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Studies on biologically Active Halogenated Compounds. IV.[1] Synthesis and Antibacterial Activity of Fluorinated Quinoline Derivatives

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Polyfluorinated derivatives of 1-alkyl-1,4-dihydro-7-methyl-4-oxoquinoline-3-carboxylic acids were synthesized and examined for antibacterial activites *in vitro*. Among the *N*-substituents, the strength of antibacterial activity of the derivatives was in the order: $CH_2CH_2F > CH_2CH_3 > CH_2CF_3 > CHF_2$. Introduction of two fluorine atoms at the 6 and 8 positions of the skeleton (**21a, b**) led to high activity, but substitution of the 7-methyl group (**20, 21, 25**) with a fluoromethyl group (**40, 41, 48**) led in general to reduced activity. Thus, 6,8-difluoro-1,4-dihydro-1-(2-fluoroethyl)-7-methyl-4-oxoquinoline-3-carboxylic acid (**21b**) showed the highest activity, almost equal to that of oxolinic acid.

Keywords—— 4-oxoquinoline-3-carboxylic acid; fluoroaniline; fluorination; fluoromethyl group; antibacterial activity

Research on new antibacterial agents[2] having a 4-oxoquinoline-3-carboxylic acid skeleton has increased since oxolinic acid[3] was found by Kaminsky *et al.* The accumulated knowledge on the structure–activity relationships shows that the substituent at the 7-position is most important for antibacterial activity, and extensive efforts have been made to introduce various substituents into this position of the skeleton.

In a series of studies[4] on the synthesis of biologically active halogenated compounds, we previously reported that replacement of the 7-methyl group by a fluoromethyl group improved the activity.

Recently, Koga *et al.*[5] found that the introduction of an electron-withdrawing group, especially fluorine, directly into the 6 or 8 position of the 4-oxoquinoline-3-carboxylic acid skeleton markedly increased the activity, and as a result, AM-715 is under development as a new antibacterial agent.

We were particularly interested in their finding that direct fluorination at the 6-position increased the activity. Thus, taking into account our previous knowledge of fluoromethylation at the 7-position as well as at the *N*-alkyl moiety of the skeleton, we synthesized various new polyfluorinated 4-oxoquinoline-3-carboxylic acids. This paper describes the synthesis and the structure–activity relationships of the above fluorinated compounds.

Chemistry

Various 6-fluoroquinolines with a 7-methyl or 7-fluoromethyl group, **20**, **21**, **25**, **40**, **41**, and **48**, were synthesized from the corresponding fluoroanilines **1**, **4**, **8**, and **13** by a method similar to that previously used in the synthesis of the 6-unsubstituted quinolines.[1]

i) Preparation of Fluoroanilines 1, 4, 8, and 13 —— 4-Fluoro-3-methylaniline (**1**) was synthesized by Valkans' procedure.[6] The synthetic routes to the new fluoroanilines **4**, **8**, and **13** are shown in Chart 1. The preparation of 2,4-difluoro-3-methylaniline (**4**) was accomplished *via* nitration of 2,6-difluorotoluene (**2**),[7] followed by reduction with stannous chloride and conc. HCl. Catalytic reduction of 2-fluoro-5-nitrobenzoic acid (**5**)[8] followed by esterification gave 5-amino-2-fluorobenzoate (**7**)[9] in a satisfactory yield. In the case of the treatment of 2,6-difluorobenzoic acid (**9**),[10] nitration proceeded without difficulty. However, catalytic reduction of **10** resulted in a complex reaction, probably due to activation of the fluorine atom

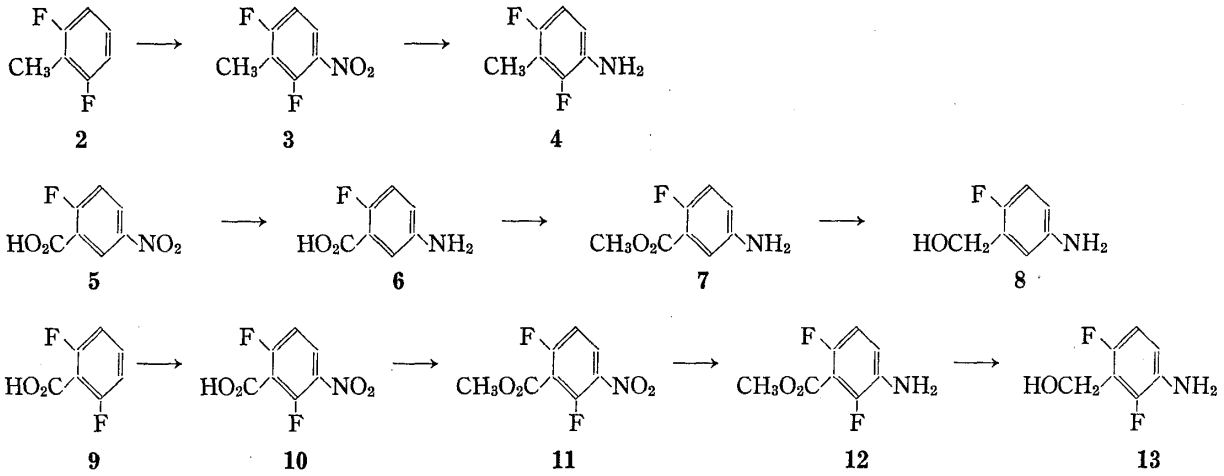
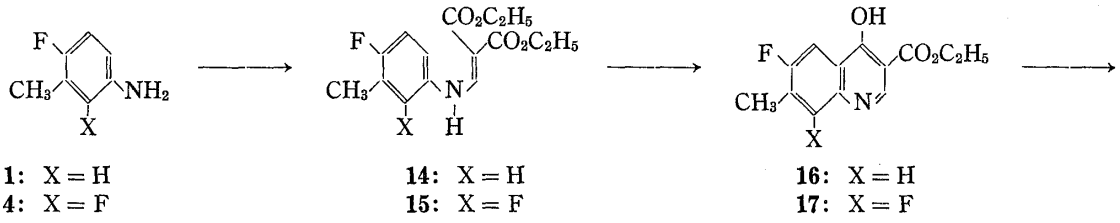


Chart 1

route A



route B

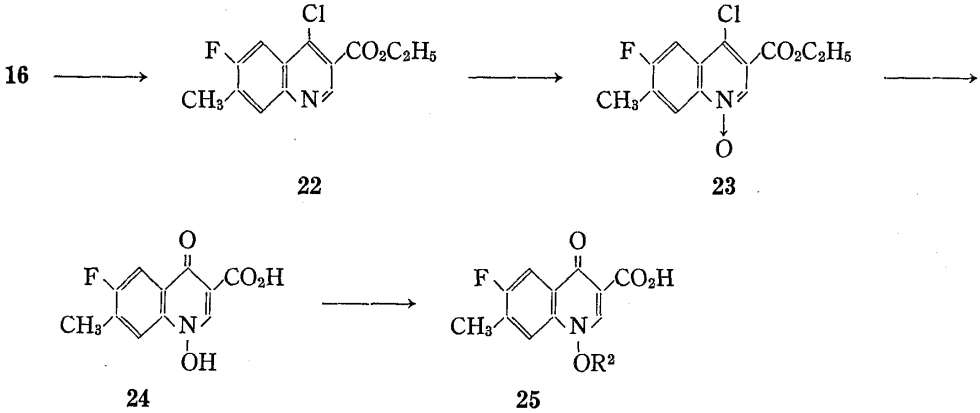


Chart 2

by the adjacent nitro group. Thus, after esterification of **10**, reduction of the nitro group was carried out with stannous chloride and conc. HCl; from the reaction mixture the desired amino compound (**12**) was easily extracted into an appropriate organic solvent. Reduction of the aminobenzoates **7** and **12** with $LiAlH_4$ gave the 3-hydroxymethylanilines **8** and **13**, which were the key intermediates of this series.

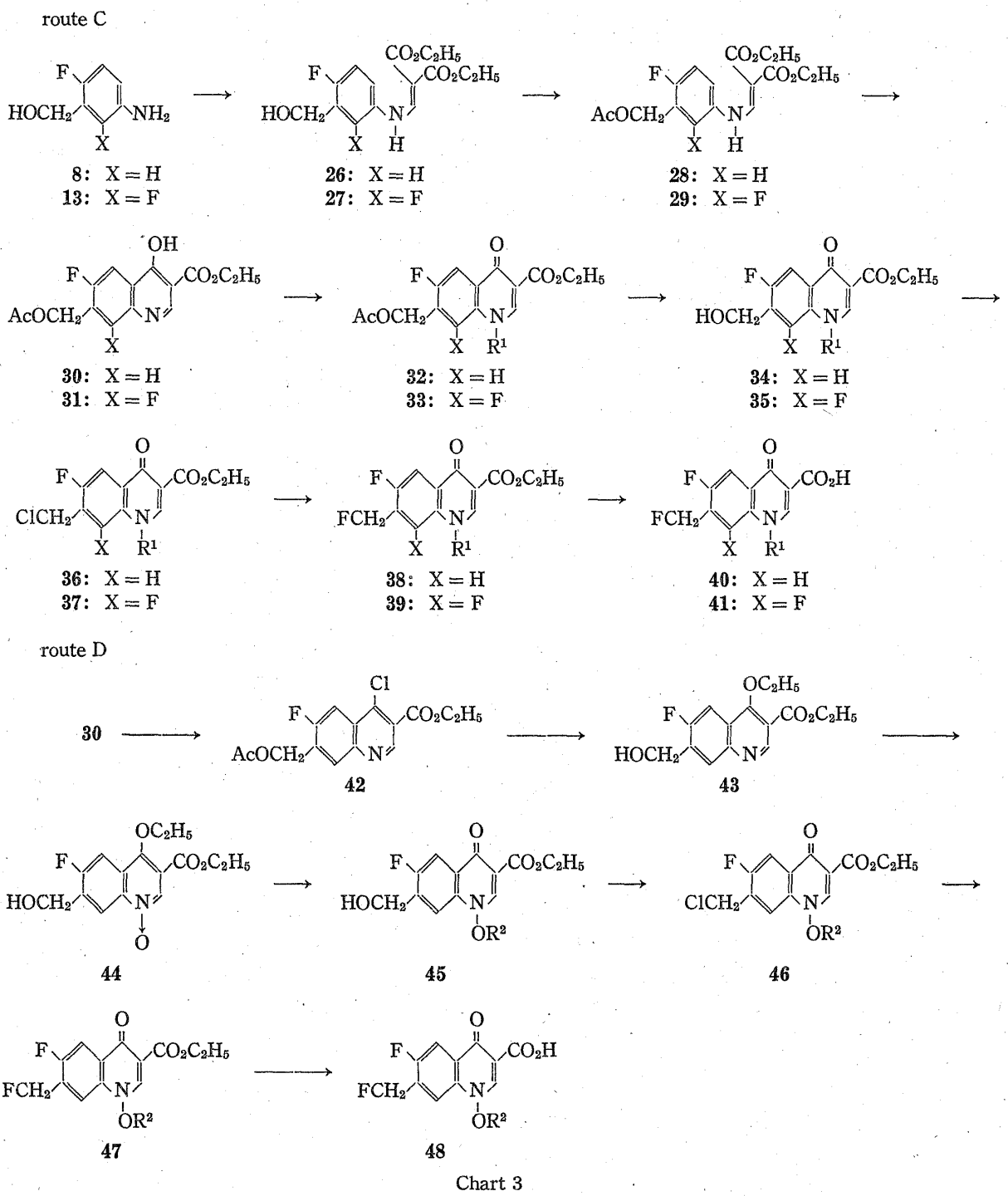


Chart 3

ii) Cyclization of Anilinomethylenemalonates 14, 15, 28, and 29——The anilinomethylenemalonates were synthesized by the reaction of the fluoroanilines with diethyl ethoxymethylenemalonate as shown in Charts 2 and 3. The hydroxymethyl group of **26** or **27** was acetylated with acetic anhydride to give the *O*-acetyl compound **28** or **29**, respectively. The thermal cyclization of the anilinomethylenemalonates **14**, **15**, **28**, and **29** was carried out in diphenyl ether to give 4-hydroxyquinoline **16**,[11] **17**, **30**, and **31**. Except among the 2,4-difluoro compounds, two positional isomers were formed by the cyclization of the monofluoroanilinomethylenemalonates as shown in Chart 4.

The ratio of the two isomers (**16** and **49**) obtained by the thermal cyclization of **14** in

diphenyl ether was estimated to be about 4 : 1 by nuclear magnetic resonance (NMR) spectral analysis. The isolation of the minor component from the mixture was very difficult because of its low solubility in organic solvents. Therefore, the mixture was derived to the *N*-ethyl compounds **18a** and **51**, which were easily separated by column chromatography. The structures of the major and minor products were assigned as **18a** and **51** on the basis of the NMR spectra. The NMR spectrum (in $CDCl_3$) of the major product showed a 3H doublet at δ 2.42 (J=2 Hz), due to aromatic methyl protons, and two 1H doublets at δ 7.23 (J=6 Hz) and 7.98 (J=10 Hz) characteristic of aromatic protons. In the case of the minor product, aromatic methyl protons (3H) deshielded with the carbonyl group absorbed at δ 2.84 as a doublet (J=3 Hz) and aromatic proton signals (2H) appeared at δ 7.2—7.35 as a multiplet. The cyclization of **28** also gave **30** as a major product with a negligible amount of **50**.

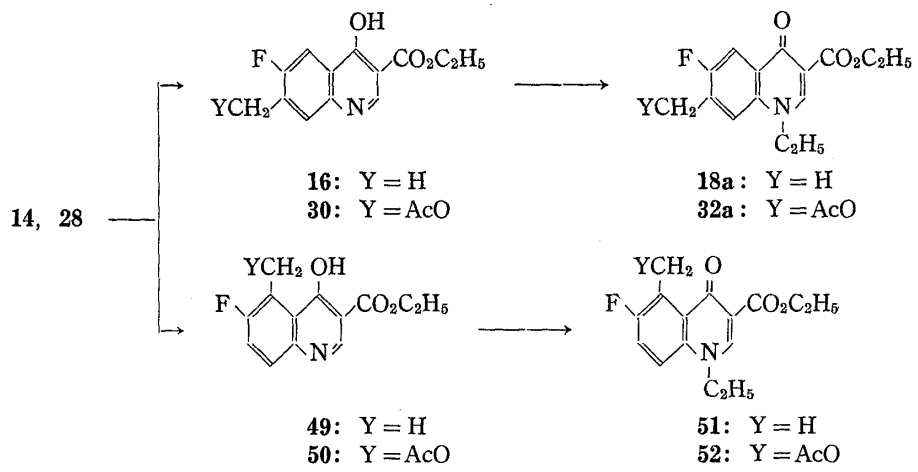


Chart 4

iii) Preparations of 7-Methyl Compounds 20, 21, and 25——1-Alkyl-1,4-dihydro-6-fluoro-7-methyl-4-oxoquinoline-3-carboxylic acids (**20**) and 1-alkyl-6,8-difluoro-1,4-dihydro-7-methyl-4-oxoquinoline-3-carboxylic acids (**21**) were prepared easily by hydrolysis of the corresponding esters **18** and **19**, which were prepared by *N*-alkylation of the 4-hydroxyquinolines **16** and **17** with alkyl halides in the presence of NaH in dimethyl formamide (DMF) (route A). The 1-vinyl compound **20g** was prepared by dehydrochlorination of the *N*-(2-chloroethyl) derivative **18f**, which was obtained by chlorination of the 2-hydroxyethyl group of compound **18e**. On the other hand, the 1-alkoxy compounds **25a, b** were prepared by alkylation of the *N*-hydroxy-3-carboxylic acid **24**, which was synthesized *via* three steps using Agui's procedure[12] (route B).

iv) Preparation of 7-Fluoromethyl Compounds 40, 41, and 48——Introduction of a fluorine atom into the 7-methyl group was achieved by use of the halogen-exchange process as a key step (route C). Heating of ethyl 1-(2-chloroethyl)-7-chloromethyl-1,4-dihydro-6-fluoro-4-oxoquinoline-3-carboxylate (**36f**) with potassium fluoride in diethyleneglycol gave rise to both fluorination of the 7-chloromethyl group and elimination of hydrogen chloride from the *N*-(2-chloroethyl) group as expected, accompanied with ester exchange at the 3-position to afford the diethyleneglycol ester of the 1-vinyl-7-fluoromethyl compound **38h**.

Though the halogen-exchange fluorination of the 6,8-difluoro compounds **37a, b** proceeded rather more smoothly than that of the 6-fluoro compounds **36**, substitution reaction of the 8-fluorine atom with the solvent was observed to give ethyl 1-alkyl-1,4-dihydro-6-fluoro-7-fluoromethyl-8-[2-(2-hydroxyethoxy)ethoxy]-4-oxoquinoline-3-carboxylate as a by-product. It is clear that the fluorine atom at the 8-position is much more reactive than that at the 6-position. 1-Alkyl-1,4-dihydro-6-fluoro-7-fluoromethyl-4-oxoquinoline-3-carboxylic acids (**40**) and 1-alkyl-6,8-difluoro-1,4-dihydro-7-fluoromethyl-4-oxoquinoline-3-carboxylic acid (**41**) were

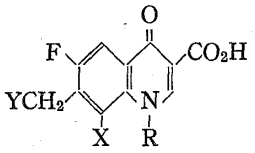
prepared by hydrolysis of the corresponding ester **38** and **39** without any problem at the 7-substituent.

On the other hand, 1-alkoxy-1,4-dihydro-6-fluoro-7-fluoromethyl-4-oxoquinoline-3-carboxylic acids (**48a, b**) were prepared from **30** *via* seven steps including the introduction of an alkoxy group at the *N*-position followed by fluoromethylation at the 7-position as shown in Chart 3 (route D).

Antibacterial Activity

The compounds synthesized here were screened for antibacterial activities against *Staphyl-*

Table I. 1-Substituted-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids



Compd. No.	Y	X	R	Method[b]	Yield (%)	mp (°C)	Recryst. solv.[d]	Formula	Analysis (%) Calcd (Found) C	H	N
20a	H	H	C_2H_5	A	80	277—279[c]	A	$C_{13}H_{12}FNO_3$	62.65 (62.76	4.85 4.93	5.62 5.70)
20b	H	H	CH_2CH_2F	A	95	286—288	A	$C_{13}H_{11}F_2NO_3$	58.42 (58.41	4.15 4.14	5.24 5.27)
20c	H	H	CH_2CF_3	A	91	295—297[c]	B	$C_{13}H_9F_4NO_3$	51.49 (51.70	2.99 3.01	4.62 4.70)
20d	H	H	CHF_2	B	72	250—252	A	$C_{12}H_8F_3NO_3$	53.14 (53.13	2.97 2.99	5.17 5.34)
20g	H	H	$CH=CH_2$	C	100	219—222	A	$C_{13}H_{10}FNO_3$	63.16 (63.40	4.08 4.28	5.67 5.66)
21a	H	F	C_2H_5	A	90	247—250	A	$C_{13}H_{11}F_2NO_3$	58.43 (58.51	4.15 4.14	5.24 5.27)
21b	H	F	CH_2CH_2F	A	100	218—220	A	$C_{13}H_{10}F_3NO_3$	54.74 (54.71	3.53 3.54	4.91 5.03)
25a	H	H	OCH_3	D	87	248—250[c]	B	$C_{12}H_{10}FNO_4$	57.37 (57.50	4.30 4.26	5.58 5.62)
25b	H	H	OCH_2CH_2F	D	85	212—215[c]	B	$C_{13}H_{11}F_2NO_4$	55.13 (55.23	3.91 3.94	4.95 5.01)
40a	F	H	C_2H_5	A	97	225—228	A	$C_{13}H_{11}F_2NO_3$	58.42 (58.30	4.15 4.14	5.24 5.40)
40b	F	H	CH_2CH_2F	A	88	240—242	A	$C_{13}H_{10}F_3NO_3$	54.74 (54.34	3.53 3.52	4.91 5.00)
40c	F	H	CH_2CF_3	A	64	256—258	B	$C_{13}H_8F_5NO_3$	48.61 (48.69	2.51 2.65	4.36 4.48)
40d	F	H	CHF_2	B	41	226—229	[e]	[f]			
40g[a]	F	H	$CH=CH_2$	C	83	203—205	A	$C_{13}H_9F_2NO_3$	58.87 (58.57	3.42 3.45	5.28 5.28)
41a	F	F	C_2H_5	A	93	201—202	B	$C_{13}H_{10}F_3NO_3$	54.74 (54.63	3.53 3.47	4.91 4.94)
41b	F	F	CH_2CH_2F	A	90	210—212	B	$C_{13}H_9F_4NO_3$	51.49 (51.15	2.99 2.90	4.62 4.69)
48a	F	H	OCH_2	A	100	227—228[c]	A	$C_{12}H_9F_2NO_4$	53.54 (53.63	3.37 3.36	5.20 5.10)
48b	F	H	OCH_2CH_2F	A	77	229—230	A	$C_{13}H_{10}F_3NO_4$	51.83 (51.90	3.35 3.32	4.65 4.71)

a) Prepared from 2-(2-hydroxyethoxy)ethyl 1,4-dihydro-6-fluoro-7-fluoromethyl-4-oxo-1-vinylquinoline-3-carboxylate.
b) See "Experimental."
c) Decomposition,
d) A=DMF; B=DMF–EtOH.
e) Not recrystallized.
f) Nor analyzed.

Table II. *In Vitro* Antibacterial Activity

Compd. No.	Minimum inhibitory concentration μg/ml				
	S. aureus 209p JC-1	*E. coli* NIHJ JC-2	*S. typhi* T-58	*K. pneumoniae* PCI 602	*P. aeruginosa* TU-408
20a	3.13	0.78	0.78	1.56	12.5
20b	3.13	0.20	0.39	0.78	6.25
20c	3.13	3.13	3.13	6.25	50
20d	>50	12.5	12.5	50	50
20g	25	3.13	3.13	3.13	25
21a	1.56	0.78	0.78	1.56	6.25
21b	1.56	0.39	0.39	0.78	6.25
25a	25	3.13	3.13	6.25	50
25b	>50	12.5	12.5	12.5	>50
40a	25	0.78	0.78	1.56	>25
40b	12.5	1.56	1.56	3.13	25
40c	6.25	1.56	3.13	3.13	>50
40g	>50	3.13	3.13	6.25	>50
41a	12.5	1.56	3.13	6.25	50
41b	6.25	0.39	0.39	1.56	25
48a	>50	3.13	6.25	6.25	>50
48b	>50	6.25	12.5	12.5	>50
MOA[a]	>50	6.25	25	6.25	>50
OA[b]	3.13	0.39	0.39	0.39	3.13
PPA[c]	12.5	0.78	1.56	3.13	6.25

a) MOA=1,4-dihydro-1-ethyl-7-methyl-4-oxoquinoline-3-carboxylic acid.
b) OA=oxolinic acid.
c) PPA=pipemidic acid.

ococcus aureus, *Escherichia coli*, *Salmonella typhi*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* by the method described in the experimental section. These results are summarized in Table II.

Introduction of a fluorine atom at the 6-position of the quinoline skeleton remarkably increased the antibacterial activity of all the compounds synthesized here, as compared with the corresponding unsubstituted compounds reported in our previous paper. Among the 6-fluoro compounds, further introduction of a fluorine atom into the 8-position generally enhanced the activity (**21**), but further replacement of the methyl group with a fluoromethyl group (**41**) rather lowered the activity.

That is, substitution of a fluorine atom into 4-oxoquinoline-3-carboxylic acid derivatives enhances the antibacterial activity most effectively at the 6-position, as has been found by Koga *et al.*, and further fluoromethylation at the 7-position has a rather negative effect, in contrast to the situation with 6-unsubstituted compounds, reported previously. Among the *N*-substituents, however, the 2-fluoroethyl group gave the best result among ethyl, vinyl alkoxy, difluoromethyl, and 2,2,2-trifluoroethyl groups. It is of interest that *N*-(2-fluoroethyl) compounds showed higher activity than the corresponding *N*-ethyl compounds among both 6-fluoro and 6,8-difluoro derivatives. Thus, among the polyfluorinated compounds, the *N*-(2-fluoroethyl)-6,8-difluoro-7-methyl compound **21b** was found to show the highest activity, almost equal to that of oxolinic acid.

Experimental

All melting points were determined on a Yamato MP-21 apparatus and are uncorrected. NMR spectra were recorded on a Hitachi RMS-4 spectrometer (60 MHz) using tetramethylsilane as an internal standard.

2,6-Difluoro-2-nitrotoluene (3)——Fuming HNO_3 (d=1.55, 7.86 g) was added dropwise to a mixture of 2,6-difluorotoluene (**2**, 17.9 g, 0.14 mol) and conc. H_2SO_4 (42 g) keeping the reaction temperature at 20—

25°C. After being stirred at the same temperature for 1.5 h, the reaction mixture was poured into ice-water (400 ml). The crystals were collected by filtration and washed with H_2O to give 19.6 g (81%) of **3**. mp 35—38°C [bp 78—80°C (4 mmHg)], NMR ($CDCl_3$) δ: 2.30 (3H, t, J=2 Hz), 6.8—7.1 (1H, m), 7.7—8.1 (1H, m). *Anal.* Calcd for $C_7H_5F_2NO_2$: C, 48.56; H, 2.91; N, 8.09. Found: C, 48.67; H, 2.85; N, 8.20.

2,4-Difluoro-3-methylaniline (**4**)——A solution of $SnCl_2$–$2H_2O$ (99.8 g, 0.44 mol) in conc. HCl (95 ml) was added to a solution of **3** (19.6 g, 0.11 mol) in MeOH (200 ml) at −15 to −5°C over a period of 1 h. This mixture was warmed slowly to room temperature and stirred for 3 h. The reaction mixture was diluted with H_2O (500 ml) and neutralized with $NaHCO_3$. The oily product was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and concentrated. The residue was distilled under reduced pressure to give pure **4** (13.7 g, 85%): bp 72—74°C (10 mmHg). NMR ($CDCl_3$) δ: 2.18 (3H, t, J=2 Hz), 3.47 (2H, s), 6.25—6.95 (2H, m). This sample was used in the next step without purification.

3-Amino-6-fluorobenzoic Acid (**6**)——A suspension of 2-fluoro-5-nitrobenzoic acid (**5**, 18.5 g, 0.1 mol) and 5% Pd on charcoal (1.8 g) in AcOH (100 ml) was shaken in an atmosphere of hydrogen (initial pressure of 3.5 kg/cm²) at 40—50°C. After cessation of hydrogen uptake, the catalyst was removed by filtration and concentration of the filtrate gave pure **6** (14.5 g 94%). mp 188—191°C (dec.). Lit. mp 190°C.[9]

Methyl 3-Amino-6-fluorobenzoate (**7**)——Thionyl chloride (15.5 g, 0.13 mol) was added to cooled methanol (100 ml) during 0.25 h at −15 to −5°C, and stirring was continued for 0.5 h at the same temperature. Powdered **6** (15.5 g, 0.1 mol) was added to the mixture in one portion. The reaction mixture was stirred for 0.5 at 0°C then overnight at room temperature. The reaction mixture was concentrated and poured into water. The mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and concentrated to give 16.4 g (97.0%) of **7**. mp 85—87°C. Lit. mp 86°C.[9] NMR ($CDCl_3$) δ: 3.65 (2H, br s), 3.90 (3H, s), 6.6—7.0 (2H, m), 7.1—7.3 (1H, m).

3-Hydroxymethyl-4-fluoroaniline (**8**)——A solution of **7** (118.3 g, 0.7 mol) in tetrahydrofuran (THF) (500 ml) was gradually added to a stirred suspension of $LiAlH_4$ (38.5 g, 1.02 mol) in THF (1000 ml) during 2 h at 0—5°C. After being stirred for 1.5 h at the same temperature, the reaction mixture was quenched by addition of H_2O (105 ml). The resulting precipitate was collected by filtration, and washed with THF. The THF solution was concentrated to dryness *in vacuo*. The residual crystals were triturated with diisopropyl ether and collected by filtration to give 86.1 g (87%) of **8**, 95—98°C. The product was recrystallized from benzene to give pure **8**, mp 94—97°C, NMR (DMSO-d_6) δ: 4.45 (2H, d, J=6 Hz), 4.88 (2H, s), 5.10 (1H, t, J=6 Hz), 6.2—6.95 (3H, m). *Anal.* Calcd for C_7H_8FNO: C, 59.57; H, 5.71; F, 13.46, N, 9.92. Found: C, 59.53; H, 5.74; F, 13.76; N, 9.85.

2,6-Difluoro-3-nitrobenzoic Acid (**10**)——A mixture of fuming HNO_3 (d=1.55, 2.52 g, 0.037 mol) and conc. H_2SO_4 (2 ml) was added dropwise to a mixture of 2,6-difluorobenzoic acid (**9**, 4.74 g, 0.03 mol) and conc. H_2SO_4 (10 g) keeping the reaction temperature at 20—25°C. After being stirred at the same temperature for 1 h, the reaction mixture was poured into ice-water (400 ml). The mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and concentrated to give 5.8 g (95%) of **10**. mp 97—100°C. NMR ($CDCl_3$) δ: 7.1—7.45 (1H, m), 8.2—8.6 (1H, m), 10.32 (1H, s). This sample was used in the next step without further purification.

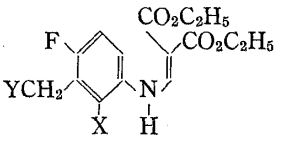
Methyl 2,6-Difluoro-3-nitrobenzoate (**11**)——Thionyl chloride (9.3 g, 0.078 mol) was added to cooled methanol (60 ml) during 0.25 h at −15 to −5°C, and stirring was continued for 0.5 h at the same temperature. Powdered **10** (12.0 g, 0.06 mol) was then added to the mixture in one portion. The whole was stirred for 0.5 h at the same temperature then overnight at room temperature. The reaction mixture was concentrated and poured into water. The mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and concentrated. Distillation of the crude product under reduced pressure gave pure crystalline **11** (5.5 g, 42%). bp 149—151°C (9 mmHg). mp 55—56°C. NMR ($CDCl_3$) δ: 4.10 (3H, s), 7.0—7.4 (1H, m), 8.1—8.6 (1H, m). *Anal.* Calcd for $C_8H_5F_2NO_4$: C, 44.25; H, 2.32; N, 6.45. Found: C, 44.24; H, 2.14; N, 6.45.

Methyl 3-Amino-2,6-difluorobenzoate (**12**)——A solution of $SnCl_2 \cdot 2H_2O$ (48.7 g, 0.216 mol) in conc. HCl (45 ml) was added dropwise to a solution of **11** (11.7 g, 0.054 mol) in MeOH (200 ml) at 5—15°C over a period of 20 min. This mixture was warmed slowly to room temperature and stirred for 20 h. This reaction mixture was diluted with H_2O (1000 ml) and neutralized with $NaHCO_3$. The oily product was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and concentrated to give 8.85 g (88%) of crude oily **12**. NMR ($CDCl_3$) δ: 3.3—4.2 (2H, br), 4.04 (3H, s), 6.6—7.2 (2H, m). This sample was used in the next step without purification.

3-Hydroxymethyl-2,4-difluoroaniline (**13**)——A solution of **12** (8.85 g, 0.047 mol) in THF (40 ml) was gradually added to a stirred suspension of $LiAlH_4$ (2.7 g, 0.071 mol) in THF (150 ml) during 45 min at −15 to −5°C. The mixture was stirred for 0.5 h at the same temperature, then additional portions of $LiAlH_4$ (1.0 g) was added to the mixture and stirring was continued at the same temperature for 20 min. This mixture was warmed at 0—5°C for 30 min. H_2O (10 ml) was added to this mixture at 0—10°C and the resulting crystals were collected by filtration, and washed with THF. The filtrate was concentrated to dryness *in vacuo*. The residual crystals were triturated with a small amount of benzene and collected by filtration to give 7.6 g (quantitative) of crude **13**, mp 54—59°C. The product was recrystallized from benzene to give yellow prisms, mp 64—66°C. NMR ($CDCl_3$) δ: 2.3—4.3 (3H, br), 4.84 (2H, t, J=1 Hz), 6.55—7.00 (2H, m). *Anal.* Calcd for $C_7H_7F_2NO$: C, 52.83; H, 4.43; N, 8.80. Found: C, 52.58; H, 4.33; N, 8.81.

Diethyl 2-Anilinomethylenemalonates (14, 15, 26, and 27). General Procedure——A mixture of a substituted aniline (**1**, **4**, **8** or **13**) and diethyl 2-ethoxymethylenemalonate (equimolar amount) was stirred at 110—120°C for 0.5—1 h, and the resulting EtOH was evaporated off. After cooling, the mixture was triturated with *n*-hexane to afford almost pure malonate, which was purified by recrystallization from a suitable solvent (listed in Table III).

TABLE III. Diethyl Anilinomethylenemalonates



Compd. No.	Y	X	Yield (%)	mp (°C)	Recryst. solv.[b]	Formula	Analysis (%) Calcd (Found) C	H	N
14[a]	H	H	91	51—52	A	$C_{15}H_{18}FNO_4$	61.01 (61.24	6.14 6.19	4.74 4.76)
15	H	F	89	80—82	B	$C_{15}H_{17}F_2NO_4$	57.50 (57.44	5.47 5.47	4.47 4.51)
26	HO	H	97	84—85	B	$C_{15}H_{18}FNO_5$	57.87 (57.87	5.83 5.78	4.50 4.36)
27	HO	F	98	120—121	C	$C_{15}H_{17}F_2NO_5$	54.71 (54.94	5.20 5.17	4.25 4.21)
28	AcO	H	86	67—70	—[c]	$C_{17}H_{20}FNO_6$	57.79 (57.69	5.71 5.61	3.96 3.95)
29	AcO	F	71	92—95	B	$C_{17}H_{19}F_2NO_6$	54.99 (55.15	5.16 5.16	3.77 3.74)

a) No data for identification in Ref. 11.
b) A=*n*-hexane; B=diisopropyl ether; C=EtOH–diisopropyl ether.
c) Not recrystallized.

Diethyl 2-(3-Acetoxymethyl-4-fluoroanilino)methylenemalonate (28)——A solution of **26** (3.11 g, 10 mmol) and acetic anhydride (1.23 g, 12 mmol) in acetic acid (5 ml) was heated for 2 h under reflux. The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in $CHCl_3$. The solution was washed with 5% aq. $NaHCO_3$ and dried over anhydrous $MgSO_4$. $CHCl_3$ was removed by distillation and the residue was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to give almost pure **28** (3.0 g, 86%, mp 67—70°C). NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7 Hz), 1.38 (3H, t, J=7 Hz), 2.14 (3H, s), 4.25 (2H, q, J=7 Hz), 4.30 (2H, q, J=7 Hz), 5.17 (2H, s), 7.0—7.2 (3H, m), 8.39 (1H, d, J=14 Hz), 10.98 (1H, d, J=14 Hz).

In a similar manner, diethyl 2-(3-acetoxymethyl-2,4-difluoroanilino)methylenemalonate (**29**) was obtained in 71% yield from **27** as colorless prisms, mp 92—95°C.

General Procedure for Preparation of Ethyl 4-Hydroxyquinoline-3-carboxylates (16, 17, 30, and 31)

Ethyl 6-Fluoro-4-hydroxy-7-methylquinoline-3-carboxylate (16)——Fine crystals of **14** (59.1 g, 0.2 mol) were added with stirring to boiling diphenyl ether (500 ml) during 5 min and stirring was continued at 250—255°C for a further 15 min. After cooling, the mixture was triturated with *n*-hexane to afford 41.4 g (83%) of a mixture of **16** and **49** (ratio=about 4: 1). Fractional recrystallizations of the mixture from DMF gave an analytically pure **16** as colorless needles, mp >300°C. NMR (CF_3CO_2D) δ: 1.58 (3H, t, J=7.5 Hz), 2.69 (3H, d, J=2.3 Hz), 4.70 (2H, q, J=7.5 Hz), 8.05 (1H, d, J=6.0 Hz), 8.20 (1H, d, J=9.0 Hz), 9.28 (1H, s). *Anal.* Calcd for $C_{13}H_{12}FNO_3$: C, 62.65; H, 4.85; N, 5.62. Found: C, 62.60; H, 4.93; N, 5.55.

In a similar manner, ethyl 6,8-difluoro-4-hydroxy-7-methylquinoline-3-carboxylate (**17**) was obtained in 73% yield from **15** as colorless needles, mp 273—275°C (DMF). NMR (CF_3CO_2D) δ: 1.58 (3H, t, J=7 Hz), 2.62 (3H, t, J=2 Hz), 4.75 (2H, q, J=7 Hz), 8.13 (1H, dd, J=8 Hz), J'=2 Hz), 9.36 (1H, s). *Anal.* Calcd for $C_{13}H_{11}F_2NO_3$: C, 58.43; H, 4.15; N, 5.24. Found: C, 58.50; H, 4.19; N, 5.30.

Ethyl 7-Acetoxymethyl-6-fluoro-4-hydroxyquinoline-3-carboxylate (**30**) was obtained in 89% yield from **28** as a brown powder, mp 286—290°C. NMR (CF_3CO_2D) δ: 1.58 (3H, t, J=7 Hz), 2.38 (3H, s), 4.72 (2H, q, J=7 Hz), 5.60 (2H, s), 8.30 (1H, d, J=9 Hz), 8.35 (1H, J=6 Hz), 9.34 (1H, s). *Anal.* Calcd for $C_{15}H_{14}FNO_5$: C, 58.63; H, 4.59; N, 4.56. Found: C, 58.70; H, 4.51; N, 4.47.

Ethyl 7-Acetoxymethyl-6,8-difluoro-4-hydroxyquinoline-3-carboxylate (**31**) was obtained in 89% yield from **29** as a colorless powder, mp 263—265°C (dec.) (DMF–EtOH). NMR (CF_3CO_2D) δ: 1.61 (3H, t, J=

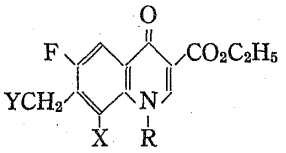
7 Hz), 2.35 (3H, s), 4.84 (2H, q, J=7 Hz), 5.75 (2H, s), 8.32 (1H, dd, J=8.5 Hz, J'=2 Hz), 9.60 (1H, s). *Anal.* Calcd for $C_{15}H_{13}F_2NO_5$: C, 55.39; H, 4.03; N, 4.31. Found: C, 55.50; H, 3.95; N, 4.39.

General Procedure for Preparation of Ethyl 1-Alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylates (18, 19, 32, and 33) (Table IV)

Typical Procedure——(a) *N*-Ethylation of **17**: NaH (66% in oil dispersion) (0.46 g, 0.0125 mol) was added to a suspension of **17** (2.67 g, 0.01 mol) in DMF (50 ml) and the mixture was stirred at room temperature for 40 min. Then, ethyl iodide (3.12 g, 0.02 mol) was added to the mixture. After being stirred at room temperature for 24 h, the reaction mixture was heated at 50—60°C for 3 h. The solvent was removed by evaporation under reduced pressure. The residual crystals were triturated with H_2O, collected by filtration, washed with 2-propanol, and then dried to give 1.95 g (66%) of ethyl 6,8-difluoro-1,4-dihydro-1-ethyl-7-methyl-4-oxoquinoline-3-carboxylate (**19a**). Recrystallization from 2-propanol gave pure **19a** as colorless needles, mp 149—151°C. NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz), 1.56 (3H, t, J=7 Hz), 2.36 (3H, t, J=2 Hz), 4.41 (2H, q, J=7 Hz), 4.2—4.7 (2H, m), 7.95 (1H, dd, J=10 Hz, J'=2 Hz), 8.37 (1H, s).

(b) *N*-Ethylation of **16** and **49**: NaH (66% in oil dispersion 2.73 g, 0.075 mol) was added to a suspension of crude **16** (15 g, 0.06 mol) in DMF (150 ml), and the mixture was stirred at room temperature for 1 h. Then, ethyl iodide (18.4 g, 0.12 mol) was added to the mixture, and the whole was stirred at room temperature for 20 h. The solvent was then removed by evaporation under reduced pressure. The residue was dissolved in $CHCl_3$ (200 ml) and the solution was washed with H_2O, dried with anhydrous $MgSO_4$, and concentrated.

TABLE IV. Ethyl 1-Substituted-1,4-dihydro-4-ouoquinoline-3-carboxylates



Compd. No.	Y	X	R	Yield (%)	mp (°C)	Recryst. solv.[d]	Formula	Analysis (%) Calcd (Found) C	H	N
18a	H	H	C_2H_5	66	178—180	A	$C_{15}H_{16}FNO_3$	64.97 (65.18	5.82 5.84	5.05 5.05)
18b	H	H	CH_2CH_2F	56	202—204	B	$C_{15}H_{15}F_2NO_3$	61.01 (60.85	5.12 5.14	4.74 4.70)
18c	H	H	CH_2CF_3	11	198—200	—[e]	[f]			
18d	H	H	CHF_2	52	198—200	B	$C_{14}H_{12}F_3NO_3$	56.19 (56.16	4.04 3.95	4.68 4.57)
18e	H	H	CH_2CH_2OH	41	205—208	B	[g]	60.68 (60.71	5.56 5.38	4.71 4.79)
18f[a]	H	H	CH_2CH_2Cl	51	226—229	B	$C_{15}H_{15}ClFNO_3$	57.79 (57.77	4.85 4.93	4.49 4.55)
19a	H	F	C_2H_5	66	149—151	C	$C_{15}H_{15}F_2NO_3$	61.01 (61.22	5.12 5.12	4.74 4.67)
19b	H	F	CH_2CH_2F	51	202—204	A	$C_{15}H_{14}F_3NO_4$	57.50 (57.74	4.50 4.52	4.47 4.47)
32a	AcO	H	C_2H_5	43	140—142	A	$C_{17}H_{18}FNO_5$	60.89 (60.76	5.41 5.36	4.18 4.23)
32b	AcO	H	CH_2CH_2F	43	151—153	A	$C_{17}H_{17}F_2NO_5$	57.79 (57.95	4.85 4.87	3.96 3.99)
32c	AcO	H	CH_2CF_3	24	141—143	C	$C_{17}H_{15}F_4NO_5$	52.45 (52.42	3.88 3.86	3.60 3.62)
32d	AcO	H	CHF_2	17	211—213	B	$C_{16}H_{14}F_3NO_5$	53.79 (53.73	3.95 3.87	3.92 3.92)
32e	AcO	H	CH_2CH_2OH	—[b]	—	—				
32f	AcO	H	CH_2CH_2Cl	66[c]	140—143	A	$C_{17}H_{17}ClFNO_5$	55.22 (55.02	4.63 4.55	3.79 3.73)
33a	AcO	F	C_2H_5	66	105—107	D	$C_{17}H_{17}F_2NO_5$	57.79 (57.70	4.85 4.86	3.96 3.95)
33b	AcO	F	CH_2CH_2F	65	141—144	C	$C_{17}H_{16}F_2NO_5$	54.99 (54.79	4.34 4.24	3.77 3.76)

a) Prepared from **18e**. *b*) Not isolated. *c*) Based on **30**. *d*) A=EtOH; B=DMF–EtOH; C=2-propanol; D=2-propanol–diisopropyl ether. *e*) Not recrystallized. *f*) Not analyzed. *g*) $C_{15}H_{16}FNO_4 \cdot 0.2H_2O$.

The residue was separated into two compounds, **18a** and **51** by column chromatography on silica gel using $CHCl_3$ as an eluent to give **18a** (11.0 g, 66%) and **51** (2.3 g, 14%). Each compound was recrystallized from a suitable solvent to afford analytically pure **18a** as colorless prisms, mp 178—180°C (EtOH) and **51** as colorless needles, mp 140—142°C (2-propanol–diisopropyl ether), respectively. NMR for **18a** ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 1.53 (3H, t, J=7 Hz), 2.42 (3H, d, J=2 Hz), 4.25 (2H, q, J=7 Hz), 4.37 (2H, q, J=7 Hz), 7.23 (1H, d, J=6 Hz), 7.98 (1H, d, J=10 Hz), 8.38 (1H, s). NMR for **51** ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 1.51 (3H, t, J=7 Hz), 2.84 (3H, d, J=3 Hz), 4.19 (2H, q, J=7 Hz), 4.38 (2H, q, J=7 Hz), 7.20—7.35 (2H, m), 8.34 (1H, s). **51** *Anal.* Calcd for $C_{15}H_{16}FNO_3$: C, 64.97; H, 5.82; N, 5.05. Found: C, 64.89; H, 5.77; N, 5.06.

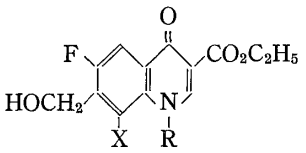
Ethyl 1-(2-Chloroethyl)-1,4-dihydro-6-fluoro-7-methyl-4-oxoquinoline-3-carboxylate (18f)——A mixture of **18e** (2.93 g, 0.01 mol), $SOCl_2$ (2.4 g, 0.02 mol), pyridine (1.6 g, 0.02 mol) and $CHCl_3$ (150 ml) was stirred at room temperature for 3.5 h. Then, additional portions of $SOCl_2$ (1.2 g, 0.01 mol) and pyridine (0.8 g, 0.01 mol) were added to the mixture and stirring was continued at room temperature for 2 h. The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in $CHCl_3$. The solution was washed with 5% aq. $NaHCO_3$, dried ($MgSO_4$), and concentrated to dryness. The residue was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to afford almost pure **18f** (1.6 g, 51%). Recrystallization from DMF–EtOH gave an analytically pure sample as colorless prisms, mp 226—229°C. NMR (DMSO-d_6) δ: 1.38 (3H, t, J=7 Hz), 2.39 (3H, d, J=2 Hz), 3.85—4.25 (2H, m), 4.22 (2H, q, J=7 Hz), 4.10—4.40 (2H, m), 7.70 (1H, d, J=10 Hz), 7.80 (1H, d, J=6 Hz), 8.60 (1H, s).

Ethyl 7-Acetoxymethyl-1-(2-chloroethyl)-1,4-dihydro-6-fluoro-4-oxoquinoline-3-carboxylate (32f)——By a procedure similar to that described above, **33f** was prepared from **32e**. mp 140—143°C. NMR (CF_3CO_2D) δ: 1.59 (3H, t, J=7 Hz), 4.18 (2H, t, J=5 Hz), 4.75 (2H, q, J=7 Hz), 4.95 (2H, s), 5.29 (2H, t, J=5 Hz), 8.42 (1H, d, J=10 Hz), 8.47 (1H, d, J=5 Hz), 9.39 (1H, s).

General Procedure for Preparation of Ethyl 1-Alkyl-1,4-dihydro-7-hydroxymethyl-4-oxoquinoline-3-carboxylates (34 and 35) (Table V)

Typical Procedure: Ethyl 1,4-dihydro-6-fluoro-7-hydroxymethyl-4-oxoquinoline-3-carboxylate (34a)——A suspension of **32a** (6.7 g, 0.02 mol) in 12.6% HCl–EtOH (230 ml) was stirred at room temperature for 19 h. The reaction mixture was concentrated to dryness and the residue was dissolved in cold H_2O. The aqueous solution was neutralized with $NaHCO_3$. The precipitate that had formed was collected by filtration and washed with H_2O and 2-propanol to afford almost pure **34a** (5.2 g, 88%), mp 188—190°C. Recrystallization

TABLE V. Ethyl 1-Substituted-1,4-dihydro-7-hydroxymethyl-4-oxoquinoline-3-carboxylates



Compd. No.	X	R	Yield (%)	mp (°C)	Recryst. solv.[b]	Formula	Analysis (%) Calcd (Found) C	H	N
34a	H	C_2H_5	88	195—196	A	$C_{15}H_{16}FNO_4$	61.43 (61.65	5.50 5.51	4.78 4.75)
34b	H	CH_2CH_2F	94	215—217	B	$C_{15}H_{15}F_2NO_4$	57.88 (57.81	4.86 4.89	4.50 4.38)
34c	H	CH_2CF_3	94	226—228	A	$C_{15}H_{13}F_4NO_4$	51.88 (51.88	3.77 3.86	4.03 4.05)
34d	H	CHF_2	60	171—173	A	$C_{14}H_{12}F_3NO_4$	53.34 (53.11	3.84 3.79	4.44 4.40)
34f	H	CH_2CH_2Cl	87	236—238[a]	B	$C_{15}H_{15}ClFNO_4$	54.97 (54.73	4.61 4.61	4.27 4.27)
35a	F	C_2H_5	83	170—172	A	$C_{15}H_{15}F_2NO_4$	57.88 (57.46	4.86 4.86	4.50 4.56)
35b	F	CH_2CH_2F	89	177—180	A	$C_{15}H_{14}F_3NO_4$	54.71 (54.73	4.29 4.22	4.25 4.21)
45a	H	OCH_3	89	177—179	A	$C_{14}H_{14}FNO_5$	56.95 (57.20	4.78 4.79	4.74 4.75)
45b	H	OCH_2CH_2F	56	178—179	A	$C_{15}H_{15}FNO_5$	55.05 (54.93	4.62 4.65	4.28 4.25)

a) Decomposition.
b) A=EtOH; B=EtOH-DMF.

from EtOH gave an analytically pure sample as colorless needles, mp 195—196°C. NMR (DMSO-d_6) δ: 1.30 (3H, t, J=7 Hz), 1.41 (3H, t, J=7 Hz), 4.23 (2H, q, J=7 Hz), 4.39 (2H, q, J=7 Hz), 4.70 (2H, d, J=5 Hz), 5.59 (1H, t, J=5 Hz), 7.79 (1H, d, J=6 Hz), 7.79 (1H, d, J=10 Hz), 8.66 (1H, s).

Ethyl 4-Chloro-6-fluoro-7-methylquinoline-3-carboxylate (22)——A suspension of crude **16** (12.5 g, 0.05 mol), which was contaminated with **49** (about 20% by weight), in a mixture of phosphoryl chloride (40 ml) and toluene (200 ml) was heated for 1.5 h under reflux. After concentration of the reaction mixture *in vacuo*, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 5% aq. $NaHCO_3$ and dried with anhydrous $MgSO_4$. After evaporation of the solvent, the residue was triturated with *n*-hexane to afford **22** (6.8 g, 50% based on crude **16**) as a pale brown powder, mp 58—65°C. NMR ($CDCl_3$) δ: 1.47 (3H, t, J=7 Hz), 2.51 (3H, d, J=2 Hz), 4.46 (2H, q, J=7 Hz), 7.89 (1H, d, J=10 Hz), 7.93 (1H, d, J=6 Hz), 9.09 (1H, s). This sample was used in the next step without purification.

Ethyl 7-Acetoxymethyl-4-chloro-6-fluoroquinoline-3-carboxylate (42)——By a procedure similar to that described for the preparation of **22**, reaction of **30** (15.4 g, 0.05 mol) and phosphoryl chloride (40 ml) afforded **42** (15.5 g, 95%) mp 93—95°C. NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7 Hz), 2.20 (3H, s), 4.49 (2H, q, J=7 Hz), 5.37 (2H, s), 7.95 (1H, d, J=10 Hz), 8.10 (1H, d, J=6 Hz), 9.10 (1H, s).

Ethyl 4-Ethoxy-6-fluoro-7-hydroxymethylquinoline-3-carboxylate (43)——A freshly prepared solution of NaOEt (0.06 mol) in EtOH (150 ml) was added to a stirred suspension of **42** (16.3 g, 0.05 mol) in absolute EtOH (150 ml) at 5°C over a period of 1 h. Then, the mixture was concentrated to dryness and the residue was extracted with $CHCl_3$. The extract was washed with H_2O, dried with anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to give almost pure **43** (9.5 g, 65%). Recrystallization from 2-propanol–diisopropyl ether gave an analytically pure sample as colorless needles, mp 110—111°C. NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7 Hz), 1.50 (3H, t, J=7 Hz), 4.28 (2H, q, J=7 Hz), 4.44 (2H, q, J=7 Hz), 4.1—4.8 (1H, br s), 4.95 (2H, s), 7.70 (1H, d, J=11 Hz), 8.25 (1H, d, J=6.5 Hz), 9.01 (1H, s). *Anal.* Calcd for $C_{15}H_{16}FNO_4$: C, 61.43; H, 5.50; N, 4.78. Found: C, 61.47; H, 5.51; N, 4.79.

4-Chloro-3-ethoxycarbonyl-6-fluoro-7-methylquinoline 1-Oxide (23)——A solution of **22** (6.7 g, 25 mmol) and *m*-chloroperbenzoic acid (80% purity, 6.5 g, 30 mmol) in $CHCl_3$ (200 ml) was stirred at room temperature for 4 h. Then, 5% aq. K_2CO_3 (100 ml) was slowly added to the reaction mixture while maintaining the temperature below 10°C over a period of 25 min and stirring was continued for a further 1 h. The organic layer was separated, washed with H_2O, and dried with anhydrous $MgSO_4$. After evaporation of the solvent, the residue was triturated with diisopropyl ether and the crystals were collected by filtration to give almost pure **23** (6.5 g, 92%) as a colorless powder, mp 100—104°C. NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7 Hz), 2.56 (3H, d, J=2 Hz), 4.46 (2H, q, J=7 Hz), 7.95 (1H, d, J=10 Hz), 8.72 (1H, d, J=6 Hz), 8.83 (1H, s). *Anal.* Calcd for $C_{13}H_{11}ClFNO_3$: C, 55.04; H, 3.91; N, 4.94. Found: C, 55.30; H, 4.00; N, 4.75.

4-Ethoxy-3-ethoxycarbonyl-6-fluoro-7-hydroxymethylquinoline 1-Oxide (44)——By a procedure similar to that used for the preparation of **23**, the quinoline **43** was oxidized with *m*-chloroperbenzoic acid to give **44** in 81% yield, mp 133—135°C. NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7 Hz), 1.57 (3H, t, J=7 Hz), 4.29 (2H, q, J=7 Hz), 4.47 (2H, q, J=7 Hz), 4.96 (2H, br s), 5.3—5.9 (1H, br), 7.66 (1H, d, J=10 Hz), 8.78 (1H, s), 8.85 (1H, d, J=6 Hz). *Anal.* Calcd for $C_{15}H_{16}FNO_5$: C, 58.25; H, 5.21; N, 4.53. Found: C, 58.44; H, 5.24; N, 4.58.

Ethyl 1-Alkoxy-1,4-dihydro-6-fluoro-7-hydroxymethyl-4-oxoquinoline-3-carboxylates (45a, b) (Table V)

Typical Procedure——A suspension of **44** (6.2 g, 0.02 mol) in methyl iodide (100 ml) was heated for 24 h under reflux. After concentration of the mixture to dryness *in vacuo*, the residue was triturated with 2-propanol and the crystals were collected by filtration to give **45a** (5.3 g, 89%). Recrystallization from EtOH gave pure **45a** as colorless needles, mp 177—179°C. NMR (DMSO-d_6) δ: 1.30 (3H, t, J=7 Hz), 4.22 (3H, s), 4.24 (2H, q, J=7 Hz), 4.73 (2H, d, J=5 Hz), 5.63 (1H, t, J=5 Hz), 7.76 (1H, d, J=10 Hz), 7.81 (1H, d, J=6 Hz), 8.91 (1H, s).

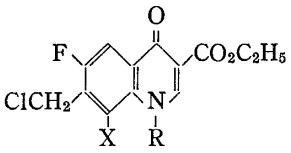
General Procedure for Preparation of Ethyl 1-Alkyl or 1-Alkoxy-7-chloromethyl-1,4-dihydro-4-oxoquinoline-3-carboxylates (36, 46, and 37) (Table VI)

Typical Procedure. Ethyl 7-Chloromethyl-1,4-dihydro-1-ethyl-6-fluoro-4-oxoquinoline-3-carboxylate (36a)——A mixture of **34a** (5.86 g, 0.02 mol), $SOCl_2$ (4.8 g, 0.04 mol), $ZnCl_2$ (2.73 g, 0.02 mol) and $CHCl_3$ (150 ml) was stirred at room temperature for 4 h. Then, additional portions of $SOCl_2$ (2.4 g, 0.02 mol) and $ZnCl_2$ (1.36 g, 0.01 mol) were added to the mixture and stirring was continued at room temperature for 2 h. After concentration of the mixture, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with cold H_2O and then with 5% aq. $NaHCO_3$. The $CHCl_3$ solution was dried with anhydrous $MgSO_4$ and the solvent was removed by evaporation. The residue was triturated with 2-propanol to afford almost pure **36a** (6.0 g, 96%). Recrystallization from EtOH gave an analytically pure sample as colorless prisms, mp 189—191°C. NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 1.57 (3H, t, J=7 Hz), 4.28 (2H, q, J=7 Hz), 4.38 (2H, q, J=7 Hz), 4.76 (2H, s), 7.56 (1H, d, J=6 Hz), 8.10 (1H, d, J=10 Hz), 8.47 (1H, s).

General Procedure for Preparation of Ethyl 1-Alkyl or 1-Alkoxy-1,4-dihydro-7-fluoromethyl-4-oxoquinoline-3- carboxylates (38, 39, and 48) (Table VII)

Typical Procedure. Ethyl 1,4-Dihydro-1-ethyl-6-fluoro-7-fluoromethyl-4-oxoquinoline-3-carboxylate (38a)——A mixture of **36a** (3.1 g, 0.01 mol), cesium fluoride (4.6 g, 0.03 mol) and diethyleneglycol (7.5 ml)

Table VI. Ethyl 1-Substituted-1,4-dihydro-7-chloromethyl-4-oxoquinoline-3-carboxylates



Compd. No.	X	R	Yield (%)	mp (°C)	Recryst. solv.[b]	Formula	Analysis (%) Calcd (Found) C	H	N
36a	H	C_2H_5	96	189—191	A	$C_{15}H_{15}ClFNO_3$	57.79 (57.84	4.85 4.89	4.49 4.53)
36b	H	CH_2CH_2F	94	188—189	A	$C_{15}H_{14}ClF_2NO_3$	54.64 (54.66	4.28 4.25	4.25 4.26)
36c	H	CH_2CF_3	90	198—200	A	$C_{15}H_{12}ClF_4NO_3$	49.26 (49.07	3.31 3.35	3.83 3.95)
36d	H	CHF_2	94	195—197	A	$C_{14}H_{11}ClF_3NO_3$	50.39 (50.20	3.32 3.35	4.20 4.16)
36f	H	CH_2CH_2Cl	91	216—218[a]	B	$C_{15}H_{14}Cl_2FNO_3$	52.04 (51.99	4.08 4.02	4.05 4.15)
37a	F	C_2H_5	95	132—134	A	$C_{15}H_{14}ClF_2NO_3$	54.64 (54.45	4.28 4.27	4.25 4.24)
37b	F	CH_2CH_2F	100	177—179	A	$C_{15}H_{13}ClF_3NO_3$	51.81 (52.00	3.97 3.74	4.03 4.05)
46a	H	OCH_3	100	106—109	C	$C_{14}H_{13}ClFNO_4$	53.60 (53.78	4.18 4.30	4.47 4.45)
46b	H	OCH_2CH_2F	68	150—153	C	$C_{15}H_{14}ClF_2NO_4$	52.11 (51.87	4.08 4.05	4.05 4.03)

a) Decomposition.
b) A=EtOH; B=EtOH–DMF; C=2-propanol.

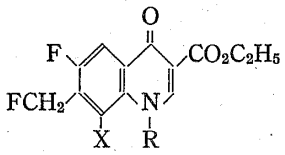
was heated at 130°C for 1.5 h with stirring. After cooling, the reaction mixture was diluted with $CHCl_3$. The mixture was washed with H_2O and dried with anhydrous $MgSO_4$. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to afford almost pure **38a** (1.7 g, 58%). Recrystallization from EtOH gave an analytical pure sample as colorless leaflets, mp 155—158°C. NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 1.57 (3H, t, J=7 Hz), 4.28 (2H, q, J=7 Hz), 4.39 (2H, q, J=7 Hz), 5.61 (2H, d, J=46 Hz), 7.52 (1H, d, J=6 Hz), 8.10 (1H, d, J=10 Hz), 8.45 (1H, s).

Ethyl 1,4-Dihydro-6-fluoro-7-fluoromethyl-4-oxo-1-vinylquinoline-3-carboxylate (38g)——A stirred mixture of **36f** (6.9 g, 0.02 mol), anhydrous KF (5.8 g, 0.1 mol) and diethyleneglycol (15 ml) was heated at 160°C for 0.5 h. After cooling, the mixture was dissolved in $CHCl_3$ and the solution was washed with H_2O. The $CHCl_3$ layer was dried with anhydrous $MgSO_4$ and the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to afford almost pure **38g** (0.4g, 7%) and 2-(2-hydroxyethoxy)ethyl 1,4-dihydro-6-fluoro-7-fluoromethyl-4-oxo-1-vinylquinoline-3-carboxylate **38h** (2.0 g, 28%). Recrystallization of crude **38g** from 2-propanol gave pure **38g** as colorless needles. mp 156—157°C. NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz), 4.42 (2H, q, J=7 Hz), 5.61 (2H, d, J=47 Hz), 5.48—5.85 (2H, m), 7.00—7.40 (1H, m), 7.57 (1H, d, J=6 Hz), 8.09 (1H, d, J=10 Hz), 8.60 (1H,s). Recrystallization of crude **38h** from EtOH–diisopropyl ether afforded pure **38h** as colorless needles. mp 113—115°C. NMR ($CDCl_3$) δ: 3.10—3.50 (1H, br s), 3.70—4.00 (6H, m), 4.40—4.60 (2H, m), 5.60 (2H, d, J=46 Hz), 5.50—5.85 (2H, m), 6.99—7.38 (1H, m), 7.55 (1H, d, J=6 Hz), 8.05 (1H, d, J=10 Hz), 8.59 (1H, s). *Anal.* Calcd for $C_{17}H_{17}F_2NO_5$: C, 57.79; H, 4.85; N, 3.96. Found: C, 57.56; H, 4.89; N, 4.06.

1,4-Dihydro-6-fluoro-1-hydroxy-6-methyl-4-oxoquinoline-3-carboxylic Acid (24)——A suspension of **23** (5.8 g, 0.02 mol) in a mixture of 1 N NaOH (80 ml) and MeOH (150 ml) was boiled for 4 h. After evaporation of MeOH, the aqueous residue was acidified with 10% HCl. The resulting precipitate was collected by filtration, washed with H_2O and dried to give almost pure **24** (4.5 g, 96%). Recrystallization from DMF–EtOH gave an analytically pure sample of **24** as a colorless powder, mp 224—225°C (dec.). NMR (CF_3CO_2D) δ: 2.73 (3H, br s), 8.23 (1H, d, J=10 Hz), 8.42 (1H, d, J=6 Hz), 9.43 (1H, s). *Anal.* Calcd for $C_{11}H_8FNO_4$: C, 55.70; H, 3.40; N, 5.91. Found: C, 55.44; H, 3.50; N, 5.90.

General Procedure for Preparation of 1-Substituted-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids (20, 21, 25, 40, 41, and 48) (Table I)

Table VII. Ethyl 1-Substituted-1,4-dihydro-7-fluoromethyl-4-oxoquinoline-3-carboxylates



Compd. No.	X	R	Yield (%)	mp (°C)	Recryst. solv.[b]	Formula	Analysis (%) Calcd (Found) C	H	N
38a	H	C_2H_5	58	155—158	A	$C_{15}H_{15}F_2NO_3$	61.01 (60.59	5.12 5.16	4.74 4.64)
38b	H	CH_2CH_2F	59	192—194	B	$C_{15}H_{14}F_3NO_3$	57.50 (57.51	4.50 4.54	4.47 4.53)
38c	H	CH_2CF_3	30	180—183	C	$C_{15}H_{12}F_5NO_3$	51.58 (51.42	3.46 3.46	4.01 3.96)
38d	H	CHF_2	6	183—185	—[c]	[d]			
38g	H	$CH^5{=}CH_2$	7	156—157	C	$C_{15}H_{13}F_2NO_3$	61.43 (61.20	4.49 4.41	4.78 4.96)
39a	F	C_2H_5	27[a]	115—117	A	$C_{15}H_{14}F_3NO_3$	57.50 (57.59	4.50 4.47	4.47 4.54)
39b	F	CH_2CH_2F	28[a]	161—163	C	$C_{15}H_{13}F_4NO_3$	54.38 (54.03	3.96 3.84	4.23 4.27)
47a	H	OCH_3	50	119—121	D	$C_{14}H_{13}F_2NO_4$	56.57 (56.43	4.41 4.41	4.71 4.55)
47b	H	OCH_2CH_2F	61	138—140	C	$C_{15}H_{14}F_3NO_4$	54.71 (54.71	4.29 4.26	4.25 4.24)

a) Reaction time was 0.5 h.
b) A=EtOH; B=DMF–EtOH; C=2-propanol; D=2-propanol–diisopropyl ether.
c) Not recrystallized.
d) Not analyzed.

Typical Examples: Method A. 1,4-Dihydro-6-fluoro-1-fluoroethyl-7-methyl-4-oxoquinoline-3-carboxylic Acid (20b)——A 1 N NaOH solution (220 ml) was added in one portion to a suspension of **18b** (29.5 g, 0.1 mol) in a mixture of EtOH (500 ml) and H_2O (280 ml) at room temperature and stirring was continued for 4 h. The clear reaction mixture was concentrated to about half of the initial volume. The concentrate was acidified with 10% HCl to give a crystalline product; 25.4 g (95%); mp 285—286°C. Recrystallization from DMF gave **20b** as colorless needles, mp 286—288°C. NMR (CF_3CO_2D) δ: 2.71 (3H, d, J=2 Hz), 4.5—5.4 (4H, m), 8.13 (1H, d, J=6 Hz), 8.39 (1H, d, J=10 Hz), 9.33 (1H, s).

Method B. 1-Difluoromethyl-1,4-dihydro-6-fluoro-7-methyl-4-oxoquinoline-3-carboxylic Acid (20d)——A solution of **18d** (1.0 g, 3.3 mmol) and Me_3SiI (90% purity) (1.67 g, 9.3 mmol) in $CHCl_3$ (30 ml) was heated for 23 h under reflux. After cooling, the reaction mixture was poured into H_2O and the resulting precipitate was collected by filtration. The precipitate was washed with H_2O and dried. The product (0.65 g, 72%) was recrystallized from DMF to give pure **20d** as colorless prisms, mp 250—252°C. NMR (CF_3CO_2D) δ: 2.73 (3H, d, J=2 Hz), 8.00 (1H, t, J=58 Hz), 8.20—8.45 (2H, m), 9.68 (1H, s).

Method C. 1,4-Dihydro-6-fluoro-7-methyl-4-oxo-1-vinylquinoline-3-carboxylic Acid (20g)——Compound **18f** (1.6 g, 5 mmol) was added to a freshly prepared solution of EtONa (35 mmol) in EtOH (50 ml), and the mixture was heated for 3.5 h under reflux. H_2O (30 ml) was added to this mixture and reflux was continued for a further 1 h. After concentration of the mixture to dryness, the residue was dissolved in H_2O and then acidified with 10% HCl. The resulting precipitate was collected by filtration, washed with H_2O and dried to give almost pure **20g** (1.35 g, quantitative). Recrystallization from DMF gave an analytically pure sample as colorless needles, mp 219—222°C. NMR (CF_3CO_2D): 2.70 (3H, d, J=2 Hz), 5.95—6.25 (2H, m), 7.35—7.75 (1H, m), 8.05 (1H, d, J=6 Hz), 8.26 (1H, d, J=10 Hz), 9.28 (1H, s).

Method D. 1,4-Dihydro-6-fluoro-1-methoxy-7-methyl-4-oxoquinoline-3-carboxylic Acid (25a)——Methyl iodide (5.7 g, 40 mmol) was added dropwise to a stirred solution of **24** (1.2 g, 5 mmol) in a mixture of 0.5 N KOH (30 ml) and MeOH (20 ml) at 40°C. Stirring was continued overnight at the same temperature. MeOH was removed from the reaction mixture by concentration *in vacuo*. The aqueous residue was acidified with 10% HCl to afford a crude product (1.1 g, 87%). Recrystallization from DMF–EtOH gave pure **25a**, mp 248—250°C (dec.). NMR (CF_3CO_2D) δ: 2.75 (3H, br s), 4.56 (3H, s), 8.25 (1H, d, J=6 Hz), 8.27 (1H, d, J=10 Hz), 9.52 (1H, s).

Antibacterial Activity Testing——Antimicrobial activities of the test compounds are shown as the minimum inhibitory concentration (MIC) determined by an agar dilution method using the serial twofold dilution technique. The concentrations of the compounds in the plates were 100, 50, 25,....1.56, 0.78 μg/ml (serial twofold dilutions). MIC was defined as the lowest concentration of a compound that prevented visible growth of bacteria after incubation at 37°C for 18 h.

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