ($CHCl_3$–EtOH)	B	89.7	$C_{17}H_{19}FN_4O_4$	56.35 (56.12)	5.29 (5.11)	5.24 (5.25)	15.46 (15.62)
30b	Et	pyrrolidinyl	>300 ($CHCl_3$–EtOH)	C	96.2	$C_{15}H_{16}FN_3O_3$	59.01 (58.80)	5.28 (5.50)	6.22 (6.27)	13.76 (13.80)
31b	Et	HO-pyrrolidinyl	293—295 (dec.) ($CHCl_3$–EtOH)	D	94.9	$C_{15}H_{16}FN_3O_4$	56.07 (56.37)	5.02 (5.03)	5.91 (6.07)	13.08 (13.12)
32b	Et	H_2N-pyrrolidinyl	201—203 (dec.) (NH_4OH)	D	91.3	$C_{16}H_{19}FN_4O_3 \cdot 2H_2O$	51.89 (51.82)	6.26 (6.36)	5.13 (5.31)	15.13 (15.02)
33b	Et	HN-piperazinyl	267—269 (dec.)[c] (NH_4OH)	E	72.8	$C_{15}H_{17}FN_4O_3 \cdot 2.5H_2O$	49.31 (49.43)	6.07 (5.93)	5.20 (5.35)	15.33 (15.38)
34b	Et	CH_3N-piperazinyl	210—211 (dec.)[d] (EtOH)	E	97.5	$C_{16}H_{19}FN_4O_3$	57.48 (57.47)	5.73 (5.70)	5.68 (5.70)	16.76 (16.68)
35b	Et	H_2N-pyrrolidinyl	251—253 (dec.) (NH_4OH)	F	95.6	$C_{15}H_{17}FN_4O_3$	56.24 (56.03)	5.35 (5.38)	5.93 (5.83)	17.49 (17.26)

a) See Experimental. *b*) The yield was not optimized. *c*) Lit.[4b] mp 250—253 °C (dec.). *d*) Lit.[4b] mp 190—192 °C (dec.).

TABLE V. *In Vitro* Antibacterial Activity of 7-Substituted 1-Ethyl-6,8-difluoro- and 6-Fluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic Acids

Compd.		Minimum inhibitory concentrations[a] (μg/ml) *Sa*[b]	*Sb*[c]	*Sp*[d]	*Ec*[e]	*Kp*[f]	*Sm*[g]	*Pa*[h]
20b	N-	1.56	0.78	25	6.25	1.56	25	100
30b	N-	1.56	1.56	50	6.25	0.78	25	>100
21b	HO-N-	25	12.5	100	6.25	1.56	50	>100
31b	HO-N-	25	12.5	>100	6.25	1.56	50	>100
26b	H_2N-N-	6.25	25	50	6.25	3.13	6.25	>100
35b	H_2N-N-	12.5	25	>100	6.25	6.25	6.25	>100
22b	H_2N-N-	3.13	12.5	12.5	25	12.5	100	>100
32b	H_2N-N-	6.25	12.5	>100	50	25	100	>100
23b	HN-N-	50	>100	>100	12.5	6.25	12.5	100
33b	HN-N-	12.5	100	>100	3.13	6.25	6.25	100
24b	CH_3N-N-	25	25	>100	3.13	1.56	12.5	100
34b	CH_3N-N-	6.25	12.5	100	1.56	1.56	6.25	>100
Cinoxacin		>100	25	>100	1.56	1.56	12.5	>100
Norfloxacin		0.39	1.56	6.25	0.1	0.39	—	0.78

a) See Experimental. *b*) *Staphylococcus aureus* 209P JC-1. *c*) *Staphylococcus aureus* SMITH. *d*) *Streptococcus pyogenes* COOK. *e*) *Escherichia coli* NIHJ JC-2. *f*) *Klebsiella pneumoniae* PCI 602. *g*) *Serratia marcescens* IFO 3736. *h*) *Pseudomonas aeruginosa* IFO 3445.

q=quartet, m=multiplet, dd=double doublet, dt=double triplet and dq=double quartet. Electron impact mass spectra (EIMS) were recorded on a Hitachi RMU-6 or JEOL JMSD-300 spectrometer. UV spectra were recorded on a Shimadzu UV-260 UV-visible recording spectrophotometer in EtOH.

Methylation of Ethyl 6,7,8-Trifluoro-4-hydroxycinnoline-3-carboxylate (1) with Methyl Iodide A mixture of **1** (2.5 g, 9.2 mmol), anhydrous K_2CO_3 (1.9 g, 13.8 mmol) and *N*,*N*-dimethylformamide (DMF) (25 ml) was heated at 60—65 °C for 20 min with stirring. Methyl iodide (3.95 g, 27.8 mmol) was added to the mixture; the solution was heated at the same temperature for an additional 1 h and then concentrated to dryness *in vacuo*. The residue was dissolved in toluene. The solution was washed with H_2O and dried over Mg_2SO_4. The solvent was evaporated off. The residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give a mixture (2.23 g, 84.8%) of ethyl 6,7,8-trifluoro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylate (**2a**) and the anhydro-base of 3-ethoxycarbonyl-6,7,8-trifluoro-4-hydroxy-2-methylcinnolinium hydroxide (**3a**) as colorless prisms. The ratio of **2a** and **3a** was estimated to be approximately 3:1 from the signal intensity of the methyl protons (**2a**: $\delta=1.42$; **3a**: $\delta=1.47$) of the ethoxycarbonyl group in the ^{1}H-NMR spectra of the mixture.

Ethylation of Ethyl 6,7,8-Trifluoro-4-hydroxycinnoline-3-carboxylate (1) with Ethyl Iodide In a similar manner to that described for the methylation, treatment of **1** (7.5 g, 27.6 mmol) with ethyl iodide (12.93 g, 82.8 mmol) gave a mixture (7.08 g, 85.5%) of ethyl 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxocinnoline-3-carboxylate (**2b**) and the anhydro-base of ethyl 3-ethoxycarbonyl-2-ethyl-6,7,8-trifluoro-4-hydroxycinnolinium hydroxide (**3b**) as colorless prisms. The ratio of the two isomers was estimated to be approximately 1:1 by ^{1}H-NMR measurement.

Hydrolysis of 2 and 3 (a) A *ca.* 3:1 mixture of **2a** and **3a** (2.10 g, 7.34 mmol) in a AcOH–H_2O–concentrated H_2SO_4 (8:6:1, v/v) mixture (30 ml) was gently refluxed for 5.5 h. The solution was concentrated to about one-third volume and then diluted with ice-water. After being alkalized with 2 N NaOH, the mixture was extracted with AcOEt. The extract was dried over Na_2SO_4 and concentrated to dryness *in vacuo*. Iso-Pr_2O was added to the residue; the resulting crystals were collected by filtration to give the anhydro-base of 6,7,8-trifluoro-4-hydroxy-2-methylcinnolinium hydroxide (**6a**) (410 mg, 26.1%) as colorless needles, mp 188—189 °C (EtOH–iso-Pr_2O). *Anal.* Calcd for $C_9H_5F_3N_2O$: C, 50.48; H, 2.35; F, 26.61; N, 13.08. Found: C, 50.40; H, 2.23; F, 26. 73; N, 12.94. EIMS *m/z*: 214 (M^+), 186. IR cm^{-1}: 1615, 1570.

The alkaline aqueous layer was adjusted to pH 2—3 with 2 N HCl and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The residue was crystallized from iso-Pr_2O. Recrystallization from EtOH–iso-Pr_2O gave 6,7,8-trifluoro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylic acid (**4a**) (1.14 g, 60.3%) as pale yellow prisms, mp 178—179 °C. *Anal.* Calcd for $C_{10}H_5F_3N_2O_3$: C, 46.53; H, 1.95; H, 22.08; N, 10.85. Found: C, 46.60; H, 2.20; F, 22.30; N, 10.81. EIMS *m/z*: 258 (M^+), 214. IR cm^{-1}: 1740, 1600, 1580.

(b) In a similar manner to procedure (a) described above, a 1:1 mixture of **2b** and **3b** (6.8 g, 22.7 mmol) was hydrolyzed to give 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic acid (**4b**) (2.75 g, 44.6%) and the anhydro-base of ethyl 2-ethyl-6,7,8-trifluoro-4-hydroxycinnolinium hydroxide (**6b**) (1.8 g, 34%), respectively. Compound **4b**: pale yellow prisms, mp 140—141 °C (EtOH–iso-Pr_2O). *Anal.* Calcd for $C_{11}H_7F_3N_2O_3$: C, 48.54; H, 2.59; F, 20.94; N, 10.29. Found: C, 48.83; H, 2.77; F, 21.01; N, 10.42. EIMS *m/z*: 272 (M^+), 228. IR cm^{-1}: 1765, 1640, 1620, 1590. Compound **6b**: colorless needles, mp 185—186 °C (AcOEt–iso-Pr_2O). *Anal.* Calcd for $C_{10}H_7F_3N_2O$: C, 52.64; H, 3.09; F, 24.98; N, 12.28. Found: C, 52.86; H, 3.42; F, 25.27; N, 12.29. EIMS *m/z*: 228 (M^+). IR cm^{-1}: 1615, 1570.

Esterification of 4 (a) Ethyl chloroformate (220 mg, 2.03 mmol) was added at −10—−5 °C to a stirred solution of **4a** (250 mg, 0.97 mmol) and Et_3N (200 mg, 2 mmol) in $CHCl_3$ (8 ml). After 20 min of stirring, dry EtOH (15 ml) was added to the solution; the whole was stirred at room temperature for 20 min and then refluxed gently for an additional 30 min. The solution was concentrated to dryness *in vacuo*. The solid residue was washed with H_2O and collected by filtration to give **2a** (230 mg, 83%) as colorless scales, mp 101—102 °C (iso-Pr_2O–hexane). *Anal.* Calcd for $C_{12}H_9F_3N_2O_3$: C, 50.36; H, 3.17; F, 19.91; N, 9.79. Found: C, 50.40; H, 3.26; F, 19.84; N, 9.75. EIMS *m/z*: 286 (M^+), 271, 241, 214. IR cm^{-1}:

1720, 1620, 1590.

(b) In a similar manner, **4b** was esterified with EtOH to give **2b** (450 mg, 81.7%) as colorless needles, mp 95—95.5 °C (iso-Pr_2O–hexane). *Anal.* Calcd for $C_{13}H_{11}F_3N_2O_3$: C, 52.01; H, 3.69; F, 18.98; N, 9.33. Found: C, 52.12; H, 3.80; F, 18.82; N, 9.34. EIMS *m/z*: 300 (M^+). IR cm^{-1}: 1720, 1620, 1590.

Methylation of Ethyl 6,7-Difluoro-4-hydroxycinnoline-3-carboxylate (7) with Dimethyl Sulfate A mixture of **7** (762 mg, 3 mmol), anhydrous K_2CO_3 (621 mg, 4.5 mmol) and DMF (20 ml) was heated at 80—90 °C for 30 min with stirring. Dimethyl sulfate (570 mg, 4.52 mmol) was added, and the mixture was heated for an additional 30 min and then concentrated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$. The solution was washed with H_2O and dried over Na_2SO_4. The solvent was evaporated off. The residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give ethyl 6,7-difluoro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylate (**8a**) and the anhydro-base of 3-ethoxycarbonyl-6,7-difluoro-4-hydroxy-2-methylcinnolinium hydroxide (**9a**). Compound **8a** (496 mg, 61.7%): colorless needles, mp 180.5—181 °C (EtOH–iso-Pr_2O). *Anal.* Calcd for $C_{12}H_{10}F_2N_2O_3$: C, 53.74; H, 3.76; F, 14.17; N, 10.44. Found: C, 53.64; H, 3.79; F, 14.23; N, 10.50. EIMS *m/z*: 268 (M^+), 223, 196, 195, 169. IR cm^{-1}: 1720, 1615, 1590. Compound **9a** (69 mg, 8.6%): colorless prisms, mp 117—118 °C (EtOH–iso-Pr_2O). *Anal.* Calcd for $C_{12}H_{10}F_2N_2O_3$: C, 53.74; H, 3.76; F, 14.17; N, 10.44. Found: C, 53.74; H, 3.63; F, 14.20; N, 10.19. EIMS *m/z*: 268 (M^+), 223, 196, 168. IR cm^{-1}: 1715, 1605.

Ethylation of Ethyl 6,7-Difluoro-4-hydroxycinnoline-3-carboxylate (7) with Diethyl Sulfate In a similar manner to that described for the methylation of **7**, treatment of **7** (695 mg, 2.74 mmol) with diethyl sulfate gave a mixture of products. The mixture was chromatographed on silica gel with $CHCl_3$–iso-Pr_2O (1 : 5) as an eluent to give ethyl 1-ethyl-6,7-difluoro-1,4-dihydro-4-oxocinnoline-3-carboxylate (**8b**) (337 mg, 43.6%) and the anhydro-base of 3-ethoxycarbonyl-2-ethyl-6,7-difluoro-4-hydroxycinnolinium hydroxide (**9b**) (189 mg, 24.5%). Compound **8b**: mp 146—147 °C (iso-Pr_2O). *Anal.* Calcd for $C_{13}H_{12}F_2N_2O_3$: C, 55.32; H, 4.29; F, 13.46; N, 9.93. Found: C, 55.39; H, 4.49; F, 13.39; N, 9.88. EIMS *m/z*: 282 (M^+), 237, 210, 182. IR cm^{-1}: 1715, 1610, 1590. Compound **9b**: mp 117—118 °C (iso-Pr_2O). *Anal.* Calcd for $C_{13}H_{12}F_2N_2O_3$: C, 55.32; H, 4.29; F, 13.46; N, 9.93. Found: C, 55.62; H, 4.15; F, 13.51; N, 9.64. EIMS *m/z*: 282 (M^+), 237, 210, 182. IR cm^{-1}: 1725, 1605.

Hydrolysis of 8 (a) A stirred mixture of **8a** (536 mg, 2 mmol) and AcOH–H_2O–concentrated H_2SO_4 (8 : 6 : 1, v/v) (15 ml) was heated at 95—100 °C for 2 h. The solution was concentrated, and the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and the solvent was evaporated off. The solid residue was recrystallized from $CHCl_3$–EtOH to give 6,7-difluoro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylic acid (**10a**) (461 mg, 96%) as colorless prisms, mp 228—229 °C. *Anal.* Calcd for $C_{10}H_6F_2N_2O_3$: C, 50.01; H, 2.52; F, 15.82; N, 11.66. Found: C, 50.07; H, 2.43; F, 15.64; N, 11.70. EIMS *m/z*: 240 (M^+), 196, 169, 140.

(b) A similar treatment of **8b** (564 mg, 2 mmol) gave 1-ethyl-6,7-difluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic acid (**10b**) (428 mg, 84.3%) as pale yellow prisms, mp 193—194 °C (EtOH). *Anal.* Calcd for $C_{11}H_8F_2N_2O_3$: C, 51.98; H, 3.17; F, 14.95; N, 11.02. Found: C, 51.98; H, 3.05; F, 15.17; N, 10.73. EIMS *m/z*: 254 (M^+), 210, 182.

The Anhydro-base of 2-Alkyl-6,7-difluoro-4-hydroxycinnolinium Hydroxide (12) (a) A mixture of **9a** (536 mg, 2 mmol) and AcOH–H_2O–concentrated H_2SO_4 (8 : 6 : 1, v/v) (15 ml) was heated at 90—95 °C for 1 h. The solution was concentrated to about one-third of the initial volume and then diluted with H_2O. The solution was adjusted to pH 8 with 2 N NaOH and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and the $CHCl_3$ was evaporated off. The solid residue was recrystallized from EtOH–iso-Pr_2O to give the anhydro-base of 6,7-difluoro-4-hydroxy-2-methylcinnolinium hydroxide (**12a**) (362 mg, 92.3%) as colorless crystals, mp 218—219 °C. *Anal.* Calcd for $C_9H_6F_2N_2O$: C, 55.11; H, 3.08; F, 19.37; N, 14.28. Found: C, 54.81; H, 2.96; F, 19.21; N, 13.98. EIMS *m/z*: 196 (M^+), 168. IR cm^{-1}: 1595, 1575.

(b) A similar treatment of **9b** (282 mg, 1 mmol) gave the anhydro-base of 2-ethyl-6,7-difluoro-4-hydroxycinnolinium hydroxide (**12b**) (184 mg, 87.6%) as colorless needles, mp 186—187 °C (iso-Pr_2O–hexane). *Anal.* Calcd for $C_{10}H_8F_2N_2O$: C, 57.15; H, 3.84; F, 18.08; N, 13.33. Found: C, 57.27; H, 3.79; F, 17.99; N, 13.44. EIMS *m/z*: 210 (M^+), 182. IR cm^{-1}: 1605.

6-Fluoro-1,4-dihydro-1-methyl-4-oxo-7-(1-piperazinyl)cinnoline-3-carboxylic Acid (13) (a) A stirred mixture of **4a** (170 mg, 0.71 mmol), anhydrous piperazine (300 mg, 3.49 mmol) and pyridine (5 ml) was heated at 80—90 °C for 45 min. The solution was concentrated to dryness *in vacuo*. The residue was dissolved in H_2O. The solution was treated with charcoal and adjusted to pH 8 with 10% AcOH. The resulting solid was collected by filtration, washed successively with H_2O and MeOH and recrystallized from diluted NH_4OH to give **13** (198 mg, 91.2%) as a pale yellow powder, mp > 300 °C. *Anal.* Calcd for $C_{14}H_{15}FN_4O_3$: C, 54.90; H, 4.94; F, 6.20; N, 18.29. Found: C, 54.71; H, 4.97; F, 6.13; N, 18.10. ^{1}H-NMR (NaOD/D_2O): 2.8—3.1 (4H, m, piperazinyl), 3.1—3.35 (4H, m, piperazinyl), 4.10 (3H, s, N-CH_3), 6.95 (1H, d, $J_{H,F}$ = 7 Hz, C_8-H), 7.75 (1H, d, $J_{H,F}$ = 13.5 Hz, C_5-H). IR cm^{-1}: 1600.

(b) A stirred mixture of **16** (65 mg, 0.25 mmol), anhydrous piperazine (162 mg, 1.88 mmol) and pyridine (3 ml) was heated at 110—120 °C for 15 h. The mixture was concentrated to dryness *in vacuo*. The residue was dissolved in aqueous AcOH. The solution was treated with charcoal and adjusted to pH 8 with diluted NH_4OH. The resulting precipitates were collected by filtration and washed with H_2O to give a mixture (51 mg) of **13** and 7-chloro-1,4-dihydro-1-methyl-4-oxo-6-(1-piperazinyl)cinnoline-3-carboxylic acid. Fractional recrystallization of the mixture from $CHCl_3$–EtOH gave an analytically pure sample of **13** (32 mg, 39.3%) as a pale yellow powder, mp > 300 °C. This sample was identical in all respects with that obtained by procedure (a). Acetylation of **13** with Ac_2O in $CHCl_3$ gave 7-(4-acetyl-1-piperazinyl)-6-fluoro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylic acid as a light yellow powder, mp 256—258 °C (dec.) ($CHCl_3$–EtOH). *Anal.* Calcd for $C_{16}H_{17}FN_4O_4 \cdot 1/4H_2O$: C, 54.47; H, 5.00; F, 5.38; N, 15.88. Found: C, 54.35; H, 4.79; F, 5.69; N, 15.85. EIMS *m/z*: 348 (M^+). ^{1}H-NMR (NaOD/D_2O): 2.20 (3H, s, $COCH_3$), 3.2—3.4 (4H, m, piperazinyl), 3.7—3.85 (4H, m, piperazinyl), 4.08 (3H, s, NCH_3), 6.83 (1H, d, $J_{H,F}$ = 8 Hz, C_8-H), 7.68 (1H, d, $J_{H,F}$ = 13.5 Hz, C_5-H). IR cm^{-1}: *ca.* 3450, 1730, 1650, 1620.

7-Chloro-6-fluoro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylic Acid (16) According to the reported method,[1] the cyclization of ethyl 3-(2,4-dichloro-5-fluorophenyl)-2-(2-methylhydrazono)-3-oxopropionate (**14**) with sodium hydride in dry dioxane gave ethyl 7-chloro-6-fluoro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylate (**15**). Hydrolysis of **15** (458 mg, 1.61 mmol), in a similar manner to that described for **8a**, gave **16** (444 mg, 82.6%) as colorless needles, mp 214—215 °C (EtOH). *Anal.* Calcd for $C_{10}H_6ClFN_2O_3$: C, 46.80; H, 2.36; Cl, 13.82; F, 7.40; N, 10.92. Found: C, 46.78; H, 2.34; Cl, 13.81; F, 7.27; N, 10.65. IR cm^{-1}: 1725, 1605, 1580. EIMS *m/z*: 256 (M^+), 212, 185, 157.

7-Substituted 1-Alkyl-6,8-difluoro- (17—28) and 6-fluoro-1,4-dihydro-4-oxocinnoline-3-carboxylic Acids (29b—35b) (Tables III—V) Method A: A mixture of **4b** (200 mg, 0.74 mmol), *ca.* 40% (w/w) aqueous dimethylamine (1 ml) and CH_3CN (5 ml) was heated at 80 °C in a sealed tube. The mixture was concentrated to dryness *in vacuo*. The residue was dissolved in H_2O. The solution was adjusted to pH 3—4 with 2 N HCl. The resulting precipitate was collected by filtration and recrystallized from EtOH to give **17b** (198 mg, 90.8%) as light yellow prisms. ^{1}H-NMR ($CDCl_3$): 1.58 (3H, dt, $J_{H,H}$ = 7 Hz, $J_{H,F}$ = 1.5 Hz, $NCH_2C\underline{H}_3$), 3.16 (6H, dd, $J_{H,F}$ = 2.8, 3.4 Hz, NCH_3), 4.83 (2H, dq, $J_{H,H}$ = 7 Hz, $J_{H,F}$ = 4 Hz, $NC\underline{H}_2CH_3$), 7.87 (1H, dd, $J_{H,F}$ = 12, 2 Hz, C_5-H).

Method B: A stirred mixture of **4b** (630 mg, 2.32 mmol), (±)-3-acetylaminopyrrolidine (450 mg, 3.52 mmol) and pyridine (15 ml) was heated at 85—90 °C for 1 h. The solution was concentrated to dryness *in vacuo*. The residue was acidified with aqueous AcOH. The resulting solid was collected by filtration, washed with H_2O and recrystallized from $CHCl_3$–EtOH to give **18b** (669 mg, 75.9%) as pale yellow needles. ^{1}H-NMR ($CDCl_3$): 1.51 (3H, dt, $J_{H,H}$ = 7 Hz, $J_{H,F}$ = 1.5 Hz, $NCH_2C\underline{H}_3$), 2.05 (3H, s, $COCH_3$), 2.1—2.3 (2H, m), 3.6—4.3 (4H, m), 4.65 (2H, dq, $J_{H,H}$ = 7 Hz, $J_{H,F}$ = 4 Hz, $NC\underline{H}_2CH_3$), 4.5—4.8 (1H, m), 7.05 (1H, d, J = 7 Hz, NH), 7.60 (1H, dd, $J_{H,F}$ = 13.5, 2 Hz, C_5-H), 15.07 (1H, br s, exchangeable with D_2O, CO_2H).

Method C: A mixture of **4b** (200 mg, 0.74 mmol) and an excess of pyrrolidine (263 mg, 3.7 mmol) in CH_3CN (6 ml) was refluxed for 10 min and then concentrated to dryness. The residue was recrystallized from EtOH–iso-Pr_2O to give **20b** (180 mg, 75.6%) as yellow prisms. ^{1}H-NMR ($CDCl_3$): 1.55 (3H, dt, $J_{H,H}$ = 7 Hz, $J_{H,F}$ = 1.5 Hz, $NCH_2C\underline{H}_3$), 1.7—2.2 (4H, m), 3.6—4.0 (4H, m), 4.78 (2H, dq, $J_{H,H}$ = 7 Hz, $J_{H,F}$ = 4 Hz, $NC\underline{H}_2CH_3$), 7.76 (1H, dd, $J_{H,F}$ = 13, 2 Hz, C_5-H), 14.78 (1H, br s, exchangeable with D_2O, CO_2H).

Method D: A mixture of **4b** (272 mg, 1 mmol) and an excess of (±)-3-hydroxypyrrolidine (435 mg, 5 mmol) in CH_3CN (5 ml)–EtOH (5 ml) was refluxed for 30 min. A similar treatment to that in method C gave **21b** (256 mg, 75.5%) as pale yellow prisms.

Method E: A stirred mixture of **10b** (110 mg, 0.43 mmol), (±)-3-aminomethylpyrrolidine (180 mg, 1.8 mmol) and pyridine (5 ml) was heated at 85—90 °C for 1 h. The solution was concentrated to dryness *in*

vacuo. The residue was dissolved in H_2O. The solution was treated with charcoal, adjusted to pH 8 with 10% AcOH and concentrated. The resulting solid was collected by filtration, washed with H_2O and recrystallized from diluted NH_4OH to give **32b** (132 mg, 82.5%) as a pale yellow powder. EIMS *m/z*: 334 (M^+), 317. ^{1}H-NMR (NaOD): 1.35 (3H, t, J=7 Hz, $NCH_2C\underline{H}_3$), 1.4—1.7 (1H, m), 1.8—2.5 (2H, m), 2.8—3.6 (4H, m), 2.75 (2H, d, J=6 Hz, $C\underline{H}_2NH_2$), 4.25 (2H, q, J=7 Hz, $NC\underline{H}_2CH_3$), 5.95 (1H, d, $J_{H,F}$=8 Hz, C_8-H), 7.45 (1H, d, $J_{H,F}$=14 Hz, C_5-H).

Method F: Compound **18b** (580 mg, 1.53 mmol) was dissolved in 10% NaOH (16 ml). The solution was heated at 80 °C for 6.5 h with stirring, acidified at pH 2 with 10% HCl, treated with charcoal and adjusted to pH 8 with 28% NH_4OH. The resulting precipitate was collected by filtration to give **26b** as a yellow powder, which was dissolved in hot 30% AcOH. The solution was treated with charcoal and concentrated to dryness *in vacuo*. The residue was diluted with H_2O and then alkalized with 28% NH_4OH. The resulting crystals were collected by filtration to give an analytically pure sample of **26b** (440 mg, 85.1%). EIMS *m/z*: 338 (M^+), 322, 294.

Method G: A 28% (w/w) NaOMe solution in MeOH (430 mg, 2.2 mmol) was added to a suspension of **4b** (300 mg, 1.1 mmol) in dry MeOH (9 ml). The mixture was gently refluxed for 15 min and then concentrated to dryness *in vacuo*. The residue was diluted with H_2O and acidified with 2 N HCl. The resulting solid was collected by filtration and recrystallized from MeOH–iso-Pr_2O to give **27b** (300 mg, 95.8%) as colorless crystals. ^{1}H-NMR ($CDCl_3$): 1.61 (3H, dt, $J_{H,H}$=7 Hz, $J_{H,F}$=1.5 Hz, $NCH_2C\underline{H}_3$), 4.25 (3H, t, $J_{H,F}$=2 Hz, OCH_3), 4.86 (2H, dq, $J_{H,H}$=7 Hz, $J_{H,F}$=3.5 Hz, $NC\underline{H}_2CH_3$), 8.00 (1H, dd, $J_{H,F}$=11, 2 Hz, C_5-H), 14.12 (1H, br s, exchangeable with D_2O, CO_2H).

Method H: A mixture of **4b** (300 mg, 1.1 mmol), 15% (w/w) CH_3SNa solution in MeOH (1.13 g, 2.4 mmol), and MeOH (6 ml) was gently refluxed for 1 h. A similar treatment to that in method G gave **28b** (280 mg, 84.8%) as hygroscopic yellow prisms. IR cm^{-1}: 3400 (br), 1760, 1630, 1580, 1565. EIMS *m/z*: 300 (M^+), 256, 241, 228. ^{1}H-NMR (CD_3OD): 1.58 (3H, dt, $J_{H,H}$=7 Hz, $J_{H,F}$=1.5 Hz, $NCH_2C\underline{H}_3$), 2.68 (3H, t, $J_{H,F}$=1.5 Hz, SCH_3), 4.88 (2H, dq, $J_{H,H}$=7 Hz, $J_{H,F}$=3.5 Hz, $NC\underline{H}_2CH_3$), 7.90 (1H, dd, $J_{H,F}$=10, 2 Hz, C_5-H).

Biological Test According to the method of Goto *et al.*,[9] the minimum inhibitory concentration (MIC) was 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.

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References and Notes

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