0.095 g (77%) of a white powder: mp 252-253 °C dec; MS, *m/e* 259 (M^+ - HCl). Anal. ($C_{17}H_{26}ClNO$) C, H, N.

***trans*-4-*n*-Propyl-7-hydroxy-8-(hydroxymethyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (4b).** A solution of 0.120 g (0.0004 mol) of **4c** in 50 mL of EtOH was hydrogenated over 0.1 g of 5% Pd/C at an initial pressure of 35 psig. When the calculated amount of H_2 was absorbed (5 h) the catalyst was removed by filtration and volatiles were removed from the filtrate under reduced pressure. The residue was recrystallized from EtOH to give 0.100 g (78%) of a white powder: mp 254-257 °C; MS, *m/e* 275 (M^+ - HCl). Anal. ($C_{17}H_{26}ClNO_2$) C, H, N.

***trans*-4-*n*-Propyl-7-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-8-carboxylic Acid Hydrochloride (4d).** Compound **4c** (0.204 g, 0.000 66 mol), 0.1243 g (0.0018 mol) of sodium formate, 0.076 g (0.0011 mol) of hydroxylamine hydrochloride, and 3 mL of formic acid were heated under reflux under A for 6 h. Volatiles were then removed under reduced pressure, and the pH of the residue was taken to 9 (pH paper) by addition of saturated $NaHCO_3$. The resulting mixture was extracted with three 30-mL portions of CH_2Cl_2. Removal of the volatiles from the pooled extracts gave a brown solid, which was chromatographed on a Chromatotron apparatus (silica: EtOAc-EtOH, 7:3). The third of three eluted bands was evaporated, and 5 mL of concentrated HCl was added to the residue. The resulting mixture was heated under reflux overnight. The white solid that separated from the cooled reaction mixture was recrystallized from MeOH-Et_2O to afford 0.072 g (30%) of a white solid: mp 277-279 °C dec; MS, *m/e* 289 (M^+ - HCl). Anal. ($C_{17}H_{24}ClNO_3$) C, H, N.

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Studies on Prodrugs. 5.[1] Synthesis and Antimicrobial Activity of *N*-(Oxoalkyl)norfloxacin Derivatives

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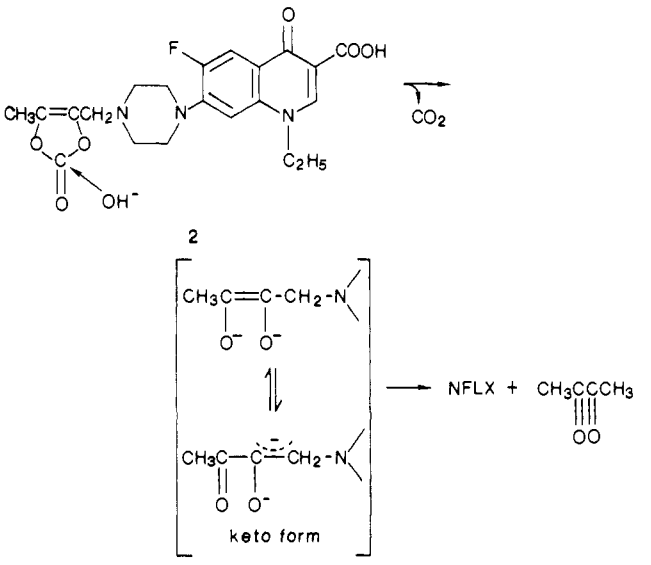
Several *N*-(oxoalkyl)norfloxacin derivatives (**3a-g**) were synthesized and evaluated for antibacterial activity in vitro and in vivo. Most of the compounds exhibited in vitro activity comparable to that of norfloxacin for Gram-positive bacteria, whereas their activity was lower than for Gram-negative bacteria. *N*-(2-Oxopropyl)norfloxacin (**3b**) liberated norfloxacin in the blood after oral administration in mice, and the serum level of norfloxacin was about 3-fold higher than that of norfloxacin itself. Thus, **3b** showed high antibacterial activity in vivo.

Since nalidixic acid has been developed as a useful therapeutic agent, a large number of analogues have been synthesized and some of them are in clinical use.[2] In the series of analogues, in particular, norfloxacin (NFLX, 1) exhibited marked and broad antibacterial activity against Gram-positive and Gram-negative bacteria.[3] Although NFLX (1) was potently active in in vitro test systems, it was found that there was still room for improvement in the activity after oral administration.[4] We have been interested in the prodrug approach of NFLX (1) and had already synthesized the unique N-masked NFLX (**2**),[1] in which we proposed that the N-masked NFLX (**2**) was hydrolyzed in the body through the keto form, as shown in Scheme I, to liberate NFLX (1) in the blood (see Chart I). Therefore, the ketone group α to the nitrogen atom was speculated to play an important part in the metabolism of this compound. In this paper, the preparation of *N*-(oxoalkyl)-substituted NFLXs (**3a-g**) is described. Furthermore, their serum levels and metabolism after oral

Scheme I



administration in mice were measured, and their antibacterial activities were evaluated in vitro and in vivo.

Chemistry. NFLX (1) was synthesized in accordance with the report of Koga et al.[3a] The N-masked NFLXs (**3a-g**) were prepared in one step using the recently described method,[1] which was the reaction of NFLX (1) with each halide (**4a-f**) without protection of the 3-carboxylic acid of NFLX. The compound (**3g**) was synthesized by means of Michael addition (Scheme II).

(1) Sakamoto, F.; Ikeda, S.; Kondo, H.; Tsukamoto, G. *Chem. Pharm. Bull.* **1985**, *33*, 4870.
(2) (a) Lesher, G. Y.; Froelich, E. J.; Gruett, M. D.; Bailery, J. H.; Brundage, R. P. *J. Med. Chem.* **1962**, *5*, 1063. (b) Minami, S.; Shono, T.; Matsumoto, J. *Chem. Pharm. Bull.* **1971**, *19*, 1426.
(3) (a) Koga, H.; Ito, A.; Murayama, S.; Suzue, S.; Irikura, T. *J. Med. Chem.* 1980, *23*, 1358. (b) Ito, A.; Hirai, K.; Inoue, M.; Koga, H.; Suzue, S.; Irikura, T.; Mitsuhashi, S. *Antimicrob. Agents Chemother.* **1980**, *17*, 103. (c) King, A.; Warren, C.; Shannon, K.; Phillips, I. *Antimicrob. Agents Chemother.* **1982**, *21*, 604.
(4) Murayama, S.; Hirai, K.; Ito, A.; Abe, Y.; Irikura, T. *Chemotherapy* **1981**, *29*(S-4), 98.

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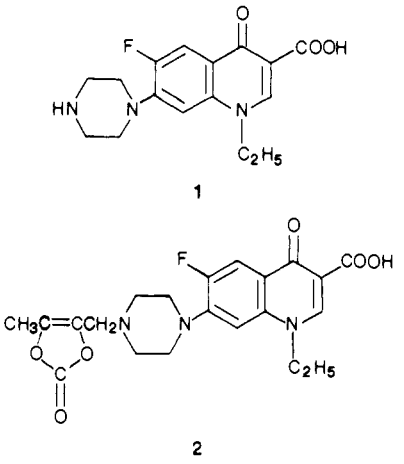
Table I. Antibiotic Activities of Compounds 3b–g

compd	microorganism[a] 1	2	3	4	5	6	7	ED_{50}[b] (*E. coli* KC-14), mg/kg, po
3b	0.39	0.39	1.56	0.20	6.25	0.78	6.25	0.95 (0.78–1.16)
3b′	0.39	0.78	0.78	0.20	3.12	0.78	6.25	3.90 (3.08–5.10)
3c	0.78	0.78	12.5	0.78	100<	3.13	50	7.13 (5.84–8.70)
3d	0.78	0.78	0.78	0.78	1.56	0.39	1.56	>7.50
3e	0.78	0.78	3.13	0.78	12.5	1.56	12.5	3.53 (2.22–5.71)
3f	0.78	0.39	3.13	0.39	6.25	1.56	6.25	6.06 (4.82–7.63)
3g	0.78	0.39	0.78	0.20	0.78	0.20	0.78	2.34 (1.58–3.46)
1	0.39	0.39	0.39	0.20	0.78	0.20	0.78	4.38 (3.34–5.80)

[a] Microorganism: 1, *Staphylococcus aureus* FDA207PJC-1; 2, *Bacillus subtilis* ATCC6633; 3, *Escherichia coli* KC-14; 4, *Klebsiella pneumoniae* IFO3512; 5, *Serratia marcescens* 16; 6, *Proteus vulgaris* OX-19; 7, *Pseudomonas aeruginosa* PAO1. [b] 95% confidence limit.

Chart I



The starting halo ketones (**4a–f**) were prepared as reported previously.[5]

The physical properties (IR, NMR, mass and elemental analyses) of these compounds (**3a–g**) were consisted with assigned structures.

Biological Results and Discussion

The in vitro antibacterial activity of compounds 1 and **3b–g** against Gram-positive and Gram-negative bacteria is shown in Table I. These compounds (**3b–g**) gave in vitro activity comparable to that of NFLX (1) against Gram-positive bacteria, but exhibited lower activity against Gram-negative ones. As the compound **3a** was unstable in solution, it was not able to be assayed. Compounds **3b–g** were stable in the same pH buffer solution as the MIC's (minimum inhibitory concentration) medium.

Then, compounds **3b–g** were tested, with oral administration, on systemic infection due to *E. coli* KC-14 in mice and were compared with NFLX (1). The evaluated median effective dose values (ED_{50}) are presented in Table I. Then, compounds **3b,e,g** showed lower in vitro activity than NFLX (1) against *E. coli* KC-14, but in vivo, exhibited higher activity. Other compounds (**3c–d,f**) showed lower activity than NFLX (1) both in vitro and in vivo.

Two possibilities were considered to account for the enhancement of the in vivo activity. One possibility was, as stated in our previous report,[1] an increase of oral absorbability by N-masking NFLX, and another possibility was that some active species were produced by metabolism after oral absorption.

(5) Compound **4a**: see Experimental Section. Compound **4b**: Levene, P. A. *Org. Synth.* **1943**, Coll. Vol. *2*, 88. Compound **4c**: Widman, O.; Wahlberg, E. *Ber. Dtsch. Chem. Ges., Ber.* **1911**, *44*, 2065. Compound **4d**: Jackson, E. L.; Pasiut, L. *J. Am. Chem. Soc.* **1927**, *49*, 2071. Compound **4e**: Favorskii, A. *J. Russ. Phys. Chem. Soc.* 44, 1339. Compound **4f**: Pfleiderer, W.; Zondler, H. *Chem. Ber.* **1966**, *99*, 3008.

Scheme II

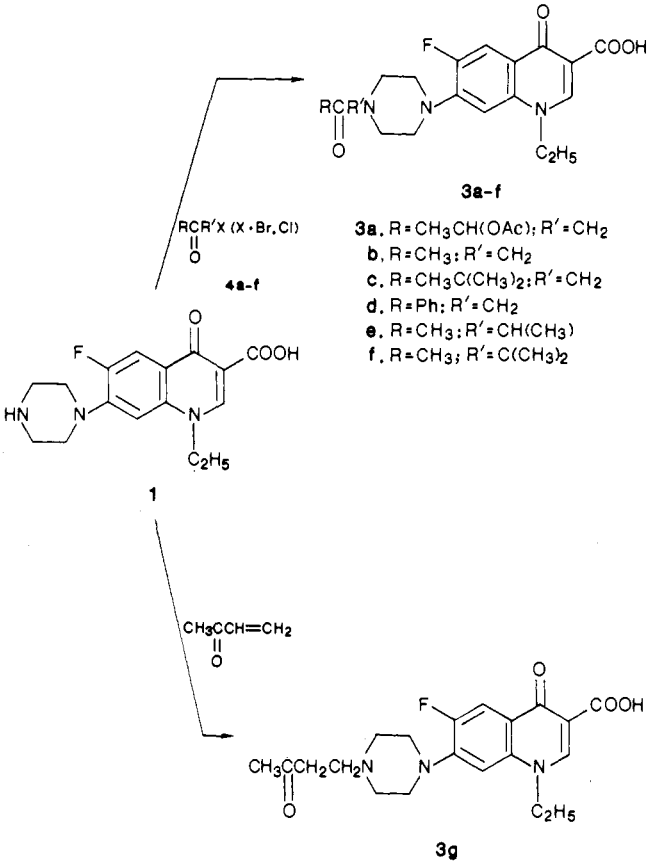


Table II. Serum Concentrations of **3b,c,g** and NFLX after Oral Administration in Mice

compd	time after administration, h 0.5	1.0	2.0	4.0	AUC[a]
3b (100 mg/kg, po)[b]					
3b	23.64	7.29	2.69	0.46	20.44
3b′	19.46	20.19	6.93	2.82	44.07
1 (NFLX)	6.33	5.74	3.96	2.62	22.01
3c (100 mg/kg, po)[b]					
3c	19.6	15.4	9.4	6.73	42.82
3c′	nd[c]	nd	nd	nd	
1 (NFLX)	nd	nd	nd	nd	
3g (100 mg/kg, po)[b]					
3g	7.06	3.55	2.22	1.18	12.87
3g′	11.08	10.8	6.28	3.44	18.53
1 (NFLX)	4.69	3.57	1.21	0.49	8.78
1 (100 mg/kg, po)					
1 (NFLX)	3.47	2.02	1.12	0.56	6.49

[a] In (μg·h)/mL. [b] A dose equivalent to 100 mg/kg of NFLX. [c] Not detected.

In order to clarify those points, we studied the blood level and biotransformation of these compounds (**3b,c,g**).

Table III. Oral Efficacy on Systemic Infections of **3b** and NFLX

compd	ED_{50}, mg/kg, po (95% confidence limit)			LD_{50},[d] mg/kg	
	S. aureus Smith[a]	*E. coli* KC-14[b]	*P. aeruginosa* E2[c]	iv	po
3b	12.6 (19.8–16.2)	0.95 (0.78–1.16)	18.5 (11.0–31.2)	684	>4000
1 (NFLX)	36.4 (23.7–55.8)	4.38 (3.34–5.80)	59.0 (44.5–78.1)	314	>4000

[a] Challenge dose: 1.1×10^7 cells/mouse. [b] Challenge dose: 5.6×10^3 cells/mouse. [c] Challenge dose: 1.4×10^3 cells/mouse. [d] A suspension of each compound in 0.5% cmc was administered, and the number of dead animals within 1 week was counted, the LD_{50} values being calculated by the method of Weil.

Table IV. Pattern of Serum Level in Mice after Oral Administration of **3b′**

compd	time after administration, h				AUC[a]
	0.5	1.0	2.0	4.0	
3b′ (100 mg/kg, po)[b]					
3b′[b]	13.6	27.1	11.8	2.21	59.2
3b	nd[c]	nd	nd	nd	
1 (NFLX)	nd	nd	nd	nd	

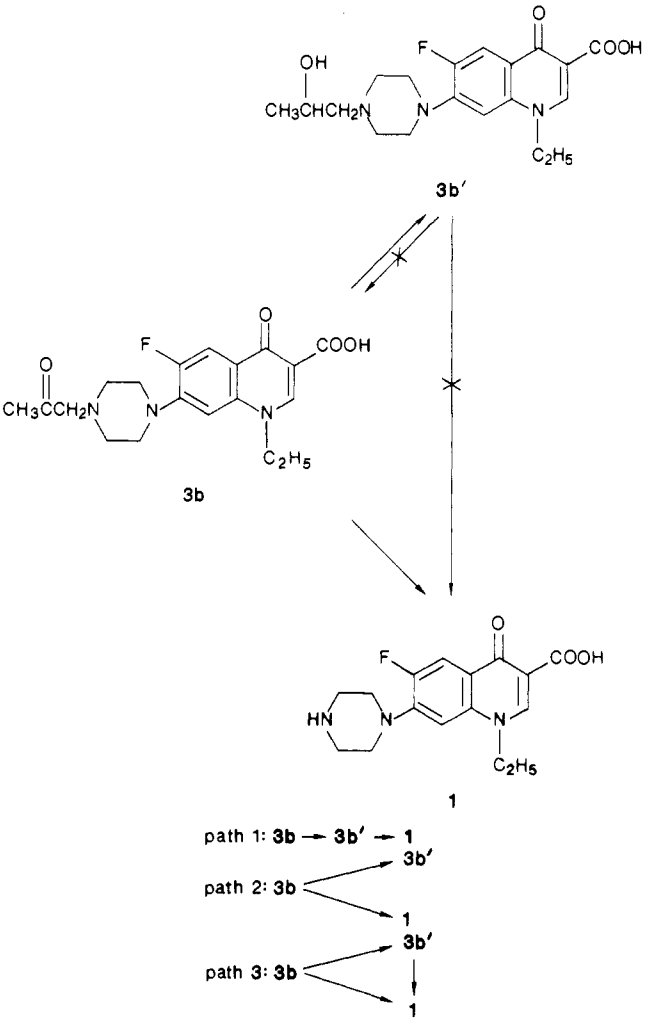
[a] In (μg·h)/mL. [b] A dose equivalent to 100 mg/kg of NFLX. [c] nd = not detected.

Thus, after oral administration in mice, the serum specimens were collected at regular time intervals, 0.5, 1.0, 2.0, and 4.0 h, and the concentrations of NFLX (1) and the original compounds (**3b,c,g**) in serum were measured individually by high-pressure liquid chromatography (HPLC) (Table II).

In compounds **3b,g**, NFLX (1) was detected together with the unchanged compound (**3b** or **3g**), while **3c** did not liberate NFLX (1). From their HPLC patterns, **3b** or **3g** was further demonstrated to be transformed to the other polar metabolite (**3b′** or **3g′**) in the reduced form. Since no metabolite is found from **3c**, it may be assumed that the bulkiness of ketone moieties on the nitrogen atom affects the metabolism of compounds **3b–g** and plays an important role for the occurrence of potent antibacterial activity in vivo. Among the compounds studied, **3b** liberated NFLX most easily, producing about a 3-fold higher serum level of NFLX than did NFLX itself, with oral administration in mice (Table II). This corresponds to the in vivo activity outlined in Table III.

The manner of biological transformation of **3b** is considered to be via three paths (1, 2, 3) as shown in Scheme III. Thus, **3b′**, which is one of the metabolites of **3b**, was synthesized, and the in vivo antibacterial activity and biological transformation after oral administration were examined in mice (Tables I and IV). The results are particularly surprising, in view of the fact that **3b′** failed to metabolize into NFLX (1) and **3b**. From those results, path 2 in Scheme III is most reasonable for the metabolic path way of **3b**. Next, we examined in rats the biological nature of **3b** in a manner similar to that given above. In rats, **3b** liberated less NFLX than in mice, but also exhibited higher in vivo activity than NFLX as shown in Table V. It is thought that this effect resulted from the combined activities of **3b**, **3b′**, and NFLX. That is to say, the increased activity of **3b** may be explained by the facts

Scheme III



that **3b** is absorbed better, gives an active metabolite, and is active by itself. In this case, generally, it is suggested that both an increase of oral absorbability by N-masking NFLX and a production of some active species by metabolism make an important contribution to enhancing the in vivo activity.

Based on many studies for N-dealkylation, any drug that undergoes oxidative dealkylation would be expected to generate the carbinolamine intermediate.[6,7] Our case may

Table V. Serum Concentration of **3b** after Oral Administration in Rats

compd	time after administration, h				AUC[a]	ED_{50},[b] (*E. coli* KC-14), mg/kg, po
	0.5	1.0	2.0	4.0		
3b (50 mg/kg, po)[c]						
3b[c]	15.31	14.0	8.88	2.49	36.9	
3b′	2.19	4.0	4.48	3.32	19.8	3.50 (1.9–6.9)
1 (NFLX)	0.45	0.75	0.38	0.24	1.9	
1 (50 mg/kg, po)						
1 (NFLX)	1.60	1.60	0.72	0.23	3.3	6.10 (4.1–8.9)

[a] In (μg·h)/mL. [b] 95% confidence limit. [c] A dose equivalent to 50 mg/kg of NFLX.

be similar; however, the clear mechanism of N-dealkylation has not yet been ascertained. The fact that in mice the ketone group (e.g., 2-oxopropyl, 3-oxobutyl group) on the nitrogen atom functions as the promoiety of NFLX is unique and opens up the possibility for a prodrug approach to amine derivatives.

Experimental Section

Melting points were determined on a Yamato capillary melting point apparatus, Model MR-21, and are uncorrected. IR spectra were recorded with a Shimadzu IR-440 instrument. All compounds were analyzed for C, H, and N, and the values were within ±0.4% of the calculated theoretical values.

In Vitro Antibacterial Activity. According to the method of Goto et al.,[8] the MICs of compounds tested in this study were determined by the serial 2-fold dilution technique, using Mueller-Hinton agar. The inoculum size was approximately 10^6 cfu/mL. The concentrations of compounds in the plates ranged from 0.006 to 100 μg/mL. MIC was defined as the lowest concentration of a compound that prevented visible growth of bacteria after incubation at 37 °C for 18 h.

In Vivo Efficacy on Systemic Infections. In vivo assay was carried out according to the general method.[9] Groups of 10 male ddy mice (20 ± 2 g) were infected with bacteria. A 0.5-mL volume of a bacterial dilution, corresponding to 10 or 100 times higher than the 50% lethal dose, was inoculated intraperitoneally. The test compounds were suspended in 0.5% sodium carboxymethyl cellulose and administered orally at 1 h postinfection. Survival rates were evaluated after 1 week.

Oral Absorbability Test. The serum concentration of NFLX in mice treated with compounds **3b,g** and NFLX itself was determined by high-pressure liquid chromatography. Test compounds were suspended in 0.5% sodium carboxymethyl cellulose and administered orally at a dose of 100 mg/kg. After 0.5, 1.0, 2.0, and 4.0 h the mice were killed by bleeding. The collected blood was centrifuged, and the test serum was adjusted. A HPLC machine was equipped with a Hitachi Model 655 pump, a Shimadzu Model SPD-2A spectrophotometric detector (at 280 nm), and a YMC A-312 column. The mobile phase consisted of 0.5% acetic acid–acetonitrile (92:8 v/v), and the flow rate was 2.0 mL/min.

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-(3-acetoxy-2-oxobutyl)-1-piperazinyl]-4-oxoquinoline-3-carboxylic Acid (3a). 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinylquinoline-3-carboxylic acid (NFLX; 0.32 g, 1.0 mmol) was added to a solution of 3-acetoxy-2-oxobutyl bromide (0.23 g, 1.1 mmol), prepared from 3-acetoxy-2-oxobutane (0.17 g, 1.3 mmol) and *N*-bromosuccinimide (0.24 g, 1.35 mmol) in carbon tetrachloride (5 mL), and potassium bicarbonate (0.11 g, 1.1 mmol) in *N,N*-dimethylformamide (3 mL). The solution was stirred at room temperature for 12 h. *N,N*-Dimethylformamide was then removed under reduced pressure. The residue was poured into water (5 mL) and extracted with chloroform (20 mL). The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated. The residual solid was crystallized from ether to give **3a** (0.24 g, 27%) as a pale-yellow powder: mp 112–118 °C dec. Anal. ($C_{22}H_{26}FN_3O_6$) H, N; C: calcd, 59.05; found, 59.66.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2-oxopropyl)-1-piperazinyl]quinoline-3-carboxylic Acid (3b). NFLX (0.16 g, 0.5 mmol) was added to a solution of 2-oxopropyl bromide (0.082 g, 0.6 mmol) and potassium bicarbonate (0.05 g, 0.5 mmol) in *N,N*-dimethylformamide (15 mL). The solution was stirred at room temperature for 1 h. The excess 2-oxopropyl bromide and *N,N*-dimethylformamide were then removed under reduced pressure. The residue was poured into water (30 mL) and extracted with chloroform (40 mL). The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated. The residual solid was recrystallized from ethanol–chloroform (5:1) to give **3b** (0.11 g, 68%) as a white crystalline solid: mp 199–202 °C dec; MS, *m/e* 375 (M^+); ^1H NMR ($CDCl_3$) δ 1.60 (t, 3 H), 2.20 (s, 3 H), 2.76 and 3.40 (m, 8 H), 3.38 (s, 1 H), 4.35 (q, 2 H), 6.82 and 8.06 (d, 2 H, aromatic), 8.64 (s, 1 H), 14.9 (s, 1 H, carboxylic acid). Anal. ($C_{19}H_{22}FN_3O_4$) C, H, N.

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-(3,3-dimethyl-2-oxobutyl)-1-piperazinyl]-4-oxoquinoline-3-carboxylic Acid (3c). NFLX (0.29 g, 0.9 mmol) was added to a solution of 3,3-dimethyl-2-oxobutyl bromide (0.32 g, 1.78 mmol) and potassium bicarbonate (0.09 g, 0.9 mmol) in *N,N*-dimethylformamide (10 mL), and by use of the same general procedure as above, a pale-yellow crystalline solid (0.24 g, 63%) was obtained: mp 215–218 °C dec; MS, *m/e* 417 (M^+); ^1H NMR (Me_2SO-d_6) δ 1.12 (s, 9 H), 1.44 (t, 3 H), 2.70 and 3.32 (m, 8 H), 3.56 (s, 2 H), 4.60 (q, 2 H), 7.18 and 7.88 (d, 2 H, aromatic), 8.92 (s, 1 H), 15.25 (s, 1 H, carboxylic acid). Anal. ($C_{22}H_{28}FN_3O_4$) C, H, N.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-phenacyl-1-piperazinyl)quinoline-3-carboxylic Acid (3d). NFLX (0.5 g, 1.56 mmol) was added to a solution of phenacyl bromide (0.37 g, 1.86 mmol) and potassium bicarbonate (0.156 g, 1.56 mmol) in *N,N*-dimethylformamide (40 mL), and by use of the same general procedure as above, a white crystalline solid (0.58 g, 65%) was obtained: mp 208–210 °C dec; MS, *m/e* 437 (M^+); ^1H NMR ($CDCl_3$) δ 1.60 (t, 3 H), 2.90 and 3.45 (m, 8 H), 3.95 (s, 2 H), 4.30 (q, 2 H), 6.88 and 8.10 (d, 2 H, aromatic), 7.52–8.0 (m, 5 H), 8.65 (s, 1 H). Anal. ($C_{24}H_{24}FN_3O_4$) C, H, N.

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-(1-methyl-2-oxopropyl)-1-piperazinyl]-4-oxoquinoline-3-carboxylic Acid (3e). NFLX (0.5 g, 1.56 mmol) was added to a solution of 3-chloro-2-butanone (0.25 g, 2.35 mmol) and potassium carbonate (0.45 g, 3.26 mmol) in *N,N*-dimethylformamide (15 mL). The solution was stirred at 50 °C for 4 h, and, using the same general procedure as above, a pale-yellow powder (0.31 g, 51%) was obtained: mp 220–224 °C dec; MS, *m/e* 389 (M^+); ^1H NMR ($CDCl_3$) δ 1.10 (d, 3 H), 1.44 (t, 3 H), 2.20 (s, 3 H), 2.68 and 3.34 (m, 8 H), 3.40 (d, 1 H), 4.56 (q, 2 H), 7.16 and 7.90 (d, 2 H, aromatic), 8.90 (s, 1 H). Anal. ($C_{20}H_{24}FN_3O_4$) C, H, N.

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-(1,1-dimethyl-2-oxopropyl)-1-piperazinyl]-4-oxoquinoline-3-carboxylic Acid (3f). NFLX (0.3 g, 0.94 mmol) was added to a solution of 1-bromo-1-methyl-2-butanone (0.31 g, 1.88 mmol) and potassium bicarbonate (0.103 g, 1.03 mmol) in *N,N*-dimethylformamide (15 mL). The solution was stirred at room temperature for 18 h, and, using the same general procedure as above, a pale-yellow powder (0.18 g, 47%) was obtained: mp 238–242 °C dec; MS, *m/e* 403 (M^+); ^1H NMR (Me_2SO-d_6) δ 1.12 (s, 6 H), 1.45 (t, 3 H), 2.21 (s, 3 H), 2.68 and 3.32 (m, 8 H), 4.50 (q, 2 H), 7.18 and 7.92 (d, 2 H, aromatic), 8.92 (s, 1 H). Anal. ($C_{21}H_{26}FN_3O_4$) C, H, N.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(3-oxobutyl)-1-piperazinyl]quinoline-3-carboxylic Acid (3g). NFLX (0.5 g, 1.56 mmol) was added to a solution of methyl vinyl ketone (0.22 g, 3.14 mmol) in chloroform (50 mL). The solution was stirred at room temperature for 2 h. The excess methyl vinyl ketone and chloroform were then removed under reduced pressure. The residual solid was recrystallized from chloroform–ethanol (1:10) to give **3g** (0.42 g, 70%) as a pale-yellow crystalline solid: mp 187–190 °C; MS, *m/e* 389 (M^+); ^1H NMR ($CDCl_3$) δ 1.55 (t, 3 H), 2.18 (s, 3 H), 2.69 (s, 4 H), 2.70 and 3.25 (m, 8 H), 4.29 (q, 2 H), 6.75 and 7.90 (d, 2 H, aromatic), 8.58 (s, 1 H). Anal. ($C_{20}H_{24}FN_3O_4$) C, H, N.

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-(2-hydroxypropyl)-1-piperazinyl]-4-oxoquinoline-3-carboxylic Acid (3b′). An excess of propylene oxide was added to a solution of NFLX (0.3 g, 0.94 mmol) in acetonitrile (50 mL). The solution was stirred at 80 °C in a sealed tube for 15 h. The excess propylene oxide and acetonitrile were then removed under pressure. The residual solid was recrystallized from ethanol–chloroform (5:1) to give **3b′** (0.28 g, 80%) as a white crystalline solid: mp 228–232 °C. Anal. ($C_{19}H_{24}FN_3O_4$) C, H, N.

Acknowledgment. We are indebted to Dr. T. Nose,

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Registry No. 1, 70458-96-7; **3a**, 103240-23-9; **3b**, 103175-73-1; **3b'**, 103240-28-4; **3c**, 103240-24-0; **3d**, 103240-25-1; **3e**, 103258-03-3; **3f**, 103240-26-2; **3g**, 103240-27-3; **4a** (X = Br), 13190-11-9; **4a** (X = H), 4906-24-5; **4b** (X = Br), 598-31-2; **4c** (X = Br), 5469-26-1; **4d** (X = Br), 70-11-1; **4e** (X = Cl), 4091-39-8; **4f** (X = Br), 815-52-1; **4g** (X = H), 78-93-3; propylene oxide, 75-56-9.

Synthesis and Aldose Reductase Inhibitory Activity of Substituted 2-Oxoquinoline-1-acetic Acid Derivatives

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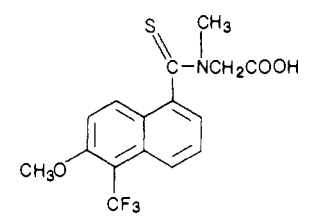
A number of 2-oxoquinoline-1-alkanoic acids that contain the *N*-acylglycine fragment found in several known inhibitors of aldose reductase were synthesized and tested in the rat lens assay. All of the target compounds were prepared by alkylation of the appropriate 2-oxoquinoline intermediates with a halo ester, followed by hydrolysis of the intermediate esters. In the rat lens assay, the 1-acetic acid derivatives **9a–e** display the highest level of aldose reductase inhibitor activity with IC_{50} values of 0.45–6.0 μM. Modification of the 1-acetic acid moiety by esterification, substitution of an α-methyl group, or insertion of an additonal methylene unit results in reduced inhibitory potency. Structure–activity data also suggests that both the benzene and 2-oxopyridine rings of **9a–e** contribute substantially toward activity and that inhibitory potency is influenced by aromatic ring substituents.

There is a growing body of evidence establishing a link between the formation and accumulation of sorbitol in ocular and nerve tissue and the development of several of the pathologies of chronic diabetes such as cataracts, retinophaty, and neuropathy.[1] Since sorbitol is formed in these tissues from glucose in a reaction mediated by the enzyme aldose reductase, one approach that has been explored to prevent or, at least, delay the onset of these diabetic pathologies has involved the development of inhibitors of aldose reductase. A large number of compounds of diverse structure have been found to inhibit this enzyme.



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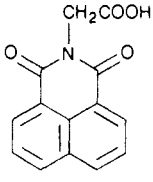

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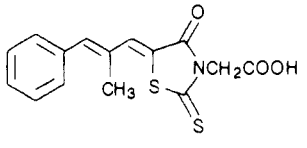

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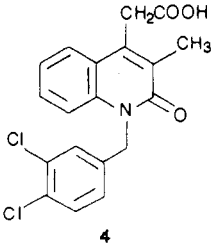

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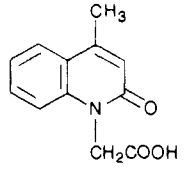

9a

Several of these inhibitors, including tolrestat (1), alrestatin (2), and ONO-2235 (3), contain an *N*-acylglycine fragment, which is believed to contribute significantly to the inhibitor–enzyme interaction.[2] This observation prompted us to synthesize and determine the aldose reductase inhibitory activity of a number of simple heterocyclic systems that contain the *N*-acylglycine fragment. One of these heterocycles, 4-methyl-2-oxoquinoline-1-acetic acid (**9a**), was found to display significant inhibitory acitivity in the rat lens assay with an IC_{50} value of 6 μM. This compound, in addition to being a derivative of **1–3**, is also related structurally to the known aldose reductase inhibitor ICI-105552 (**4**).[3] Herein we report the synthesis and enzyme inhibitory activity of **9a** as well as a number of other 2-oxoquinolines designed to explore structure–activity relationships among this class of aldose reductase inhibitors.

Chemistry

Several 2-oxoquinoline-1-acetic acids (**9a–e**) and -1-(2-propanoic acids) (**11a–c**) as well as a -1-(3-propanoic acid) (**13**) and 2-oxopyridine-1-acetic acid (**16**) were prepared for evaluation as inhibitors of aldose reductase (Table I). All of these compounds were synthesized by the general method reported by Potts of Yao for the preparation of 2-oxoquinoline-1-acetic acid.[4] Therefore, alkylation of the sodium salts of 2-oxoquinolines **7a–c** with ethyl bromoacetate provided the intermediate esters **8a–c**. Alkaline hydrolysis of the crude esters yielded the acetic derivatives **9a–c** upon neutralization (Scheme I). Similarly, the 1-(2-propanoic acid) **11a–c** and 1-(3-propanoic acid) **13** were prepared by alkylation of **7a–c** with ethyl 2-bromopropionate and ethyl 3-chloropropionate, respectively, and 2-oxopyridine-1-acetic acid (**16**) by alkylation of **14** with ethyl bromoacetate (Scheme I). The intermediate 2-oxoquinolines **7b–c** were prepared by converting quinolines **5b–c** to the corresponding *N*-oxides **6b–c** and then treating these *N*-oxides with acetic anhydride, followed by ammonium hydroxide as described by Pettit and co-workers

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