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Synthetic Chemotherapeutic Agents. II.[1] Synthesis of 2-Substituted Thiazolo[5,4-*f*]quinoline Derivatives. (2)[2]

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In order to search for new antimicrobial agents, a number of 2-substituted 6-ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic acids were prepared. Nucleophilic reactions of the 2-methylsulfonyl derivative (**6** or **13**) gave the 2-alkoxy (**12**), 2-cyano (**14**), 2-amino (**15** and **19**) and other derivatives. By using the 2-cyano compound (**3** or **14**), various derivatives were also prepared, *e.g.*, the 2-amidine (**24h**), 2-imido-ether (**27**), 2-carbamoyl (**26** and **30**) and other derivatives. Formation of the 9-ethoxy compound (**33**) by ethylation of the 8-decarboxylated compound (**34**) was also described.

These compounds obtained were tested for their antimicrobial activities *in vitro*. The 2-cyano (**14**), 2-carbamoyl (**26**), 2-diethylaminoethylcarbamoyl (**30f**) and some other derivatives showed the stronger activities than nalidixic acid. The most active compound, **30f**, exhibited the activities against *Escherichia coli* resistant to nalidixic acid, but had no activity against *Ps. aeruginosa*.

The preceding paper[1] of this series reported the synthetic methods for the 2-methylthiothiazolo[5,4-*f*]quinoline-8-carboxylic acid derivatives. The present paper deals with the synthesis of various 2-substituted thiazolo[5,4-*f*]quinoline-8-carboxylic acids from the 2-methylthio derivatives and their antimicrobial activities.

In order to activate the 2-methylthio group, ethyl 6-ethyl-6,9-dihydro-2-methylthio-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylate (**7**)[1] was oxidized with potassium permanganate or hydrogen peroxide to give the 2-methylsulfonyl derivative (**6**). When the compound (**7**) was oxidized with one molar equivalent of hydrogen peroxide, the 2-methylsulfinyl derivative (**8**) was isolated, being convertible into **6** by further oxidation. The compound (**6**) was also obtained by ethylation of the 2-methylsulfonyl derivative (**5**)[1] which was prepared by oxidation of **4**[1] in a similar manner.

Treatment of the ester (**6**) with sodium hydrogensulfide or sodium cyanide gave the corresponding 2-mercapto-8-carboxylic acid ester (**2**) which was convertible into the acid (**1**) by hydrolysis, or the 2-cyano-8-ester (**3**), respectively. Reaction of **6** with sodium ethoxide, however, resulted in the formation of the 2-ethoxy-8-acid (**12b**)[1] owing to the simultaneous hydrolysis of the ester group at the 8 position. In a similar manner, **12a—d** were obtained by reaction of the 2-chloro-8-ester (**11**)[1] with sodium alkoxide.

The 2-cyano-8-acid (**14**) was prepared by oxidation of the 2-methylthio-8-acid (**10**),[1] followed by treatment of the resulting 2-methylsulfonyl-8-acid (**13**) with potassium cyanide.

According to the method of Van Duzee[4] who described the oxidative conversion of the mercapto group into the hydroxy group in the benzothiazole derivatives, the 2-methylthio-8-acid (**10**) was oxidized with sodium hypochlorite in sodium hydroxide solution to yield the 2-oxo-8-acid (**9**). The compound (**9**) also obtained by hydrolysis of **6**, **11** or **12b** with a mixture of hydrochloric acid in acetic acid or with potassium hydroxide solution, was an important

1) Part I: R. Dohmori, S. Kadoya, I. Takamura, and N. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **24**, 130 (1976).
2) A part of this work was presented at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 1974.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
4) E.M. Van Duzee, U.S. Patent 2179987 (1937) [*C. A.*, **34**, 1690 (1940)].

intermediate for the synthesis of the N-3 substituted derivatives which will be mentioned in a subsequent paper.

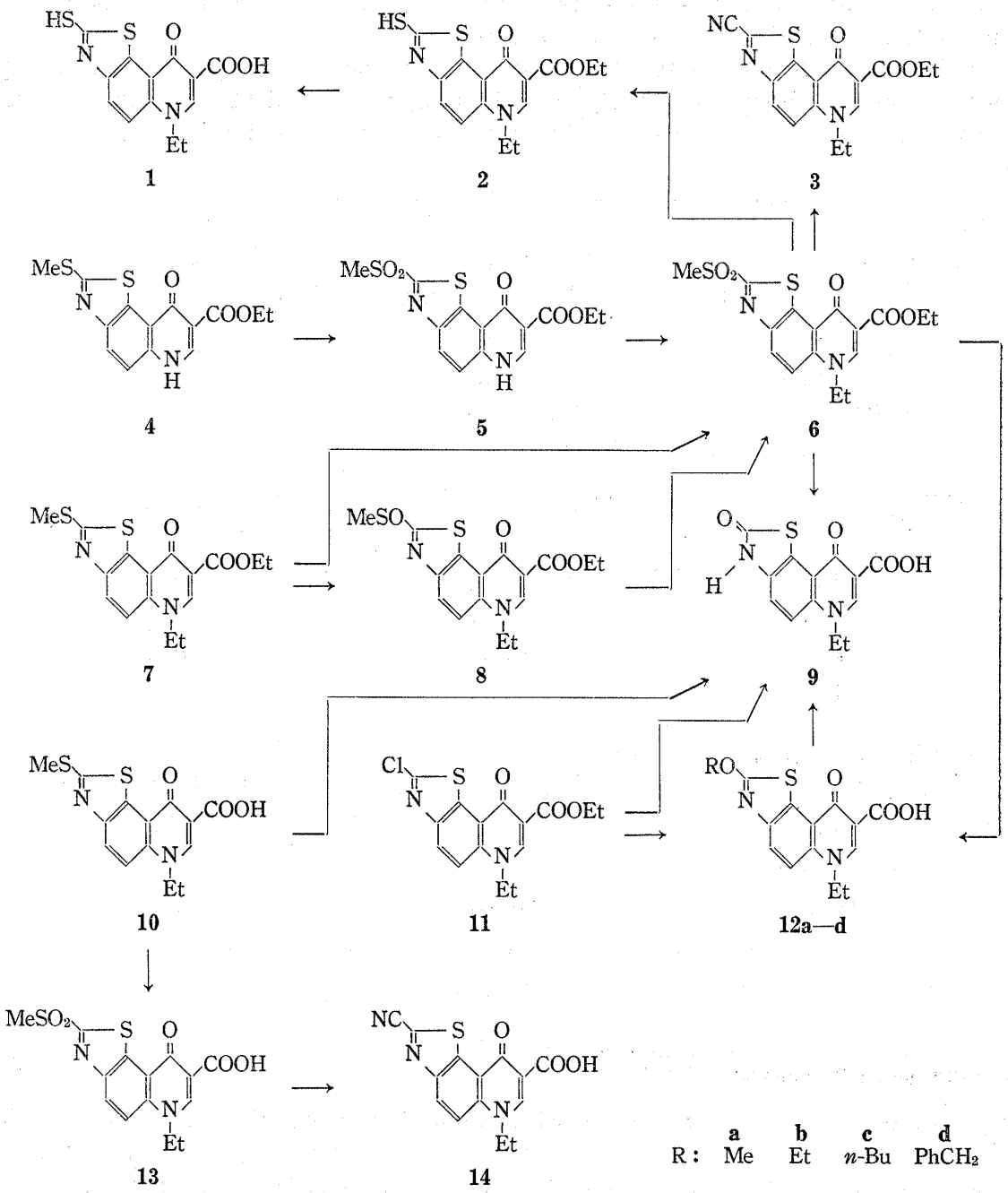


Chart 1

In the case of reaction of **6** with amines, various products formed depending upon the strength of basicity and the amounts of the amines used. Reaction of **6** with a slight excess of primary amines afforded mainly the 2-substituted 8-carboxylic acid esters (**18c** and **d**) which were easily convertible into the corresponding acids (**19c** and **d**) by hydrolysis. Treatment of **6** with a large excess of primary amines gave chiefly 2-substituted 8-carboxamides (**16b—e**) of which the hydrolysis with diluted sulfuric acid, however, afforded a mixture of the corresponding acids (**19b** and **c**) and the decarboxylated products (**17b** and **c**). The acids (**19a, b** and **d**) were more easily obtainable by treatment of **13** with primary amines.

Reaction of **6** with a large excess of more basic secondary amines, *e.g.*, aqueous dimethylamine or morpholine, gave mainly the 2-substituted 8-carboxylic acid (**15b** or **f**, respectively)

as a result of hydrolysis of the 8-ester group rather than amidation. Treatment of **6** with a more basic amine, aqueous diethylamine, however, did not provide the 2-diethylamino-8-carboxylic acid (**15c**) but the 2-oxo-8-carboxylic acid (**9**) resultant from hydrolysis of both the 2-methylsulfonyl and 8-ethoxycarbonyl groups.

Reaction of the 2-chloro-8-ester (**11**)[1] with nucleophilic reagents proceeded similarly as that of the 2-methylsulfonyl-8-ester (**6**) except that the reaction of **11** with aqueous diethylamine gave the 2-diethylamino-8-acid (**15c**) but not the 2-oxo derivative (**9**).

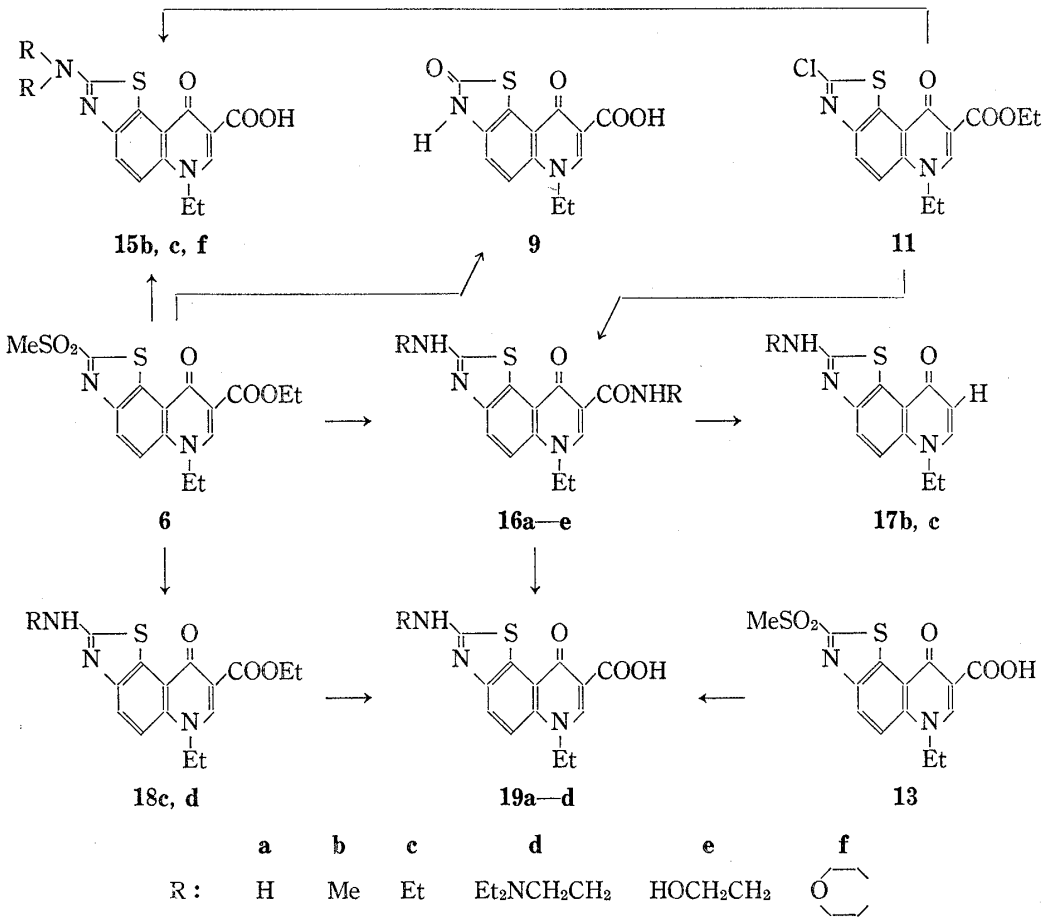


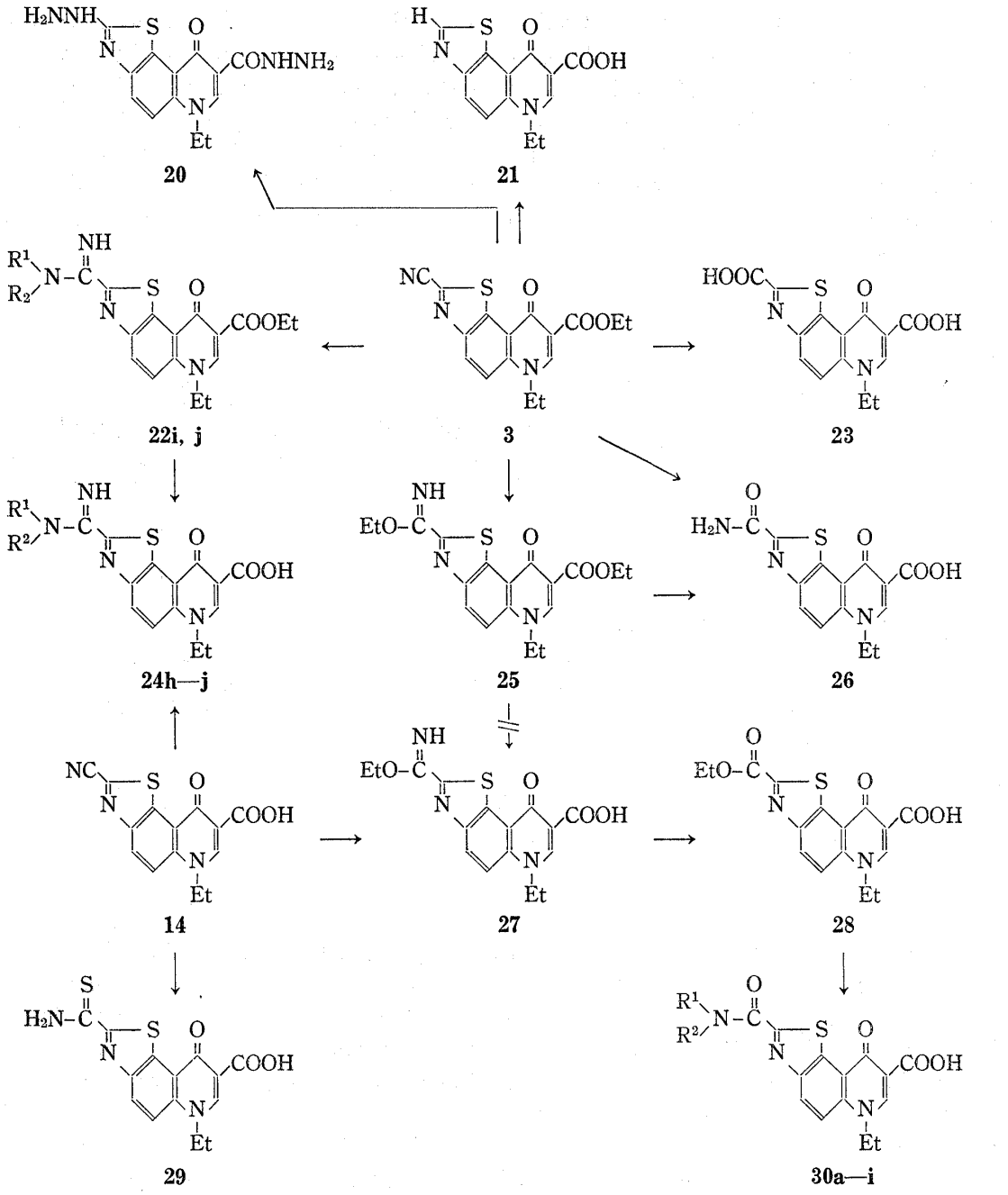
Chart 2

Hydrolysis of the 2-cyano-8-ester (**3**) with sodium hydroxide solution gave the 2,8-dicarboxylic acid (**23**), with a mixture of hydrochloric acid in acetic acid gave the 2-carbamoyl-8-acid (**26**), and with a mixture of sodium nitrite in sulfuric acid, however, afforded the decarboxylated product (**21**) which was identical with the sample obtained in the preceding paper.[1]

Reaction of **3** with gaseous hydrochloric acid in ethanol yielded a hygroscopic salt of imido-ether (hydrochloride of **25**) which was difficult to purify. However, it was found that reaction of **3** with potassium carbonate in ethanol easily afforded a stable imido-ether (**25**), which was also obtainable by treatment with sodium ethoxide in ethanol.[5] Hydrolysis of **25** with sodium hydroxide solution gave the 2-carbamoyl-8-acid (**26**) in place of the ethoxyformimidoyl acid (**27**) which could be obtained by reaction of the 2-cyano-8-acid (**14**) with potassium carbonate in ethanol. Treatment of **14** with gaseous hydrogen sulfide in dimethylformamide (DMF) gave the 2-thiocarbamoyl-8-acid (**29**).

5) *a*) F.C. Schaffer and G.A. Peters, *J. Org. Chem.*, **26**, 412 (1961); *b*) D.W. Henry, *J. Med. Chem.*, **12**, 303 (1969).

Treatment of the cyano compound (**3** or **14**) with hydroxylamine gave the amidoxime (**22j** or **24j**, respectively), and reaction of **14** with morpholine gave the amidine (**24h**) as a product of addition reactions. Reaction of **3** or **14** with hydrazine at room temperature gave also the corresponding addition product, **22i** or **24i**, respectively. At elevated temperatures, the 2-cyano-8-acid (**14**) gave also the amidrazone (**24i**) as an addition product, while the more soluble 2-cyano-8-ester (**3**) afforded the unexpected 2-hydrazino-8-carboxylic acid hydrazide (**20**) as a result of substitution reaction. The ester (**22i** or **j**) was hydrolyzed with diluted sodium hydroxide or hydrochloric acid solution to give the acid (**24i** or **j**, respectively).



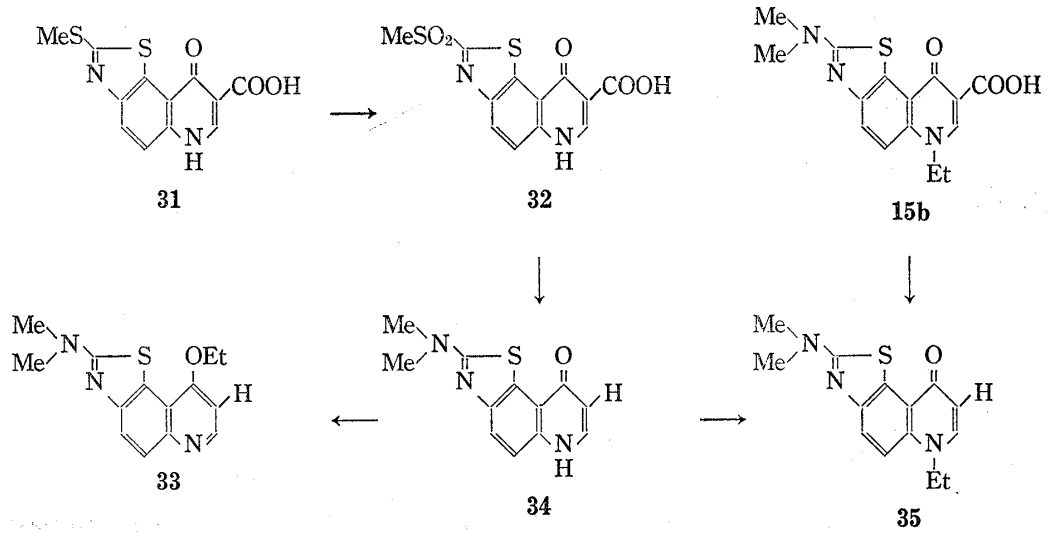
	a	b	c	d	e	f	g	h	i	j
R^1:	H	H	H	H	H	H	Et		H	H
R^2:	Et	*n*-Bu	$HO(CH_2)_2$	$HO(CH_2)_3$	$MeCH(OH)CH_2$	$Et_2N(CH_2)_2$	$HO(CH_2)_2$		H_2N	HO

Chart 3

The 2-ethoxycarbonyl-8-acid (**28**) prepared by reaction of the imido-ether (**27**) with diluted hydrochloric acid, was treated with amines or hydrazine to give the 2-carbamoyl-8-acids (**30a—h**) or the 2-hydrazinocarbonyl-8-acid (**30i**), respectively.

The 2-methylsulfonyl-8-acid (**32**) was prepared by oxidation of the corresponding 2-methylthio-8-acid (**31**).[1] The acid (**32**) was heated with 30% aqueous dimethylamine at 100° in a sealed tube for 3.5 hr to give a decarboxylated 2-dimethylamino product (**34**) as a result of substitution reaction at the 2 position and the simultaneous decarboxylation at the 8 position. This decarboxylation of **32** is of interest because of its mild reaction conditions, in view of the fact that the decarboxylation of pyridine- and quinoline-3-carboxylic acids needs generally vigorous conditions.[6]

Ethylation of the decarboxylation product (**34**) with ethyl iodide in the presence of potassium carbonate in DMF afforded, in almost equal yields, not only the O-ethyl product (**33**) but also the N-ethyl product (**35**) which was proved to be identical with the product obtained by decarboxylation of **15b**. Since ethylation of various thiazolo[5,4-*f*]quinoline derivatives which have a carboxy group at the 8 position resulted only in the formation of the N-ethyl products as described in the preceding paper,[1] the hydrogen bonding between the 8-carboxy and 9-hydroxy groups or the steric hindrance of the 8-carboxy group may be the factor which prevents the O-ethylation.



31 **32** **15b**

33 **34** **35**

Chart 4

2-Substituted 6-ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic acids prepared in this work were tested for their antibacterial activities *in vitro* against various gram-negative and -positive bacteria. In the series of the compounds which have an ethyl group at the 6 position and a carboxy group at the 8 position, the 2-cyano (**14**), amidoxime (**24j**), carbamoyl (**26**), imido-ether (**27**) and diethylaminoethylcarbamoyl (**30f**) derivatives showed the stronger activities than nalidixic acid, but exhibited no activities against *Ps. aeruginosa*. The cross-resistances of bacteria to both nalidixic acid and these compounds except for **30f** were observed. Further details on these antibacterial activities and their structure-activity relationships will be reported in near future.

6) *a*) E. Klinsberg, "The Chemistry of Heterocyclic Compounds," Vol. 14, Part III, A. Weissberger, ed., Wiley Interscience, New York, 1962, p. 189; *b*) C.C. Price and R.M. Roberts, "Organic Syntheses," Coll. Vol. III ed. by E.C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 272.

Experimental[7]

Ethyl 6-Ethyl-6,9-dihydro-2-mercapto-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylate (2) and Its Acid (1)——A suspension of **6** (0.92 g) and NaSH hydrate (1.40 g) in water (14 ml) was stirred at 90—100° for 1 hr. The solid separated, on acidification, was recrystallized from DMF to afford **2** (0.68 g, 81%) as pale yellow needles, mp 282—284°. *Anal.* Calcd. for $C_{15}H_{14}O_3N_2S_2$: C, 53.87; H, 4.22; N, 8.38. Found: C, 53.68; H, 4.29; N, 8.47.

A suspension of **2** (0.32 g) in conc. HCl–90% AcOH (1: 11, 6 ml) was refluxed for 1 hr. Water was added to the mixture, and the product deposited was recrystallized from DMF to give **1** (0.10 g, 34%) as yellow needles, mp 310—311° (decomp.). *Anal.* Calcd. for $C_{13}H_{10}O_3N_2S_2$: C, 50.96; H, 3.29; N, 9.15. Found: C, 51.04; H, 3.23; N, 8.79.

Reaction of 6 with KCN——A mixture of **6** (2.70 g) and KCN (1.20 g) in DMSO (50 ml) was stirred at 80° for 5 min. After cooling, the crystals deposited were filtered and dissolved in $CHCl_3$, and the solution was washed with water, dried and treated with activated charcoal. Evaporation of the solvent gave **3** (2.00 g, 87%) as needles. An analytical sample was prepared by recrystallization from $CHCl_3$, mp 259—262°. *Anal.* Calcd. for $C_{16}H_{13}O_3N_3S$: C, 58.71; H, 4.00; N, 12.84. Found: C, 58.87; H, 4.04; N, 12.56.

Oxidation of 4 with $KMnO_4$——To a suspension of **4**[1] (0.96 g) in AcOH (50 ml) was added dropwise 7.5% aq. $KMnO_4$ solution (12 ml) over a period of 55 min with stirring at 35—40°. The suspension was further stirred at the same temperature for 10 min, and then treated with $NaHSO_3$. Water was added to the suspension and the product deposited was recrystallized from DMF–ether to give **5** (0.68 g, 64%) as a crystalline powder, mp 302° (decomp.). This product was identical with the authentic sample obtained by the alternative method in the preceding paper.[1]

Ethyl 6-Ethyl-6,9-dihydro-2-methylsulfonyl-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylate (6)——i) A solution of **7**[1] (1.04 g) in AcOH (50 ml) was treated with 7.5% $KMnO_4$ solution (12 ml) in a similar manner as described above and the product was recrystallized from dichloroethane to give **6** (0.80 g, 70%) as prisms, mp 235—236°. *Anal.* Calcd. for $C_{16}H_{16}O_5N_2S_2$: C, 50.52; H, 4.24; N, 7.36. Found: C, 50.54; H, 3.96; N, 7.60.

A mixture of **7** (3.48 g) and 30% H_2O_2 solution (7 ml) in AcOH (140 ml) was stirred at 50—60° for 2 hr. After the careful evaporation of the solvent, the product deposited (1.09 g) was recrystallized from $CHCl_3$ to give **6** (0.73 g, 19%) as prisms, mp 236°, IR spectrum (KBr) of which was identical with that of the sample obtained above. From the filtrate of the concentrated reaction mixture was obtained the crude product (0.92 g) which was shown by its TLC to be a mixture of **6** and **8** in about 1: 4 ratio.

ii) A mixture of **5**[1] (0.64 g), K_2CO_3 (0.83 g) and EtI (0.71 g) in DMF (12 ml) was stirred at 80° for 10 hr. The filtrate of the reaction mixture was concentrated and the $CHCl_3$ solution of the residue was washed with water, dried and evaporated. The residue was treated with ether and crystallized from $CHCl_3$ to give **6** (0.57 g, 82%) melting at 235°, identical with the authentic sample obtained by the method (i).

iii) A mixture of **8** (0.18 g) and 30% H_2O_2 solution (0.4 ml) in AcOH (4 ml) was stirred at 50—60° for 1.5 hr. The separated crystals on cooling were washed with water and dried to give **6** (0.11 g, 60%), mp 234—236°, which was identified with the sample obtained by method (i).

Partial Oxidation of 7 with H_2O_2——A mixture of **7**[1] (1.05 g, 3 mmoles) and 30% H_2O_2 solution (0.4 ml, 3.9 mmoles) in AcOH (35 ml) was stirred at 60—70° for 4 hr. After the careful evaporation of the solvent, the crystals deposited were recrystallized from $CHCl_3$–MeOH to give **8** (0.50 g, 45%) as needles, mp 232—233°. *Anal.* Calcd. for $C_{16}H_{16}O_4N_2S_2$: C, 52.73; H, 4.43; N, 7.68. Found: C, 52.45; H, 4.35; N, 7.89.

6-Ethyl-2,3,6,9-tetrahydro-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (9)——i) By Hydrolysis of **6**: a) A suspension of **6** (0.38 g) in 10% KOH (7.6 ml) was stirred at 80° for 1.5 hr. The precipitate on acidification was recrystallized from DMF to give **9** (0.24 g, 83%) as needles, mp above 300°. *Anal.* Calcd. for $C_{13}H_{10}O_4N_2S$: C, 53.80; H, 3.47; N, 9.65. Found: C, 53.57; H, 3.47; N, 9.89. b) The acidic hydrolysis of **6** with conc. HCl–AcOH (1: 11), however, was unsuccessful.

ii) By Oxidative Hydrolysis of **10**: To a suspension of **10**[1] (0.32 g) in 2N NaOH (10 ml) was added NaOCl solution (10% of active chlorine) (5 ml) dropwise with stirring below 10° during 30 min. After stirring at the same temperature for 1 hr, the suspension was heated at 90° for 1 hr. A small quantity of undissolved substances was removed by filtration and the filtrate was acidified. The separated crystals were recrystallized from DMF to give **9** (0.24 g, 83%), identical with the sample obtained above.

iii) By Hydrolysis of **11**: a) A suspension of **11**[1] (1.00 g) in 10% KOH (25 ml) was refluxed for 30 min. The precipitate on acidification was recrystallized from DMF to give **9** (0.20 g, 23%), identical with the authentic **9**. b) A mixture of **11** (0.34 g) in conc. HCl–AcOH (1: 11) (5.1 ml) was stirred at 110° for 2 hr. Recrystallization from DMF gave **9** (0.12 g, 40%).

iv) By Hydrolysis of **12b**: a) A mixture of **12b** (0.12 g) in 1N KOH (8 ml) was refluxed for 1 hr. The resulting solid, on acidification, was recrystallized from DMF to give **9** (0.073 g, 78%), identical with the sam-

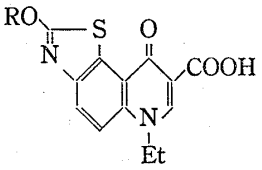
7) All melting points are uncorrected. Thin-layer chromatography (TLC) was carried out on Merck Kieselgel GF_{254} using $CHCl_3$–MeOH (10: 1) as developing solvent and plates were examined under ultraviolet light.

ple obtained by method (i). b) The compound (**12b**, 0.10 g) was also hydrolyzed with HCl–AcOH to give **9** (0.060 g, 67%).

2-Alkoxy-6-ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic Acids (12a—d) (Table I)——i) A mixture of **6** (1.90 g) in NaOEt solution (Na 0.35 g, EtOH 50 ml) was stirred at 60—70° for 1 hr and evaporated *in vacuo*. Water was added to the residue and a small quantity of insoluble materials was removed by filtration, and the filtrate was acidified with dil. HCl. The product deposited was recrystallized from DMF to give **12b** (1.12 g, 71%) as needles, mp 234—240°. This product was identical in IR spectrum with the authentic sample obtained by the alternative method in the preceding paper.[1]

ii) In a similar manner described above, the reaction of **11** with sodium alkoxides gave **12a—d**. Details are summarized in Table I.

Table I. 2-Alkoxy-6-ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic Acids (**12**)



Compd. No.	R	mp (°C)	Recrystn. solvents	Yield (%)	Formula	Analysis (%); Calcd. (Found) C	H	N
12a	Me	>320	DMF	42	$C_{14}H_{12}O_4N_2S$	55.26 (55.34)	3.97 (3.80)	9.21 (9.46)
12b[a]	Et	234—236	DMF	47	$C_{15}H_{14}O_4N_2S$	56.60 (56.29)	4.43 (4.20)	8.80 (8.98)
12c	*n*-Bu	199—200	$CHCl_3$–ether	70	$C_{17}H_{18}O_4N_2S$	58.95 (58.82)	5.24 (5.29)	8.09 (8.25)
12d	$PhCH_2$	216—217	DMF	44	$C_{20}H_{16}O_4N_2S$	63.25 (62.93)	4.24 (4.13)	7.36 (7.51)

a) The alternative preparation of this compound was described in the preceding paper.[1]

Oxidation of 10 with $KMnO_4$——To a stirred suspension of **10**[1] (0.20 g) in AcOH (10 ml) was added dropwise 7.5% $KMnO_4$ solution (5 ml) at 35—40° during 40 min. The mixture was further stirred for 1 hr, and was worked up as described in the preparation of **5**. Recrystallization from DMF gave **13** (0.12 g, 55%) as needles, mp 290—291°. *Anal.* Calcd. for $C_{14}H_{12}O_5N_2S_2$: C, 47.71; H, 3.43; N, 7.95. Found: C, 47.62; H, 3.29; N, 8.24.

Reaction of 13 with KCN——A mixture of **13** (4.75 g) and KCN (1.90 g) in DMSO (120 ml) was stirred at 120° for 10 min. The resulting precipitate on cooling was dissolved in water, and the solution was acidified with AcOH. The crystals separated were recrystallized from DMF to give **14** (2.65 g, 59%) as pale yellow needles, mp 264—267°. *Anal.* Calcd. for $C_{14}H_9O_3N_3S$: C, 56.18; H, 3.03; N, 14.04. Found: C, 56.10; H, 2.93; N, 14.36.

2-Dialkylamino-6-ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic Acids (15b, c, and f) (Table II)——i) A mixture of **6** (1.14 g, 3.0 mmoles) in 30% aq. dimethylamine (60 ml, 0.39 mole) was heated at 110—120° in a sealed tube for 17 hr. A small amount of insoluble materials was filtered and the filtrate was concentrated *in vacuo*. Recrystallization of the residue from DMF gave **15b** (0.59 g, 62%) as pale yellow plates, mp 294—296° (decomp.).

Reaction of **6** with aq. morpholine in a similar manner gave **15f** in 67% yield.

ii) A mixture of **11** (0.34 g, 1.0 mmole) in 30% aq. diethylamine (16 ml, 66 mmoles) was heated at 110—120° in a sealed tube for 5.5 hr. Recrystallization from DMF gave **15c** (0.18 g, 52%) as pale yellow needles, mp 242—243°.

The compound (**15b**) was obtained in 56% yield by the reaction of **11** with aq. dimethylamine in a similar manner.

Reaction of 6 with Diethylamine——A mixture of **6** (0.38 g, 1.0 mmole) in 40% aq. diethylamine (20 ml, 0.15 mole) was heated at 110° in a sealed tube for 10 hr. The mixture was concentrated and the residue was crystallized from DMF to give **9** (0.22 g, 76%), identified with the authentic sample prepared by hydrolysis of **6** as previously described.

N-Alkyl 2-Alkylamino-6-ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxamides (16a—e) (Table II)——i) A mixture of **11**[1] (0.34 g, 1.1 mmoles) and 30% aq. methylamine (16 ml, 135 mmoles) was

heated at 110—120° in a sealed tube for 20 hr. Recrystallization from EtOH gave **16b** (0.21 g, 66%) as prisms, mp 300—301° (decomp.).

In a similar manner, **16a** was obtained in 58% yield by the reaction of **11** (1.0 mmole) with conc. NH_4OH (0.47 mole).

ii) A mixture of **6** (0.38 g, 1.0 mmole) and 70% aq. ethylamine (7.0 g, 0.1 mole) in water (7 ml) was heated at 110—120° in a sealed tube for 20 hr. The mixture was concentrated and the residue which showed on its TLC three spots of **16c**, **19c**, and **18c**, was successively washed with dil. KOH and water, and then crystallized from DMF. The $CHCl_3$ solution of the resulting crystals was chromatographed on silica gel. The fraction eluted with $CHCl_3$–MeOH was crystallized from MeOH to give **16c** (0.082 g, 23%) as needles, mp 265—266°.

Reaction of **6** (1.0 mmole) with aq. methylamine (27 mmoles), 2-diethylaminoethylamine (10 mmoles) or aq. 2-hydroxyethylamine (50 mmoles) in a similar manner gave **16b**, **16d**, or **16e**, respectively, in a yield of 76, 74, or 26%.

Attempted Hydrolysis of 16b or c (Table II)——i) Formation of **17b** and **19b** from **16b**: A mixture of **16b** (0.60 g), conc. H_2SO_4 (10 ml), AcOH (10 ml) and water (5 ml) was stirred at 110—120° for 24 hr. The mixture was neutralized with dil. NH_4OH and the crystals separated were dissolved in hot MeOH and filtered. The filtrate was cooled to give **17b** (0.24 g, 44%) as plates, mp 292—294°. The residue was dissolved in 10% KOH and the solution was acidified with AcOH. The separated solid was recrystallized from DMF to give **19b** (0.10 g, 18%) as needles, mp 318—319° (decomp.).

ii) Formation of **17c** and **19c** from **16c**: Hydrolysis of **16c**, in a similar manner, gave **17c** (37%) and **19c** (38%).

Ethyl 2-Alkylamino-6-ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylates (18c and d) (Table II)——i) A mixture of **6** (1.90 g, 5 mmoles) and 70% aq. ethylamine (1.0 g, 16 mmoles) in water (7 ml) was heated at 110—120° in a sealed tube for 20 hr. After evaporation of the solvent, the residue was crystallized from DMF to give **18c** (0.75 g, 43%) as pale yellow needles, mp 311—312° (decomp.).

ii) The compound (**18d**) was prepared in 27% yield by the reaction of **6** (0.76 g, 2 mmoles) with aq. 2-diethylaminoethylamine (0.46 g, 4 mmoles) in a similar manner.

2-Alkylamino-6-ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic Acids (19a—d) (Table II)——i) A mixture of **13** (0.35 g) and 30% aq. methylamine (16 ml) was heated at 110—120° in a sealed tube for 19 hr. Recrystallization from DMF gave **19b** (0.16 g, 53%) as needles, mp 318—319° (decomp.).

The compound (**19a**·HCl) was similarly prepared by the reaction of **13** with conc. NH_4OH in 44% yield.

ii) A solution of **18c** (0.35 g) in conc. HCl–90% AcOH (1: 11) (7 ml) was refluxed for 2 hr. The residue, on evaporation, was crystallized from MeOH to give **19c**·HCl (0.29 g, 80%) as plates, mp 261—262° (decomp.).

The compound (**19d**·HCl) was obtained in a similar manner by hydrolysis of **18d** in 81% yield.

Reaction of 3 with Hydrazine Giving Substitution Product (20)——A mixture of **3** (0.33 g) and $NH_2NH_2 \cdot H_2O$ (6 ml) in EtOH (50 ml) was refluxed for 1.5 hr. The deposited solid on cooling was recrystallized from DMF to give **20** (0.21 g, 66%) as pale yellow needles, mp above 320°. *Anal.* Calcd. for $C_{13}H_{14}O_2N_6S$: C, 49.05; H, 4.43; N, 26.40. Found: C, 48.74; H, 4.64; N, 26.34.

Hydrolysis of 3 with $NaNO_2$ in H_2SO_4: Formation of the 2-Decarboxylated Product (21)——A mixture of **3** (0.33 g) in conc. H_2SO_4 (1 ml) was stirred at 100° for 30 min and cooled. To the mixture was added dropwise aq. $NaNO_2$ solution (0.13 g of $NaNO_2$) under ice-cooling. After stirring at 50° for 1.5 hr, the reaction mixture was poured into ice-water and the solid deposited was recrystallized from DMF to give **21** (0.10 g, 38%) as a powder, mp above 315°, identified with the authentic sample obtained in the preceding paper.[1]

Reaction of 3 with Hydrazine(22i)——A suspension of **3** (0.30 g) and $NH_2NH_2 \cdot H_2O$ (6 ml) in EtOH (50 ml) was stirred at room temperature for 1.5 hr. The solid separated was recrystallized from DMF to give **22i** (0.13 g, 40%) as a pale yellow powder, mp 301° (decomp.). *Anal.* Calcd. for $C_{16}H_{17}O_3N_5S$: C, 53.47; H, 4.77; N, 19.49. Found: C, 53.50; H, 4.76; N, 19.60.

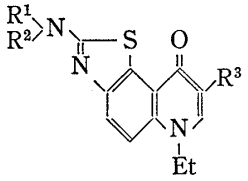
6-Ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-2,8-dicarboxylic Acid (23)——A suspension of **3** (0.30 g) in 2N NaOH (15 ml) was stirred for 10 hr under refluxing. After cooling, the deposited solid was collected and dissolved in water. The separated solid, on acidification, was recrystallized from DMF to give **23** (0.22 g, 69%) as a powder, mp 285—289° (decomp.). *Anal.* Calcd. for $C_{14}H_{10}O_5N_2S$: C, 52.83; H, 3.17; N, 8.80. Found: C, 52.81; H, 2.99; N, 8.74.

Reaction of 14 with Morpholine——A mixture of **14** (0.30 g) and morpholine (0.17 g) in DMF (2 ml) was stirred at 100° for 10 hr. The solid separated was collected by filtration in warm and recrystallized from DMF to give **24h** (0.093 g, 22%) as yellow prisms, mp 246° (decomp.). *Anal.* Calcd. for $C_{18}H_{18}O_4N_4S$: C, 55.95; H, 4.70; N, 14.50. Found: C, 55.89; H, 4.81; N, 14.26.

6-Ethyl-2-hydrazinoformimidoyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (24i)——i) A mixture of **14** (0.30 g) and $NH_2NH_2 \cdot H_2O$ (6 ml) in EtOH (50 ml) was stirred at room temperature for 6 hr. The solid separated was recrystallized from DMF–EtOH to give **24i** (0.17 g, 52%) as pale yellow needles, mp above 320°. *Anal.* Calcd. for $C_{14}H_{13}O_3N_5S$: C, 50.75; H, 3.95; N, 21.14. Found: C, 50.50; H, 4.20; N, 20.83.

Refluxing for 2 hr, instead of stirring at room temperature, gave also **24i** in 51% yield but did not afford the substitution product (*cf.* **20**).

Table II. 2-Amino (or 2-Alkylamino)-6-ethyl Thiazolo[5,4-*f*]quinoline Derivatives



Compd. No.	R^1	R^2	R^3	mp (°C)	Recryst. solvent	Yield(%) /starting material	Formula	Analysis (%); Calcd. (Found) C	H	N
15b	Me	Me	COOH	294—296 (decomp.)	DMF	**62/6**	$C_{15}H_{15}O_3N_3S$	56.76 (57.23)	4.76 (4.67)	13.24 (13.37)
15c	Et	Et	COOH	242—243	DMF	**52/11**	$C_{17}H_{19}O_3N_3S$	59.11 (58.82)	5.54 (5.36)	12.17 (12.34)
15f	O		COOH	307—309 (decomp.)	DMF	**67/6**	$C_{17}H_{17}O_4N_3S$	56.81 (56.79)	4.77 (4.75)	11.69 (11.58)
16a	H	H	$CONH_2$	>320	DMF	**58/11**	$C_{13}H_{12}O_2N_4S$[a]·1/2H_2O	52.52 (52.68)	4.41 (4.25)	18.84 (19.13)
16b	H	Me	CONHMe	300—301 (decomp.)	EtOH	**66/11**	$C_{15}H_{16}O_2N_4S$	56.95 (56.98)	5.10 (5.03)	17.71 (17.73)
16c	H	Et	CONHEt	265—266	MeOH	**23/6**	$C_{17}H_{20}O_2N_4S$	59.28 (59.22)	5.85 (5.60)	16.27 (16.24)
16d	H	DEAE[b]	DEAEA[b]	194—195	acetone	**74/6**	$C_{25}H_{38}O_2N_6S$	61.70 (61.34)	7.87 (7.96)	17.27 (16.95)
16e	H	HE[b]	HEA[b]	274—276 (decomp.)	DMF	**26/6**	$C_{17}H_{20}O_4N_4S$[a]·1/2H_2O	52.98 (53.26)	5.49 (5.31)	14.54 (14.78)
17b	H	Me	H	292—294	MeOH	**44/16b**	$C_{13}H_{13}ON_3S$	60.21 (60.53)	5.05 (4.94)	16.20 (16.27)
17c	H	Et	H	258—259	AcOEt	**37/16c**	$C_{14}H_{15}ON_3S$	61.52 (61.66)	5.53 (5.57)	15.37 (15.16)
18c	H	Et	COOEt	311—312 (decomp.)	DMF	**43/6**	$C_{17}H_{19}O_3N_3S$	59.11 (58.89)	5.54 (5.36)	12.17 (11.95)
18d	H	DEAE[b]	COOEt	308—309 (decomp.)	DMF	**27/6**	$C_{21}H_{28}O_3N_4S$	60.55 (60.49)	6.78 (6.72)	13.45 (13.16)
19a	H	H	COOH	324—326 (decomp.)	DMF	**44/13**	$C_{13}H_{11}O_3N_3S$[a]·HCl·H_2O	45.42 (45.57)	4.10 (4.34)	12.22 (11.97)
19b	H	Me	COOH	318—319 (decomp.)	DMF	**53/13**	$C_{14}H_{13}O_3N_3S$	55.44 (55.28)	4.32 (4.35)	13.85 (14.01)
19c	H	Et	COOH	261—262 (decomp.)	MeOH	**80/18c**	$C_{15}H_{15}O_3N_3S$[a]·HCl·1/2H_2O	49.65 (49.73)	4.72 (4.85)	11.58 (11.62)
19d	H	DEAE[b]	COOH	291—292 (decomp.)	DMF	**81/18d**	$C_{19}H_{24}O_3N_4S$[a]·HCl·1/2H_2O	52.59 (52.33)	6.04 (5.85)	12.91 (13.24)

a) IR (Nujol) spectrum exhibited a O–H band of water near 3400 cm^{-1}.
b) DEAE=$Et_2NCH_2CH_2$, DEAEA=$CONHCH_2CH_2NEt_2$, HE=$HOCH_2CH_2$, HEA=$CONHCH_2CH_2OH$

ii) A mixture of **22i** (0.13 g) in 10% NaOH (0.6 ml) was refluxed for 1 hr. The separated solid, on acidification, was recrystallized from DMF to give **24i** (0.042 g, 32%) as a yellow powder, mp above 320°, identical with the sample obtained above.

6-Ethyl-6,9-dihydro-2-hydroxyaminoformimidoyl-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (24j)——i) A solution of **22j** (0.18 g) in conc. HCl–90% AcOH (1: 11) (3 ml) was stirred at 100° for 1 hr. The solid separated was recrystallized from DMF to give **24j** (0.093 g, 55%) as a pale yellow powder, mp above 300°. *Anal.* Calcd. for $C_{14}H_{12}O_4N_4S$: C, 50.60; H, 3.64; N, 16.86. Found: C, 50.43; H, 3.90; N, 16.65.

ii) A mixture of **14** (0.30 g), K_2CO_3 (0.20 g) and NH_2OH·HCl (0.20 g) in water (2 ml) was refluxed for 1 hr. The solid separated was recrystallized from DMF–EtOH to give **24j** (0.20 g, 62%) as a pale yellow powder, identical with the sample obtained above.

Ethyl 2-Ethoxyformimidoyl-6-ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylate (25)——i) To a mixture of **3** (0.20 g) in EtOH (20 ml) was added a solution of K_2CO_3 (0.40 g) in water (3 ml) and the mixture was stirred at room temperature for 6 hr. The $CHCl_3$ solution of the solid separated was washed with

water and concentrated. Recrystallization from EtOH gave **25** (0.12 g, 52%) as needles, mp 236° (decomp.). *Anal.* Calcd. for $C_{18}H_{19}O_4N_3S$: C, 57.90; H, 5.13; N, 11.25. Found: C, 57.90; H, 4.87; N, 11.21.

ii) To a suspension of **3** (0.33 g) in anhyd. EtOH (5 ml) was added NaOEt solution (0.08 g of Na, 10 ml of EtOH) and the mixture was stirred for 3 hr under refluxing. The separated solid on cooling was worked up in a similar manner as described above to give **25** (0.20 g, 54%) as needles, mp 238° (decomp.), identical with the sample obtained above.

2-Carbamoyl-6-ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (26)——i) By Hydrolysis of **3**: A mixture of **3** (0.25 g) in conc. HCl–90% AcOH (1: 11) (10 ml) was refluxed for 1 hr. The solid separated, on addition of water, was recrystallized from DMF to give **26** (0.16 g, 68%) as needles, mp above 310°. *Anal.* Calcd. for $C_{14}H_{11}O_4N_3S$: C, 52.99; H, 3.49; N, 13.24. Found: C, 52.83; H, 3.57; N, 13.28.

ii) By Hydrolysis of **25**: A mixture of **25** (0.12 g, 0.3 mmole) in 10% NaOH (4 ml, 0.6 mmole) was stirred at 80—90° for 30 min. The solid separated, on acidification with AcOH, was recrystallized from DMF to give **26** (0.071 g, 77%) as needles, identical with the sample obtained above.

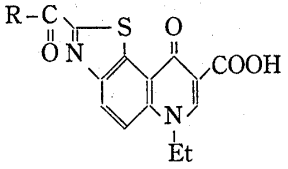
2-Ethoxyformimidoyl-6-ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (27)——i) To a suspension of **14** (0.60 g) in EtOH (50 ml) was added a solution of K_2CO_3 (1.20 g) in water (9 ml) and the mixture was stirred at room temperature for 10 hr. The solid separated was washed with EtOH and dissolved in water. The precipitate, on acidification, was recrystallized from DMF to give **27** (0.35 g, 50%) as yellow needles, mp 248° (decomp.). *Anal.* Calcd. for $C_{16}H_{15}O_4N_3S$: C, 55.64; H, 4.38; N, 12.17. Found: C, 55.39; H, 4.49; N, 12.40.

ii) Dry gaseous HCl was bubbled into a suspension of **14** (2.99 g) in EtOH (150 ml) under ice-cooling for 2.5 hr. The pink solid separated was poured into water (100 ml), and the suspension was stirred at room temperature for 30 min. The yellow crystals deposited were recrystallized from DMF to give **27** (2.45 g, 69%) as yellow needles, mp 248° (decomp.), identical with the sample obtained above.

Treatment of 27 with HCl——A solution of **27** (1.42 g) in 10% HCl (24 ml) was stirred at room temperature for 3 hr. The solid deposited was recrystallized from DMF to give **28** (0.93 g, 67%) as pale yellow needles, mp 255° (decomp.). *Anal.* Calcd. for $C_{16}H_{14}O_5N_2S$: C, 55.49; H, 4.07; N, 8.09. Found: C, 55.36; H, 4.02; N, 8.40.

Reaction of 14 with H_2S——Into a solution of **14** (0.30 g) in DMF (10 ml) was bubbled gaseous H_2S under ice-cooling for 3 hr. After being kept on standing overnight, the solid separated was recrystallized from DMF

Table III. 2-(N-Substituted)carbamoyl Thiazolo[5,4-*f*]quinoline Derivatives



Compd. No.	R	mp (°C)	Yield[a] (%)	Formula	Analysis (%); Calcd. (Found) C	H	N
30a	EtNH	>300	54	$C_{16}H_{15}O_4N_3S$[b]·1/2H_2O	54.23 (53.92)	4.55 (4.41)	11.86 (12.08)
30b	*n*-BuNH	>300	67	$C_{18}H_{19}O_4N_3S$	57.89 (57.53)	5.13 (5.02)	11.25 (11.32)
30c	$HOCH_2CH_2NH$	>300	36	$C_{16}H_{15}O_5N_3S$	53.18 (52.89)	4.18 (4.24)	11.63 (11.87)
30d	$HOCH_2CH_2CH_2NH$	>300	75	$C_{17}H_{17}O_5N_3S$	54.39 (54.62)	4.56 (4.56)	11.19 (10.99)
30e	$MeCH(OH)CH_2NH$	>300	24	$C_{17}H_{17}O_5N_3S$	54.39 (54.11)	4.56 (4.61)	11.19 (11.36)
30f	$Et_2NCH_2CH_2NH$	296 (decomp.)	68	$C_{20}H_{24}O_4N_4S$	57.68 (57.58)	5.81 (5.60)	13.45 (13.14)
30g	$HOCH_2CH_2(Et)N$	229—231	56	$C_{18}H_{19}O_5N_3S$	56.38 (55.95)	4.99 (4.73)	10.96 (11.26)
30h		323—324 (decomp.)	73	$C_{18}H_{17}O_5N_3S$	55.81 (55.55)	4.42 (4.37)	10.85 (10.66)
30i	H_2NNH	>330	51	$C_{14}H_{12}O_4N_4S$	50.60 (50.76)	3.64 (3.58)	16.86 (16.79)

a) All compounds were recrystallized from DMF. *b*) IR (Nujol) spectrum exhibited a O-H band of water at 3450 cm^{-1}.

to give **29** (0.20 g, 60%) as brownish needles, mp 320° (decomp.). *Anal.* Calcd. for $C_{14}H_{11}O_3N_3S_2$: C, 50.44; H, 3.33; N, 12.60. Found: C, 50.09; H, 3.29; N, 12.77.

Amidation of 28 (Table III)——i) A mixture of **28** (0.18 g) and 70% aq. ethylamine (5 ml) was heated in a sealed tube at 100° for 2 hr. Excess reagent was evaporated and the residue was crystallized from DMF to give **30a** (0.12 g, 54%) as pale yellow needles, mp above 310°.

ii) The compounds (**30b**—**h**) were prepared in a similar manner as described above. Yields of the products and their analytical data are recorded in Table III.

Reaction of 28 with NH_2NH_2 (Table III)——A mixture of **28** (0.35 g) and $NH_2NH_2 \cdot H_2O$ (6 ml) in EtOH (50 ml) was refluxed for 2 hr. The solid separated was recrystallized from DMF to give **30i** (0.18 g, 51%) as pale yellow needles, mp above 300°.

Oxidation of 31 with $KMnO_4$——To a suspension of **31**[1] (1.46 g) in AcOH (73 ml) was added dropwise 7.5% $KMnO_4$ (53 ml) at 30—35° over a period of 3 hr. After stirring for 1 hr, the mixture was treated with $NaHSO_3$ and ice. The solid separated was dried to give a pale yellow powder (1.06 g) which was shown to be a mixture of **32** and **31** (10: 3 ratio) by its nuclear magnetic resonance (NMR) spectrum. A part of this powder (0.50 g) was suspended in AcOH (50 ml) and was added dropwise 7.5% $KMnO_4$ (12 ml) at 40—45° over a period of 1.5 hr. The solid separated, on addition of $NaHSO_3$ and ice, was recrystallized from DMF to give **32** (0.20 g, 26%) as needles, mp 311—313° (decomp.). *Anal.* Calcd. for $C_{12}H_8O_5N_2S_2$: C, 44.44; H, 2.49; N, 8.64. Found: C, 44.53; H, 2.47; N, 8.82.

Reaction of 32 with Dimethylamine: Formation of 8-Decarboxylated Product (34)——A mixture of **32** (0.13 g) and 30% aq. dimethylamine (2 ml) was heated at 100° in a sealed tube for 3.5 hr. Excess reagent was evaporated and the solid separated, on addition of water, was recrystallized from MeOH to give **34** (0.033 g, 34%) as pale yellow needles, mp 308—310° (decomp.). *Anal.* Calcd. for $C_{12}H_{11}ON_3S$: C, 58.76; H, 4.52; N, 17.13. Found: C, 58.44; H, 4.73; N, 17.41.

Ethylation of 34: Formation of O-Ethyl (33) and N-Ethyl (35) Products——A mixture of **34** (0.25 g), EtI (0.32 g) and K_2CO_3 (0.14 g) in DMF (5 ml) was stirred at 90—95° for 2.5 hr. After concentration, the reaction mixture was treated with water and filtered. The solid remained was recrystallized from AcOEt to give the O-ethyl product, **33** (0.10 g, 36%), as pale yellow needles, mp 163—165°. UV λ_{max}^{MeOH} nm: 272, 318. *Anal.* Calcd. for $C_{14}H_{15}ON_3S$: C, 61.52; H, 5.53; N, 15.37. Found: C, 61.19; H, 5.74; N, 15.51.

The filtrate of the reaction mixture was cooled and the crystals deposited were recrystallized from AcOEt to give the N-ethyl product, **35** (0.090 g, 33%), as pale yellow prisms, mp 230—233°. UV λ_{max}^{MeOH} nm: 276, 319, 369. *Anal.* Calcd. for $C_{14}H_{15}ON_3S$: C, 61.52; H, 5.53; N, 15.37. Found: C, 61.35; H, 5.36; N, 15.33.

Decarboxylation of the 2-Dimethylamino Derivative (15b): Alternative Synthesis of 35——A mixture of **15b** (0.26 g), conc. H_2SO_4 (5 ml), AcOH (5 ml) and water (3 ml) was heated at 110—120° for 43 hr, and diluted with water. After being made alkaline with conc. NH_4OH, the mixture was extracted with $CHCl_3$. The residue obtained from the extract was washed with 10% KOH and crystallized from AcOEt to give **35** (0.072 g, 30%) as a powder, mp 231—232°, identical with the sample obtained above.

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