[Chem. Pharm. Bull. 24(1) 147—155 (1976)]

UDC 547.789'831.057.09 : 615.31.076.7

Synthetic Chemotherapeutic Agents. III.[1a] Synthesis of 3-Substituted Thiazolo[5,4-*f*]quinoline Derivatives. (1)[2]

Shizuo Kadoya, Norio Suzuki, Isao Takamura, and Renzo Dohmori

Research Institute, Daiichi Seiyaku Co., Ltd.[3]

(Received April 3, 1975)

For the search of the more active antimicrobial compounds than the 2,6-disubstituted derivatives, 3,6-disubstituted 2,3,6,9-tetrahydro-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic acid (**1**, **3**, **7**, **8**, **11**, **20**, **21**, and **22**) were synthesized from the 2-oxo-6-substituted thiazolo[5,4-*f*]quinoline derivatives (**2**, **17**, or **18**).

Thermal rearrangement of the 2-methylthio derivative (**23**) gave the 2-thioxo-3-methyl derivative (**24**), which was converted into the 2-oxo-3-methyl derivative (**26**) by reaction with mercuric acetate. The 2-ethoxy derivative (**27**) was also thermally rearranged to give the 2-oxo-3-ethyl derivative (**8b**).

The 3,6-disubstituted compounds obtained in this work showed the stronger activities against gram-negative and gram-positive bacteria *in vitro* than nalidixic acid and the 2,6-disubstituted derivatives prepared in the previous work. 6-Ethyl-2,3,6,9-tetrahydro-3-methyl-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic acid (**8a**) exhibited the strongest activities among these compounds against many gram-negative bacteria including *E. coli* resistant to nalidixic acid and *Ps.* aeruginosa, and against some gram-positive bacteria.

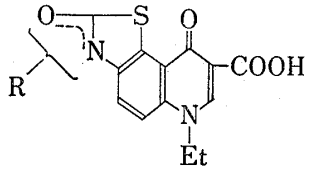
In the previous papers[1] we described the synthetic methods for various 2-substituted thiazolo[5,4-*f*]quinoline derivatives. Since several 2-substituted derivatives have exhibited potent antimicrobial activities against many gram-negative bacteria except for *Ps. aeruginosa*, we further synthesized a number of thiazolo[5,4-*f*]quinoline derivatives to search for active compounds against *Ps. aeruginosa*. The present paper deals with the synthesis of 3-substituted thiazolo[5,4-*f*]quinoline derivatives and their antimicrobial activities.

Reaction of 6-ethyl-2,3,6,9-tetrahydro-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic acid (**2**)[1a] with several alkyl halides in dimethylformamide (DMF) in the presence of potassium carbonate gave the N-3-substituted 6-ethyl-8-carboxylic acid esters (**4a**—**h**). Hydrolysis of these esters afforded the corresponding carboxylic acids (**8a**—**h**) in good yields, but did not provide the 2-oxo-8-acid (**2**) which was easily obtainable by hydrolysis of the 2-ethoxy derivative as described in the preceding paper.[1a] Ultraviolet (UV) spectral data of **2** resemble very closely those of the N-alkyl derivatives as shown in Table I, showing that **2** exists as the 2-oxo form rather than the 2-hydroxy tautomer similar to the tautomerism of the 2-hydroxybenzothiazoles.[4] It can therefore be presumed that, in these alkylation reactions, the N-3 alkylation took place in preference to the O-2 alkylation. The 3-methyl derivative (**8a**) could directly be synthesized by treatment of **2** with methyl iodide in aqueous alkaline solution.

Treatment of **2** with ethyl chloroacetate and potassium carbonate in DMF gave the diester (**6**), from which the di-carboxylic acid (**7**) was obtained by complete hydrolysis of the ester groups. Reaction of **2** with 2-diethylaminoethyl chloride in DMF in the presence of

1) *a*) Part II: S. Kadoya, I. Takamura, N. Suzuki, and R. Dohmori, *Chem. Pharm. Bull.* (Tokyo), **24**, 136, (1976); *b*) Part I: R. Dohmori, S. Kadoya, I. Takamura, and N. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **24**, 130 (1976).
2) This work was presented partly at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 1974.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
4) *a*) R.C. Elderfield (ed.), "Heterocyclic Compounds," Vol. 5, John Wiley and Sons, Inc., New York, 1957, p. 551; *b*) H. Zinner and W. Nimmich, *J. Prakt. Chem.*, **14**, 139 (1961).

Table I. UV Spectral Data of Thiazolo[5,4-*f*]quinoline Derivatives



R	λ_{max}^{MeOH} nm (log ε)	
	O-Alkyl derivatives[1a]	N-Alkyl derivatives (8)
Me	258.5(4.47), 267.5(4.46)	263.0(4.63)
Et	259.0(4.34), 268.0(4.34)	263.0(4.69)
n-Bu	259.5(4.45), 268.5(4.45)	263.5(4.53)
$PhCH_2$	259.5(4.47), 268.5(4.47)	263.5(4.38)
H[1a]	261.0(4.42)	

Ph=phenyl

triethylamine provided the 3-(2-diethylaminoethyl) derivative (**1**). Acetylation of **2** with acetic anhydride in pyridine gave its 3-acetate (**3**).

The 3-vinyl derivative (**11**) was prepared as follows. The acid (**2**) was converted, *via* its acid chloride, into the ethyl ester (**5**), the reaction of which with 2-chloroethyl bromide afforded the 3-(2-chloroethyl) derivative (**10**). The same compound (**10**) was also obtainable by reaction of **5** with ethylene oxide, followed by treatment of the product (**9**) with thionyl chloride. Elimination of hydrogen chloride from **10** by use of sodium ethoxide, with simultaneous hydrolysis of the ester group, gave the desired 3-vinyl-8-acid (**11**).

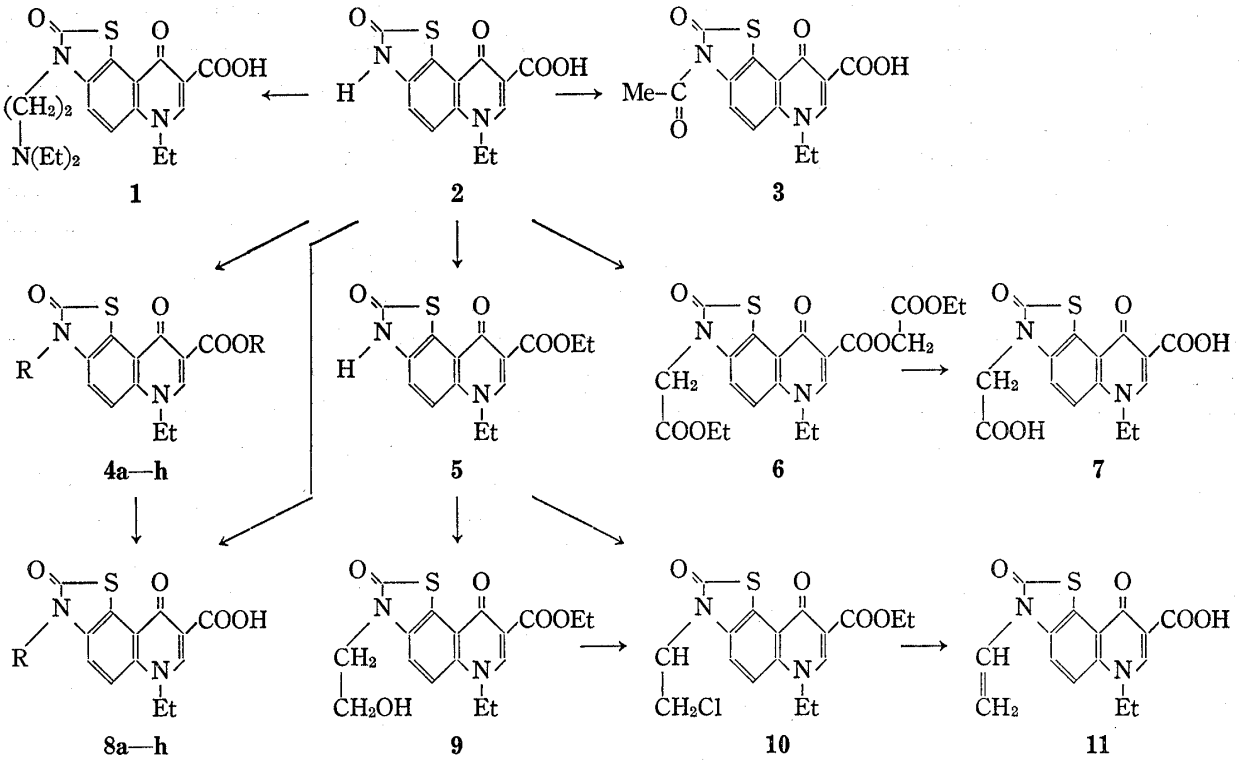


Chart 1

Synthetic routes for the 3,6-disubstituted derivatives other than the 6-ethyl compounds were shown in Chart 2. The compound (**12**)[1b] was treated alkyl halides to yield the 6-alkyl derivatives (**13a—e**), the oxidation of which gave the 2-methylsulfonyl-6-alkyl derivatives (**14a—e**). The 6-allyl derivative (**14f**), however, was prepared from **15**[1a] in order to avoid the oxidative reactions which would destroy the 6-allyl group. The 2-methylsulfonyl-8-esters (**14a—d** and **f**) thus obtained were hydrolyzed to give the 2-oxo-6-alkyl-8-acids (**18a—d** and **f**). Hydrolysis of the 6-ethoxycarbonylmethyl derivative (**14e**) afforded the di-acid (**17**). Treatment of **17** with ethyl chloroacetate gave the tri-ester (**16**), which was hydrolyzed to yield the tri-acid (**20**). Reaction of **17** with dimethyl sulfate in aqueous alkaline solution gave the 3-methyl-8-acid (**21**). Methylation of the 6-alkyl derivatives (**18b—d**) in aqueous alkaline solution gave also the 3-methyl-8-acids (**22b—d**). Treatment of the 6-methyl derivative (**18a**) with methyl iodide in the presence of potassium carbonate in DMF afforded the 3,6-dimethyl ester (**19**), which was then converted into the acid (**22a**) by acidic hydrolysis. The compound (**22f**) was similarly prepared by methylation of **18f** in DMF and hydrolysis of the resulting ester.

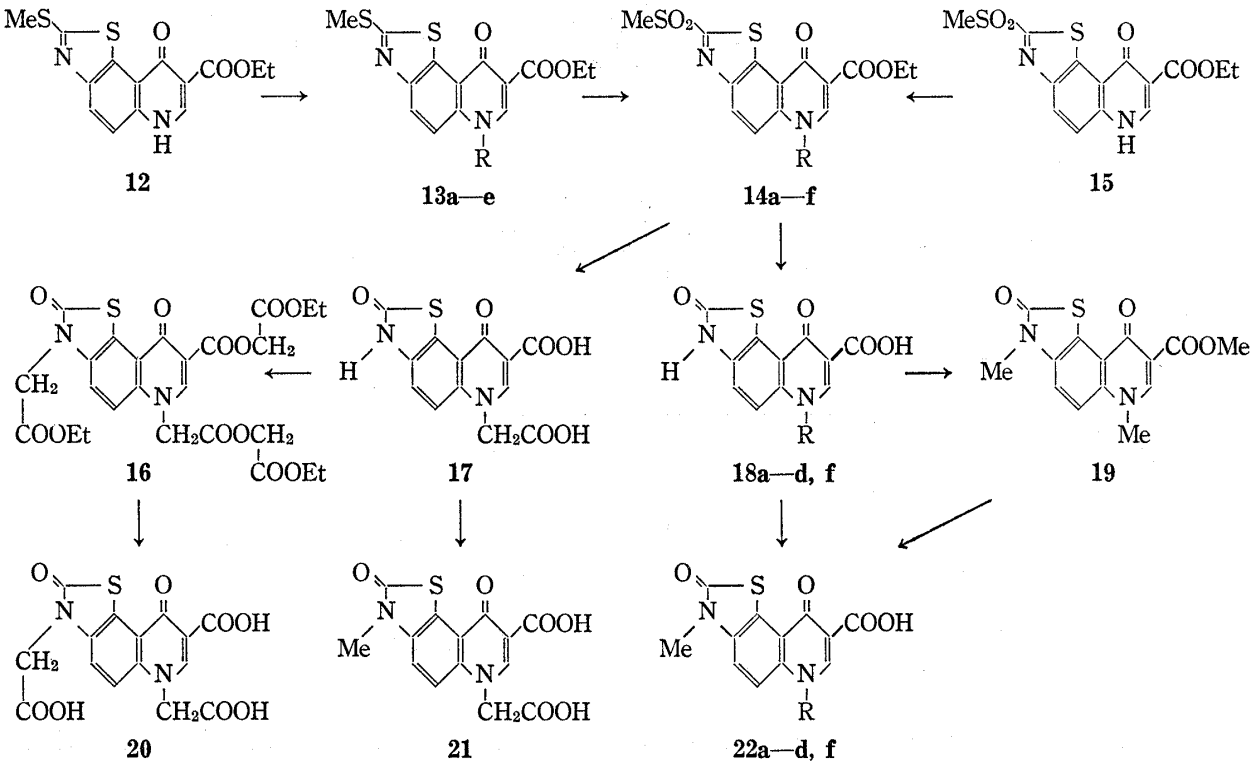


Chart 2

According to the method of Reed, *et al.*[5] and D'Amico, *et al.*[6] who described the thermal rearrangement of the methyl group from the S atom to the N atom in benzothiazoles, we undertook an alternative synthesis of the 3-methyl derivative (**25**) from the 2-methylthio ester (**23**). Heating of **23** at 200—230° in the presence of iodine or potassium iodide, followed by hydrolysis of the resulting 3-methyl-2-thioxo-8-ester (**24**) gave the 3-methyl-2-thioxo-8-acid (**25**). The structure of **24** was confirmed by its conversion into the 2-oxo-8-acid (**8a**). The

5) F.P. Reed, A. Robertson, and W.A. Sexton, *J. Chem. Soc.*, **1939**, 473.
6) J.J. D'Amico, S.T. Webster, R.T. Campbell, and C.E. Twine, *J. Org. Chem.*, **30**, 3628 (1965).

ester (**24**) was treated with mercuric acetate, according to the method of Gueden, *et al.*[7] to give the 2-oxo-8-ester (**26**), which was then hydrolyzed to the 3-methyl-2-oxo-8-acid (**8a**).

This rearrangement was similarly applied to the 2-alkoxy derivative. The 2-ethoxy acid (**27**)[1a] was heated in the presence of potassium iodide to afford the 3-ethyl-2-oxo-8-acid (**8b**). However, heating of the 2-benzyloxy derivative (**28**)[1a] gave no 3-benzyl product (**29**) but the 2-oxo derivative (**2**) as a result of elimination of the benzyloxy group.

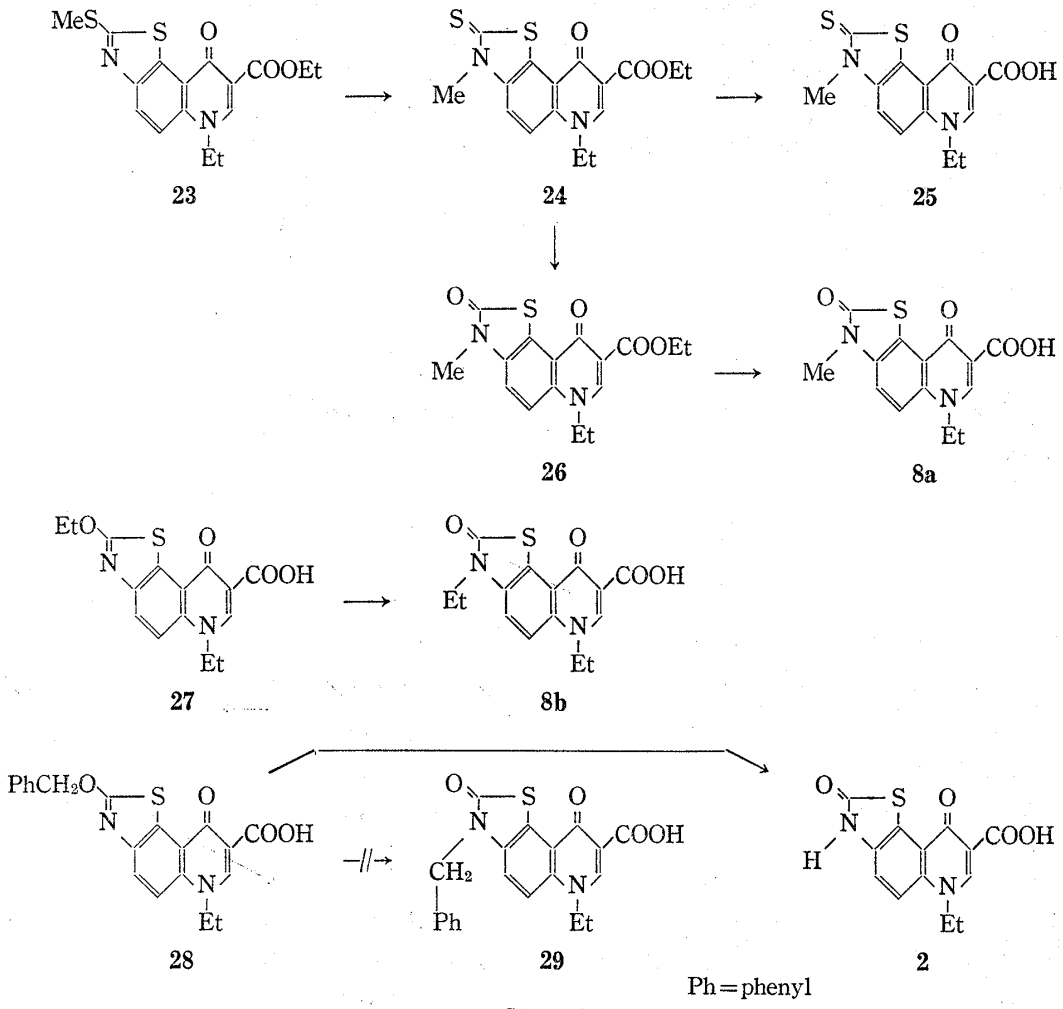


Chart 3

These compounds prepared in this work were tested for their antimicrobial activities against various bacteria *in vitro*. Many compounds showed the stronger activity than nalidixic acid or 2-substituted thiazolo[5,4-*f*]quinoline derivatives obtained in the previous work.[1] The 3-methyl-6-ethyl-8-carboxylic acid (**8a**) showed the strongest activity against both gram-negative bacteria including *Ps. aeruginosa* and several gram-positive bacteria, and furthermore rendered bacteria no cross-resistance with nalidixic acid.

Details on the structure-activity relationship will be reported in near future.

Experimental[8]

6-Ethyl-3-(2-diethylaminoethyl)-2, 3, 6, 9-tetrahydro-2, 9-dioxothiazolo[5, 4-*f*]quinoline-8-carboxylic Acid (1)——A mixture of 2[1a] (0.87 g), 2-diethylaminoethyl chloride (0.62 g) and Et_3N (0.73 g) in DMF (17 ml)

7) C. Gueden and J. Vialle, *Bull. Soc. Chim. France*, 1973, 270.

8) All melting points are uncorrected. UV spectra were measured on a Hitachi Recording Spectrophotometer 323. NMR spectra were recorded on a JEOLCO Model JNM 4H-100 Spectrometer or a Hitachi Perkin-Elmer R-20B using tetramethylsilane as an internal standard.

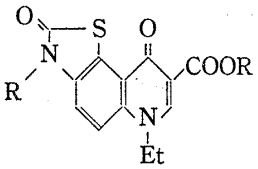
was stirred at 90° for 2 hr. After evaporation of the solvent, water was added to the residue and the undissolved materials were filtered. The filtrate was concentrated and the residue was washed with MeOH and crystallized from DMF to give **1**·HCl (0.45 g, 38%) as needles, mp 286—289° (decomp.). *Anal.* Calcd. for $C_{19}H_{23}O_4N_3S$·HCl: C, 53.58; H, 5.68; N, 9.87. Found: C, 53.25; H, 5.83; N, 9.77.

Acetylation of 2 Giving 3——A suspension of **2**[1a] (0.58 g), Ac_2O (5 ml) and pyridine (5 ml) was refluxed for 4.5 hr. After evaporation of the solvent, the residue was washed with water and two times recrystallized from DMF to give **3** (0.10 g, 15%) as needles, mp 313—314° (decomp.). *Anal.* Calcd. for $C_{15}H_{12}O_5N_2S$: C, 54.21; H, 3.64; N, 8.43. Found: C, 54.56; H, 3.78; N, 8.47. UV λ_{max}^{MeOH} nm: 261.5.

Alkylation of 2 with Alkyl Halides Giving 4a—h——i) A mixture of **2**[1a] (0.58 g), MeI (1.05 g) and K_2CO_3 (0.41 g) in DMF (12 ml) was stirred at 90° for 1.5 hr. After concentration of the mixture, the residue was washed with water and crystallized from MeOH to give **4a** (0.51 g, 80%) as needles, mp 274—275°. *Anal.* Calcd. for $C_{15}H_{14}O_4N_2S$: C, 56.60; H, 4.43; N, 8.80. Found: C, 56.43; H, 4.16; N, 8.85.

ii) The compounds (**4a—h**) were prepared in a similar manner as described above. Details are summarized in Table II.

Table II. 3-Substituted Thiazolo[5,4-*f*]quinoline Esters (**4**)



Compd. No.	R	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Analysis (%); Calcd. (Found) C	H	N
4b	Et	235—237	MeOH	75	$C_{17}H_{18}O_4N_2S$	58.95 (58.65)	5.24 (4.98)	8.09 (7.82)
4c	*n*-Pr	217—218	MeOH	80	$C_{19}H_{22}O_4N_2S$	60.95 (61.06)	5.92 (5.88)	7.48 (7.30)
4d	*n*-Bu	201—202	MeOH	72	$C_{21}H_{26}O_4N_2S$	62.67 (62.97)	6.51 (6.57)	6.96 (6.93)
4e	allyl	202—204	MeOH	58	$C_{19}H_{18}O_4N_2S$	61.60 (61.36)	4.90 (4.63)	7.56 (7.48)
4f	$PhCH_2$	227—229	$CHCl_3$	71	$C_{27}H_{22}O_4N_2S$	68.92 (68.74)	4.71 (4.45)	5.95 (6.12)
4g	$MeCOCH_2$	263 (decomp.)	MeOH	57	$C_{19}H_{18}O_6N_2S$	56.71 (56.42)	4.51 (4.53)	6.96 (7.09)
4h	BRPN[a]	255—257	$CHCl_3$	28	$C_{29}H_{20}O_6N_2SBr_2$	50.89 (50.94)	2.95 (2.81)	4.09 (4.43)

a) BRPN=Br-C$_6$H$_4$-$COCH_2$

Ph=phenyl

Ethyl 6-Ethyl-2,3,6,9-tetrahydro-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylate (5)——A suspension of **2**[1a] (20.0 g) in $SOCl_2$ (150 ml) was stirred at room temperature for 3 hr. To the mixture was added CH_2Cl_2 and the solid obtained was poured into anhyd. EtOH. After stirring for 30 min, the suspension was concentrated and the residue was washed with water. Recrystallization from DMF–MeOH gave **5** (20.4 g, 93%) as pale yellow needles, mp above 300°. *Anal.* Calcd. for $C_{15}H_{14}O_4N_2S$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.65; H, 4.71; N, 8.91.

Reaction of 2 with Ethyl Chloroacetate——A mixture of **2**[1a] (0.58 g), ethyl chloroacetate (0.54 g) and K_2CO_3 (0.55 g) in DMF (12 ml) was stirred at 100—110° for 1 hr. After evaporation of the solvent, the residue was washed with water and crystallized from MeOH to give **6** (0.69 g, 77%) as pale yellow needles, mp 218—220°. *Anal.* Calcd. for $C_{21}H_{22}O_8N_2S$: C, 54.53; H, 4.80; N, 6.06. Found: C, 54.41; H, 4.56; N, 6.25.

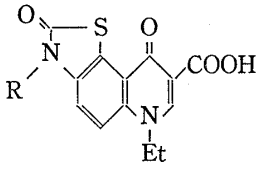
Hydrolysis of 6——A suspension of **6** (0.60 g) in conc. HCl–90% AcOH (1: 11) (5 ml) was refluxed for 35 min. The solid separated on cooling was recrystallized from DMF to give **7** (0.32 g, 65%) as needles, mp 288—289° (decomp.). *Anal.* Calcd. for $C_{15}H_{12}O_6N_2S$·1/2DMF: C, 51.49; H, 4.06; N, 9.10. Found: C, 51.71; H, 4.06; N, 9.01. NMR (CF_3COOH, 100 MHz) δ: 1.85 (3H, t, J=7.5 Hz, $NCH_2\underline{CH_3}$), 3.27 and 3.37 (each 1.5 H, each s, $N(CH_3)_2$), 5.02 (2H q, J=7.5 Hz, $NC\underline{H_2}CH_3$), 5.26 (2H, s, NCH_2COOH), 8.18 and 8.36 (each 1H, each d, J=9 Hz, 4- and 5-H), 8.38 (0.5H, s, HCON<), 9.43 (1H, s, 7-H).

3-Substituted 6-Ethyl-2,3,6,9-tetrahydro-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic Acids (8a—h)——i) A suspension of **4a** (0.32 g) in conc. HCl–90% AcOH (1 : 11) (5 ml) was refluxed for 1.5 hr. The solid separated was recrystallized from DMF to give **8a** (0.21 g, 70%) as needles, mp above 300°. *Anal.* Calcd. for $C_{14}H_{12}O_6N_2S$: C, 55.25; H, 3.98; N, 9.21. Found: C, 54.97; H, 3.85; N, 9.31.

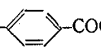
The compounds (**8b—h**) were prepared in a similar manner. Details were summarized in Table III.

ii) To a solution of **2**[1a] (0.29 g) in 1N NaOH (5 ml) was added MeI (0.71 g) in EtOH (4 ml) and the resulting solution was stirred at 70° for 1.5 hr. The solid separated on acidification was recrystallized from DMF to give **8a** (0.20 g, 66%), identical with the sample obtained above.

TABLE III. 3-Substituted Thiazolo[5,4-*f*]quinoline Acids (**8**)



Compd. No.	R	mp (°C)	Yield[a] (%)	Formula	Analysis (%); Calcd. (Found) N	H	C
8b	Et	>300	91	$C_{15}H_{14}O_4N_2S$	56.60 (56.55)	4.43 (4.41)	8.80 (8.57)
8c	*n*-Pr	>320	68	$C_{16}H_{16}O_4N_2S$	57.82 (57.46)	4.85 (4.84)	8.43 (8.28)
8d	*n*-Bu	272—274 (decomp.)	79	$C_{17}H_{18}O_4N_2S$	58.94 (58.63)	5.24 (5.30)	8.09 (8.34)
8e	allyl	300—301 (decomp.)	70	$C_{16}H_{14}O_4N_2S$	58.17 (58.38)	4.27 (4.23)	8.48 (8.73)
8f	$PhCH_2$	274—275	63	$C_{20}H_{16}O_4N_2S$	63.15 (62.83)	4.24 (4.01)	7.36 (7.60)
8g	$MeCOCH_2$	299 (decomp.)	70	$C_{16}H_{14}O_5N_2S$	55.48 (55.33)	4.07 (4.17)	8.09 (8.24)
8h	BRPN[b]	321—322 (decomp.)	78	$C_{21}H_{15}O_5N_2SBr$	51.75 (51.47)	3.10 (3.12)	5.75 (5.98)

a) All compounds were recrystallized from DMF. b) BRPN=Br-  -$COCH_2$

Ph=phenyl

Reaction of 5 with Ethylene Oxide——To an ice-cooled suspension of **5** (2.50 g) in DMF (50 ml) was bubbled through ethylene oxide for 2 hr. The resulting solution was heated at 120° in a sealed tube for 6 hr. After evaporation of the solvent, the residue was crystallized from DMF to give **9** (1.10 g, 39%) as pale yellow needles, mp 279—282°. *Anal.* Calcd. for $C_{17}H_{18}O_5N_2S$: C, 56.33; H, 5.01; N, 7.73. Found: C, 56.20; H, 5.06; N, 7.77.

Ethyl 3-(2-Chloroethyl)-6-ethyl-2,3,6,9-tetrahydro[5,4-*f*]quinoline-8-carboxylate (10)——i) A suspension of **9** (4.90 g) in $SOCl_2$ (50 ml) was stirred at 60—70° for 2 hr. After being kept for two days, the reaction mixture was poured onto ice, neutralized, and extracted with $CHCl_3$. The extract was washed with water and concentrated. Recrystallization from $CHCl_3$–EtOH gave **10** (3.16 g, 61%) as needles, mp 283—285°. *Anal.* Calcd. for $C_{17}H_{17}O_4N_2SCl$: C, 53.61; H, 4.50; N, 7.36. Found: C, 53.31; H, 4.45; N, 7.45.

ii) A mixture of **5** (1.27 g), K_2CO_3 (2.21 g) and 2-bromoethyl chloride (1.14 g) in DMF (30 ml) was stirred at 100° for 1 hr. The mixture was concentrated and extracted with $CHCl_3$. Recrystallization from $CHCl_3$–EtOH gave **10** (1.19 g, 78%) as needles, identical with the sample obtained above.

Reaction of 10 with NaOEt——A mixture of **10** (2.30 g) in NaOEt solution (0.42 g of Na, and 300 ml of anhyd. EtOH) was refluxed for 5 hr. After evaporation of the solvent, the residue was dissolved in water and acidified. Recrystallization of the resulting solid from DMF gave **11** (1.32 g, 69%) as yellow needles, mp above 300°. *Anal.* Calcd. for $C_{15}H_{12}O_4N_2S$: C, 56.94; H, 3.82; N, 8.86. Found: C, 56.66; H, 4.03; N, 9.11.

Alkylation of 12 with Alkyl Halides——i) A mixture of **12**[1b] (22.4 g), *n*-butyl bromide (24.0 g) and K_2CO_3 (27.3 g) in DMF (400 ml) was stirred at 70—80° for 3 hr. The reaction mixture was concentrated and extracted with $CHCl_3$. The residue, on evaporation of the solvent, was crystallized from benzene–petrobenzine to give **13c** (20.5 g, 78%) as needles, mp 132—135°. *Anal.* Calcd. for $C_{18}H_{20}O_3N_2S_2$: C, 57.43; H, 5.35; N, 7.47. Found: C, 57.08; H, 5.15; N, 7.47.

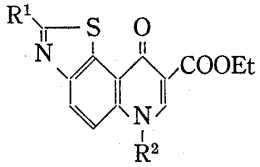
ii) The compounds (**13a**, **b**, **d**, and **e**) were prepared in a similar manner as described above. Details are summarized in Table IV.

Ethyl 6-Substituted 6,9-Dihydro-2-methylsulfonyl-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylate (14a—f)——i) To a suspension of **13c** (20.5 g) in AcOH (300 ml) was dropwise added 8% $KMnO_4$ solution (200 ml) during 1 hr at room temperature. After stirring for 1.5 hr, the suspension was treated with $NaHSO_3$. The solid remained was recrystallized from MeOH to give **14c** (18.4 g, 68%) as needles, mp 201—203°. *Anal.* Calcd. for $C_{18}H_{20}O_5N_2S_2$: C, 52.94; H, 4.94; N, 6.86. Found: C, 52.72; H, 4.85; N, 6.86.

ii) The compounds (**14a**, **b**, **d**, and **e**) were prepared in a similar manner as described in the method (i). Details are summarized in Table IV.

iii) A mixture of **15**[1b] (6.40 g), K_2CO_3 (8.28 g) and allyl bromide (7.26 g) in DMF (100 ml) was stirred at 80—90° for 1 hr. The reaction mixture was worked up as described in the preparation of **13c**. Recrystallization from DMF–EtOH gave **14f** (4.19 g, 59%) as needles, mp 228—231°. *Anal.* Calcd. for $C_{17}H_{16}O_5N_2S_2$: C, 52.04; H, 4.11; N, 7.14. Found: C, 52.02; H, 4.04; N, 7.02.

Table IV. 2-Methylthio(or 2-Methylsulfonyl)-6-alkyl Thiazolo[5,4-*f*]quinoline Derivatives



Compd. No.	R^1	R^2	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Analysis (%); Calcd. (Found) C	H	N
13a	MeS	Me	291—292 (decomp.)	DMF	65	$C_{15}H_{14}O_3N_2S_2$	53.87 (53.60)	4.22 (4.22)	8.38 (8.69)
13b	MeS	*n*-Pr	178—181	benzene	75	$C_{17}H_{18}O_3N_2S_2$	56.33 (56.25)	5.00 (5.03)	7.73 (7.54)
13d	MeS	$PhCH_2$	257—260	DMF	83	$C_{21}H_{18}O_3N_2S_2$	61.45 (61.16)	4.42 (4.49)	6.82 (6.56)
13e	MeS	$EtOOCCH_2$	202—205	DMF–MeOH	67	$C_{18}H_{18}O_5N_2S_2$	53.19 (52.87)	4.46 (4.55)	6.89 (6.83)
14a	$MeSO_2$	Me	>310	DMF	71	$C_{15}H_{14}O_5N_2S_2$	49.17 (49.43)	3.85 (3.85)	7.65 (7.65)
14b	$MeSO_2$	*n*-Pr	243—246	DMF	86	$C_{17}H_{18}O_5N_2S_2$	51.77 (51.87)	4.60 (4.74)	7.10 (7.13)
14d	$MeSO_2$	$PhCH_2$	208—210	$CHCl_3$–MeOH	77	$C_{21}H_{18}O_5N_2S_2$	57.00 (56.87)	4.10 (4.10)	6.33 (6.29)
14e	$MeSO_2$	$EtOOCCH_2$	195—198	DMF–MeOH	79	$C_{18}H_{18}O_7N_2S_2$	49.30 (49.36)	4.14 (4.03)	6.39 (6.38)

Ph=phenyl

Reaction of 17 with Ethyl Chloroacetate——A mixture of **17** (1.28 g), ethyl chloroacetate (5.49 g) and K_2CO_3 (6.21 g) in DMF (100 ml) was stirred at 100° for 40 min. The reaction mixture was treated as described in the preparation of **13c**. Recrystallization from $CHCl_3$–MeOH gave **16** (1.38 g, 62%) as a powder, mp 197—200° (decomp.). *Anal.* Calcd. for $C_{25}H_{26}O_{12}N_2S$: C, 51.91; H, 4.53; N, 4.84. Found: C, 51.96; H, 4.43; N, 4.79.

Hydrolysis of 14a—f——i) Preparation of **17**: A mixture of **14e** (15.3 g) in 10% NaOH (130 ml) was refluxed for 2 hr. The separated solid, on acidification, was washed with water and recrystallized from DMF–MeOH to give **17** (7.92 g, 71%) as needles, mp above 300°. *Anal.* Calcd. for $C_{13}H_8O_6N_2S \cdot 1/2DMF$; C, 48.80; H, 3.24; N, 9.81. Found: C, 48.56; H, 3.28; N, 9.95. NMR (CF_3COOH, 60 MHz) δ: 3.27 and 3.37 (each 1.5 H, each s, $N(CH_3)_2$), 5.80 (2H, s, $C\underline{H}_2COOH$), 8.10 and 8.36 (each 1H, each d, $J=10$ Hz, 4- and 5-H), 8.37 (0.5H, s, HCON<), 9.52 (1H, s, 7-H).

ii) Preparation of **18c**: A mixture of **14c** (4.08 g) in 10% NaOH (45 ml) was refluxed for 1 hr. The solid obtained, on acidification, was recrystallized from DMF to give **18c** (2.35 g, 74%) as needles, mp above 300°. *Anal.* Calcd. for $C_{15}H_{14}O_4N_2S$: C, 56.60; H, 4.43; N, 8.80. Found: C, 56.28; H, 4.55; N, 9.00.

iii) The compounds (**18a**, **b**, **d**, and **f**) were prepared in a similar manner as described above. Details are summarized in Table V.

Reaction of 18a with MeI——A mixture of **18a** (0.55 g), MeI (1.14 g) and K_2CO_3 (0.69 g) in DMF (12 ml) was stirred at 80—90° for 3 hr. The reaction mixture was worked up as usual and the solid obtained was recrystallized from DMF to give **19** (0.47 g, 77%) as needles, mp 324—326° (decomp.). *Anal.* Calcd. for $C_{14}H_{12}O_4N_2S$: C, 55.26; H, 3.97; N, 9.21. Found: C, 55.07; H, 3.86; N, 9.05.

Hydrolysis of 16——A mixture of **16** (1.16 g) in 1N HCl–90% AcOH (30 ml) was stirred at 100° for 3 hr. The solid separated, on addition of water, was recrystallized from DMF–MeOH to give **20** (0.53 g, 70%) as a powder, mp 298° (decomp.). *Anal.* Calcd. for $C_{15}H_{10}O_8N_2S \cdot H_2O$: C, 45.45; H, 3.05; N, 7.07. Found: C, 45.32; H, 2.81; N, 7.25. This compound showed a O–H band of water at 3450 cm^{-1} in IR (Nujol) spectrum.

Reaction of 17 with Dimethyl Sulfate——To a solution of **17** (0.96 g) in 5% KOH (16 ml) was added dropwise Me_2SO_4 (0.95 g) and the solution was stirred at room temperature for 4 hr. The solid deposited, on acidification, was washed with water and recrystallized from DMF–MeOH to give **21** (0.59 g, 57%) as a powder, mp 298—300° (decomp.). *Anal.* Calcd. for $C_{14}H_{10}O_6N_2S$: C, 50.30; H, 3.02; N, 8.38. Found: C, 50.12; H, 3.19; N, 8.13.

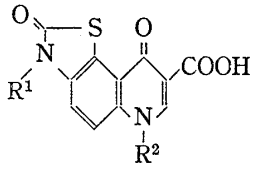
6-Substituted 2,3,6,9-Tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic Acids (22a—d and f)——i) A mixture of **19** (0.30 g) in 1N HCl–90% AcOH (5 ml) was refluxed for 1 hr and the solid obtained, on addition of water, was recrystallized from DMF to give **22a** (0.24 g, 83%) as needles, mp above 320°. *Anal.* Calcd. for $C_{13}H_{10}O_4N_2S$: C, 53.79; H, 3.47; N, 9.65. Found: C, 54.00; H, 3.56; N, 9.89.

ii) The compounds (**22b—d**): A solution of **18c** (0.95 g) in 5% KOH (16 ml) was treated with Me_2SO_4 (0.95 g) and stirred at room temperature for 4 hr. The solid deposited, on acidification, was recrystallized from DMF to give **22c** (0.52 g, 52%) as needles, mp 304—305° (decomp.). *Anal.* Calcd. for $C_{16}H_{16}O_4N_2S$: C, 57.81; H, 4.85; N, 8.43. Found: C, 57.65; H, 4.76; N, 8.58.

The derivatives (**22b** and **d**) were prepared in a similar manner as described above. Details were summarized in Table V.

iii) A mixture of **18f** (1.21 g), MeI (2.82 g) and K_2CO_3 (2.76 g) in DMF (100 ml) was stirred at 100° for 1 hr. The residue, on evaporation of the reaction mixture, was washed with water and dried to give the crude product, mp above 300°, 1.26 g. This ester (0.66 g), without further purification, was hydrolyzed in 1N HCl–90% AcOH (10 ml) with stirring at 100° for 2 hr. The solid obtained, on addition of water, was recrystallized from DMF to give **22f** (0.53 g, 80%) as needles, mp 312° (decomp.). *Anal.* Calcd. for $C_{15}H_{12}O_4N_2S$: C, 56.95; H, 3.83; N, 8.86. Found: C, 56.81; H, 3.94; N, 8.79.

Table V. 6-Substituted or 3,6-Disubstituted Thiazolo[5,4-*f*]quinoline Acids



Compd. No.	R^1	R^2	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Analysis (%); Calcd. (Found) C	H	N
18a	H	Me	>310	DMF	51	$C_{12}H_8O_4N_2S$	52.17 (52.44)	2.92 (3.07)	10.14 (10.49)
18b	H	*n*-Pr	>300	DMF	64	$C_{14}H_{12}O_4N_2S$	55.25 (55.16)	3.98 (4.17)	9.21 (8.90)
18d	H	$PhCH_2$	>300	DMF	78	$C_{18}H_{12}O_4N_2S$	61.35 (61.53)	3.43 (3.59)	7.95 (8.22)
18f	H	allyl	>300	DMF–MeOH	77	$C_{14}H_{10}O_4N_2S$	55.62 (55.31)	3.33 (3.32)	9.27 (8.97)
22b	Me	*n*-Pr	>300	DMF	60	$C_{15}H_{14}O_4N_2S$	56.59 (56.41)	4.43 (4.66)	8.80 (8.81)
22d	Me	$PhCH_2$	>300	DMF	81	$C_{19}H_{14}O_4N_2S$	62.28 (62.51)	3.85 (3.97)	7.65 (7.93)

Ph=phenyl

Rearrangement of 2-Methylthio Derivative (23) Giving 2-Thioxo-3-methyl Derivative (24)——A mixture of **23**[1b] (1.72 g) and I_2 (0.13 g) was heated at the bath temperature of 200—230° for 30 min. After cooling, the solid remained was washed with $(C_2H_5)_2O$ and recrystallized from DMF to give **24** (1.05 g, 61%) as pale yellow plates, mp 324—326° (decomp.). *Anal.* Calcd. for $C_{16}H_{16}O_3N_2S_2$: C, 55.15; H, 4.63; N, 8.04. Found: C, 55.41; H, 4.42; N, 8.40.

Repetition of the above reaction with KI (0.08 g) in place of I_2 proceeded to give also **22** (1.18 g, 69%).

Hydrolysis of 24——A mixture of **24** (0.30 g) in 1N HCl–90% AcOH (10 ml) was refluxed for 2 hr. The solid separated, on cooling, was recrystallized from DMF to give **25** (0.20 g, 70%) as pale yellow needles, mp 322—323° (decomp.). *Anal.* Calcd. for $C_{14}H_{12}O_3N_2S_2$: C, 52.49; H, 3.78; N, 8.74. Found: C, 52.58; H, 3.92; N, 9.05.

Conversion of 2-Thioxo Derivative (24) into 2-Oxo Derivative (26)——A mixture of **24** (1.00 g) and mercuric acetate (3.0 g) in DMF (60 ml) was stirred at 120—130° for 1.5 hr. After cooling, the insoluble materials were removed by filtration and the filtrate was concentrated. The residue was extracted with $CHCl_3$ and the extract was evaporated to dryness. Recrystallization from MeOH gave **26** (0.44 g, 46%) as needles, mp 262—265°. *Anal.* Calcd. for $C_{16}H_{16}O_4N_2S$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.68; H, 4.86; N, 8.73.

Hydrolysis of 26——A mixture of **26** (0.33 g) in 1N HCl–90% AcOH (6 ml) was stirred at 100° for 2 hr. Usual work-up of the reaction mixture gave the crude product, which was recrystallized from DMF to give **8a** (0.22 g, 72%) as needles, mp above 300°. This product was identical in IR spectrum with an authentic sample obtained from **2**.

Rearrangement of 2-Ethoxy Derivative (27) Giving 2-Oxo-3-ethyl Derivative (8b)——A mixture of **27**[1a] (0.74 g) and KI (0.04 g) was heated at the bath temperature of 255—265° for 30 min. After cooling, the reaction mixture was washed successively with MeOH and water. Recrystallization from DMF gave **8b** (0.32 g, 44%) as needles, mp above 320°, identical with an authentic sample prepared from **4a**.

Attempted Rearrangement of 2-Benzyloxy Derivative (28): Formation of 2-Oxo Derivative (2)——A mixture of **28**[1a] (0.19 g) and KI (0.01 g) was heated at the bath temperature of 220—240° for 30 min. After cooling, the solid remained was recrystallized from DMF–MeOH to give **2** (0.073 g, 48%) as a yellow powder, mp above 300°. The product was identical with an authentic sample prepared in the preceding paper.[1a]

Acknowledgement The authors are indebted to Dr. N. Koga, director of this institute, and Dr. G. Ohta for their support and encouragement. Thanks are also due to the members of the analytical section of this institute for the elemental analyses.