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Studies on biologically Active Haloganenated Compounds. III.[1] Synthesis and Antibacterial Activity of 7-Fluoromethyl-1,8-naphthyridine and Quinoline Derivatives

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Some novel compounds having a fluoromethyl group at the C_7-position on 1-alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid and on 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid were prepared and their antibacterial activities were examined *in vitro*. In a series of quinolines, no striking difference of antibacterial activities between the 7-fluoromethyl and 7-methyl derivatives was observed. However, the activity was increased in the series of 1,8-naphthyridines by replacement of the methyl group with the fluoromethyl group. As regards the N_1-substituents, the 2-fluoroethyl compound showed a higher activity than the others.

Keywords——4-oxo-1,8-naphthyridine-3-carboxylic acid; 4-oxoquinoline-3-carboxylic acid; fluorination; fluoromethyl group; antibacterial activity

Numerous investigations of 1-alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids and 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids have been carried out in the hope of finding useful antibacterial agents since Lesher *et al.*[2] discovered that nalidixic acid exhibited a marked antibacterial activity against gram-negative bacilli. During the last two decades, closely related compounds such as oxolinic acids,[3] piromidic acid,[4] pipemidic acid,[5] and AB-206[6] have been found. An extensive study[7] on the structure-activity relationships has shown that the substituent at the 7-position of the aromatic ring has a significant effect on the activity, and the N_1-substituent also plays an important role. Among the various N_1-substituents, smaller radicals, especially the ethyl group, generally give the best result. In some cases, however, the N_1-ethyl group can be replaced by a 2-fluoroethyl, vinyl, or methoxy group without lowering the activity.

In a series of studies[1] on the synthesis of biologically active halogenated compounds, we reported that introduction of a fluoromethyl group into the 4(3*H*)-quinazolinone ring gave rise to a remarkable increase in CNS depressant activity and a dramatic reduction of toxicity.

Our next target for the introduction of the fluoromethyl group into a heterocyclic molecule was nalidixic acid and related compounds, since we hoped that the replacement of the 7-methyl group with a fluoromethyl group would lead to enhancement of the antibacterial activity of the mother compounds. Some N_1 2-fluoroethyl or 2,2,2-trifluoroethyl analogs with a 7-fluoromethyl group have attracted our interest largely because of their increased fat solubility due to the introduction of multiple fluorine atoms.[8]

This paper describes the synthesis and antibacterial activity of fluorinated derivatives of 1,8-naphthyridine and quinoline.

Chemistry

Among the synthetic routes for the 7-fluoromethyl derivatives of both 1,8-naphthyridine and quinoline, fluorination of the 7-chloromethyl group of ethyl 1-alkyl-7-chloromethyl-1,4-dihydro-4-oxo-1,8-naphthyridine (or quinoline)-3-carboxylate (**4** or **10**) was a key step in this study, as shown in Chart 1. The choice of a suitable fluorinating agent was required in each

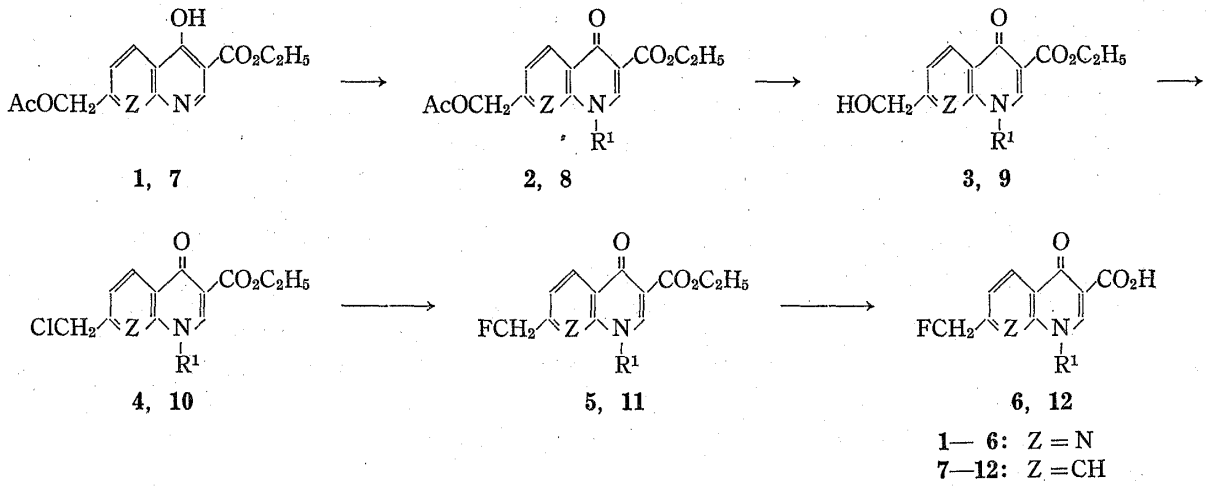


Chart 1

reaction depending on the stability of the substituent (R^1) at the N_1 as well as the reactivity of the chlorine atom, which is influenced by the conjugated nitrogen atom at the neighboring 8-position of 1,8-naphthyridine.

(a) **Preparation of 7-Chloromethyl-1,8-naphthyridines 4**——The reaction conditions for *N*-alkylation of ethyl 7-acetoxymethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**1**), which was prepared according to the method of Lesher,[9] depended upon the reactivity of the alkyl halide used: the alkylation proceeded easily with ethyl iodide or *p*-chlorobenzyl chloride at room temperature, and with 2-fluoroethyl bromide at 60°C. However, when alkyl halides with low boiling points and/or less reactivity such as 2,2,2-trifluoroethyl iodide and difluoromethyl chloride were used, it was necessary to carry out the reaction in a sealed glass vessel at 120°C.

Deacetylation of 7-acetoxymethyl-1-alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates (**2**) was achieved with HCl–EtOH at room temperature to afford the hydroxymethyl derivatives **3**, which were chlorinated with $SOCl_2$–$ZnCl_2$ to give the corresponding 7-chloromethyl compounds **4a—e**. The results are summarized in Tables 4,5, and 6.

(b) **Preparation of 7-Chloromethylquinolines 10**——Gould–Jacobs cyclization of diethyl 3-acetoxymethylanilinomethylenemalonate (**15**) gave two isomers, the 7-acetoxymethyl and 5-acetoxymethyl quinoline derivatives (**7** and **16**) shown in Chart 2. The major isomer **7** was easily isolated by recrystallization of the crude mixture from dimethylformamide (DMF). The structural assignment of **7** was based on the results of elemental analysis and nuclear magnetic resonance (NMR) spectroscopy. In the NMR spectrum (in CF_3CO_2D) of **7**, the methylene signal of a CH_2OAc group appeared at δ 5.56 (2H, s) and four aromatic proton signals were observed at δ 7.96 (1H, d, J=8.5 Hz), 8.12 (1H, s), 8.69 (1H, d, J=8.5 Hz), and 9.33 (1H, s). The absorption pattern of the aromatic protons supports the structure **7**. It was difficult to isolate the minor isomer **16** in a pure state. The NMR spectrum (in CF_3CO_2D) of **16** contaminated with **7** exhibited, in addition to the absorption due to **7**, a singlet at δ 5.92 assignable to methylene protons of the CH_2OAc group, a 3H multiplet at δ 7.8—8.4 characteristic of aromatic protons on the benzene ring, and a singlet at δ 9.36 due to C_2–H. The ratio of **7** and **16** in the crude mixture was estimated to be about 4: 1 by NMR measurement. *N*-Alkylation of **7** followed by deacetylation and chlorination at the C_7-substituent gave **10a—e** as shown in Chart 1.

On the other hand, 7-chloromethyl-1-alkoxyquinoline derivatives (**10h, i**) were prepared from **7** *via* 5 steps (**7**→**17**→**18**→**19**→**9**→**10**), including selective alkylation of the corresponding *N*-oxide (**19**) as shown in Chart 3, followed by chlorination (Chart 1).

(c) **Fluorination of the 7-Chloromethyl Derivatives 4 and 10**——Potassium fluoride (KF) is one of the most common fluorinating agents the displacement of chlorine, and we used it

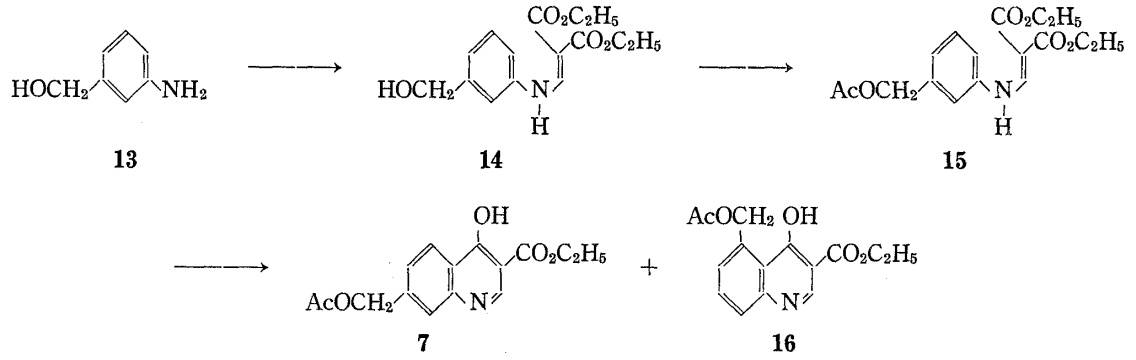


Chart 2

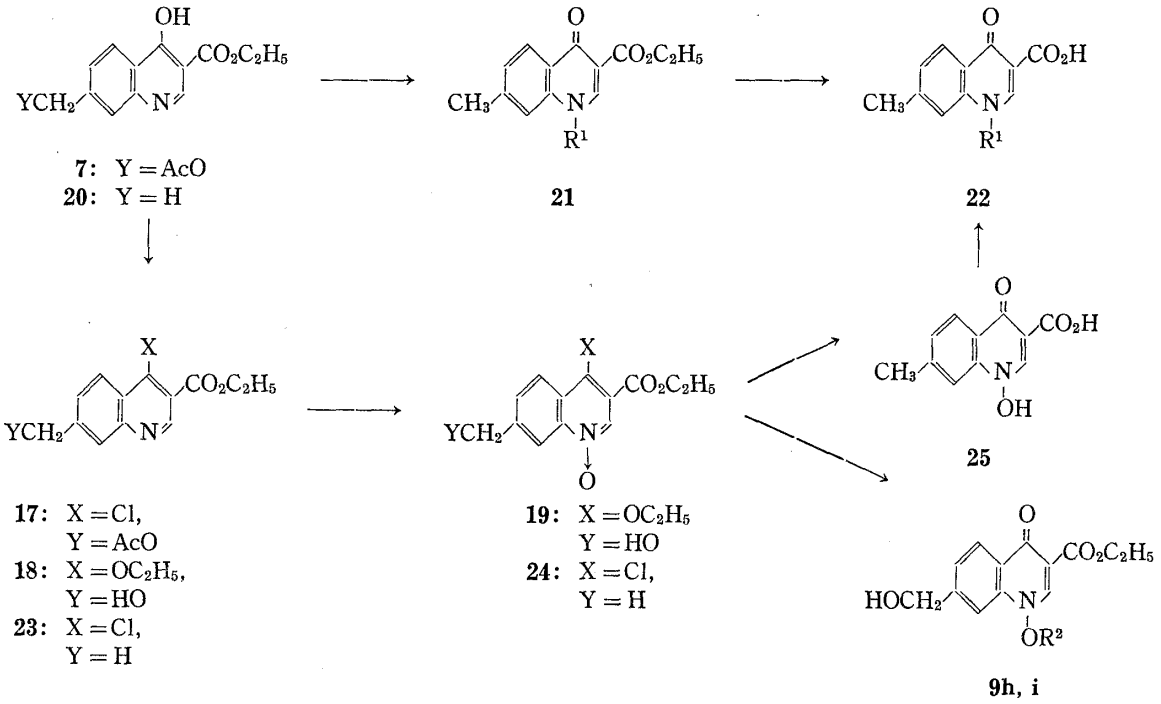


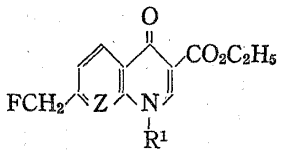
Chart 3

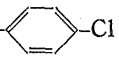
without difficulty to give the fluoromethyl derivatives of 4(3*H*)-quinazolinone as described in the previous papers.[1] In fact, in some quinolines **10** with a stable substituent such as an ethyl group at the N_1-position, replacement of the 7-chloromethyl group with fluoromethyl proceeded under the same reaction conditions as used previously. However, a partial ester exchange at the 3-carboxylate was observed during the fluorination reaction in diethyleneglycol. Moreover, when the 2-chloroethyl derivatives **10f** was treated with KF, elimination of hydrogen chloride and partial ester exchange took place simultaneously to form a mixture of the ethyl ester (**11g**) and 2-(2-hydroxyethoxy)ethyl ester (**11k**) of 1,4-dihydro-7-fluoromethyl-4-oxo-1-vinylquinoline-3-carboxylic acid.

On the other hand, in the cases of 1,8-naphthyridines, the basicity of KF would be unfavorable for the fluorination reaction **4a** was rapidly decomposed and polymerized into a tar on heating with KF at 160°C in diethyleneglycol.

The use of potassium hydrogen difluoride (KHF_2), an acidic fluorinating agent, gave a better result on heating with **4a** at 160°C. In contrast, when **4b** was treated with KHF_2 under the same reaction conditions, the desired 7-fluoromethyl compound (**5b**) was hardly obtained. In this case, sensitivity of the 2-fluoroethyl group substituted at the N_1-position to diethyl-

Table I. 7-Fluoromethyl Compounds **5** and **11**



Compd. No.	Z	R^1	Reagent	Yield (%)	mp (°C)	Recryst. solv.[a]	Formula	Analysis (%) Calcd (Found) C	H	N
5a	N	C_2H_5	KHF_2	36	137—139	A	$C_{14}H_{15}FN_2O_3$	60.42 (60.33	5.43 5.60	10.07 9.88)
5b	N	CH_2CH_2F	CsF	64	136—138	B	$C_{14}H_{14}F_2N_2O_3$	56.75 (56.67	4.76 4.73	9.46 9.56)
5c	N	CH_2CF_3	$CsF(KHF_2)$	33(27)	180—181	C	$C_{14}H_{12}F_4N_2O_3$	50.61 (50.69	3.64 3.63	8.43 8.42)
5d	N	CH_2-  -Cl	KHF_2	32	136—137	D	$C_{19}H_{16}ClFN_2O_3$	60.89 (60.78	4.30 4.21	7.48 7.56)
5e	N	CHF_2	$CsF(KHF_2)$	37(29)	105—106	E	$C_{13}H_{11}F_3N_2O_3$	52.00 (52.14	3.69 3.77	9.33 9.34)
11a	CH	C_2H_5	KF	16	156—157	A	$C_{15}H_{16}FNO_3$	64.97 (64.78	5.82 5.94	5.05 5.02)
11b	CH	CH_2CH_2F	CsF	56	190—192	D	$C_{15}H_{15}F_2NO_3$	61.01 (60.89	5.12 5.10	4.74 4.81)
11c	CH	CH_2CF_3	CsF	32	175—176	A	$C_{15}H_{13}F_4NO_3$	54.38 (54.33	3.96 4.00	4.23 4.16)
11g	CH	$CH=CH_2$	KF	3	111—112	E	$C_{15}H_{14}FNO_3$	65.45 (65.35	5.13 5.16	5.09 4.95)
11h	CH	OCH_3	CsF	58	115—117	E	$C_{14}H_{14}FNO_4$	60.21 (60.36	5.05 5.13	5.02 5.00)
11i	CH	OCH_2CH_2F	CsF	61	130—131	A	$C_{15}H_{15}F_2NO_4$	57.87 (57.76	4.86 4.83	4.50 4.47)

a) A=2-propanol; B=AcOEt–diisopropyl ether; C=AcOEt; D=EtOH; E=2-propanol–diisopropyl ether.

eneglycol (solvent) would be enhanced by the acidity of KHF_2, resulting in a complicated polymerized product.

Under these circumstances, the use of cesium fluoride (CsF) was found to give the best results: *e.g.*, when **4b** was treated with CsF in diethyleneglycol at 120°C, the yield of **5b** reached 64%. Thus, most of the fluorination reactions were carried out with CsF, which has weaker basicity than KF. The results are listed in Table I.

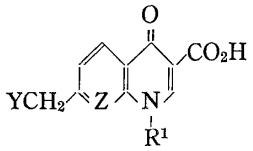
(d) **Hydrolysis of the Ethyl Carboxylates 5 and 11**——The ethyl carboxylates **5** and **11** were easily hydrolyzed with aqueous sodium hydroxide to give the corresponding carboxylic acids **6** and **12** except in one instance, the 1-difluoromethyl derivative **5e**. The difluoromethyl group was very sensitive to aqueous alkali and easily decomposed. Compound **6e** was prepared under neutral conditions using trimethylsilyl iodide. The results are listed in Table II.

To aid in the biological evaluation of the fluoromethyl group at C_7 on the skeleton, some 7-methyl derivatives **22** were prepared from **20** by application of the well-known procedures[6,11] shown in Chart 3.

Antibacterial Activity

The compounds synthesized here were screened for antibacterial activities against *Staphylocous aureus*, *Escherichia coli*, *Salmonella typhi*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* by the method described in the experimental section. These results are summarized in Table III. Replacement of 7-methyl with fluoromethyl in a series of 1,8-naphthyridines generally increased the activity. As regards the N_1-substituents in this series, the 2-fluoroethyl derivative (**6b**) showed a higher activity that the ethyl derivative (**6a**), while replacement with

TABLE II. 4-Oxo-1,8-naphthyridine-3-carboxylic Acids (**6**) and 4-Oxoquinoline-3-carboxylic Acids (**12** and **22**)



Compd. No.	Z	Y	R^1	Yield (%)	mp (°C)	Recryst. solv.[e]	Formula	Analysis (%) Calcd (Found) C	H	N
6a	N	F	C_2H_5	94	224—227	A	$C_{12}H_{11}FN_2O_3$	57.60 (57.28	4.40 4.77	11.20 11.40)
6b	N	F	CH_2CH_2F	90	195—197	B	$C_{12}H_{10}F_2N_2O_3$	53.73 (53.76	3.76 3.78	10.45 10.48)
6c	N	F	CH_2CF_3	96	178—181[c]	C	$C_{12}H_8F_4N_2O_3$	47.38 (47.32	2.65 2.76	9.21 9.14)
6d	N	F	CH_2-C$_6$H$_4$-Cl	85	240—241	B	$C_{17}H_{12}ClFNO_3$	58.88 (58.97	3.49 3.46	8.08 8.22)
6e	N	F	CHF_2	24	155—158	—[f]	[g]			
12a	CH	F	C_2H_5	98[a]	261—263	B	$C_{13}H_{12}FNO_3$	62.65 (62.46	4.85 5.00	5.62 5.90)
12b	CH	F	CH_2CH_2F	96	250—251	A	$C_{13}H_{11}F_2NO_3$	58.42 (58.21	4.15 4.14	5.24 5.20)
12c	CH	F	CH_2CF_3	85	253—257	B	$C_{13}H_9F_4NO_3$	51.49 (51.47	2.99 3.04	4.62 4.67)
12g	CH	F	$CH=CH_2$	92[b]	226—228	A	$C_{13}H_{10}FNO_3$	63.15 (62.93	4.08 4.11	5.67 5.62)
12h	CH	F	OCH_3	88	202—203	A	$C_{12}H_{10}FNO_4$	57.37 (57.42	4.01 4.02	5.58 5.55)
12i	CH	F	OCH_2CH_2F	100	189—192	A	$C_{13}H_{11}F_2NO_4$	55.12 (55.12	3.91 3.78	4.95 5.03)
22a	CH	H	C_2H_5	96	279—281[d]	A	—			
22b	CH	H	CH_2CH_2F	92	285—287	A	$C_{13}H_{12}FNO_3$	62.65 (62.74	4.85 4.85	5.85 5.62)
22c	CH	H	CH_2CF_3	88	289—291[c]	A	$C_{13}H_{10}F_3NO_3$	54.74 (55.03	3.53 3.53	4.91 5.13)
22e	CH	H	CHF_2	43	240—242	B	$C_{12}H_9F_2NO_3$	56.92 (56.68	3.58 3.58	5.53 5.52)
22g	CH	H	$CH=CH_2$	96	263—264	A	$C_{13}H_{11}NO_3$	68.11 (68.15	4.84 4.96	6.11 6.16)
22h	CH	H	OCH_3	69	230—232	B	$C_{12}H_{11}NO_4$	61.80 (62.17	4.75 4.88	6.01 6.09)
22i	CH	H	OCH_2CH_2F	64	207—208	B	$C_{13}H_{12}FNO_4$	58.57 (58.66	4.56 4.62	5.23 5.30)

a) Prepared from 2-(2-hydroxyethoxy)ethyl 1-ethyl-1,4-dihydro-7-fluoromethyl-4-oxoquinoline-3-carboxylate.
b) Prepared from 2-(2-hydroxyethoxy)ethyl 1,4-dihydro-7-fluoromethyl-4-oxo-1-vinylquinoline-3-carboxylate.
c) Decomposition.
d) Ref. 10, mp 283—284°C.
e) A=DMF; B=DMF–EtOH; C=EtOH.
f) Not recrystallized.
g) Not analyzed.

2,2,2-trifluoroethyl (**6c**) lowered the activity. The higher fat solubility of the 2,2,2-trifluoroethyl or *p*-chlorobenzyl group would not be effective because of the effect of bulkiness of the N_1-substituent. Thus, the highest antibacterial activity was observed in the 7-fluoromethyl-N_1-(2-fluoroethyl) compound (**6b**), which exhibited much higher activity than nalidixic acid. In the case of the quinoline derivatives, replacement with 7-fluoromethyl did not cause a marked improvement in activity compared with the corresponding 7-methyl compounds. However, among the N_1-substituents, the activities of the 2-fluoroethyl compounds (**12b** and

22b) were higher than those of the difluoromethyl (**22e**) and 2,2,2-trifluoroethyl (**12c** and **22c**) derivatives, or those of the ethyl, vinyl, methoxy, and 2-fluoroethoxy compounds. From the above results we may conclude that introduction of a fluoromethyl group at C_7 on the 1,8-naphthyridine nucleus increases the antibacterial activity, and that replacement of the N_1-substituent with a 2-fluoroethyl group can further improve the activity in both the 1,8-naphthyridine and the quinoline compounds.

Table III. *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
Nalidixic acid	>50	6.25	6.25	6.25	>50
6a	12.5	0.78	6.25	1.56	>50
6b	12.5	0.39	0.78	1.56	50
6c	6.25	6.25	6.25	6.25	>50
6d	50	>50	>50	>50	>50
12a	>50	6.25	6.25	6.25	>50
12b	50	6.25	3.13	3.13	>50
12c	>50	3.13	6.25	6.25	>50
12g	>50	25	50	25	50
12h	>50	12.5	50	25	>50
12i	>50	25	>50	50	>50
22a	>50	6.25	12.5	6.25	>50
22b	>50	1.25	3.13	3.13	>50
22c	>50	12.5	12.5	25	>50
22e	>50	25	>50	>50	>50
22g	>50	12.5	25	12.5	>50
22h	>50	12.5	25	25	>50
22i	>50	50	>50	50	>50

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.

General Procedure for Preparation of Ethyl 7-Acetoxymethyl-1-alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates (2) and Ethyl 7-Acetoxymethyl-1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylates (8) (Table IV)

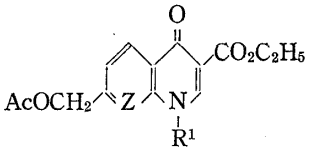
Typical Examples: A. Ethyl 7-Acetoxymethyl-1,4-dihydro-1-ethyl-4-oxo-1,8-naphthyridine-3-carboxylate (2a)——Sodium hydride (55% in oil dispersion. 5.2 g, 0.12 mol) was added portionwise to a stirred suspension of ethyl 7-acetoxymethyl-4-hydroxy-1,8-naphthyridine-3-carboxylate[9] (1, 29.0 g, 0.1 mol) in 1500 ml of DMF at room temperature. The mixture was stirred for 1 h at the same temperature. Then, ethyl iodide (31.2 g, 0.2 mol) was added to the reaction mixture and stirring was continued at room temperature for 20 h. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (1000 ml). The solution was washed with H_2O and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was triturated with EtOH (100 ml) and the crystals were collected by filtration to give **2a** (20.8 g), mp 129—133°C. From the mother liquor, a further crop of **2a** (3.7 g, mp 130—133°C) was obtained by chromatography on silica gel using $CHCl_3$ as an eluent. Recrystallization from EtOH gave analytically pure **2a** as colorless needles, mp 132—133°C. NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz), 1.51 (3H, t, J=7 Hz), 2.22 (3H, s), 4.42 (2H, q, J=7 Hz), 4.49 (2H, q, J=7 Hz), 5.33 (2H, s), 7.43 (1H, d, J=9 Hz), 8.67 (1H, s), 8.79 (1H, d, J=9 Hz).

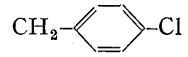
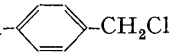
B. Ethyl 7-Acetoxymethyl-1-(2-chloroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (8f)——Sodium hydride (61% in oil dispersion, 0.5 g, 0.0125 mol) was added to a suspension of ethyl 7-acetoxymethyl-4-hydroxyquinoline-3-carboxylate (7, 2.89 g, 0.01 mol) in DMF (50 ml), and the mixture was stirred at room temperature for 1 h. Then, ethylene chlorohydrin (2.42 g, 0.03 mol) was added to the reaction mixture. The reaction mixture was stirred at 120°C for 20 h and concentrated to dryness under reduced pressure. The residue was dissolved in $CHCl_3$ (50 ml). The $CHCl_3$ solution was washed with H_2O and dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by trituration of the crystalline residue with EtOH (50 ml)

gave crude ethyl 7-acetoxymethyl-1,4-dihydro1-(2-hydroxyethyl)-4-oxoquinoline-3-carboxylate (1.72 g). A mixture of the above product (1.72 g), $SOCl_2$ (1.86 g, 0.015 mol), pyridine (1.24 g, 0.015 mol), and $CHCl_3$ (100 ml) was stirred at room temperature for 20.5 h, then the reaction mixture was concentrated to dryness and the residue was extracted with $CHCl_3$ (100 ml). The extract was washed with 5% aqueous $NaHCO_3$ and dried over 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 **8f** (1.08 g). Recrystallization from EtOH gave analytically pure **8f** as colorless needles, mp 135—136°C. NMR (DMSO-d_6) δ: 1.30 (3H, t, J=7 Hz), 2.13 (3H, s), 4.12 (2H, q, J=7 Hz), 4.29 (2H, t, J=6 Hz), 4.77 (2H, J=6 Hz), 5.24 (2H, s), 7.43 (1H, d, J=9 Hz), 7.78 (1H, s), 8.22 (1H, d, J=9 Hz), 8.66 (1H, s).

General Procedure for Preparation of Ethyl 1-Alkyl-1,4-dihydro-7-hydroxymethyl-4-oxo-1,8-naphthyridine-3-carboxylates (3) and Ethyl 1-Alkyl-1,4-dihydro-7-hydroxymethyl-4-oxoquinoline-3-carboxylates (9) (Table V)

Table IV. 7-Acetoxymethyl Compounds **2** and **8**



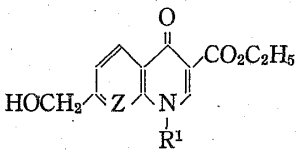
Compd. No.	Z	R^1	Reaction conditions: Reagent	Temp. (°C)	Time (h)	Yield (%)
2a	N	C_2H_5	C_2H_5I	r.t.	19	77
2b	N	CH_2CH_2F	FCH_2CH_2Br	60	16	70
2c	N	CH_2CF_3	CF_3CH_2I	120	8	56
2d	N			r.t.	24	70
2e	N	CHF_2	CHF_2Cl	120	5	66
8a	CH	C_2H_5	C_2H_5I	60	15	64
8b	CH	CH_2CH_2F	FCH_2CH_2Br	60	24	70
8c	CH	CH_2CF_3	CF_3CH_2I	120	17	28
8f [a]	CH	CH_2CH_2Cl	$HOCH_2CH_2Cl$	120	20	30[b]

Compd. No.	mp (°C)	Recryst. solv.[c]	Formula	Analysis (%) Calcd (Found) C	H	N
2a	132—133	A	$C_{16}H_{18}N_2O_5$	60.37 (60.36)	5.70 (5.71)	8.80 (8.75)
2b	162—163	B	$C_{16}H_{17}FN_2O_5$	57.14 (57.45)	5.10 (5.34)	8.33 (8.59)
2c	138—139	B	$C_{16}H_{15}F_3N_2O_5$	51.61 (51.47)	4.06 (4.05)	7.53 (7.54)
2d	148—149	C	$C_{21}H_{19}ClN_2O_5$	60.80 (60.88)	4.62 (4.68)	6.75 (6.71)
2e	121—122	B	$C_{15}H_{14}F_2N_2O_5$	52.94 (52.89)	4.15 (4.15)	8.23 (8.17)
8a	142—144	A	$C_{17}H_{19}NO_5$	64.34 (64.33)	6.04 (6.16)	4.41 (4.37)
8b	157—159	A	$C_{17}H_{18}FNO_5$	60.89 (60.73)	5.41 (5.47)	4.18 (4.12)
8c	171—172	D	$C_{17}H_{16}F_3NO_5$	54.99 (55.11)	4.34 (4.33)	3.77 (4.00)
8f [a]	135—136	A	$C_{17}H_{18}ClNO_5$	58.04 (58.15)	5.16 (5.13)	3.98 (4.01)

a) Prepared from **7** *via* 2 steps. See "Experimental."
b) Based on **7**.
c) A=EtOH; B=AcOEt; C=2-propanol; D=EtOH–diisopropyl ether.

Typical Example: Ethyl 1,4-Dihydro-1-(2-fluoroethyl)-7-hydroxymethyl-4-oxo-1,8-naphthyridine-3-carboxylate (3b)——A solution of **2b** (16.8 g, 0.05 mol) in 10% HCl–EtOH (500 ml) was allowed to stand at room temperature for 18 h. After evaporation of the solvent, the residue was dissolved in cold H_2O (300 ml) and the solution was neutralized with $NaHCO_3$. An oily product was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was triturated with EtOH to give **3b** (13.2 g) as a pale yellow powder. Recrystallization from EtOH gave analytically pure **3b** as colorless needles, mp 153—154°C. (dec.). NMR (DMSO-d_6) δ: 1.30 (3H, t, J=7 Hz), 4.0—5.8 (9H, m), 7.60 (1H, d, J=9 Hz), 8.54 (1H, d, J=9 Hz), 8.73 (1H, s).

TABLE V. 7-Hydoxymethyl Compounds **3** and **9**



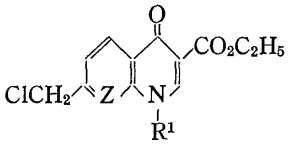
Compd. No.	Z	R^1	Yield (%)	mp (°C)	Recryst. solv.[c]	Formula	Analysis (%) Calcd (Found) C	H	N
3a	N	C_2H_5	93	171—172[b]	A	—			
3b	N	CH_2CH_2F	90	153—154	A	$C_{14}H_{15}FN_2O_4$	57.14 (57.25	5.14 5.11	9.52 9.61)
3c	N	CH_2CF_3	91	171—172	B	$C_{14}H_{13}F_3N_2O_4$	50.91 (50.90	3.97 3.94	8.48 8.54)
3d	N	CH_2-C$_6$H$_4$-Cl	96	151—154	C	$C_{19}H_{17}ClN_2O_4$	61.22 (61.08	4.60 4.69	7.51 7.46)
3e	N	CHF_2	63	111—112	D	$C_{13}H_{12}F_2N_2O_4$	52.34 (52.21	4.06 4.15	9.39 9.36)
9a	CH	C_2H_5	71	173—175	A	$C_{15}H_{17}NO_4$	65.44 (65.46	6.22 6.31	5.09 5.10)
9b	CH	CH_2CH_2F	95	177—180	A	$C_{15}H_{16}FNO_4$	61.43 (61.14	5.50 5.40	4.78 4.65)
9c	CH	CH_2CF_3	81	189—190	C	$C_{15}H_{14}F_3NO_4$	54.74 (54.66	4.29 4.30	4.25 4.22)
9f	CH	CH_2CH_2Cl	90	218—221	E	$C_{15}H_{16}ClNO_4$	58.16 (58.21	5.21 5.23	4.52 4.57)
9h	CH	OCH_3	70[a]	146—151	C	$C_{14}H_{15}NO_5$	60.64 (60.43	5.45 5.66	5.05 4.98)
9i	CH	OCH_2CH_2F	27[a]	139—140	C	$C_{15}H_{16}FNO_5$	58.25 (58.29	5.22 5.24	4.53 4.50)

a) Prepared from **19**.
b) Ref. 12, mp 173.5—174°C.
c) A=EtOH; B=AcOEt; C=2-propanol; D=2-propanol–diisopropyl ether; E=DMF–EtOH.

General Procedure for Preparation of Ethyl 1-Alkyl-7-chloromethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates (4) and Ethyl 1-Alkyl-7-chloromethyl-1,4-dihydro-4-oxoquinoline-3-carboxylates (10) (Table XI)
Typical Example: Ethyl 7-Chloromethyl-1,4-dihydro-1-ethyl-4-oxo-1,8-napthhyridine-3-carboxylate (4a)——$SOCl_2$ (9.5 g, 0.04 mol) was added dropwise to a stirred suspension of **3a** (11.0 g, 0.04 mol) and $ZnCl_2$ (5.4 g, 0.04 mol) in $CHCl_3$ (300 ml) at room temperature. The stirring was continued for 3.5 h. The reaction mixture was concentrated to dryness and the residue was dissolved in $CHCl_3$ (200 ml). The solution was washed with H_2O and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation and the residue was triturated with 2-propanol to afford almost pure **4a** (9.8 g). Recrystallization from 2-propanol gave a pure sample of **4a** as colorless needles, mp 135—137°C. NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz), 1.53 (3H, t, J=7 Hz), 4.43 (2H, q, J=7 Hz), 4.52 (2H, q, J=7 Hz), 4.76 (2H, s), 7.53 (1H, d, J=7 Hz), 8.64 (1H, s), 8.77 (1H, d, J=8 Hz).

General Procedure for Preparation of Ethyl 1-Alkyl-1,4-dihydro-7-fluoromethyl-4-oxo-1,8-naphthyridine-3-carboxylates (5) and Ethyl 1-Alkyl-1,4-dihydro-7-fluoromethyl-4-oxoquinoline-3-carboxylates (11) (Table I)
i) **Typical Procedure using Potassium Hydrogen Difluoride as a Fluorinating Reagent**——A mixture of **4a** (2.94 g, 0.01 mol), potassium hydrogen difluoride (3.91 g, 0.05 mol) and diethyleneglycol (10 ml) was

Table VI. 7-Chloromethyl Compounds **4** and **10**



Compd. No.	Z	R^1	Yield (%)	mp (°C)	Recryst. solv.[a]	Formula	Analysis (%) Calcd (Found) C	H	N
4a	N	C_2H_5	83	135—137	A	$C_{14}H_{15}ClN_2O_3$	57.05 (56.87	5.13 5.30	9.51 9.20)
4b	N	CH_2CH_2F	93	139—140	B	$C_{14}H_{14}ClFN_2O_3$	53.77 (53.74	4.51 4.53	8.96 9.00)
4c	N	CH_2CF_3	47	152—153	B	$C_{15}H_{12}ClF_3N_2O_3$	48.22 (48.34	3.47 3.46	8.03 8.02)
4d	N	CH_2-C$_6$H$_4$-Cl	89	154—155	A	$C_{19}H_{16}Cl_2N_2O_3$	58.22 (58.49	4.12 4.29	7.16 7.16)
4e	N	CHF_2	38	116—117	C	$C_{13}H_{11}ClF_2N_2O_3$	49.30 (49.10	3.50 3.49	8.85 8.71)
10a	CH	C_2H_5	89	133—134	B	$C_{15}H_{16}ClNO_3$	61.23 (61.44	5.49 5.59	4.77 4.88)
10b	CH	CH_2CH_2F	93	186—188	D	$C_{15}H_{15}ClFNO_3$	57.79 (57.62	4.85 4.88	4.49 4.44)
10c	CH	CH_2CF_3	92	204—205	D	$C_{15}H_{13}ClF_3NO_3$	51.81 (51.62	3.77 3.98	4.03 3.98)
10f	CH	CH_2CH_2Cl	82	219—221	E	$C_{15}H_{15}Cl_2NO_3$	54.89 (55.10	4.61 4.72	4.27 4.47)
10h	CH	OCH_3	86	118—119	F	$C_{14}H_{14}ClNO_4$	56.86 (57.02	4.77 4.86	4.74 4.73)
10i	CH	OCH_2CH_2F	75	147—149	B	$C_{15}H_5ClFNO_4$	54.97 (55.06	4.61 4.54	4.27 4.36)

a) A=2-propanol; B=AcOEt; C=diisopropyl ether; D=EtOH; E=DMF; F=2-propanol–diisopropyl ether.

heated at 160°C for 1 h. After cooling, the reaction mixture was poured into H_2O (100 ml) and extracted with $CHCl_3$. The extract was dried over anhydrous $MgSO_4$ and concentrated, then the residue was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to afford almost pure **5a** (1.35 g). Recrystallization from 2-propanol gave analytically pure **5a** as colorless plates, mp 137—139°C. NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7 Hz), 1.52 (3H, t, J=7 Hz), 4.45 (2H, q, J=7 Hz), 4.48 (2H, q, J=7 Hz), 5.59 (2H, d, J=47 Hz), 7.59 (1H, d, J=8 Hz), 8.68 (1H, s), 8.87 (1H, d, J=8 Hz).

In a similar manner, **5c**, **5d** and **5e** were prepared.

ii) Typical Procedure using Potassium Fluoride as a Fluorinating Reagent——A mixture of **10a** (5.87 g, 0.02 mol), anhydrous potassium fluoride (5.81 g, 0.1 mol) and diethyleneglycol (8 ml) was stirred at 160°C for 1 h. After cooling, the mixture was worked up as described above, including the purification by column chromatography on silica gel, to afford **11a** (0.90 g) as colorless prisms and 2-(2-hydroxyethoxy)ethyl 1-ethyl-1,4-dihydro-7-fluoromethyl-4-oxoquinoline-3-carboxylate (**11j**, 1.28 g, mp 139—142°C) as colorless prisms. The *Rf* values of **11a** and **11j** on thin layer chromatography (TLC) (silica gel plate, $CHCl_3$–MeOH=20: 1) were 0.48 and 0.24, respectively. NMR for **11a** ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz), 1.56 (3H, t, J=7 Hz), 4.27 (2H, q, J=7 Hz), 4.39 (2H, q, J=7 Hz), 5.55 (2H, d, J=46 Hz), 7.32 (1H, d, J=8 Hz), 7.43 (1H, s), 8.48 (1H, s), 8.52 (1H, d, J=8 Hz). NMR for **11j** ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 3.3—4.6 (11H, m), 5.62 (2H, d, J=46 Hz), 7.45 (1H, d, J=8 Hz), 7.78 (1H, s), 8.25 (1H, d, J=8 Hz), 8.67 (1H, s). The sample of **11j** was used in the next step without further purification.

In a similar manner, **11g** and 2-(2-hydroxyethoxy)ethyl 1,4-dihydro-7-fluoromethyl-4-oxo-1-vinylquinoline-3-carboxylate (**11k**) were obtained from **10f** in 3 and 30% yields, respectively. An analytical sample of **11g**, which was recrystallized from EtOH–diisopropylether, melted at 111—112°C; NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 4.39 (2H, q, J=7 Hz), 5.4—5.8 (2H, m), 5.51 (2H, d, J=46 Hz), 6.95—7.4 (2H, m), 7.42 (1H, s), 8.47 (1H, d, J=8 Hz), 8.57 (1H, s). Recrystallization of crude **11k** from EtOH gave analytically pure **11k** as a colorless powder, mp 116—118°C. NMR ($CDCl_3$) δ: 3.5—4.0 (7H, m), 4.35—4.6 (2H, m), 5.45—5.85 (2H, m), 5.49 (2H, d, J=46 Hz), 6.95—7.3 (1H, m), 7.29 (1H, d, J=8 Hz), 7.39 (1H, s), 8.36 (1H, d, J=8 Hz), 8.54 (1H, s). *Anal.* Calcd for $C_{17}H_{18}FNO_5$: C, 60.89; H, 5.41; N, 4.16. Found: C, 60.88; H, 5.39;

N, 4.14.

iii) **Typical Procedure using Cesium Fluoride as a Fluorinating Reagent**——A mixture of **4b** (3.13 g, 0.01 mol), anhydrous cesium fluoride (4.77 g, 0.03 mol) and diethyleneglycol (5 ml) was stirred at 120°C for 80 min. After cooling, the mixture was worked up in the manner described above to afford **5b** (1.9 g). NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 4.2—5.3 (6H, m), 5.50 (2H, d, J=46 Hz), 7.53 (1H, d, J=9 Hz), 8.59 (1H, s), 8.90 (1H, d, J=9 Hz).

In a similar manner, fluorinations of **4c**, **4e**, **10b**, **10c**, **10h** and **10i** were carried out to afford the corresponding fluoromethyl derivatives, **5c**, **5e**, **11b**, **11c**, **11h** and **11i**.

General Procedure for Preparation of 1-Alkyl-1,4-dihydro-7-fluoromethyl-4-oxo-1,8-naphthyridine-3-carboxylic Acids (6) and 1-Alkyl-1,4-dihydro-7-fluoromethyl-4-oxoquinoline-3-carboxylic Acids (12) (Table 2)

Typical Examples: **A. 1,4-Dihydro-1-ethyl-7-fluoromethyl-4-oxo-1,8-naphthylidine-3-carboxylic Acid (6a)**——A suspension of **5a** (2.78 g, 0.01 mol) in EtOH (100 ml) and 0.5 N NaOH (50 ml) was stirred at room temperature for 2 h. Most of the EtOH was removed *in vacuo* and the aqueous residue was acidified with 10% HCl. The precipitate which had formed was collected by filtration, washed with H_2O, and dried to give almost pure **6a** (2.35 g) as a colorless powder. Recrystallization from DMF gave a pure sample of **6a** as colorless needles, mp 224—227°C. NMR (CF_3CO_2D) δ: 1.77 (3H, t, J=7 Hz), 5.15 (2H, q, J=7 Hz), 5.77 (2H, d, J=46 Hz), 8.26 (1H, d, J=8.5 Hz), 9.18 (1H, d, J=8.5 Hz), 9.67 (1H, s).

B. 1-Difluoromethyl-1,4-dihydro-7-fluoromethyl-4-oxo-1,8-naphthyridine-3-carboxylic Acid (6e)——A mixture of **5e** (90 mg, 0.3 mmol) and commercial 90% trimethylsilyl iodide (170 mg, 0.75 mmol) in $CHCl_3$ (5 ml) was heated under reflux for 20 h. Then the same weight of trimethylsilyl iodide was further added to the reaction mixture and the whole was again heated for 24 h. After cooling, the reaction mixture was transferred into a separatory funnel and washed with H_2O. The $CHCl_3$ layer was dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to afford **6e** (20 mg) as a colorless powder, mp 155—158°C. NMR ($CDCl_3$) δ: 5.57 (2H, d, J=46 Hz), 7.25 (1H, d, J=9 Hz), 8.31 (1H, t, J=60 Hz), 8.85 (1H, d, J=9 Hz), 9.15 (1H, s).

Diethyl 2-(3-Hydroxymethylanilino)methylenemalonate (14)——A mixture of 3-hydroxymethylaniline (**13**, 4.57 g, 0.037 mol) and diethyl ethoxymethylenemalonate (9.66 g, 0.037 mol) was heated with stirring at 110—120°C for 0.5 h, then cooled. The resulting crystals were triturated with *n*-hexane and collected by filtration to give crude **14** (10.6 g, 97%). Recrystallization from *n*-hexane–diisopropyl ether gave analytically pure **14** as colorless needles, mp 58—59°C. NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7 Hz), 1.36 (3H, t, J=7 Hz), 3.06 (1H, br s), 4.22 (2H, q, J=7 Hz), 4.27 (2H, q, J=7 Hz), 4.66 (2H, s), 6.86—7.42 (4H, m), 8.43 (1H, d, J=13.5 Hz), 10.93 (1H, d, J=13.5 Hz). *Anal.* Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.47; H, 6.47; N, 4.82.

Diethyl 2-(3-Acetoxymethylanilino)methylenemalonate (15)——Acetic anhydride (1.23 g, 0.012 mol) was added to a solution of **14** (2.93 g, 0.01 mol) in AcOH (5 ml) and then the mixture was kept at 55—60°C for 20 h with stirring. After concentration of the reaction mixture, the residue was dissolved in H_2O (50 ml) and neutralized with $NaHCO_3$. The separated oil was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to afford almost pure **15** (3.24 g, 97%) as an oily substance. NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7 Hz), 1.37 (3H, t, J=7 Hz), 2.12 (3H, s), 4.24 (2H, q, J=7 Hz), 4.30 (2H, q, J=7 Hz), 5.09 (2H, s), 6.9—7.5 (4H, m), 8.46 (1H, d, J=13.5 Hz), 10.97 (1H, d, J=13.5 Hz).

Ethyl 7-Acetoxymethyl-4-hydroxyquinoline-3-carboxylate (7)——Compound **15** (16.8 g, 0.05 mol) was added portionwise to boiling diphenyl ether (180 ml) for 5 min and the reaction mixture was kept at 250—255°C for 15 min. After cooling, the mixture was triturated with 300 ml of *n*-hexane to afford 9.4 g of a mixture of the desired compound **7** and ethyl 5-acetoxymethyl-4-hydroxyquinoline-3-carboxylate (**16**), which was formed by cyclization at the 2-position on the benzene ring of **15**. Recrystallization of the mixture from DMF gave pure **7** (5.4 g, 37%) as colorless needles, mp 258—260°C. NMR (CF_3CO_2D) δ: 1.57 (3H, t, J=7 Hz), 2.37 (3H, s), 4.70 (2H, q, J=7 Hz), 5.56 (2H, s), 7.96 (1H, d, J=8.5 Hz), 8.12 (1H, s), 8.69 (1H, d, J=8.5 Hz), 9.33 (1H, s). From the mother liquor, a small amount of **16** contaminated with **7** was obtained; mp 200—230°C. The NMR spectrum of **16** in CF_3CO_2D was estimated to be as follows from the spectrum of this mixture, δ: 1.57 (3H, t, J=7 Hz), 2.38 (3H, s), 4.70 (2H, q, J=7 Hz), 5.92 (2H, s), 7.8—8.4 (3H, m), 9.36 (1H, s).

Ethyl 7-Acetoxymethyl-4-chloroquinoline-3-carboxylate (17)——A suspension of **7** (2.89 g, 0.01 mol) in a mixture of phosphoryl chloride (8 ml) and toluene (40 ml) was heated under reflux for 35 min. After cooling, the mixture was concentrated to dryness *in vacuo*. Addition of H_2O to the residue gave an aqueous mixture, which was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to afford **17** (2.28 g, 74%), as a pale brown powder, mp 64—66°C. Recrystallization from diisopropyl ether gave an analytically pure sample of **17** as colorless needles, mp 65—66°C. NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7 Hz), 2.20 (3H, s), 4.54 (2H, q, J=7 Hz), 5.37 (2H, s), 7.65 (1H, dd, J=9 Hz, J'=2 Hz), 8.13 (1H, br s), 8.41 (1H, d, J=9 Hz), 9.23 (1H, s). *Anal.* Calcd for $C_{15}H_{14}ClNO_4$: C, 58.54; H, 4.59; Cl, 11.52; N, 4.55. Found: C, 58.52; H, 4.66, Cl, 11.56; N, 4.51.

Ethyl 4-Ethoxy-7-hydroxymethylquinoline-3-carboxylate (18)——Finely powdered **17** (3.08 g, 0.01 mol) was added portionwise to a stirred solution of sodium ethoxide [which had been freshly prepared from Na (0.253 g, 0.011 mol) and anhydrous EtOH (35 ml)], at below 5°C over a period of 20 min. The stirring was continued at the same temperature for 30 min and then at room temperature for 2 h. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ and the solution was washed with H_2O. The $CHCl_3$ solution was dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was purified by column chromatography on silica gel using ethyl acetate as an eluent to give almost pure **18** (1.67 g, 61%), mp 77—79°C. Recrystallization from diisopropyl ether afforded an analytically pure sample of **18** as colorless needles, mp 78—79°C. NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz), 1.48 (3H, t, J=7 Hz), 4.26 (2H, q, J=7 Hz), 4.41 (2H, q, J=7 Hz), 4.65—5.30 (1H, br s), 4.87 (2H, s), 7.46 (1H, dd, J=9 Hz, J'=2 Hz), 8.04 (1H, s), 8.10 (1H, d, J=9 Hz), 9.01 (1H, s). *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.68; H, 6.31; N, 5.07.

4-Ethoxy-3-ethoxycarbonyl-7-hydroxymethylquinoline 1-Oxide (19)——*m*-Chloroperbenzoic acid (80% purity, 1.72 g, 8 mmol) was added to a stirred solution of **18** (1.1 g, 4 mmol) in $CHCl_3$ (50 ml) at 5—10°C. Stirring was continued at room temperature for 2.5 h. Aqueous K_2CO_3 (5%, 50 ml) was added to the reaction mixture at a temperature below 10°C, and the mixture was kept at room temperature for 1 h with stirring. The $CHCl_3$ layer was separated and dried over $MgSO_4$. After removal of the solvent by evaporation, the residue was triturated with Et_2O to afford crude **19** (0.8 g, 69%) as a pale brown powder, mp 116—120°C. Recrystallization from a mixture of 2-propanol and diisopropyl ether gave a pure sample of **19** as pale yellow needles, mp 124—125°C. NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7 Hz), 1.52 (3H, t, J=7 Hz), 4.25 (2H, q, J=7 Hz), 4.44 (2H, q, J=7 Hz), 4.84 (2H, s), 5.05—5.45 (1H, br s), 7.53 (1H, dd, J=9 Hz, J'=2 Hz), 7.93 (1H, d, J=9 Hz), 8.47 (1H, br s), 8.75 (1H, s). *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.45; H, 5.98; N, 4.72.

Ethyl 1,4-Dihydro-7-hydroxymethyl-1-methoxy-4-oxoquinoline-3-carboxylate (9h)——A mixture of **19** (0.87 g, 3 mmol) and methyl iodide (10 ml) was heated under reflux for 4 h. The mixture was concentrated to dryness and the residue was triturated with a mixture of Et_2O and 2-propanol to afford crude **9h** (0.58 g) as a pale brown powder, mp 143—149°C. Recrystallization from 2-propanol gave an analytically pure sample of **9h** as colorless needles, mp 146—151°C. NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7 Hz), 4.00 (1H, br s), 4.13 (3H, s), 4.23 (2H, q, J=7 Hz), 4.72 (2H, s), 7.18 (1H, dd, J=9 Hz, J'=2 Hz), 7.50 (1H, s), 8.05 (1H, d, J=9 Hz), 8.55 (1H, s).

In a similar manner, the 2-fluoroethoxy derivative **9i** was prepared. The result are listed in Table V.

General Procedure for Preparation of Ethyl 1-Alkyl-1,4-dihydro-7-methyl-4-oxoquinoline-3-carboxylates (21) (Table VII)

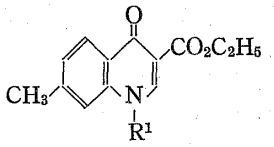
Typical Examples: A. Ethyl 1,4-Dihydro-1-(2-fluoroethyl)-7-methyl-4-oxoquinoline-3-carboxylate (21b)——NaH (61% in oil dispersion, 1.0 g, 0.025 mol) was added to a suspension of ethyl 4-hydroxy-7-methylquinoline-3-carboxylate[11] (**20**, 4.62 g, 0.02 mol) in DMF (100 ml), and the mixture was stirred at room temperature for 1 h. Then, 2-fluoroethyl bromide (5.1 g, 0.04 mol) was added to the reaction mixture and stirring was continued at 60°C for 22.5 h. The solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (200 ml) and the solution was washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was triturated with 2-propanol (20 ml) and the crystals were collected by filtration to give **21b** (3.8 g, mp 186—189°C). Recrystallization from EtOH gave analytically pure **21b** as colorless needles, mp 191—192°C. NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 2.48 (3H, s), 4.36 (2H, q, J=7 Hz), 4.25—5.30 (4H, m), 7.12 (1H, s), 7.18 (1H, d, J=8 Hz), 8.36 (1H, d, J=8 Hz), 8.38 (1H, s).

B. Ethyl 1-(2-Chloroethyl)-1,4-dihydro-7-methyl-4-oxoquinoline-3-carboxylate (21f)——NaH (61% in oil dispersion, 2.0 g, 0.05 mol) was added portionwise to a suspension of **20** (9.24 g, 0.04 mol) in DMF (100 ml), and the mixture was stirred at room temperature for 1 h. Then, ethylene chlorohydrin (10.0 g, 0.125 mol) was added to the reaction mixture and the whole was stirred at 120 °C for 22 h then concentrated under reduced pressure. The residue was washed with H_2O and 2-propanol and dried to give crude ethyl 1,4-dihydro-1-(2-hydroxyethyl)-7-methyl-4-oxoquinoline-3-carboxylate (8.5 g). A mixture of the above crude crystals (8.5 g), $SOCl_2$ (4.8 g), pyridine (1.6 g), and $CHCl_3$ (200 ml) was stirred at room temperature for 2 h. The reaction mixture was washed with 5% aqueous $NaHCO_3$ and dried over 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 **21f** (2.5 g). Recrystallization from DMF–EtOH gave analytically pure **21f** as colorless prisms, mp 214—217°C. NMR (DMSO-d_6) δ: 1.30 (3H, t, J=7 Hz), 2.50 (3H, s), 4.08 (2H, t, J=5 Hz), 4.24 (2H, q, J=7 Hz), 4.77 (2H, t, J=5 Hz), 7.30 (1H, d, J=8 Hz), 7.63 (1H, s), 8.15 (1H, d, J=8 Hz), 8.64 (1H, s).

General Procedure for Preparation of 1-Alkyl-1,4-dihydro-7-methyl-4-oxoquinoline-3-carboxylic Acids (22a—c, e, and g) (Table II)——Compounds **21a, b** and **c** were hydrolyzed with NaOH in aqueous EtOH in the same manner as described for preparing **12** to afford the corresponding carboxylic acids (**22a, b** and **c**). **22e** was obtained by the reaction of the corresponding ester (**21e**) with trimethylsilyl iodide in the same manner as described for the preparation of **6e**.

1,4-Dihydro-7-methyl-4-oxo-1-vinylquinoline-3-carboxylic Acid (22g)——Compound **21f** (1.47 g, 5 mmol) was added to a freshly prepared solution of sodium ethoxide (35 mmol) in EtOH (50 ml) and the mixture

TABLE VII. Ethyl 1-Substituted-1,4-dihydro-7-methyl-4-oxoquinoline-3-carboxylates (21)



Compd. No.	R^1	Reaction Conditions: Reagent	Temp. (°C)	Time (h)	Yield (%)	mp (°C)	Recryst. solv.[d]	Formula	Analysis (%) Calcd (Found): C	H	N
21a	C_2H_5	C_2H_5I	r.t.	15	58	150—151[c]	A	$C_{15}H_{17}NO_3$	69.48 (69.57	6.61 6.68	5.40 5.71)
21b	CH_2CH_2F	FCH_2CH_2Br	60	24	69	191—192	B	$C_{15}H_{19}FNO_3$	64.97 (65.18	5.82 5.85	5.05 5.00)
21c	CH_2CF_3	CF_3CH_2I	120	14	29	179—181	B	$C_{15}H_{14}F_3NO_3$	57.50 (57.48	4.50 4.55	4.47 4.50)
21e	CHF_2	CHF_2Cl	120	16	64	185—187	B	$C_{14}H_{13}F_2NO_3$	59.78 (59.83	4.66 4.69	4.98 4.97)
21f[a]	CH_2CH_2Cl	$HOCH_2CH_2Cl$	120	22	21[b]	214—217	C	$C_{15}H_{16}ClNO_3$	61.33 (61.29	5.49 5.65	4.77 4.83)

a) Prepared from **20** *via* 2 steps. See "Experimental."
b) Based on **20**.
c) Ref. 10, mp 218—219°C.
d) A=CH_3CN; B=EtOH; C=DMF–EtOH.

was heated under reflux for 3 h. Then, H_2O (30 ml) was added to the reaction mixture and heating was continued for a further 1 h. After removal of EtOH from the reaction mixture under reduced pressure, the aqueous residue was acidified with 10% HCl. The resulting precipitate was collected by filtration and washed with H_2O to give almost pure **22g** (1.1 g, 96%) as a colorless powder, mp 261—263°C. Recrystallization from DMF afforded an analytically pure sample of **22g**, mp 263—264°C. NMR (CF_3CO_2D) δ: 2.80 (3H, s), 5.90—6.30 (2H, m), 7.30—7.70 (1H, m), 7.75—8.00 (1H, m), 7.98 (1H, s), 8.67 (1H, d, J=8 Hz), 9.30 (1H, s).

Ethyl 4-Chloro-7-methylquinoline-3-carboxylate (23)——A suspension of **20** (11.56 g, 0.05 mol) in a mixture of phosphoryl chloride (40 ml) and toluene (200 ml) was heated under reflux for 30 min. The reaction mixture was worked up in the manner described for the preparation of **17** to afford 12.5 g (quantitative yield) of **23** as a brown powder, mp 46—49°C. NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7 Hz), 2.54 (3H, s), 4.46 (2H, q, J=7 Hz), 7.42 (1H, dd, J=8.5 Hz, J'=2 Hz), 7.83 (1H, br s), 8.18 (1H, d, J=8.5 Hz), 9.10 (1H, s).

4-Chloro-3-ethoxycarbonyl-7-methylquinoline 1-Oxide (24)——*m*-Chloroperbenzoic acid (80% purity, 12.8 g, 0.06 mol) was added portionwise to a stirred solution of **23** (12.9 g, 0.05 mol) in $CHCl_3$ (400 ml) at 5—10°C. Stirring was continued at room temperature for 2.5 h and the reaction mixture was worked up in the manner described for the preparation of **19** to afford **24** (8.80 g, 60%) as a brown powder, mp 65—70°C. NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7 Hz), 2.65 (3H, s), 4.47 (2H, q, J=7 Hz), 7.50 (1H, d, J=8 Hz), 8.32 (1H, d, J=8 Hz), 8.60 (1H, s), 9.01 (1H, s).

1,4-Dihydro-1-hydroxy-7-methyl-4-oxoquinoline-3-carboxylic Acid (25)——A solution of **24** (7.97 g, 0.03 mol) in a mixture of MeOH (45 ml) and 2 N NaOH (60 ml) was heated under reflux for 4 h. After removal of MeOH from the reaction mixture, the aqueous residue was acidified with 10% HCl. The precipitate was collected by filtration, washed with H_2O and dried to give almost pure **25** (4.87 g, 74%) as a colorless powder, mp 230—231°C. Recrystallization from DMF–MeOH afforded a pure sample of **25** as colorless needles, mp 230—231°C. NMR (CF_3CO_2D) δ: 2.80 (3H, s), 7.91 (1H, d, J=8 Hz), 8.31 (1H, s), 8.62 (1H, d, J=8 Hz), 9.47 (1H, s). *Anal.* Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.21; H, 4.34; N, 6.53.

1-Alkoxy-1,4-dihydro-7-methyl-4-oxoquinoline-3-carboxylic Acids (22h and i) (Table II)

Typical Example: 1,4-Dihydro-7-methyl-1-methoxy-4-oxoquinoline-3-carboxylic Acid (22h)——Methyl iodide (5.68 g, 40 mmol) was added dropwise to a stirred solution of **25** (1.1 g, 5 mmol) in a mixture of 0.5 N KOH (30 ml) and MeOH (20 ml) at 38—40°C, and the stirring was continued overnight at the same temperature. After concentration of the reaction mixture under reduced pressure, the aqueous residue was acidified with 10% HCl. The resulting precipitate was collected by filtration, washed with H_2O and dried to afford almost pure **22h** (0.8 g, 69%). Recrystallization from DMF–EtOH afforded analytically pure **22h** as colorless needles, mp 230—232°C. NMR (CF_3CO_2D) δ: 2.83 (3H, s), 4.54 (3H, s), 7.94 (2H, d, J=8 Hz), 8.15 (1H, br s), 8.66 (1H, d, J=8 Hz), 9.53 (1H, s).

In the same manner, 1-(2-fluoroethoxy)derivative (**22i**) was prepared.

Antibacterial Activity Testing——Antibacterial activities of the test compounds are shown as the mini-

mum inhibitory concentration (MIC) determined by an agar dilution method using the serial twofold dilution technique. The concentrations of the compounds in the heart infusion agar plates used were 100, 50, 25..1.56, 0.78 μg/ml. MIC was defined as the lowest concentration of a compound that prevented visible growth after the incubation of bacteria at 37°C for 18 h.

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