Studies on Pyridonecarboxylic Acids [1]. 2. Synthesis and Antibacterial Activity of 8-Substituted-7-fluoro-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acids

Jun Segawa*, Masahiko Kitano, Kenji Kazuno, Masami Tsuda,
Ichiro Shirahase, Masakuni Ozaki, Masato Matsuda and Masahiro Kise*

Research Laboratories, Nippon Shinyaku Co., Ltd.,
Nishioji Hachijo, Minamiku, Kyoto, 601, Japan

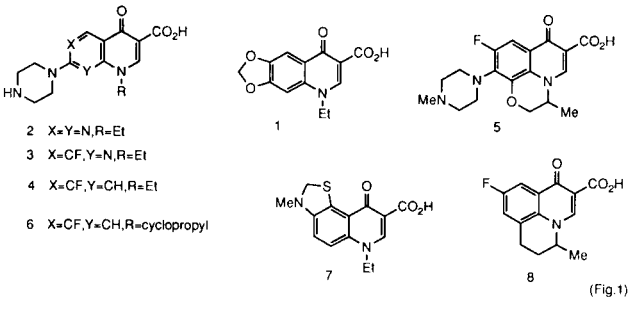
Received January 27, 1992

A series of 8-substituted-7-fluoro-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic acids was prepared and evaluated for antibacterial activity. These compounds were synthesized from ethyl 2-mercaptoquinoline-3-carboxylates **17** which were obtained from anilines **11** by a route involving an intramolecular cyclization reaction.

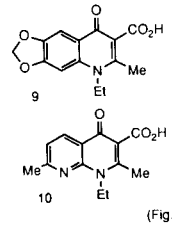
J. Heterocyclic Chem., **29**, 1117 (1992).

Since the discovery of nalidixic acid by Lesher in 1962 [2], a large number of related derivatives, collectively known as "quinolones", have been synthesized. The earlier derivatives such as oxolinic acid **1** [3] and pipemidic acid **2** [4] have been used as gram-negative antibacterial agents. Recently, more highly effective broad-spectrum antibacterial agents that contain fluorine atom have been synthesized. Compounds such as enoxacin **3** [5], norfloxacin **4** [6], ofloxacin **5** [7] and ciprofloxacin **6** [8] are included in this later group.

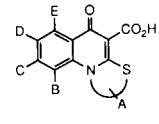
Within the "quinolone" class of antibacterial agents, there is also a series of potent tricyclic compounds containing a three-atom bridge connecting the vicinal positions of quinolones. This series includes oxolinic acid **1**, tioxacin **7** [9], flumequine **8** [10], and ofloxacin **5** (Figure 1). On the other hand, the introduction of a methyl group in the C-2 position resulted completely inactive compounds **9** [11] and **10** [12] (Figure 2). There was a suggestion that in these agents the coplanarity of C-3 carboxyl and C-4 carbonyl groups was inhibited by the bulky C-2 substituent and as a result the interaction between the drug and target enzyme was weakened [13]. In our search for potent quinolone analogs, we have been studying tricyclic compounds characterized by an S-bridge between the N-1 substituent and the C-2 of quinolone [14] with a thought that antibacterial activity might be retained if the steric hindrance of the C-2 substituent to the C-3 carboxyl group were minimized (Figure 3). We found that the title compounds had excellent antibacterial activity. This result indicates that the sulfur atom in the C-2 position of quinolone improves antibacterial activity when a substituent of the sulfur atom has little steric effect on the C-3 carboxyl group. In this paper we describe the synthesis and antibacterial activity of 8-substituted-7-fluoro-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic acid derivatives (Figure 2).

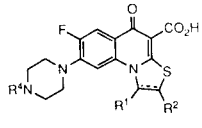


(Fig.1)



(Fig.2)

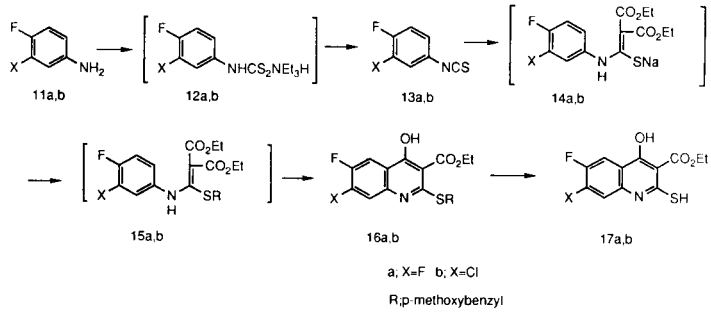

(Fig.3)


(Fig.4)

Chemistry.

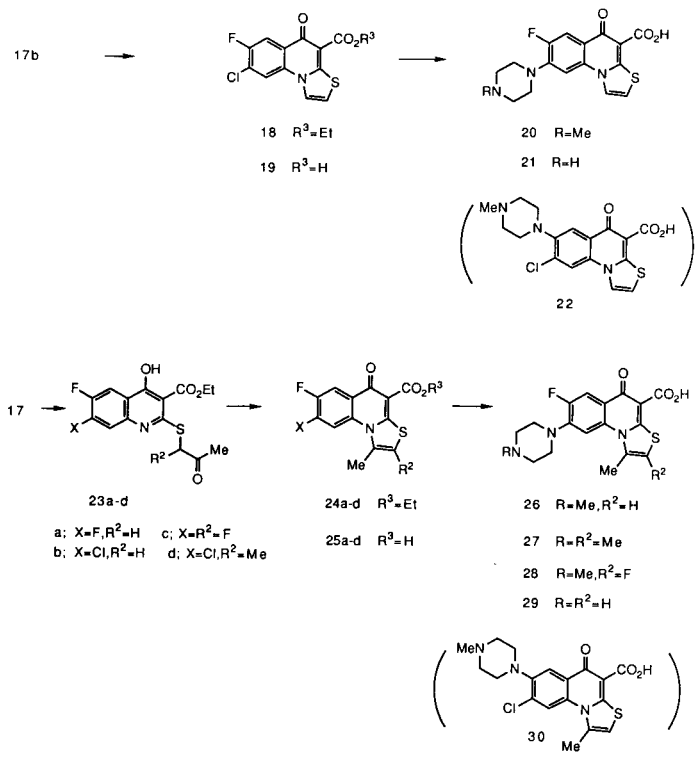
The synthesis to key compounds **17** is illustrated in Scheme 1. Treatment of anilines **11** with carbon disulfide in the presence of triethylamine gave triethylammonium dithiocarbamates **12**, which without purification, were treated with ethyl chloroformate to give isothiocyanates **13** [15]. The reaction of **13** with diethyl malonate in the presence of 1.1 moles equivalent of sodium hydride in THF

Scheme 1



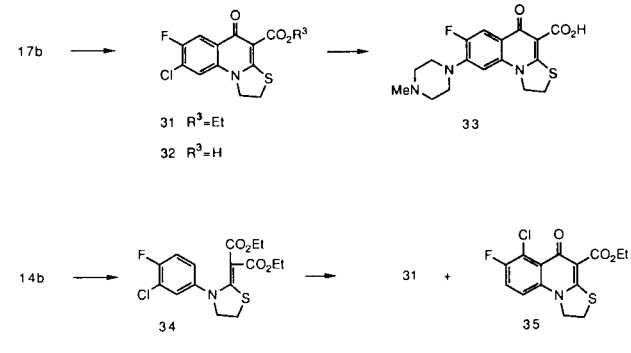
yielded sodium salts of aminomercaptomethylenemalonates **14**, which were converted to *p*-methoxybenzyl ethers **15** by treatment with *p*-methoxybenzyl chloride. Cyclization was performed in the usual manner [16]. Compounds

Scheme 2



15 were heated in diphenyl ether to afford quinolones **16**. The pmr spectrum (in deuteriochloroform) of **16b** shows signals at δ 7.70 (d, J = 10 Hz) for the proton in the 5-position and at δ 7.72 (d, J = 6 Hz) for the proton in the 8-position. The *p*-methoxybenzyl group of **16** was removed with trifluoromethanesulfonic acid and trifluoroacetic acid in anisole [17] to give key intermediates, ethyl 2-mercaptoquinoline-3-carboxylates **17**. The synthesis to 5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic acids from **17** is shown in Scheme 2. Hantzsch's method was used to prepare these compounds [18]. The reaction of **17b** with bromoacetal in the presence of potassium bicarbonate followed by treatment with concentrated sulfuric acid afforded the tricyclic ester **18**. Alkaline hydrolysis of **18** afforded the corresponding carboxylic acid **19**. The nucleophilic substitution reaction of **19** with 1-methylpiperazine gave the desired 8-substituted derivative **20** along with the 7-substituted compound **22**. Similarly **21** was obtained from **19** and piperazine. 1-Methyl derivatives **26-29** were synthesized *via* ethyl 2-acetonylthioquinoline-3-carboxylate derivatives **23a-23d** [18]. The reaction of **17a** with chloroacetone gave the thioether **23a**, which was treated with concentrated sulfuric acid to afford the tricyclic ester **24a**. Alkaline hydrolysis of **24a** afforded the corresponding carboxylic acid **25a**. Similarly, **25b** and **25d** were prepared from **17b** *via* **24b** and **24d**. On the other hand, **25c** was obtained directly from **23c** by treatment with fuming sulfuric acid. The reaction of the 7-fluoro derivative **25a** with 1-methylpiperazine gave the desired 8-substituted compound **26** as the sole product. On the other hand, 8-chloro derivative **25b** gave a mixture of **26** and the 7-substituted compound **30**. Similar results were obtained from the reaction of **25c** or **25d** with piperazine or 1-methylpiperazine. The synthesis to 1,2-dihydro-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic acid **33** from **17b** is shown in Scheme 3. Compound **17b** was treated with 1,2-dibromoethane to afford the tricyclic ester **31**, which was hydrolyzed to give the corresponding carboxylic acid **32**. Compound **32** was then treated with 1-methylpiperazine to give

Scheme 3



8-substituted derivative **33** as a sole product. This result is in contrast to that of the reaction of unsaturated analog **19**. An alternative pathway to the intermediate **31** from **14b** was then investigated. Treatment of **14b** with 1,2-dibromoethane gave the thiazolidine derivative **34**, which was cyclized by heating in polyphospholic acid [19] to give **31** and the isomer **35** in an approximately two to three ratio.

Biology.

Table 1 summarizes the *in vitro* antibacterial activity of the 5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic acids against four gram-positive organisms (*Staphylococcus aureus* 209-P JC, *Staphylococcus aureus* Smith, *Micrococcus luteus* ATCC 9341 and *Bacillus subtilis* ATCC 6633) and seven gram-negative organisms (*Escherichia coli* NIHJ JC-2, *Escherichia coli* KC-14, *Klebsiella pneumoiae* K-1966, *Serratia marcescens* IFO 3736, *Proteus vulgaris* HX-19, *Pseudomonas aeruginosa* E-2 and *Acinetobacter calcoaceticus 54*). The data for norfloxacin **4** is included for comparison. 5-Oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic acids with no substituent in either the C-1 or C-2 positions, **20,21**, or with a methyl group in the C-1 position, **26,29**, show greater activity than norfloxacin **4**. This finding reveals that the thiazole ring fused to the quinoline nuclei improves antibacterial activity, but the introduction of substituents in the C-2 position, **27,28**, results in a loss of activity. The activity of 1,2-dihydro derivative **33** is similar to that of norfloxacin **4**.

EXPERIMENTAL

All melting points were determined in capillary tubes on a Büchi melting point apparatus and were uncorrected. Elemental analyses were performed on a Yanaco CHN Corder MT-3 elemental analyzer, and C,H,N values were within 0.4% of the theoretical values. Pmr spectra were determined on a Varian XL-200 or a Hitachi R-24-B spectrometer with tetramethylsilane as an internal standard, and chemical shifts are given in ppm (δ). Pmr spectra of all compounds obtained were consistent with assigned structures. The ir spectra recorded on a Shimadzu IR-453-U-03 spectrometer. Mass spectra were recorded on a JEOL JMS-SX102 spectrometer at 70eV ionization potential. Analyses (hplc) were carried out with Shimadzu LC-6A liquid chromatograph. Column chromatography separations were carried out on Wako Gel C-200 and C-300. Yields are of purified products and are not optimized.

3,4-Difluorophenyl Isothiocyanate (**13a**).

To a stirred solution of 3,4-difluoroaniline **11a** (200 g, 1.549 moles) in triethylamine (470 g, 4.644 moles) was added dropwise carbon disulfide (130 g, 1.700 moles) under ice cooling. The reaction mixture was allowed to stand at the same temperature overnight. The resultant precipitate was collected by filtration, washed with ether, and dried to give 449 g (95%) of triethylammonium 3,4-difluorophenyldithiocarbamate (**12a**) as a colorless powder, which without further purification, was suspended in 800 ml of chloroform and triethylamine (163.2 g, 1.613 moles). To this suspension was added dropwise ethyl chloroformate (175 g, 1.613 moles) under ice cooling. After stirring at room temperature for 3.5 hours, the reaction mixture was washed with water, dried, and concentrated to dryness under reduced pressure to give an oily

Table 1

In Vitro Antibacterial Activity of 5-Oxo-5*H*-thizolo[3,2-*a*]quinoline-4-carboxylic Acids

Minimal Inhibitory Concentration(MIC), μg/ml [a]

	Organism										
Compound	Sa	Sa(s)	MI	Bs	Ec(N)	Ec	Kp	Sm	Pv	Pa	A
20	0.1	0.05	0.78	0.006	0.1	0.01	0.1	0.39	0.006	0.39	0.39
21	0.025	0.05	0.78	0.006	0.05	0.006	0.025	0.2	0.01	0.2	0.78
26	0.01	0.05	0.78	0.003	0.025	0.01	0.05	0.39	0.1	0.39	0.2
27	1.56	0.78	0.78	0.2	3.13	1.56	1.56	6.25	0.39	100	6.25
28	0.39	0.2	0.78	0.025	0.05	0.1	0.05	0.39	0.025	1.56	0.2
29	0.025	0.01	0.39	0.006	0.025	0.006	0.01	0.2	0.002	0.39	0.2
33	0.2	0.2	12.5	0.1	0.1	0.05	0.1	0.2	0.025	1.56	0.78
4	0.2	0.39	12.5	0.2	0.05	0.05	0.05	0.2	0.05	0.78	3.13

[a] According to the method of the MIC Committee of the Japan Society of Chemotherapy, the MIC(in micrograms per milliliter) was determined by the twofold agar dilution method using sensitivity test agar (Nissui, Tokyo, Japan): the bacterial inocula contained approximately 10^6 colony-forming units/ml and bacterial growth was observed after incubation for 20 hours at 37°.

Organisms selected for inclusion in the table are: Sa, *Staphylococcus aureus* 209-P JC; Sa(s), *Staphylococcus aureus* Smith; MI, *Micrococcus luteus* ATCC 9341; BS, *Bacillus subtilis* ATCC 6633; Ec(N), *Escherichia coli* NIHJ JC-2; Ec, *Escherichia coli* KC-14; Kp, *Klebsiella pneumoiae* K-1966; Sm, *Serratia marcescens* IFO 3736; Pv, *Proteus vulgaris* HX-19; Pa, *Pseudomonas aeruginosa* E-2; A, *Acinetobacter calcoaceticus* 54.

residue. The crude oil was purified by column chromatography using *n*-hexane to afford 186.17 g (74% from **11a**) of (**13a**), bp 68-70°/4 mm Hg; ir: 2050, 1600, 1500 cm^{-1}; pmr (deuteriochloroform): δ 6.75-7.30 (m, 3H, aromatic); ms: (m/z) 171 (M^+).

According to the same method, 3-chloro-4-fluorophenyl isothiocyanate (**13b**) was prepared from **11b** in 91% yield. Compound **13b** had bp 115-117°/11 mm Hg; ir (neat): 2000, 1580, 1480 cm^{-1}; pmr (deuteriochloroform): δ 6.95-7.56 (m, 3H, aromatic); ms: (m/z) 187 (M^+).

Ethyl 6,7-Difluoro-4-hydroxy-2-(*p*-methoxybenzylthio)quinoline-3-carboxylate (**16a**).

To a suspension of 2.90 g (0.060 mole) of sodium hydride (50% in oil) in 60 ml of THF was added dropwise diethyl malonate (8.81 g, 0.055 mole) under ice cooling. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. To this suspension was added dropwise **13a** (9.41 g, 0.055 mole) under ice cooling. Then the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction mixture was kept in a refrigerator overnight. The resultant precipitate was collected by filtration, washed with ether, and dried to give 18.7 g (96%) of sodium salt of diethyl 3,4-difluorophenylamino(mercapto)methylenemalonate (**14a**), which was used in the successive reaction without purification. To a solution of **14a** (18.7 g, 0.053 mole) in 30 ml of DMF was added dropwise *p*-methoxybenzylchloride (8.30 g, 0.053 mole) under ice cooling. After stirring at the same temperature for 30 minutes, the reaction mixture was gradually brought to room temperature and stirred for 2 hours. The resultant mixture was poured into water and extracted with chloroform. The organic layer was washed with water, dried, and concentrated to dryness under reduced pressure to give 15.9 g (67%) of diethyl 3,4-difluorophenylamino(*p*-methoxybenzylthio)methylenemalonate (**15a**) as an oil. Without purification, **15a** (15.9 g, 0.0352 mole) was dissolved in 60 ml of diphenyl ether and heated at 250° for 12 minutes. After cooling, the reaction mixture was diluted with 150 ml of *n*-hexane. The resulting precipitate was collected by filtration and recrystallized from ethyl acetates to afford 7.7 g (35% from **13a**) of **16a**, mp 151°; ir (potassium bromide): 1665, 1590, 1430 cm^{-1}; pmr (deuteriochloroform): δ 1.47 (t, J = 7 Hz, 3H, CH_2CH_3), 3.74 (s, 3H, OCH_3), 4.36 (s, 2H, SCH_2), 4.47 (q, J = 7 Hz, 2H, CH_2CH_3), 6.73 (d, J = 9 Hz, 2H, 3',5'-H), 7.24 (d, J = 9 Hz, 2H, 2',6'-H), 7.44 (dd, J = 8 Hz, 11 Hz, 1H), 7.80 (dd, J = 9 Hz, 10 Hz, 1H), 13.20 (s, 1H, OH).

Anal. Calcd. for $C_{20}H_{17}F_2NO_4S$: C, 59.25; H, 4.23; N, 3.45. Found: C, 59.22; H, 3.91; N, 3.46.

According to the same procedure, ethyl 7-chloro-6-fluoro-4-hydroxy-2-(4-methoxybenzylthio)quinoline-3-carboxylate (**16b**) was prepared. Compound **16b** was obtained in 41% yield from **13a**, mp 142°; ir (potassium bromide): 1650, 1585, 1410 cm^{-1}; pmr (deuteriochloroform): δ 1.42 (t, J = 8 Hz, 3H, CH_2CH_3), 3.69 (s, 3H, OCH_3), 4.32 (s, 2H, SCH_2), 4.45 (q, J = 8 Hz, 2H, CH_2CH_3), 6.75 (d, J = 9 Hz, 2H, 3',5'-H), 7.27 (d, J = 9 Hz, 2H, 2',6'-H), 7.70 (d, J = 10 Hz, 1H, 5-H), 7.72 (d, J = 6 Hz, 1H, 8-H), 13.16 (s, 1H, OH).

Anal. Calcd. for $C_{20}H_{17}ClFNO_4S$: C, 56.94; H, 4.06; N, 3.32. Found: C, 57.06; H, 4.08; N, 3.40.

Ethyl 6,7-Difluoro-4-hydroxy-2-mercaptoquinoline-3-carboxylate (**17a**).

To a solution of trifluoromethanesulfonic acid (12.8 g, 0.085 mole), trifluoroacetic acid (58.3 g, 0.511 mole) and anisole (92.2 g, 0.085 mole) was gradually added **16a** (5.76 g, 0.014 mole) in a small portion at −5°. After stirring at the same temperature for 30 minutes, the mixture was allowed to warmed to room temperature and stirred for 2 hours. The reaction mixture was concentrated under reduced pressure below 40°. The residue was dissolved in 20% aqueous sodium hydroxide and the solution was washed with ether. The aqueous layer was separated, acidified with acetic acid and kept at 0° overnight. The precipitate was collected by filtration, washed with water, and dried to give 3.64 g (90%) of **17a**, mp 208° dec; ir (potassium bromide): 3100, 1645, 1595 cm^{-1}; pmr (trifluoroacetic acid): δ 1.62 (t, J = 7 Hz, 3H, CH_2CH_3), 4.74 (q, J = 7 Hz, 2H, CH_2CH_3), 7.68 (dd, J = 7 Hz, 9 Hz, 1H, 8-H), 8.20 (dd, J = 8 Hz, 9 Hz, 1H, 5-H).

Anal. Calcd. for $C_{12}H_9F_2NO_3S$: C, 50.53; H, 3.18; N, 4.91. Found: C, 50.65; H, 3.08; N, 4.70.

According to the same method ethyl 7-chloro-6-fluoro-4-hydroxy-2-mercaptoquinoline-3-carboxylate (**17b**) was prepared from **16b** in 84% yield. Compound **17b** had mp 220° dec; ir (potassium bromide): 1635, 1585 cm^{-1}; pmr (trifluoroacetic acid): δ 1.65 (t, J = 7 Hz, 3H, CH_2CH_3), 4.80 (q, J = 7 Hz, 2H, CH_2CH_3), 8.00 (d, J = 6 Hz, 1H, 8-H), 8.12 (d, J = 9 Hz, 1H, 5-H).

Anal. Calcd. for $C_{12}H_9ClFNO_3S$: C, 47.77; H, 3.01; N, 4.64. Found: C, 47.89; H, 3.00; N, 4.41.

Ethyl 8-Chloro-7-fluoro-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylate (**18**).

A mixture of **17b** (3.0 g, 10 mmoles), bromoacetaldehyde diethyl acetal (2.9 g, 15 mmoles) and potassium bicarbonate (2.7 g, 20 mmoles) in 20 ml of DMF was stirred at 80° for 12 hours. After concentration of the reaction mixture under reduced pressure, the residue was taken up in water and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness to afford a crude solid, which without further purification, was dissolved in concentrated sulfuric acid. After heating at 90° for 20 minutes, the reaction mixture was poured into ice-water. The resulting precipitate was collected by filtration and recrystallized from DMF to give 2.6 g (80%) of **18**, mp 257-258° dec; ir (potassium bromide): 1660, 1610, 1480 cm^{-1}; pmr (trifluoroacetic acid): δ 1.66 (t, J = 7 Hz, 3H, CH_2CH_3), 4.82 (q, J = 7 Hz, 2H, CH_2CH_3), 8.04 (d, J = 5 Hz, 1H, 2-H), 8.38 (d, J = 9 Hz, 1H, 6-H), 8.62 (d, J = 6 Hz, 1H, 9-H), 8.92 (d, J = 5 Hz, 1H, 1-H).

Anal. Calcd. for $C_{14}H_9ClFNO_3S$: C, 51.46; H, 2.78; N, 4.29. Found: C, 51.55; H, 2.57; N, 3.95.

8-Chloro-7-fluoro-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**19**).

To a solution of sodium hydroxide (0.5 g, 12 mmoles) in 70 ml of ethanol and 70 ml of water was added **18** (1.94 g, 6 mmoles) and refluxed for 2 hours. After cooling, the solution was acidified with acetic acid and the resulting precipitate was collected and recrystallized from DMF to afford 1.3 g (73%) of **19**, mp 310-315° dec; ir (potassium bromide): 3125, 1690, 1595 cm^{-1}; pmr (trifluoroacetic acid): δ 8.05 (d, J = 5 Hz, 1H, 2-H), 8.37 (d, J = 8 Hz, 1H, 6-H), 8.63 (d, J = 6 Hz, 1H, 9-H), 8.92 (d, J = 5 Hz, 1H, 1-H).

Anal. Calcd. for $C_{12}H_5ClFNO_3S$: C, 48.42; H, 1.69; N, 4.71. Found: C, 48.84; H, 1.48; N, 4.40.

7-Fluoro-8-(4-methyl-1-piperazinyl)-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**20**) and 8-Chloro-7-(4-methyl-1-piperazinyl)-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**22**).

A mixture of **19** (0.50 g, 1.7 mmoles), 1-methylpiperazine (2.53

g, 25.2 mmoles) and 15 ml of pyridine was refluxed for 75 hours. The reaction mixture was concentrated under reduced pressure to afford a crude mixture of **20** and **22**. Column chromatography eluting with 10% methanol in chloroform afforded 0.32 g (52%) of **20** (Rf = 0.34 methanol:chloroform 1:5), mp 305-308° dec; ir (potassium bromide): 1680, 1630 cm^{-1}; pmr (trifluoroacetic acid): δ 3.18 (s, 3H, NCH_3), 3.30-4.60 (m, 8H, piperazine), 7.80 (d, J = 6 Hz, 1H, 9-H), 7.96 (d, J = 5 Hz, 1H, 2-H), 8.24 (d, J = 12 Hz, 1H, 6-H), 8.91 (d, J = 5 Hz, 1H, 1-H).

Anal. Calcd. for $C_{17}H_{16}FN_3O_3S$: C, 56.50; H, 4.46; N, 11.63. Found: C, 56.28; H, 4.45; N, 11.68.

Elution also afforded 0.094 g (14%) of **22** (Rf = 0.46), mp 254-255° dec; ir (potassium bromide): 1675, 1580 cm^{-1}; pmr (trifluoroacetic acid): δ 3.21 (s, 3H, NCH_3), 3.4-4.2 (m, 8H, piperazine), 8.10 (d, J = 5 Hz, 1H, 2-H), 8.30 (s, 1H, 6-H), 8.66 (s, 1H, 9-H), 8.97 (d, J = 5 Hz, 1H, 1-H).

Anal. Calcd. for $C_{17}H_{16}ClN_3O_3S{\cdot}0.5H_2O$: C, 52.78; H, 4.43; N, 10.86. Found: C, 52.94; H, 4.32; N, 10.91.

7-Fluoro-5-oxo-8-(1-piperazinyl)-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**21**).

A mixture of **19** (10.0 g, 0.034 mole), piperazine (29.0 g, 0.34 mole) and 250 ml of pyridine was refluxed for 55 hours. After cooling, the resulting precipitate was collected by filtration and dissolved in 10% aqueous sodium hydroxide solution. After filtration, the filtrate was neutralized with acetic acid. The resultant precipitate was collected and recrystallized from DMF to afford 4.78 g (41%) [20] of **21**, mp 288° dec; ir (potassium bromide): 1670, 1630 cm^{-1}; pmr (trifluoroacetic acid): δ 3.50-4.30 (m, 8H, piperazine), 7.85 (d, J = 7 Hz, 1H, 9-H), 7.96 (d, J = 6 Hz, 1H, 2-H), 8.25 (d, J = 12 Hz, 1H, 6-H), 8.96 (d, J = 6 Hz, 1H, 1-H).

Anal. Calcd. for $C_{16}H_{14}FN_3O_3S$: C, 55.32; H, 4.06; N, 12.10. Found: C, 55.52; H, 4.14; N, 12.37.

Ethyl 6,7-Difluoro-4-hydroxy-2-(2-oxopropyl)thio-3-carboxylate (**23a**).

To a 70 ml of absolute ethanol was added 0.41 g (17.5 mmoles) of sodium under ice cooling. To this solution was added **17a** (5.00 g, 17.5 mmoles) and stirred for 1.5 hours, and was added dropwise chloroacetone (3.56 g, 38.6 mmoles) at the same temperature and allowed to warm to room temperature. After stirring for 3.5 hours, the reaction mixture was poured into ice-water. The resulting precipitate was collected, washed with water, ethanol and ether to give 5.46 g (87%) of **23a**, mp 195-196° dec; ir (potassium bromide): 3200, 1670, 1600 cm^{-1}; pmr (trifluoroacetic acid): δ 1.63 (t, J = 7 Hz, 3H, CH_2CH_3), 2.10 (s, 3H, CH_3), 3.77 and 4.00 (d, J = 12 Hz, 2H, SCH_2CO), 4.79 (q, J = 7 Hz, 2H, CH_2CH_3), 8.18 (dd, J = 8 Hz, 8 Hz, 1H, 5-H), 9.01 (dd, J = 6 Hz, 12 Hz, 1H, 8-H).

Anal. Calcd. for $C_{15}H_{13}F_2NO_4S$: C, 52.78; H, 3.84; N, 4.10. Found: C, 52.87; H, 3.74; N, 4.06.

According to the same method, compounds **23b-23d** were prepared.

Ethyl 7-Chloro-6-fluoro-4-hydroxy-2-(2-oxopropyl)thioquinoline-3-carboxylate (**23b**).

This compound was obtained in 86% yield, mp 239-242°.

Anal. Calcd. for $C_{16}H_{15}ClFNO_4S$: C, 51.69; H, 4.07; N, 3.77. Found: C, 51.52; H, 4.41; N, 3.56.

Ethyl 6,7-Difluoro-4-hydroxy-2-(1-fluoro-2-oxopropyl)thioquinoline-3-carboxylate (**23c**).

This compound was obtained in 89% yield, pmr (deuteriochloroform): δ 1.65 (t, J = 8 Hz, 3H, CH_2CH_3), 2.10 (s, 3H, $COCH_3$), 4.80 (q, J = 8 Hz, 2H, CH_2CH_3), 6.20 (d, J = 54 Hz, 1H, SCHCO), 8.42 (dd, J = 7 Hz, 9 Hz, 1H, 5-H), 9.00 (dd, J = 7 Hz, 9 Hz, 1H, 8-H).

Ethyl 7-Chloro-6-fluoro-4-hydroxy-2-(1-methyl-2-oxopropyl)thioquinoline-3-carboxylate (**23d**).

This compound was obtained in 96% yield, mp 222-224° dec; ir (potassium bromide): 3220, 1680, 1600 cm^{-1}; pmr (trifluoroacetic acid): δ 1.65 (t, J = 7 Hz, 3H, CH_2CH_3), 1.73 (d, J = 7 Hz, 3H, $SCHCH_3$), 1.92 (s, 3H, $COCH_3$), 4.23 (q, J = 7 Hz, 1H, $SCHCH_3$), 4.37 (q, J = 7 Hz, 2H, CH_2CH_3), 8.22 (d, J = 8 Hz, 1H, 5-H), 9.16 (d, J = 6 Hz, 1H, 8-H).

Anal. Calcd. for $C_{16}H_{15}ClFNO_4S$: C, 51.69; H, 4.06; N, 3.69. Found: C, 51.72; H, 4.32; N, 3.52.

Ethyl 7,8-Difluoro-1-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylate (**24a**).

To cooled (0°) concentrated sulfuric acid (55 ml) was added portionwise **23a** (5.46 g, 16.0 mmoles) and stirred for 1 hour at the same temperature. The reaction mixture was poured into ice-water and the resulting precipitate was collected by filtration, washed with water, dried to give 4.60 g (89%) of **24a**, mp 256-257° dec; ir (potassium bromide): 3090, 1655, 1610 cm^{-1}; pmr (trifluoroacetic acid): δ 1.68 (t, J = 7 Hz, 3H, CH_2CH_3), 3.26 (s, 3H, CH_3), 4.86 (q, J = 7 Hz, 2H, CH_2CH_3), 7.75 (s, 1H, 2-H), 8.60 (dd, J = 8 Hz, 8 Hz, 1H, 6-H), 8.80 (dd, J = 6 Hz, 11 Hz, 1H, 9-H).

Anal. Calcd. for $C_{15}H_{11}F_2NO_3S$: C, 55.72; H, 3.43; N, 4.33. Found: C, 55.70; H, 3.56; N, 4.28.

According to the same procedure **24b** and **24d** were prepared.

Ethyl 8-Chloro-7-fluoro-1-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylate (**24b**).

This compound was obtained in 72% yield, mp 291-293° dec; ir (potassium bromide): 1695, 1670, 1605 cm^{-1}; pmr (trifluoroacetic acid): δ 1.66 (t, J = 7 Hz, 3H, CH_2CH_3), 3.23 (s, 3H, CH_3), 4.80 (q, J = 7 Hz, 2H, CH_2CH_3), 7.66 (s, 1H, 2-H), 8.39 (d, J = 8 Hz, 1H, 6-H), 8.93 (d, J = 6 Hz, 1H, 9-H).

Anal. Calcd. for $C_{15}H_{11}ClFNO_3S$: C, 53.03; H, 3.26; N, 4.12. Found: C, 52.47; H, 3.47; N, 4.57.

Ethyl 8-Chloro-7-fluoro-1,2-dimethyl-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylate (**24d**).

This compound was obtained in 90% yield, mp 223-227° dec; ir (potassium bromide): 1660, 1610 cm^{-1}; pmr (trifluoroacetic acid): δ 1.74 (t, J = 7 Hz, 3H, CH_2CH_3), 2.76 (s, 3H, 2-CH_3), 3.23 (s, 3H, 1-CH_3), 4.85 (q, J = 7 Hz, 2H, CH_2CH_3), 8.46 (d, J = 8 Hz, 1H, 6-H), 9.00 (d, J = 6 Hz, 1H, 9-H).

Anal. Calcd. for $C_{16}H_{13}ClFNO_3S$: C, 54.31; H, 3.70; N, 3.95. Found: C, 54.62; H, 3.81; N, 4.07.

7,8-Difluoro-1-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**25a**).

This compound was prepared from **24a** by the same procedure used to prepare **19** from **18**.

Compound **25a** had mp 270-280° dec; ir (potassium bromide): 1690, 1610 cm^{-1}; pmr (trifluoroacetic acid): δ 3.25 (s, 3H, CH_3), 7.68 (s, 1H, 2-H), 8.52 (dd, J = 6 Hz, 8 Hz, 1H, 6-H), 8.71 (dd, J = 6 Hz, 8 Hz, 1H, 9-H).

Anal. Calcd. for $C_{13}H_7F_2NO_3S$: C, 52.88; H, 2.39; N, 4.74.

Found; C, 53.05; H, 2.40; N, 4.61.

According to the same procedure compounds **25b** and **25d** were prepared.

8-Chloro-7-fluoro-1-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**25b**).

This compound was obtained in 88% yield, mp 317-319°; ir (potassium bromide): 1695, 1590 cm^{-1}; pmr (trifluoroacetic acid): δ 3.26 (s, 3H, CH_3), 7.72 (s, 1H, 2-H), 8.46 (d, J = 8 Hz, 1H, 6-H), 8.98 (d, J = 6 Hz, 1H, 9-H).

Anal. Calcd. for $C_{13}H_7ClFNO_3S$: C, 50.09; H, 2.26; N, 4.49. Found: C, 50.32; H, 2.37; N, 4.37.

8-Chloro-7-fluoro-1,2-dimethyl-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**25d**).

This compound was obtained in 94% yield, mp 294-296° dec; ir (potassium bromide): 1690, 1590 cm^{-1}; pmr (trifluoroacetic acid): δ 2.70 (s, 3H, 2-CH_3), 3.14 (s, 3H, 1-CH_3), 8.46 (d, J = 8 Hz, 1H, 6-H), 8.95 (d, J = 6 Hz, 1H, 9-H).

Anal. Calcd. for $C_{14}H_9ClFNO_3S$: C, 51.62; H, 2.78; N, 4.29. Found: C, 51.84; H, 2.69; N, 4.51.

2,7,8-Trifluoro-1-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**25c**).

To cooled (0°) fuming sulfuric acid (24 ml) was added portionwise **23c** (3.95 g, 11 mmoles) and allowed to warm to room temperature. After stirring for 4 hours, the reaction mixture was poured into ice-water. The resulting precipitate was collected by filtration and recrystallized from DMF to give 1.3 g (38%) of **25c**, mp 285-286° dec; ir (potassium bromide): 1695, 1600 cm^{-1}; pmr (trifluoroacetic acid): δ 3.16 (d, J = 4 Hz, 3H, CH_3), 8.62 (dd, J = 9 Hz, 9 Hz, 1H, 6-H), 8.74 (dd, J = 6 Hz, 12 Hz, 1H, 9-H).

Anal. Calcd. for $C_{13}H_6F_3NO_3S$: C, 49.85; H, 1.93; N, 4.47. Found: C, 49.78; H, 1.80; N, 4.52.

7-Fluoro-1-methyl-8-(4-methyl-1-piperazinyl)-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**26**) and 8-Chloro-1-methyl-7-(4-methyl-1-piperazinyl)-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**30**).

Method A.

Compounds **26** and **30** were prepared from **25b** using a similar experimental procedure as the preparation of **20** and **22** from **19**.

Compound **26** was obtained in 34% yield, mp 288-290° dec; ir (potassium bromide): 1695, 1630 cm^{-1}; pmr (trifluoroacetic acid): δ 3.22 (s, 3H, 1-CH_3), 3.27 (s, 3H, NCH_3), 3.3-4.4 (m, 8H, piperazine), 7.67 (s, 1H, 2-H), 8.25 (d, J = 6 Hz, 1H, 9-H), 8.36 (d, J = 12 Hz, 1H, 6-H).

Anal. Calcd. for $C_{18}H_{18}FN_3O_3S$: C, 57.59; H, 4.83; N, 11.19. Found: C, 57.42; H, 4.93; N, 11.03.

Compound **30** was obtained in 26% yield, mp 291-293° dec; ir (potassium bromide): 1690, 1590 cm^{-1}; pmr (trifluoroacetic acid): δ 3.22 (s, 3H, 1-CH_3), 3.22 (s, 3H, NCH_3), 3.3-4.2 (m, 8H, piperazine), 7.68 (s, 1H, 2-H), 8.29 (s, 1H, 6-H), 8.96 (s, 1H, 9-H).

Anal. Calcd. for $C_{18}H_{18}ClN_3O_3S$: C, 55.17; H, 4.63; N, 10.72. Found: C, 55.11; H, 4.70; N, 10.63.

Method B.

A mixture of **25a** (0.295 g, 1 mmole), piperazine (0.344 g, 4 mmoles) and 2 ml of pyridine was heated at 100° for 2 hours. After cooling, the resultant precipitate was collected and recrystallized from a mixture of DMF and ethanol to give 0.264 g (73%) of **26**, whose ir and pmr spectrum was identical with those of **26** prepared by method A.

7-Fluoro-1,2-dimethyl-8-(4-methyl-1-piperazinyl)-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**27**).

A mixture of **25b** (1.0 g, 3.1 mmoles), 1-methylpiperazine (3.1 g, 31.0 mmoles) and 40 ml of pyridine was refluxed for 40 hours. The reaction mixture was concentrated under reduced pressure. The residue was treated with water, and the resulting precipitate was collected by filtration and recrystallized from pyridine to afford 0.34 g (31%) [20] of **27**, mp 283-285° dec; ir (potassium bromide): 1690, 1630 cm^{-1}; pmr (trifluoroacetic acid): δ 2.67 (s, 3H, 2-CH_3), 3.12 (s, 3H, 1-CH_3), 3.22 (s, 3H, NCH_3), 3.3-4.5 (m, 8H, piperazine), 8.17 (d, J = 6 Hz, 1H, 9-H), 8.34 (d, J = 12 Hz, 1H, 6-H).

Anal. Calcd. for $C_{19}H_{20}FN_3O_3S$: C, 58.59; H, 5.17; N, 10.78. Found: C, 58.71; H, 5.18; N, 10.51.

2,7-Difluoro-1-methyl-8-(4-methyl-1-piperazinyl)-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**28**).

A mixture of **25c** (0.30 g, 0.96 mmole), 1-methylpiperazine (0.19 g, 1.9 mmoles) and 20 ml of DMF was heated at 85° for 4 hours and allowed to stand at room temperature overnight. The resulting precipitate was collected by filtration and recrystallized from DMF to give 0.23 g (61%) of **28**, mp 255-260° dec; ir (potassium bromide): 1690, 1620 cm^{-1}; pmr (trifluoroacetic acid): δ 3.20 (s, 3H, 1-CH_3), 3.20 (s, 3H, NCH_3), 2.8-4.5 (m, 8H, piperazine), 8.20 (d, J = 6 Hz, 1H, 9-H), 8.30 (d, J = 12 Hz, 1H, 6-H).

Anal. Calcd. for $C_{18}H_{17}F_2N_3O_3S$: C, 54.95; H, 4.36; N, 10.68. Found: C, 55.01; H, 4.22; N, 10.61.

7-Fluoro-1-methyl-5-oxo-8-(1-piperazinyl)-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**29**).

Method C.

Compound **29** was prepared from **25b** using a similar experimental procedure as the preparation of **21** from **19**.

Compound **29** was obtained in 13% yield [17], mp 284-286° dec; ir (potassium bromide): 1700, 1635 cm^{-1}; pmr (trifluoroacetic acid): δ 3.28 (s, 3H, CH_3), 3.7-4.8 (m, 8H, piperazine), 7.71 (s, 1H, 2-H), 8.35 (d, J = 7 Hz, 1H, 9-H), 8.42 (d, J = 12 Hz, 1H, 6-H).

Anal. Calcd. for $C_{17}H_{16}FN_3O_3S \cdot 0.5H_2O$: C, 55.13; H, 4.63; N, 11.34. Found: C, 55.63; H, 4.61; N, 11.34.

Method D.

A mixture of **25a** (0.295 g, 1.00 mmole), piperazine (0.344 g, 4.0 mmoles) and 2 ml of pyridine was heated at 100° for 2 hours. After cooling, the resulting precipitate was collected by filtration, washed with ethanol and recrystallized from a mixture of DMF and ethanol to give 0.264 g (73%) of **29**, whose ir and pmr spectrum was identical with those of **29** prepared by method C.

Ethyl 8-Chloro-7-fluoro-1,2-dihydro-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylate (**31**).

Method E.

A mixture of **17b** (3.0 g, 10 mmoles), 1,2-dibromoethane (1.9 g, 10 mmoles), potassium bicarbonate (4.1 g, 30 mmoles) and 10 ml of DMF was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and treated with water. The precipitated solid was collected, washed with

water and recrystallized from ehanol to afford 3.3 g (94%) of **31**, mp 278°; ir (potassium bromide): 1750, 1680 cm^{-1}; pmr (trifluoroacetic acid): δ 1.65 (t, J = 7 Hz, 3H, CH_2CH_3), 3.82 (t, J = 9 Hz, 2H, SCH_2), 4.79 (q, J = 7 Hz, 2H, CH_2CH_3), 5.23 (t, J = 9 Hz, 2H, NCH_2), 7.96 (d, J = 6 Hz, 1H, 9-H), 8.19 (d, J = 8 Hz, 1H, 6-H).

Anal. Calcd. for $C_{14}H_{11}ClFNO_3S \cdot 0.25H_2O$: C, 50.61; H, 3.49; N, 4.22. Found: C, 50.69; H, 3.24; N, 4.07.

Method F.

A mixture of **14b** (10.00 g, 27.0 mmoles), 1,2-dibromoethane (12.20 g, 64.0 mmoles), potassium bricarbonate (8.98 g, 64.0 mmoles) and 200 ml of DMF was stirred at room temperature for 3 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated under reduced pressure to give an oil which was triturated with *n*-hexane to give 7.0 g (70%) of diethyl 3-(3-chloro-4-fluorophenyl)-1,3-thiazolidine-2-ylidenemalonate (**34**), mp 112-113°; ir (potassium bromide): 1705, 1660 cm^{-1}; pmr (trifluoroacetic acid): δ 1.19 (t, J = 8 Hz, 6H, CH_2CH_3), 3.18 (t, J = 7 Hz, 2H, SCH_2), 3.78 (t, J = 7 Hz, 2H, NCH_2), 3.95 (q, J = 8 Hz, 4H, CH_2CH_3), 6.9-7.4 (m, 3H, aromatic).

Anal. Calcd. for $C_{16}H_{17}ClFNO_4S$: C, 51.41; H, 4.58; N, 3.75. Found: C, 51.26; H, 4.51; N, 3.87.

A mixture of **34** (7.15 g, 19.0 mmoles) and 71 g of polyphosphoric acid was heated at 120° for 2 hours. After cooling, the reaction mixture was poured into ice-water and the precipitated solid was collected by filtration. The crude solid was purified by column chromatography eluting with chloroform to give 2.97 g (47%) of **31**, which was identical in all respects with an authentic specimen of **31** prepared by the method E. Elution also afforded 2.04 g (33%) of ethyl 6-chloro-7-fluoro-1,2-dihydro-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylate (**35**), mp 278°; ir (potassium bromide): 1710, 1680 cm^{-1}; pmr (trifluoroacetic acid): δ 1.63 (t, J = 7 Hz, 3H, CH_2CH_3), 3.85 (t, J = 7 Hz, 2H, SCH_2), 4.78 (q, J = 7 Hz, 2H, CH_2CH_3), 5.28 (t, J = 7 Hz, 2H, NCH_2), 7.7-8.1 (m, 2H, 8-H, 9-H).

Anal. Calcd. for $C_{14}H_{11}ClFNO_3S$: C, 51.46; H, 3.39; N, 4.29. Found: C, 51.38; H, 3.25; N, 4.11.

8-Chloro-7-fluoro-1,2-dihydro-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic Acid (**32**).

To a solution of sodium hydroxide (2.4 g, 60.0 mmoles) in 105 ml of water and 75 ml of ethanol was added **31** (8.2 g, 25.9 mmoles) and refluxed for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water. The solution was acidified with acetic acid and the resulting precipitate was collected by filtration, washed with ethanol and ether to afford 6.04 g (78%) of **32**, mp 318°; ir (potassium bromide): 1700, 1590 cm^{-1}; pmr (trifluoroacetic acid): δ 3.82 (t, J = 8 Hz, 2H, SCH_2), 5.23 (t, J = 8 Hz, 2H, NCH_2), 8.00 (d, J = 6 Hz, 1H, 9-H), 8.23 (d, J = 9 Hz, 1H, 6-H).

Anal. Calcd. for $C_{12}H_7ClFNO_3S$: C, 48.09; H, 2.35; N, 4.67. Found: C, 48.28; H, 2.14; N, 4.37.

7-Fluoro-1,2-dihydro-8-(4-methyl-1-piperazinyl)-5-oxo-5*H*-thiazolo-[3,2-*a*]quinoline-4-carboxylic Acid (**33**).

A mixture of **32** (0.501 g, 1.67 mmoles), 1-methylpiperazine (2.513 g, 25.31 mmoles) and 15 g of pyridine was refluxed for 27 hours. The reaction mixture was concentrated under reduced pressure to afford a crude solid, which was purified by column chromatography eluting with 5% methanol in chloroform to give 0.499 g (82%) of **33**, mp 267-271° dec; ir (potassium bromide): 1695, 1625 cm^{-1}; pmr (trifluoroacetic acid): δ 3.35-4.50 (m, 10H, piperazine SCH_2), 5.18 (t, J = 8 Hz, 2H, NCH_2), 7.18 (d, J = 6 Hz, 1H, 9-H), 8.12 (d, J = 13 Hz, 1H, 6-H).

Anal. Calcd. for $C_{17}H_{18}FN_3O_3S$: C, 56.19; H, 4.99; N, 11.56. Found: C, 55.81; H, 4.67; N, 11.28.

REFERENCES AND NOTES

[1] This is part **2** in a series of Studies on Pyridonecarboxylic acids, Part **1**. J. Segawa, M. Kitano, K. Kazuno, M. Matsuoka, I. Shirahase, M. Ozaki, M. Matsuda, Y. Tomii and M. Kise, *J. Med. Chem.*, in preparation.

[2] G. Y. Lesher, E. J. Froelich, M. D. Gruett, J. H. Bailey and R. P. Brundage, *J. Med. Pharm. Chem.*, **5**, 1063 (1962).

[3] D. Kaminsky and R. I. Meltzer, *J. Med. Chem.*, **11**, 160 (1968).

[4] J. Matsumoto and S. Minami, *J. Med. Chem.*, **18**, 74 (1975).

[5] J. Matsumoto, T. Miyamoto, A. Minamida, Y. Nishimura, H. Egawa and H. Nishimura, *J. Med. Chem.*, **27**, 292 (1984).

[6] H. Koga, A. Itoh, S. Murayama, S. Suzue and T. Irikura, *J. Med. Chem.*, **23**, 1358 (1980).

[7] K. Sato, Y. Matsuura, M. Inoue, T. Une, Y. Osada, H. Ogawa and S. Mitsuhashi, *Antimicrob. Agents Chemother.*, **22**, 548 (1982).

[8] R. Wise, J. M. Andrews and L. J. Edwards, *Antimicrob. Agents Chemother.*, **23**, 559 (1983).

[9] R. Dohmori, S. Kadoya, I. Takamura and N. Suzuki, *Chem. Pharm. Bull.*, **24**, 130 (1976).

[10] J. F. Gerster, US Patent 3,896,131.

[11a] H. Agui, T. Mitani, A. Izawa, T. Komatsu and T. Nakagome, *J. Med. Chem.*, **20**, 791 (1977); [b] L. A. Mitscher, H. E. Gracey, J. W. Clark and J. Suzuki, *J. Med. Chem.*, **21**, 485 (1978).

[12] S. Nishigaki, N. Mizushima, F. Yoneda and H. Takahashi, *J. Med. Chem.*, **14**, 638 (1971).

[13] H. Koga, Structure-Activity Relationships and Drug Design of the Pyridonecarboxylic Acid Type (Nalidixic Acid Type) Synthetic Antibacterial Agents, *KNRZAN*, **136**, 177 (1982).

[14a] S. Matsumura, M. Kise, M. Ozaki, S. Tada, K. Kazuno, H. Watanabe, K. Kunimoto and M. Tsuda, Japan Patent Kokai 57-136588; [b] H. Enomoto, M. Kise, M. Ozaki, M. Kitano and I. Morita, Japan Patent Kokai 58-103393; [c] M. Kise, M. Kitano and I. Morita, Japan Patent Kokai 58-105965; [d] M. Kise, M. Kitano, M. Ozaki, K. Kazuno, I. Shirahase, Y. Tomii and J. Segawa, Japan Patent Kokai 63-107990; [e] M. Kise, M. Kitano, M. Ozaki, K. Kazuno, M. Matsuda, I. Shirahase and Y. Tomii, Japan Patent Kokai 1-230584; [f] M. Kise, M. Kitano, M. Ozaki, K. Kazuno, M. Matsuda and I. Shirahase, Japan Patent Kokai 1-294680.

[15] M. L. Moore and F. S. Crossley, *Org. Synth.*, **III**, 599 (1955).

[16] C. C. Price and R. M. Roberts, *Org. Synth.*, **III**, 272 (1955).

[17] H. Yajima, K. Kitagawa, T. Segawa, M. Nakano and K. Kataoka, *Chem. Pharm. Bull.*, **23**, 3299 (1975).

[18a] A. Hantzsch, *Ber.*, **21**, 942 (1888); [b] R. H. Wiley, D. C. England and L. C. Behr, *Org. React.*, **6**, 367 (1951).

[19a] B. Staskun, *J. Org. Chem.*, **29**, 1153 (1964); [b] J. Moszew, *Zesz. Nauk Uniw. Jagiellon Pr. Chem.*, **10**, 7 (1965); *Chem. Abstr.*, **66**, 28128 (1967); [c] A. K. Sen and K. Mitra, *J. Indian Chem. Soc.*, **43**, 327 (1960); *Chem. Abstr.*, **65**, 8871 (1966).

[20] Low yields caused by the formation of 7-substituted derivatives which were not isolated.