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Studies on Quinoline Derivatives and Related Compounds. 5.[1] Synthesis and Antimicrobial Activity of Novel 1-Alkoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids

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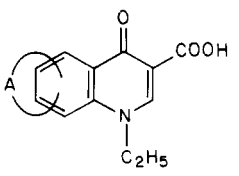
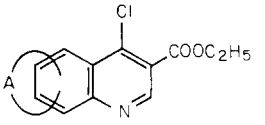
A series of novel 1-alkoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids was synthesized and screened as antimicrobial agents. The most active compounds in vitro against gram-negative microorganisms and *Staphylococcus aureus* were 1,4-dihydro-1-methoxy-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**22**), 1,2,6,9-tetrahydro-6-methoxy-9-oxofuro[3,2-*f*]quinoline-8-carboxylic acid (**30**), and 2,3,6,9-tetrahydro-6-methoxy-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic acid (**34**). These compounds had antigram-negative activity comparable to that of the corresponding *N*-ethyl derivatives **1**, **2**, and **4**. Their serum levels and urinary recovery rates in rats, however, were significantly improved relative to the latter compounds (**1**, **2**, and **4**).

Since the finding that oxolinic acid (1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid, **1**)[2] exhibited potent in vitro antimicrobial activity against gram-negative microorganisms and *Staphylococci*, many related quinoline derivatives have been synthesized for examination of their antibacterial activity against gram-negative microorganisms.[3] These compounds, however, are poorly absorbed from the gastrointestinal tract and as a result their usefulness as chemotherapeutic agent is limited.

The purpose of this investigation is to obtain new quinoline derivatives, which possess improved pharmacokinetic properties and retain the antibacterial activity of the parent compounds, by structural modification. All the previously synthesized derivatives of this type of compounds have an alkyl group at the nitrogen atom. In view of the structure–activity relationship that the alkyl group at the nitrogen atom seemed to play an important role in enhancing the activity, we became interested in the preparation of compounds having an alkoxy group at the nitrogen atom, in order to examine whether the substituent consisting of a highly polar oxygen atom would confer physiochemical and biological properties on the quinoline molecule different from those conferred by the alkyl group.

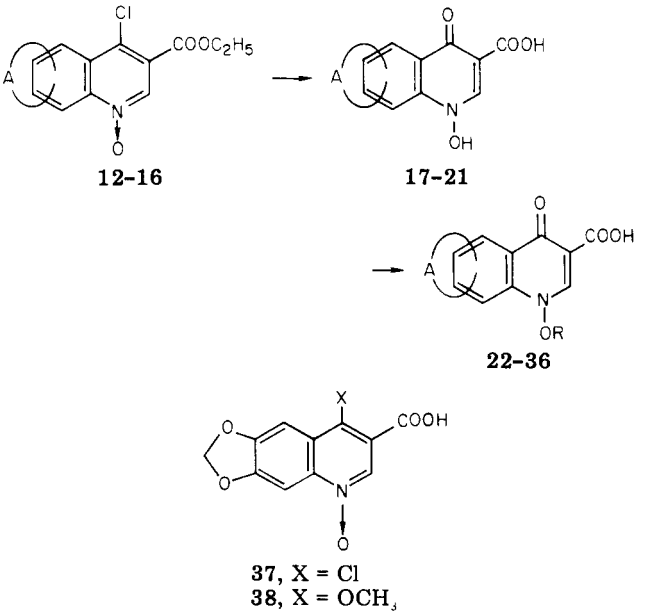


1, A = 6,7-OCH_2O-
2, A = 6,7-OCH_2CH_2-
3, A = 5,6-CH_2OCH_2O-
4, A = 5,6-$SC(=O)N(CH_3)$-
5, A = 7,8-$CH_2CH_2CH_2$-



6, A = 6,7-OCH_2O-
7, A = 6,7-OCH_2CH_2-
8, A = 5,6-CH_2CH_2O-
9, A = 5,6-CH_2OCH_2O-
10, A = 5,6-SC(Cl)=N-
11, A = 7,8-$CH_2CH_2CH_2$-

Scheme I



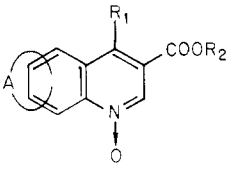
12–16 **17–21** **22–36**

37, X = Cl
38, X = OCH_3

Chemistry. Ethyl 4-chloro-3-quinolinecarboxylates (**6–11**) employed as starting materials were prepared by the method described in the literature[4] and converted to 3-carboethoxy-4-chloroquinoline 1-oxides (**12–16**) by oxidation with *m*-chloroperbenzoic acid in chloroform. In order to synthesize 1,4-dihydro-1-hydroxy-4-oxo-3-quinolinecarboxylic acids (**17–21**), hydrolysis of **12** under a variety of conditions was attempted and the best results were obtained when sodium hydroxide and aqueous methanol were used.

In this conversion of **12** to **17**, the formation of the intermediates **37** and **38** was observed by NMR study.

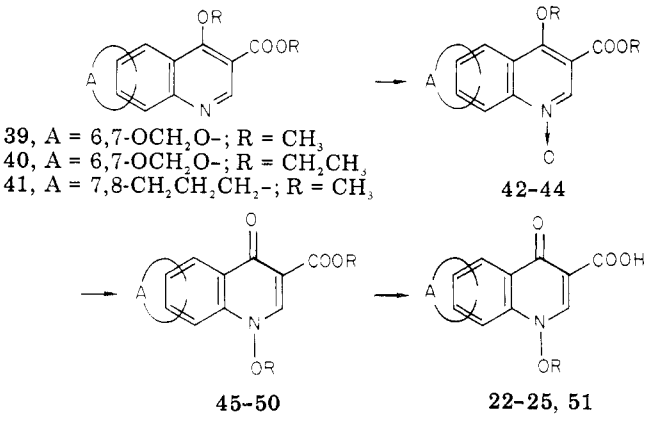
Table I. 4-Substituted 3-Carboalkoxyquinoline 1-Oxides



Compd	A	R_1	R_2	Mp, °C	Recrystn solvent	Yield,[a] %	Formula[b]
12	6,7-OCH_2O-	Cl	C_2H_5	189-190	EtOAc-$CHCl_3$	56	$C_{13}H_{10}ClNO_5$
13	6,7-$O(CH_2)_2$-	Cl	C_2H_5	162-163 dec	EtOAc-$CHCl_3$	85	$C_{14}H_{12}ClNO_4$
14	5,6-$(CH_2)_2O$-	Cl	C_2H_5	167-168 dec	EtOAc-$CHCl_3$	65	$C_{14}H_{12}ClNO_4$
15	5,6-CH_2OCH_2O-	Cl	C_2H_5	168-169 dec	EtOAc-$CHCl_3$	83	$C_{14}H_{12}ClNO_5$
16	5,6-SC(Cl)=N-	Cl	C_2H_5	206-208	EtOAc-$CHCl_3$	80	$C_{13}H_8Cl_2N_2O_3$
42	6,7-OCH_2O-	OMe	CH_3	203-204	MeOH	80	$C_{13}H_{11}NO_6$
43	6,7-OCH_2O-	OEt	C_2H_5	148-149	*n*-Hexane-EtOAc	82	$C_{15}H_{15}NO_6$
44	7,8-$(CH_2)_3$-	OMe	CH_3	132-134 dec	EtOAc	85	$C_{15}H_{15}NO_4$

[a] Yields are of purified product and are not maximal. [b] All compounds were analyzed for C, H, and N; analytical results were within ±0.4% of the theoretical values.

Scheme II



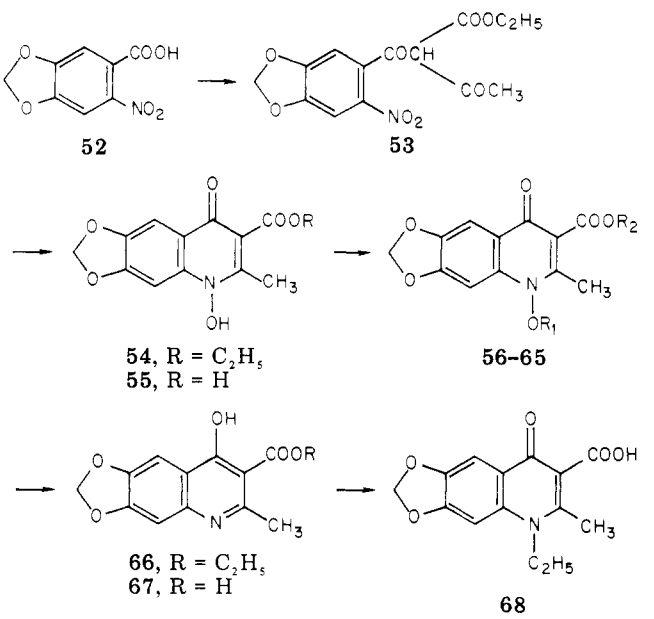
39, A = 6,7-OCH_2O-; R = CH_3
40, A = 6,7-OCH_2O-; R = CH_2CH_3
41, A = 7,8-$CH_2CH_2CH_2$-; R = CH_3

42-44

45-50

22-25, 51

Scheme III



52

53

54, R = C_2H_5
55, R = H

56-65

66, R = C_2H_5
67, R = H

68

Other 4-chloroquinoline *N*-oxides (**13–16**) were converted to **18–21** by analogous hydrolysis. Compounds **17–21** thus obtained were converted to 1-alkoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**22–36**) by alkylation with an appropriate alkyl halide, followed by acid hydrolysis (Scheme I).

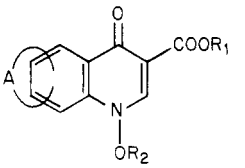
An alternative method, as shown in Scheme II, for the preparation of compounds **22–25** and **51** was investigated. 4-Alkoxy-3-quinolinecarboxylates (**39–41**) were prepared in 80–90% yields by treatment of **6** and **11** with sodium alkoxide. Oxidation of **39–41** with *m*-chloroperbenzoic acid in chloroform afforded 4-alkoxy-3-carboalkoxyquinoline 1-oxides (**42–44**). Heating **42–44** with excess alkyl iodide gave 1-alkoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylates (**45–50**) which led to the desired acids **22–25** and **51** by acid hydrolysis. The physical properties and yields of **12–36** and **42–51** are listed in Tables I and II.

Furthermore, we planned to synthesize 1-alkoxy- (**61–65**) and 1-ethyl-1,4-dihydro-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acids (**68**), in which the substituents at the nitrogen atom are sterically hindered, for the purpose of examining the effect of the methyl group at the C_2 position on the antibacterial activity.

The syntheses of compounds **61–65** and **68** are shown in Scheme III. The intermediates (**54** and **55**) for **61–65** were prepared by analogy to the method by which ethyl 1,4-dihydro-1-hydroxy-2-methyl-4-oxo-3-quinolinecarboxylate was obtained.[5] 3,4-Methylenedioxy-6-nitrobenzoic acid (**52**)[6] was chlorinated to give the acid chloride, which condensed with sodium ethyl acetoacetate to afford ethyl 2-(3,4-methylenedioxy-6-nitrobenzoyl)acetoacetate (**53**). Reductive cyclization of **53** with stannous chloride gave ethyl 1,4-dihydro-1-hydroxy-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (**54**). The reaction was also effected by the use of sodium borohydride in place of stannous chloride. Alkylation of **54** with an appropriate alkyl halide in the presence of potassium carbonate and aqueous ethanol gave ethyl 1-alkoxy-1,4-dihydro-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylates (**56–60**), which were converted to the corresponding acids **61–65** by acid hydrolysis (see Table III). On the other hand, alkaline hydrolysis of **56–58** gave 4-hydroxy-2-methyl-6,7-methylenedioxy-3-quinolinecarboxylic acid (**67**) in 80–90% yields. Compound **67** was also prepared by alkaline hydrolysis of compound **66**, which was obtained by catalytic hydrogenolysis of **54** using Raney nickel. In alkaline hydrolysis of **56**, the silver mirror test of the reaction solution gave a positive result. With compound **58**, benzaldehyde was isolated as its 2,4-dinitrophenylhydrazone. From these observations, the formation of **67** from **56–58** is explained by a probable mechanistic pathway as given in Scheme IV. Elimination of a proton of an alkoxy group and subsequent electronic shifts would produce **67** and an aldehyde.

Compound **61–65** were also prepared by alkylation of 1,4-dihydro-1-hydroxy-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**55**), obtained by hydrolysis

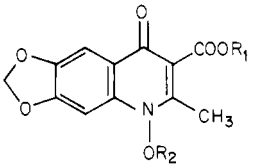
Table II. 1-Substituted 1,4-Dihydro-4-oxo-3-quinolinecarboxylic Acids and Their Esters



Compd	A	R_1	R_2	Procedure[c]	Mp, °C	Recrystn solvent	Yield,[a] %	Formula[b]
17	6,7-OCH_2O-	H	H	A	255-256 dec		95	$C_{11}H_7NO_6$
18	6,7-$O(CH_2)_2$-	H	H	A	271-272 dec		98	$C_{12}H_9NO_5$
19	5,6-$(CH_2)_2O$-	H	H	A	272-273 dec		97	$C_{12}H_9NO_5$
20	5,6-CH_2OCH_2O-	H	H	A	>350		96	$C_{12}H_9NO_6$
21	5,6-SC(=O)NH-	H	H	A	>300		95	$C_{11}H_6N_2O_5S$
22	6,7-OCH_2O-	H	CH_3	B, D	264 dec	DMF	94,[d] 86[e]	$C_{12}H_9NO_6$
23	6,7-OCH_2O-	H	CH_2CH_3	B, D	258-259 dec	DMF	80,[d] 84[e]	$C_{13}H_{11}NO_6$
24	6,7-OCH_2O-	H	$CH_2CH=CH_2$	B, D	309-310 dec	DMF	85,[d] 90[e]	$C_{14}H_{11}NO_6$
25	6,7-OCH_2O-	H	$CH(CH_3)_2$	B, D	185-186	DMF-H_2O	85,[d] 90[e]	$C_{14}H_{13}NO_6$
26	6,7-OCH_2O-	H	$(CH_2)_2CH_3$	B	210-211	MeOH-$CHCl_3$	74	$C_{14}H_{13}NO_6$
27	6,7-OCH_2O-	H	CH_2CH_2OH	B	245-246 dec	DMF	78	$C_{13}H_{11}NO_7$
28	6,7-OCH_2O-	H	CH_2-c-C_3H_5	B	210-211	AcOH	51	$C_{15}H_{13}NO_6$
29	6,7-OCH_2O-	H	CH_2Ph	B	242-244 dec	DMF	61	$C_{18}H_{13}NO_6$
30	6,7-$O(CH_2)_2$-	H	CH_3	B	267-268 dec	DMF	95	$C_{13}H_{11}NO_5$
31	5,6-$(CH_2)_2O$-	H	CH_3	B	228-229 dec	DMF	94	$C_{13}H_{11}NO_5$
32	5,6-CH_2OCH_2O-	H	CH_3	B	247-249 dec	DMF-H_2O	90	$C_{13}H_{11}NO_6$
33	5,6-CH_2OCH_2O-	H	$CH_2CH=CH_2$	B	244-245 dec	DMF-H_2O	91	$C_{15}H_{13}NO_6$
34	5,6-SC(=O)-N(CH_3)-	H	CH_3	B	312-315 dec	DMF	65	$C_{13}H_{10}N_2O_5S$
35	5,6-SC(=O)-N($CH_2CH=CH_2$)-	H	$CH_2CH=CH_2$	B	253-255	DMF	70	$C_{17}H_{14}N_2O_5S$
36	5,6-SC(=O)-N(CH_2Ph)-	H	CH_2Ph	B	245-246	EtOAc	55	$C_{25}H_{18}N_2O_5S$
45	6,7-OCH_2O-	CH_3	CH_3	C	223-224 dec	MeOH	80	$C_{13}H_{11}NO_6$
46	6,7-OCH_2O-	C_2H_5	CH_3	C	184-185	EtOAc-EtOH	95	$C_{14}H_{13}NO_6$
47	6,7-OCH_2O-	C_2H_5	C_2H_5	C	130-131	EtOAc	89	$C_{15}H_{15}NO_6$
48	6,7-OCH_2O-	C_2H_5	$CH_2CH=CH_2$	C	140-141	EtOAc	60	$C_{16}H_{15}NO_6$
49	6,7-OCH_2O-	C_2H_5	$CH(CH_3)_2$	C	148-149	EtOAc	50	$C_{16}H_{17}NO_6$
50	7,8-$(CH_2)_3$-	CH_3	CH_3	C	199-200	EtOAc	55	$C_{15}H_{15}NO_4$
51	7,8-$(CH_2)_3$-	H	CH_3	D	250 dec	DMF	95	$C_{14}H_{13}NO_4$

[a,b] See corresponding footnotes in Table I. [c] Capital letters refer to procedures in the Experimental Section. [d] Yield in procedure B. [e] Yield in procedure D.

Table III. 1-Alkoxy-1,4-dihydro-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic Acids and Their Esters



Compd	R_1	R_2	Procedure[c]	Mp, °C	Recrystn solvent	Yield,[a] %	Formula[b]
56	CH_2CH_3	CH_3	G	151-152	EtOH	88	$C_{15}H_{15}NO_6$
57	CH_2CH_3	CH_2CH_3	G	112-113	Benzene-petroleum ether	77	$C_{16}H_{17}NO_6$
58	CH_2CH_3	CH_2Ph	G	135-136	Benzene	93	$C_{21}H_{19}NO_6$
59	CH_2CH_3	$CH_2CH=CH_2$	G	118-120	Benzene-petroleum ether	96	$C_{17}H_{17}NO_6$
60	CH_2CH_3	$CH(CH_3)_2$	G		A pale yellow oil	80	$C_{17}H_{19}NO_6$
61	H	CH_3	H, I	251 dec	DMF	60,[d] 71[e]	$C_{13}H_{11}NO_6$
62	H	C_2H_5	H, I	220 dec	DMF	70,[d] 75[e]	$C_{14}H_{13}NO_6$
63	H	CH_2Ph	H, I	237 dec	DMF-H_2O	75,[d] 68[e]	$C_{19}H_{15}NO_6$
64	H	$CH_2CH=CH_2$	H, I	233 dec	DMF-H_2O	80,[d] 92[e]	$C_{15}H_{13}NO_6$
65	H	$CH(CH_3)_2$	H, I	192-193	DMF-H_2O	75,[d] 78[e]	$C_{15}H_{15}NO_6$

[a-c] See corresponding footnotes in Table II. [d] Yield in procedure H. [e] Yield in procedure I.

of **54** with an appropriate alkyl halide.

1-Ethyl-1,4-dihydro-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**68**) was prepared from **66** by sodium hydride and ethyl iodide in dimethylformamide. The structures of all compounds were confirmed by their NMR spectra and elementary analyses.

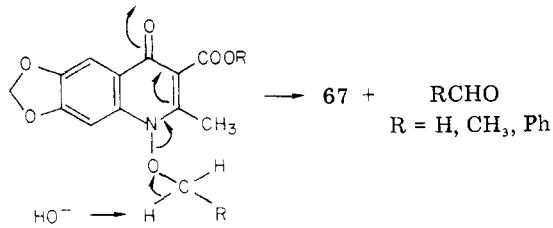
Biological Results and Discussion. Table IV summarizes the in vitro antibacterial activity against several gram-negative bacteria and *Staphylococcus aureus* for 1,4-dihydro-4-oxo-3-quinolinecarboxylic acids (**17–36, 51, 61–65,** and **68**) and esters (**45–50** and **56–60**) synthesized. The data for compounds **1–5** were included for comparison. The MIC's for compounds **17–21, 29, 45–50,** and **56–68** are greater than 200 μg/mL. The activities of **22, 30,** and **34** in the 6,7-methylenedioxyquinoline, furo[2,3-*g*]quinoline, and thiazolo[5,4-*f*]quinoline series are almost comparable to those of the corresponding N^1-ethyl derivatives (**1, 2,** and **4**), respectively. Gram-negative bacterial strains tested

Table IV. In Vitro Antibacterial Activity[a]

Compd	Min inhibitory concn, μg/mL				
	S. aureus 209P	*E. coli* NIHJ	*P. mirabilis* GN 2425	*P. aeruginosa* 104	*K. pneumoniae* PCI-602
Oxolinic acid	3.13	0.39	0.39	6.25	0.78
2	6.25	0.2	0.39	12.5	0.2
3	3.13	6.25	12.5	>200	NT[b]
4	3.13	0.1	0.39	>200	0.2
5	3.13	1.56	6.25	50	0.39
22	6.25	0.39	0.39	12.5	0.39
23	25	3.13	50	100	1.56
24	12.5	6.25	50	200	3.13
25	25	6.25	50	200	3.13
26	50	100	200	100	>200
27	100	100	100	100	>200
28	50	50	100	>200	>200
30	6.25	0.78	0.39	12.5	0.2
31	50	100	>200	>200	50
32	25	12.5	200	>200	12.5
33	50	>200	>200	>200	>200
34	6.25	0.2	0.39	12.5	0.2
35	50	100	>200	>200	200
36	1.56	>200	>200	>200	>200
51	25	12.5	50	>200	3.13

[a] See Experimental Section. [b] NT, not tested.

Scheme IV



56-58

in the present investigation are highly susceptible to these compounds and inhibited at a concentration less than 1 μg/mL except for *Pseudomonas aeruginosa*. This does not hold in the series of 1,3-dioxino[4,5-*f*]quinoline (**32**) and cyclopenta[*h*]quinoline (**51**), where the compounds with an N^1-methoxy group show inferior activity to those of **3** and **5** with an N^1-ethyl group.

Extension of carbon chains of the N^1-alkoxy group results in marked decrease in activity as observed in the series of compounds **22–29**, **32**, **33**, and **34–36**. It is interesting that 6-ethyl-1,2,6,9-tetrahydro-9-oxofuro[3,2-*f*]quinoline-8-carboxylic acid (**31**) exhibited no activity in view of the significant activity observed in the isomeric compound **30**. Substitution of an N^1-alkoxy by a hydroxy group (compounds **17–21**) and introduction of a methyl group into position 2 (compounds **61–65**) result in complete loss of activity.

Absorption and Excretion. The three compounds, **22**, **30**, and **34**, which showed significant antigram-negative activity were selected for absorption studies, and their serum levels (Table V) and urinary recovery rates (Table VI) in rats were compared with those of their N^1-ethyl counterparts.

As observed in Table V, each N^1-methoxy derivative produced much higher serum levels compared to the corresponding N^1-ethyl derivative. Of three N^1-methoxy compounds tested, **22** exhibited the most remarkable increase in the serum levels. The recovery rate in the urine collected over a period of 24 h was also increased on each N^1-methoxy compound (Table VI).

In Vivo Activity. Finally, 1,4-dihydro-1-methoxy-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**22**), which seemed most promising on the basis of the data

Table V. Serum Levels in Rats[a]

Compd	Mean drug levels, μg/mL				
	0.5 h	1.0 h	2.0 h	4.0 h	6.0 h
Oxolinic acid	0.7	1.5	4.7	4.8	2.7
22	11.6	27.8	22.3	19.5	1.5
2	0.9	1.3	2.8	1.25	NT[b]
30	6.2	4.7	4.0	1.7	NT
4	0.3	0.36	0.32	0.45	0.36
34	2.9	4.5	3.7	1.9	NT

[a] See Experimental Section. [b] NT, not tested.

Table VI. Urinary Recovery in Rats[a]

Compd	% of dose recovered
Oxolinic acid	2.4
22	7.5
2	9.6
30	11.0
4	0.3
34	1.8

[a] See Experimental Section.

Table VII. Effect on Systemic Infections in Mice on Oral Administration[a]

Compd	*E. coli* 0111		*P. mirabilis* GN2425	
	MIC	ED_{50}	MIC[b]	ED_{50}
Oxolinic acid	0.39	20	0.39	48
22	0.39	7.2	0.39	30

[a] See Experimental Section. [b] Taken from Table IV.

obtained, was tested on *E. coli* 0111 and *Proteus mirabilis* GN 2425 infections in mice with oral administration (Table VII). Compound **22** proved to be more effective than oxolinic acid (**1**).

Thus, by substituting the N^1-ethyl group of 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**1**), 5-ethyl-2,3,5,8-tetrahydro-8-oxofuro-[2,3-*g*]quinoline-7-carboxylic acid (**2**), and 6-ethyl-2,3,6,9-tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]-quinoline-8-carboxylic acid (**4**) with a methoxy group, it was successful to improve the pharmacokinetic properties

without altering their in vitro antibacterial activity. Compound **22** was selected as a result of the present investigation for further studies and is presently undergoing clinical trial.

Experimental Section

Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and were uncorrected. All ^1H NMR spectra were taken in CF_3COOH with Varian T-60 spectrometer and compared with Me_4Si as an internal standard. In thin-layer chromatography silica gel on plastic sheet (Spotfilm fluorescent, Tokyo Kasei Kogyo Co., Ltd.) was used throughout this work unless otherwise stated.

All compounds were analyzed for C, H, and N. Analytical results were within ±0.4% of the theoretical values.

4-Alkoxy-3-quinolinecarboxylates (39–41). To a stirred solution containing 2.53 g (0.11 mol) of Na and 300 mL of an anhydrous alcohol was added 0.1 mol of an ethyl 4-chloro-3-quinolinecarboxylate (**6** or **11**). After being heated under reflux for 3 h, the solution was concentrated to dryness in vacuo. The resulting solid was washed with H_2O, collected by filtration, and dried. Recrystallization from EtOH afforded **39–41** as colorless needles in 80–90% yields.

Methyl 4-Methoxy-6,7-methylenedioxy-3-quinolinecarboxylate (39). This compound had mp 148–149 °C: NMR ($CDCl_3$) δ 3.97 (s, CH_3), 4.07 (s, CH_3), 6.12 (s, CH_2), 7.3, 7.4, and 8.98 (each s, ring protons). Anal. ($C_{13}H_{11}NO_5$) C, H, N.

Ethyl 4-Ethoxy-6,7-methylenedioxy-3-quinlinecarboxylate (40). This compound had mp 85–86 °C: NMR ($CDCl_3$) δ 1.43 (t, CH_3), 1.5 (t, CH_3), 4.23 (q, CH_2), 4.43 (q, CH_2), 6.13 (s, CH_2), 7.27, 7.38, and 8.98 (each s, ring protons). Anal. ($C_{13}H_{11}NO_5$) C, H, N.

Methyl 4-Methoxy-7,8-cyclopentano-3-quinolinecarboxylate (41). This compound had mp 115–117 °C: NMR ($CDCl_3$) δ 4.0 (s, CH_3), 4.13 (s, CH_3), 1.93–2.6 and 2.97–3.67 (each m, $CH_2CH_2CH_2$), 4.47 (d, ring proton), 4.86 (d, ring proton), 9.23 (s, C-2 proton). Anal. ($C_{15}H_{15}NO_3$) C, H, N.

Oxidation of 4-Alkoxy- (39–41) and 4-Chloro-3-quinolinecarboxylates (6–11). To a stirred solution containing 10 mmol of **39–41** or **6–11** and 100 mL of $CHCl_3$ was added 20 mmol of *m*-chloroperbenzoic acid at room temperature. Stirring was continued for a further 12–14 h. The disappearance of a starting material was confirmed by TLC using EtOAc as a solvent. To the resulting solution was portionwise added 50 mL of 5% aqueous K_2CO_3 over a period of 30 min at the range of 0–5 °C with stirring. After stirring at the same temperature for 10 min the solution was stirred at room temperature for 1 h. The $CHCl_3$ layer was separated, washed with H_2O, and evaporated to dryness in vacuo, yielding the crude *N*-oxide which was recrystallized from the solvent indicated in Table I.

1,4-Dihydro-1-hydroxy-4-oxo-3-quinolinecarboxylic Acids (17–21). Procedure A. A suspension containing 10 mmol of a 3-carboethoxy-4-chloroquinoline 1-oxide (**12–16**), 40 mmol of NaOH, 20 mL of H_2O, and 15 mL of MeOH was heated under reflux for 4 h. After evaporation of the MeOH the resulting solution was heated at 90–95 °C for 1 h. Acidification of the solution to pH 1–2 by the addition of 6 N HCl precipitated an analytically pure product (**17–21**) as a white solid.

1-Alkoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids (22–36). Procedure B. To a stirred solution containing 10 mmol of a 1,4-dihydro-1-hydroxy-4-oxo-3-quinolinecarboxylic acid (**17–21**), 30 mmol of 85% KOH, 60 mL of H_2O, and 40 mL of MeOH was portionwise added 40 mmol of an appropriate alkyl halide (methyl, ethyl, allyl, isopropyl, and *n*-butyl iodide, and 2-hydroxyethyl, cyclopropylmethyl and benzyl bromide as alkyl halides were used) at 35–40 °C over a period of 30 min. The resulting solution was maintained at the same temperature with stirring for 10 h. The reaction mixture was diluted with H_2O (ca. 50 mL) and acidified to pH 1 by the addition of 6 N HCl. The MeOH was evaporated at atmospheric pressure and the resulting suspension was heated at 90–95 °C with stirring for 1 h. After cooling, the deposited solid was collected by filtration, washed with H_2O, and dried. Recrystallization from the solvent shown in Table II afforded the pure product (**22–36**).

1-Alkoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylates (45–50). Procedure C. A mixture containing 10 mmol of a 4-alkoxy-3-carboalkoxyquinoline 1-oxide (**42–44**) and 30 mL of an appropriate alkyl iodide was heated under reflux for 4 h. An excess reagent was distilled off and the resulting solid was recrystallized from the solvent shown in Table II.

Hydrolysis of Esters 45–50. Procedure D. A mixture containing an ester (**45–50**) and a tenfold volume of 6 N HCl was heated under reflux with stirring for 3 h. After cooling, a white solid that deposited was collected by filtration and washed with H_2O and dried. Recrystallization from the solvent shown in Table II afforded an acid (**22–25** or **51**).

Ethyl 2-(3,4-Methylenedioxy-6-nitrobenzoyl)acetoacetate (53). A mixture of 21.1 g of 3,4-methylenedioxy-6-nitrobenzoic acid (**52**) and 50 mL of $SOCl_2$ was stirred at 50–60 °C for 1 h. After evaporation of excess $SOCl_2$ in vacuo, the resulting red oil (25.6 g) was portionwise added to the solution containing 5.2 g of Na, 15 g of ethyl acetoacetate, and 67 mL of anhydrous EtOH at 5–10 °C over a period of 30 min. The mixture was kept at the same temperature with stirring overnight. The EtOH was distilled off in vacuo, and the resulting residue was washed with 1 N HCl (ca. 100 mL) and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried over $MgSO_4$, and evaporated, yielding a yellow solid. Recrystallization from EtOH gave 14.5 g (45%) of **53** as yellow prisms: mp 95–97 °C; NMR ($CDCl_3$) δ 0.98 (CH_3, t), 2.52 (CH_3, s), 3.07 (CH_2, q), 6.18 (CH_2, s), 6.68 and 7.63 (each s, ring protons), 9.1 (CH, br s). Anal. ($C_{14}H_{13}NO_8$) C, H, N.

Ethyl 1,4-Dihydro-1-hydroxy-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (54). Procedure E. To a stirred mixture containing 0.75 g (20 mmol) of $NaBH_4$, 40 mL of H_2O, and 0.05 g of 5% palladium on charcoal was added a solution containing 3.23 g (10 mmol) of **53** and 45 mL of MeOH in a current of N_2 over a period of 5 min. An exothermic reaction set in and the temperature of the mixture rose to 50–60 °C. After stirring at room temperature for 1 h, the palladium on charcoal was removed by filtration. The filtrate was acidified to pH 1 by the addition of 6 N HCl. The MeOH was distilled under reduced pressure. The residual solid was washed with H_2O and collected by filtration. Recrystallization from aqueous DMF gave 1.05 g (36%) of **54** as colorless prisms: mp 213 °C dec; NMR (Me_2SO-d_6) δ 1.12 (t, CH_3), 2.42 (s, CH_3), 4.27 (q, CH_2), 6.0 (s, CH_2), 7.3 and 7.4 (each s, ring protons). Anal. ($C_{14}H_{13}NO_6$) C, H, N.

Procedure F. Dry HCl was introduced to a mixture containing 12 g (60 mmol) of 95% $SnCl_2$ and 42 mL of AcOH at room temperature until the solution became clear. To this solution was added 3.23 g (10 mmol) of **53**, and the introduction of HCl continued. The contents of the flask was stirred throughout the entire operation. In time a white crystalline substance separated and the reduction was continued until the reaction mass had cooled to room temperature. The precipitate was collected and washed first with H_2O containing a little AcOH and then with H_2O. Recrystallization from aqueous DMF gave 1.67 g (62%) of **54**, mp 214 °C dec. The IR spectrum was identical with that of a sample prepared by procedure E.

1,4-Dihydro-1-hydroxy-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic Acid (55). A mixture containing 3 g of **54** and 20 mL of 5% aqueous KOH was heated at 90–95 °C with stirring for 2 h. After cooling, the resulting solution was treated with charcoal and the filtrate acidified to pH 6 by the addition of 6 N HCl. A white solid that precipitated was collected by filtration, washed with H_2O, and dried. Recrystallization from aqueous DMF gave 1.13 g (42%) of **55** as colorless prisms: mp 254–255 °C dec. Anal. ($C_{12}H_9NO_6$) C, H, N.

Ethyl 1-Alkoxy-1,4-dihydro-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylates (56–70). Procedure G. A mixture containing 2.9 g (10 mmol) of **54**, 30 mL of 33% aqueous K_2CO_3, and 30 mL of EtOH was stirred at room temperature for 1 h. An appropriate alkyl halide (methyl, ethyl, allyl, and isopropyl iodide, and benzyl bromide as alkyl halides were used, 25 mmol) was added, and the resulting mixture was stirred at room temperature for 2 h and then at 40–45 °C for 5 h. After evaporation of EtOH in vacuo, the residue was extracted with EtOAc and the extract washed with H_2O, dried over $MgSO_4$, and evaporated in vacuo, yielding a crude product (**56–60**), which was recrystallized from the solvent shown in Table III.

1-Alkoxy-1,4-dihydro-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic Acids (61–65). Procedure H. A mixture containing 2.63 g (10 mmol) of **55**, 1.9 g (20 mmol) of 85%

KOH, 30 mL of H_2O, 30 mL of MeOH, and 30 mmol of an appropriate alkyl iodide was stirred at 35–40 °C for 4 h. The mixture was acidified to pH 1 by the addition of 6 N HCl. After evaporation of the MeOH at atmospheric pressure the mixture was heated at 90–95 °C with stirring for 1 h. The resulting white solid was collected by filtration, washed with H_2O, and dried. Recrystallization from aqueous DMF gave the acid (**61–65**).

Procedure I. A mixture containing 10 mmol of an ester (**56–60**) and 70 mL of 1 N HCl was refluxed for 3 h. After cooling the resulting white solid was collected by filtration, washed with H_2O, and dried. Recrystallization from aqueous DMF gave an analytically pure product (**61–65**).

Ethyl 4-Hydroxy-2-methyl-6,7-methylenedioxy-3-quinolinecarboxylate (66). A mixture containing 2.9 g (10 mmol) of **56**, 1 mL of AcOH, 100 mL of EtOH, 1 g of EtOH, and Raney nickel (W-11) was hydrogenated at 70–80 °C at atmospheric pressure. The reduction stopped when the calculated amount of H_2 had been absorbed. After evaporation of the solvent the residue was dissolved in hot DMF. The DMF solution was filtered while hot and the filtrate evaporated to dryness in vacuo, yielding a white solid. Recrystallization from DMF gave 1.3 g (47%) of **66** as colorless prisms: mp 292 °C dec; NMR (Me_2SO-d_6) δ 1.28 (t, CH_3), 2.37 (s, CH_3), 4.25 (q, CH_2), 6.95 and 7.40 (each s, ring protons). Anal. ($C_{14}H_{13}NO_5$) C, H, N.

4-Hydroxy-2-methyl-6,7-methylenedioxy-3-quinolinecarboxylic Acid (67). Procedure J. A mixture containing 2.75 g of **66** and 40 mL of 5% aqueous KOH was heated under reflux for 3 h. After cooling, the resulting solution was acidified to pH 1 by the addition of 6 N HCl. A white solid that precipitated was collected by filtration, washed with H_2O, and dried. Recrystallization from DMF gave 2.0 g (81%) of **67** as colorless prisms, mp 340 °C dec. Anal. ($C_{12}H_9NO_5$) C, H, N.

Procedure K. A mixture containing 10 mmol of an ethyl 1-alkoxy-1,4-dihydro-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (**56–58**) and 50 mL of 5% KOH was heated under reflux for 2 h. The resulting solution was acidified to pH 1 by the addition of 6 N HCl. A white solid that precipitated was collected by filtration, washed with H_2O, and dried. Recrystallization from DMF gave **67** in 80–90% yields.

In hydrolysis of **58**, benzaldehyde was separated from the reaction mixture by steam distillation and converted to 2,4-dinitrophenylhydrazone, mp 238–239 °C, undepressed on admixture with an authentic sample.

1-Ethyl-1,4-dihydro-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic Acid (68). A mixture containing 2.75 g (10 mmol) of **66**, 40 mL of DMF, and 0.76 g (20 mmol) of 63% NaH (in mineral oil) was stirred at 80–90 °C for 30 min. To the resulting mixture was added 2.6 g (16.6 mmol) of EtI at 70–80 °C. The same temperature was maintained for an additional 2 h. This was followed by an additional 1.3 g (8.6 mmol) of EtI and 2 h of stirring at 70–80 °C. Being kept at room temperature overnight, the reaction mixture was concentrated under reduced pressure. H_2O was added to the residue and the mixture extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and dried over $MgSO_4$. Evaporation of the solvent to dryness yielded 2 g of a fawn solid, which was stirred at 90–95 °C in 6 N HCl for 3 h. After cooling, the precipitate was collected by filtration, washed with H_2O, and recrystallized from DMF, yielding 1 g (55%) of **68** as colorless needles: mp 305 °C dec; NMR (CF_3COOH) δ 1.4 (t, CH_3), 3.17 (s, CH_3), 4.73 (q, CH_2), 6.33 (s, CH_2), 7.73 and 7.77 (each s, ring protons). Anal. ($C_{14}H_{13}NO_5$) C, H, N.

In Vitro Antibacterial Activity. The twofold dilution method used by Turner et al.[7] was employed for the determination of the MIC (μg/mL). The test organisms were inoculated into trypticase soy broth (BBL) and incubated at 37 °C for 24 h.

Experimental Infection in Mice. Male ICR mice weighing 19–21 g were used. The test organisms, which were cultured for 18 h in heart infusion broth (Difco), were suspended in sterile 5% gastric mucin which was diluted in heart infusion broth (Difco). The mice were inoculated intraperitoneally with 0.2 mL of an appropriate dilution of test organisms (1–10 MLD). Compounds **1** and **22** were micronized and suspended in 0.5% carboxymethylcellulose. Five groups of eight infected mice were treated orally at 0.5 and 6 h postinfection with doubling dilutions of the antimicrobial agent to be tested. The 50% effective dose (ED_{50}, mg/kg) was calculated from the survival rates at 1 week after challenge.

Serum Levels and Urinary Recovery Rates. Three to five male Wistar rats per each group weighing approximately 200 g and fasting for 12 h were orally administered 50 mg/kg of compounds **1**, **2**, **4**, **22**, **30**, and **34** in 0.5% carboxymethylcellulose by gavage. Food was withheld for 4 h after the administration. Blood samples collected from the descending aorta and pooled urine (0–24 h) were bioassayed with *E. coli* B. A cylinder cup method which was used for the assay of oxolinic acid by Ringel[8] was employed. The serum levels were determined from the standard curve using serum as a diluent. Urine was diluted in $^1/_{15}$ M phosphate buffer (pH 7.2) and urine levels were determined from the standard curve using $^1/_{15}$ M phosphate buffer (pH 7.2).

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