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

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A method of synthesizing for 3,6-disubstituted 2,9-dioxo-2,3,6,9-tetrahydrothiazolo-[5,4-*f*]quinoline-8-carboxylic acids *via* the thiazolium salts was studied and proved to be practical. The reactions of the thiazolium salt with various nucleophilic reagents afforded several new derivatives. Gould-Jacobs reaction of the benzothiazole-2-ones and benzothiazole-2-thione derivatives were also carried out.

In Part III of this series, we reported that 3,6-disubstituted 2,9-dioxo-2,3,6,9-tetrahydrothiazolo[5,4-*f*]quinoline derivatives showed excellent antibacterial activities against gram-negative and gram-positive bacteria *in vitro*. Consequently, our interest was focused on the more convenient synthesis of these and other new derivatives. The present paper deals with the experiments on reaction of thiazolium salts and formation of thiazoloquinolines from benzothiazolones.

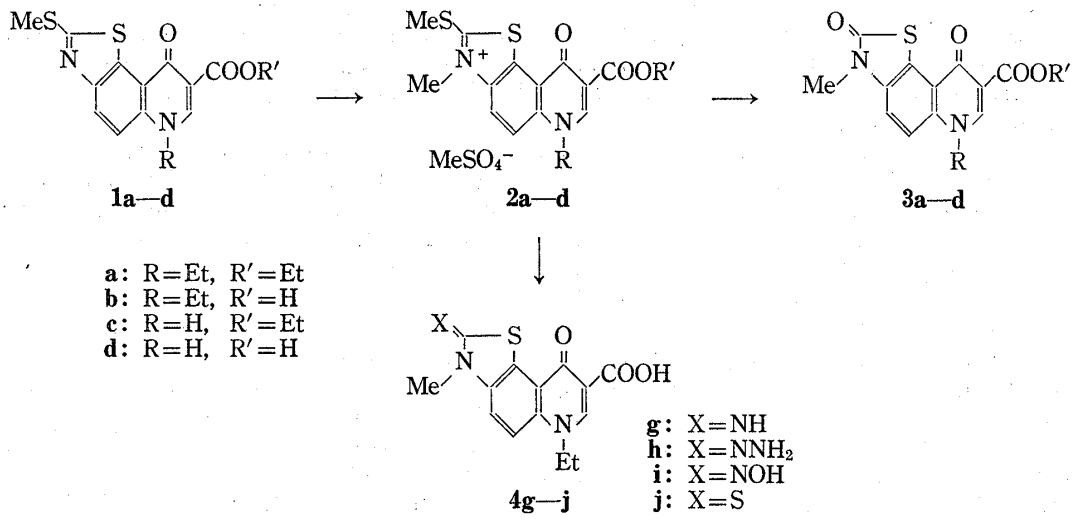


Chart 1

Since Sexton[4] described in 1939 the nucleophilic substitution reactions of N,S-dialkylbenzothiazolium salt, a few papers of this subject have been published. Recently, Sohar, *et al.*[5] reported on the reaction of 2-methylthio-3-methylbenzothiazolium iodide, showing that the 2-methylthio group is convertible into the 2-oxo- or 2-imino group. We applied these reactions to the synthesis of the thiazoloquinoline derivatives. On reaction with dimethyl

1) Part III: S. Kadoya, N. Suzuki, I. Takamura, and R. Dohmori, *Chem. Pharm. Bull.* (Tokyo), **24**, 147 (1976).
2) A part of this work was presented at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April 1974.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
4) W.A. Sexton, *J. Chem. Soc.*, **1939**, 470.
5) *a*) P. Sohar, G.H. Denny, Jr. and R.D. Babson, *J. Heterocyclic Chem.*, **6**, 163 (1969); *b*) *Idem, ibid.*, **7**, 1369 (1970).

sulfate, ethyl 6-ethyl-6,9-dihydro-2-methylthio-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylate (**1a**) gave the corresponding thiazolium salt (**2a**), which was active in nucleophilic reactions. Treatment of **2a** with aqueous sodium hydroxide at room temperature, liberating methylmercaptane, produced the 2-oxo ester (**3a**) which was hydrolyzed with acids to the corresponding acid (**3b**).[1] Heating **2a** in an alkaline solution gave **3b** in one step in a good yield. This method was preferable for the synthesis of **3b**. **1b—d** were also converted into **3b—d** *via* corresponding quaternary salts (**2b—d**), respectively. Further, treatment of **2b** with ammonia, hydrazine hydrate and hydroxylamine, as nucleophilic reagents smoothly gave the corresponding 2-imino-3-methylthiazoloquinoline derivatives (**4g—i**) respectively. Reaction of **2b** with potassium hydrogen sulfide afforded the corresponding 2-thioxo derivative (**4j**), identical with an authentic sample[1] obtained by hydrolysis of the thermal rearrangement product of **1a**.

In a similar procedure 6-(2-diethylaminoethyl)-6,9-dihydro-2-methylthio-9-oxothiazolo-[5,4-*f*]quinoline-8-carboxylic acid (**5m**) was converted into the corresponding 3-methyl-2-oxothiazoloquinoline derivative (**6m**) *via* its thiazolium salt. Further, **6n** obtained from **5n** was treated with ethylene oxide to give 2-hydroxyethyl 2,3,6,9-tetrahydro-6-(2-hydroxyethyl)-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylate (**7**), from which the corresponding carboxylic acid (**8**) was prepared by hydrolysis. Treatment of **7** with thionyl chloride gave the corresponding dichloro derivative (**10**), which was converted to the 6-chloroethyl-8-carboxylic acid (**11**) by acidic hydrolysis and to the 6-vinyl acid (**9**) by reaction with sodium ethoxide.

In the second approach to the synthesis of **3b**, we undertook a new process by ring closure of diethyl N-(2,3-dihydro-3-methyl-2-oxobenzothiazol-6-yl)aminomethylenemalonate (**17q**) prepared from **12** as shown in Chart 3. When **17q** was heated in Dowtherm A, a mixture which showed two spots in thin-layer chromatography (TLC) was obtained. The nuclear

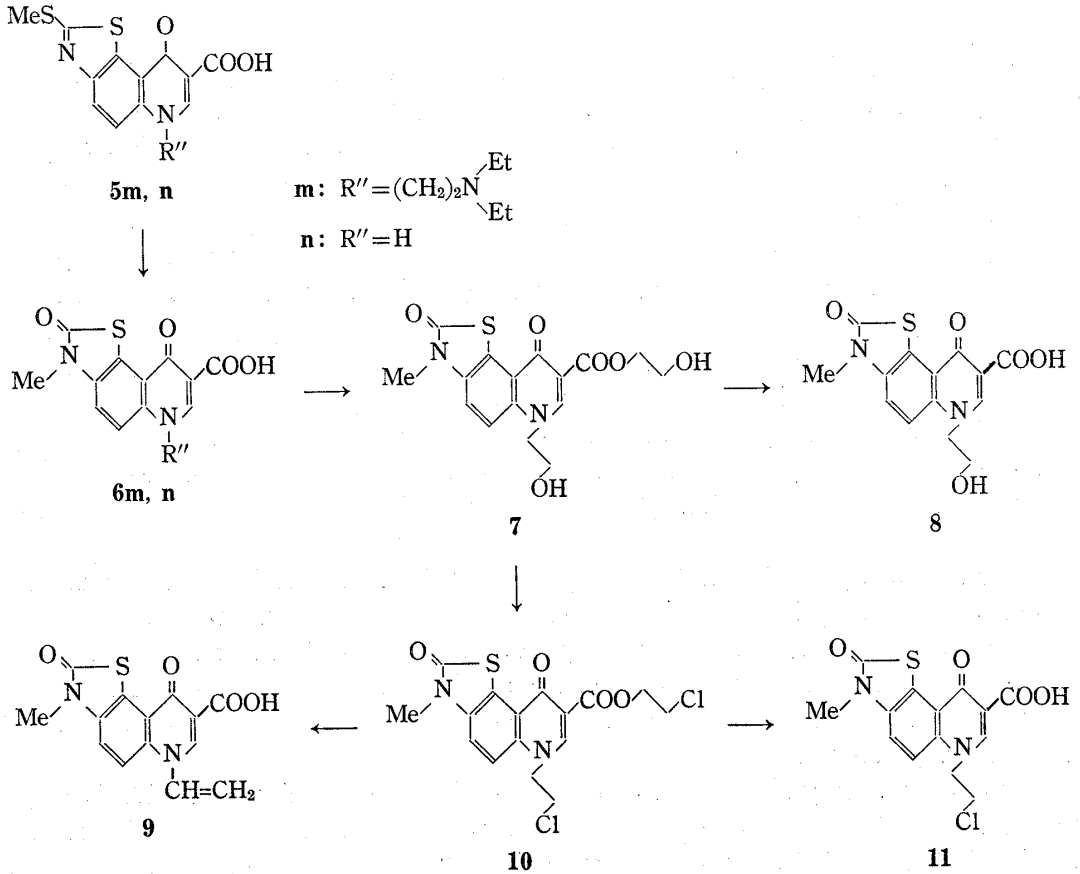


Chart 2

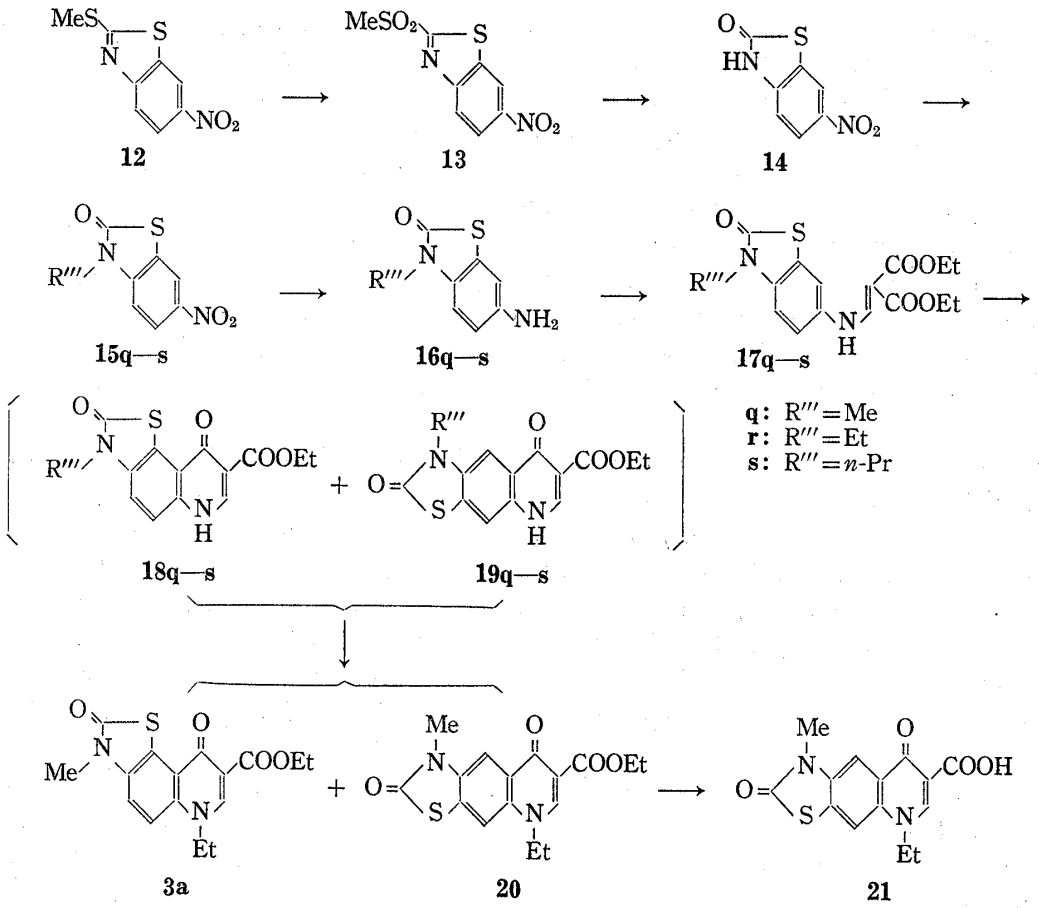


Chart 3

magnetic resonance (NMR) spectrum of the mixture exhibited two parts of doublets (8.15 and 8.34 ppm) and two singlets (8.34 and 8.43 ppm) assignable to the aromatic proton signals of the angular type compound (**18q**) and those of linear type compound (**19q**), respectively, as shown in Fig. 1. From the intensities of the signals (3.82 and 3.85 ppm) corresponding to the N-CH_3, the mixture appeared to consist of equal amounts of **18q** and **19q**. The products (**18q** and **19q**) were difficult to separate from each other, because they were sparingly soluble in various organic solvents. N-6-Ethyl derivatives (**3a** and **20**) introduced from the mixture were purified by preparative TLC. The compound mp 259—262° (**3a**), being identical with a sample synthesized previously,[1] was angular type. The other compound (mp 243—245°) obtained from the more mobile fraction, showed to be isomeric with **3a**, from the results of its elemental analysis and mass spectrum (M^+ 332) measurement. Its NMR signals for aromatic protons observed as two singlets at 8.52 and 8.42 ppm, proved its structure to be linear type, *e.g.* the thiazolo[4,5-*g*]quinoline (**20**). It was converted into the corresponding acid (**21**) by hydrolysis.

When **17r** (R'''=Et) and **17s** (R'''=*n*-Pr) were cyclized in a similar manner, the reaction products were presumed by their TLC and NMR spectra to be the mixtures of angular thiazoloquinoline derivatives (**18r, s**) and linear compounds (**19r, s**) in about 1:1 ratio, respectively; the results were similar to that in the case of the cyclization of the 2-oxo-3-methyl compound (**17q**). Thus the effect of the substituent at the N-3 position could not be observed upon the direction of the ring closure.

The result of the ring-closure reaction of the 2-oxobenzothiazole derivatives (**17q—s**) led our attention to the effect of substituents at the 2 position upon the direction of ring closure. The intermediate, benzothiazolium salt (**22**) obtained from **12** was treated with hydrogen sulfide in alkaline solution to give the 2-thioxo derivative (**23**). The compound

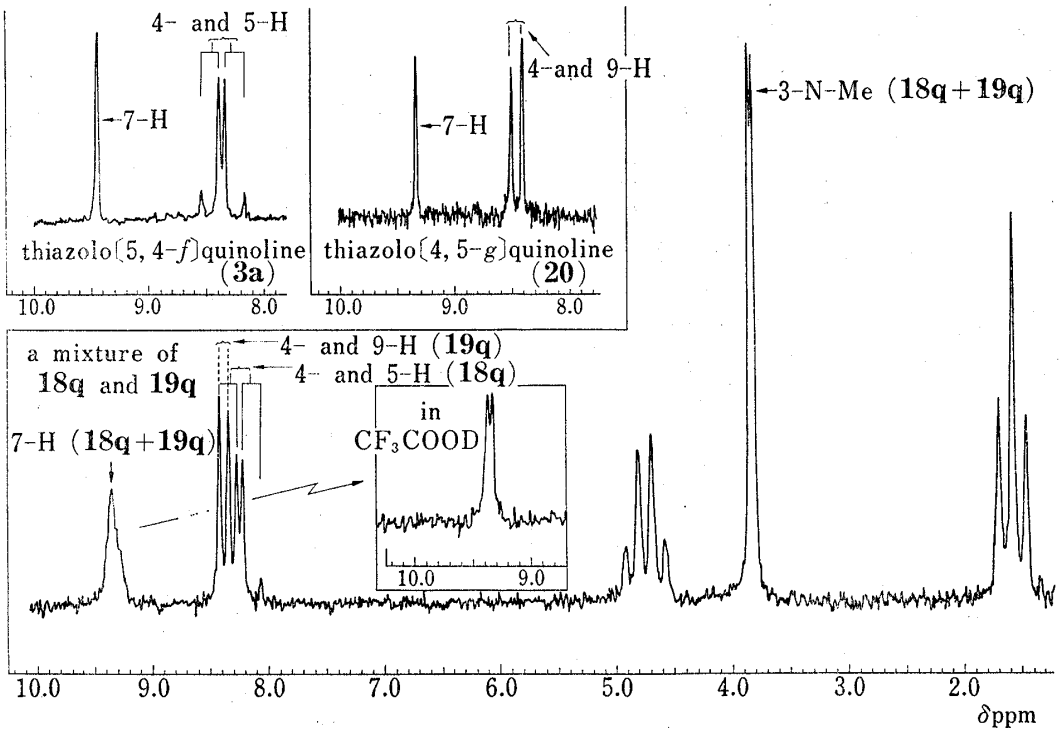


Fig. 1. NMR Spectra of Thiazoloquinoline Derivatives (**18q**+**19q**, **3a** and **20**) in CF_3COOH

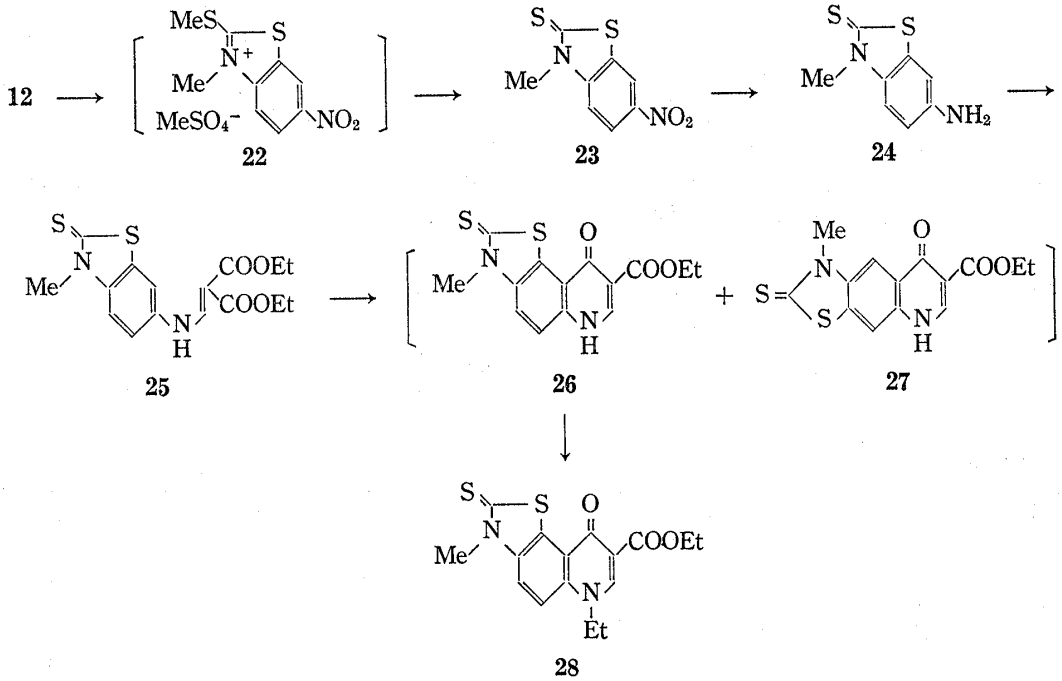


Chart 4

(**23**) was further converted to the anil derivative (**25**) *via* the amino derivative (**24**). Heating of **25** in Dowtherm A gave the cyclization product which was presumed to be a mixture of an angular thiazoloquinoline (**26**) and a linear compound (**27**) in about 4: 1 ratio. After ethylation of the mixture, the main product was purified by recrystallization from dimethylformamide (DMF), and identified with the product (**28**) obtained from **1a** by thermal rearrangement reaction.[1)]

It was reported in the previous paper[6] that the ring-closure of 2-substituted benzothiazoles affords exclusively the angular thiazoloquinolines. Now we have obtained a mixture of the angular compound and linear one (cyclization products at 7- and 5-position, respectively) from 3-substituted 2-oxobenzothiazole derivatives. It is known that the bromination of 6-aminobenzothiazole occurs predominantly at 7-position.[7] However, the electron density at 5-position of 6-aminobenzothiazole derivative appears to be higher than that at 7-position from the data of its NMR spectrum.[6,8] These facts suggest that the electron density can not be an important factor in the cyclization of benzothiazoles. On the other hand, in the cyclization of 2-substituted benzothiazoles, the intermediate for angular thiazoloquinoline exsists as a resonance hybrid between **29** and **29′**, and is more stabilized than that (**30**) for linear one, in analogy with the explanation on the cyclization of benzimidazole by Ishiwata, *et al.*[9] In the case of 3-substituted 2-oxobenzothiazoles which lack the aromaticity in the hetero ring, the angular intermediate (**31**) seems to be nearly the same as the linear one (**32**) in the energy level. Therefore, it may be presumed that the direction of cyclization of benzothiazoles and 2-oxobenzothiazoles depends on the stability of the intermediate rather than on the electron density. We can not, however, clearly account for the result on the cyclization of 3-substituted 2-thioxobenzothiazole derivative and further studies are required.

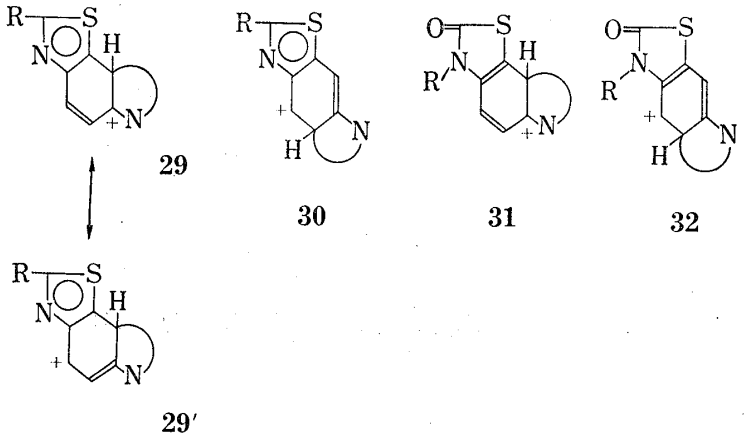


Chart 5

The compounds obtained in this work were tested for their antibacterial activities. Some compounds among them, *e.g.* **11** showed superior activity than that of nalidixic acid *in vitro*. The linear thiazoloquinoline derivative (**21**) was by far less active than the corresponding angular compound (**3b**) against all the bacteria tested. Antibacterial activities of these compounds and the structure-activity relationship will be shown elsewhere.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were obtained on a Hitachi EPI-G2 spectrophotometer. Hitachi Perkin-Elmer R-20B spectrometer (60 MHz) was used for measurement of NMR spectra and chemical shifts (δ) are given in ppm from TMS as standard signal. Abbreviation: s=singlet, d=doublet, t=triplet and m=multiplet. Mass spectra were run on a Hitachi RMS-4 mass spectrometer. TLC was carried out on Merck's Silica gel GF_{254} with a solvent system of Rf^1, $CHCl_3$–MeOH (10: 1); Rf^2, $CHCl_3$–MeOH (10: 2).

General Procedure of 6,9-Dihydro-3-methyl-2-methylthio-9-oxothiazolo[5,4-*f*]quinolinium Methylsulfates (2a—d)——A mixture of **1**[6] (0.01 mol), Me_2SO_4 (3.78 g) in DMF (30 ml) was heated at 100° for 5 hr with stirring. After cooling, resulting precipitate was collected, washed with MeOH and dried to give **2** as pale yellow needles.

6) Part I: R. Dohmori, S. Kadoya, I. Takamura, and N. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **24**, 130 (1976).
7) E.R. Ward and C.H. Williams, *J. Chem. Soc.*, **1965**, 2248.
8) NMR spectrum ($CDCl_3$, 60 MHz) of diethyl N-(2-methylthio-6-benzothiazolyl)aminomethylenemalonate exhibited the signals for aromatic protons at 7.12 (doubled d, J=9.0 and 2.0 Hz, 5-H), 7.45 (d, J=2.0 Hz, 7-H) and 7.78 ppm (d, J=9.0 Hz, 4-H). The corresponding peaks for 3-methyl-2-oxobenzothiazole derivative, however, were observed at 7.02—7.20 ppm and were unable to assign for each proton.
9) S. Ishiwata and Y. Shiokawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 2455 (1969).

8-Ethoxycarbonyl-6-ethyl-6,9-dihydro-3-methyl-2-methylthio-9-oxothiazolo[5,4-*f*]quinolinium Methylsulfate (**2a**): **2a** was obtained from **1a** in a similar manner except that benzene was used instead of DMF as the solvent. Yield, 84%. The product was used to next step without purification.

8-Carboxy-6-ethyl-6,9-dihydro-3-methyl-2-methylthio-9-oxothiazolo[5,4-*f*] quinolinium Methylsulfate (**2b**): Yield, 75%. mp 248—249° (decomp.). *Anal.* Calcd. for $C_{16}H_{18}O_7N_2S_3$: C, 43.04; H, 4.06; N, 6.27. Found: C, 42.71; H, 3.97; N, 6.07.

8-Ethoxycarbonyl-6,9-dihydro-3-methyl-2-methylthio-9-oxothiazolo[5,4-*f*]quinolinium Methylsulfate (**2c**): Yield 86%, mp 230—231° (decomp.). *Anal.* Calcd. for $C_{16}H_{18}O_7N_2S_3$: C, 43.04; H, 4.06; N, 6.27. Found: C, 43.48; H, 4.16; N, 6.18.

8-Carboxy-6,9-dihydro-3-methyl-2-methylthio-9-oxothiazolo[5,4-*f*] quinolinium Methylsulfate (**2d**): Yield 66%, mp 278—279° (decomp.). *Anal.* Calcd. for $C_{14}H_{14}O_7N_2S_3$: C, 40.18; H, 3.37; N, 6.69. Found: C, 40.57; H, 3.46; N, 7.07.

General Procedure of 2,3,6,9-Tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline Derivatives (3a—d) ——A solution of **2a** or **2c** (0.01 mol) in 2% NaOH (20 ml) was warmed at 40° for 10 min and allowed to stand overnight at room temperature. The resulting precipitate was collected and its recrystallization from EtOH or DMF gave **3a** or **3c**, respectively. In the case of **2b** or **2d**, the quaternary salt was treated with 10% NaOH at room temperature for 15 min and the reaction mixture was acidified. The resulting crystalline mass (**3b** or **3d**) was collected.

Ethyl 6-Ethyl-2,3,6,9-tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylate (**3a**): Yield 82%, needles (from DMF), mp 261—265°. It was identical with the authentic sample.[1]

6-Ethyl-2,3,6,9-Tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (**3b**): Yield 84%, needles, mp>300°. It was identical with an authentic sample.[1]

Ethyl 2,3,6,9-Tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylate (**3c**): Crude product was obtained quantitatively and immediately converted into the corresponding acid (**3d**) by acidic hydrolysis. Total yield, 74%.

2,3,6,9-Tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (**3d**): Yield 94%, needles mp>300°. *Anal.* Calcd. for $C_{12}H_8O_4N_2S$: C, 52.17; H, 2.95; N, 10.14. Found: C, 51.78; H, 2.95; N, 9.88.

6-Ethyl-2,3,6,9-tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (3b)——a) A suspension of **3a** (0.20 g) in conc. HCl-90% AcOH (1: 11 in volume) (4 ml) was refluxed for 0.5 hr. The resulting precipitate was collected, washed and dried to give the crude product (0.15 g; 83%). Recrystallization from DMF gave **3b** as needles, mp>300°. It was identical with an authentic sample.[1]

b) **2a** (4.60 g) was added in 2% NaOH (45 ml) and the mixture was heated at 80—85° for 1 hr. The solid obtained by acidification of the reaction mixture was collected and recrystallized from DMF to give **3b** (2.70 g; 89%).

6-Ethyl-2,3,6,9-tetrahydro-2-imino-3-methyl-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (4g)——A solution of **2b** (0.44 g), water (10 ml) and conc. NH_4OH (2 ml) was allowed to stand for 4 hr at room temperature and concentrated. The separated crystals were collected and recrystallized from DMF to give **4g** (0.12 g; 40%) as yellow needles, mp>300°. *Anal.* Calcd. for $C_{14}H_{13}O_3N_3S$: C, 55.42; H, 4.32; N, 13.85. Found: C, 55.50; H, 4.28; N, 13.35.

6-Ethyl-2-hydrazono-2,3,6,9-tetrahydro-3-methyl-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (4h) ——A solution of **2b** (0.87 g), water (10 ml) and $NH_2NH_2 \cdot H_2O$ (0.50 g) was allowed to stand for 3 days at room temperature. The red prisms separated were collected. Yield, 0.49 g (77%). mp>300°. *Anal.* Calcd. for $C_{14}H_{14}O_3N_4S$: C, 52.82; H, 4.43; N, 17.60. Found: C, 53.14; H, 4.53; N, 17.79.

6-Ethyl-2,3,6,9-tetrahydro-2-hydroxyimino-3-methyl-9-oxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (4i) ——A solution prepared from $NH_2OH \cdot HCl$ (1.24 g), K_2CO_3 (0.83 g) and water (10 ml), was added to a solution of **2b** (0.87 g) in water (10 ml). After 0.5 hr, the separated crystals were collected and recrystallized from DMF–MeOH to give **4i** (0.54 g; 86%) as yellow needles, mp 299—301° (decomp.). *Anal.* Calcd. for $C_{14}H_{13}O_4N_3S$: C, 52.66; H, 4.10; N, 13.16. Found: C, 52.78; H, 4.15; N, 13.45.

6-Ethyl-2,3,6,9-tetrahydro-3-methyl-9-oxo-2-thioxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (4j)—— To a solution of **2b** (2.00 g) in water (50 ml) was added 20% KSH (20 ml). The reaction mixture was kept at room temperature for 10 min and warmed at 50° for 10 min and finally acidified with dil. HCl. The separated precipitate was recrystallized from DMF to give pale yellow needles (1.40 g; 90%), mp>300°. The IR spectrum of the product was identical with that of an authentic sample.[1]

6-(2-Diethylamino)ethyl-2,3,6,9-tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (6m)——A mixture of **5m**[6] (4.36 g), Me_2SO_4 (3.78 g) in DMF (30 ml) was stirred at 100—110° for 7 hr and cooled. The resulting precipitate was collected and washed with DMF. The quaternary salt obtained above was dissolved in water and made basic with aqueous NaOH. The reaction mixture was allowed to stand at room temperature overnight, and acidified with AcOH. The resulting crystalline mass was recrystallized from DMF-MeOH to give **6m** (1.90 g; 48%). Drying this sample *in vacuo* at 130° overnight gave a powder, mp 215—218°. *Anal.* Calcd. for $C_{18}H_{21}O_4N_3S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.11; H, 5.35; N, 10.83.

2,3,6,9-Tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (6n)——The quaternary salt of **5n** was prepared from **5n**[6] (4.38 g), Me_2SO_4 (5.67 g) and DMF (100 ml) in 66% yield and was converted into **6n** quantitatively in a similar manner described for the synthesis of **6m**. Recrystallization from DMF gave pure **6n** as needles, mp>300°.

2-Hydroxyethyl 2,3,6,9-Tetrahydro-6-(2-hydroxyethyl)-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylate (7)——To a suspension of **6n** (3.20 g) in DMF was introduced gaseous ethylene oxide. The mixture was heated in a sealed tube for 2 days at 120°. After cooling, separated crystals were recrystallized from DMF to give **7** (3.16 g; 75%) as a powder, mp 297—300°. *Anal.* Calcd. for $C_{16}H_{16}O_6N_2S$: C, 52.74; H, 4.43; N, 7.69. Found: C, 52.80; H, 4.79; N, 8.03.

2,3,6,9-Tetrahydro-6-(2-hydroxyethyl)-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (8)——A mixture of **7** (0.30 g) and conc. HCl-90% AcOH (1: 11) (60 ml) was refluxed for 1 hr. Water was added to the reaction mixture and the resulting solid was recrystallized from DMF to give **8** (0.26 g; 97%) as a needles, mp 295—300°. *Anal.* Calcd. for $C_{14}H_{12}O_5N_2S$: C, 51.76; H, 3.88; N, 8.17. Found: C, 51.82; H, 4.01; N, 8.21.

2,3,6,9-Tetrahydro-3-methyl-2,9-dioxo-6-vinylthiazolo[5,4-*f*]quinoline-8-carboxylic Acid (9)——To a solution prepared from Na (92 mg) and anhyd. EtOH (50 ml) was added **10** (0.40 g), and the mixture was refluxed for 2.5 hr. After evaporation of the solvent, water was added to the residue and undissolved material was filtered off. The filtrate was adjusted to pH 4 with HCl and the precipitate was collected. Recrystallization from DMF gave **9** (0.12 g; 38%) as pale yellow needles, mp>300°. *Anal.* Calcd. for $C_{14}H_{10}O_4N_2S$: C, 55.62; H, 3.33; N, 9.27. Found: C, 55.31; H, 3.46; N, 8.95.

2-Chloroethyl 6-(2-Chloroethyl)-2,3,6,9-tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylate (10)——A mixture of **7** (2.50 g) and $SOCl_2$ (25 ml) was gently refluxed for 1 hr, concentrated and poured on ice. After neutralization, the resulting solid was recrystallized from DMF to give pale yellow needles, **10** (2.03 g; 74%), mp 270—273°. *Anal.* Calcd. for $C_{16}H_{14}O_4N_2SCl_2$: C, 47.89; H, 3.52; N, 6.88. Found: C, 48.30; H, 3.78; N, 7.38.

6-(2-Chloroethyl)-2,3,6,9-tetrahydro-3-methyl-2,9-dioxothiazolo[5,4-*f*]quinoline-8-carboxylic Acid (11)——A mixture of **10** (0.36 g in conc. HCl–90% AcOH (1: 11) (7 ml) was refluxed for 2.5 hr. After cooling, the separated precipitate was recrystallized from DMF to give **11** (0.23 g; 76%) as pale yellow needles, mp >300°. *Anal.* Calcd. for $C_{14}H_{11}O_4N_2SCl$: C, 49.63; H, 3.27; N, 8.27. Found: C, 50.03, H, 3.57; N, 8.46.

2-Methylsulfonyl-6-nitrobenzothiazole (13)——To a stirred suspension of **12** (34.0 g) in AcOH (400 ml) was added dropwise 10% $KMnO_4$ (200 ml) and the reaction mixture was stirred for 1 hr. Then $NaHSO_3$ was added to the mixture until it became to colorless. The resulting precipitate was recrystallized from EtOH to give **13** (32.5 g; 84%) as needles, mp 182—186°. *Anal.* Calcd. for $C_8H_6O_4N_2S_2$: C, 37.20; H, 2.34; N, 10.85. Found: C, 37.02; H, 2.46; N, 10.63.

6-Nitrobenzothiazolone (14)——A mixture of **13** (32.5 g) and 5% NaOH (500 ml) was stirred at 100° for 1 hr. The reaction mixture was acidified and extracted with AcOEt. After evaporation of the solvent, the residue was crystallized from EtOH to give **14** (22 g; 92%) as pale yellow needles, mp 245—248°. *Anal.* Calcd. for $C_7H_4O_3N_2S$: C, 42.85; H, 2.06; N, 14.28. Found: C, 42.59; H, 1.89; N, 14.27.

2,3-Dihydro-3-methyl-6-nitro-2-oxobenzothiazole (15q)——A mixture of **14** (2.61 g), powdered K_2CO_3 (5.38 g), MeI (7.05 g) and EtOH (50 ml) was refluxed for 3.5 hr, concentrated and extracted with $CHCl_3$. The residue obtained from the extract was crystallized from acetone–EtOH to give **15q** as pale yellow needles (1.69 g; 62%), mp 163—165°. *Anal.* Calcd. for $C_8H_6O_3N_2S$: C, 45.71; H, 2.89; N, 13.33. Found: C, 45.95; H, 2.86; N, 13.05.

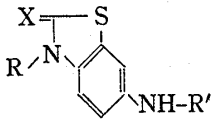
3-Ethyl-2,3-dihydro-6-nitro-2-oxobenzothiazole (15r)——A mixture of **14** (26.1 g), K_2CO_3 (53.8 g), EtI (80 g) in DMF (200 ml) was stirred at 90—100° for 2 hr, and concentrated. Water was added to the residue and the resulting precipitate was collected. Recrystallization from $CHCl_3$–EtOH gave **15r** (25.2 g; 87%) as pale yellow needles, mp 198—201°. *Anal.* Calcd. for $C_9H_8O_3N_2S$: C, 48.20; H, 3.60; N, 12.49. Found: C, 48.36; H, 3.51; N, 12.46.

2,3-Dihydro-6-nitro-3-propyl-2-oxobenzothiazole (15s)——**15s** was obtained from **14** (26.1 g), K_2CO_3 (53.8 g) and *n*-propyl bromide (80.0 g) in DMF (300 ml) in a similar manner described for **15r**. Yield, 24.5 g (79%). Pale yellow needles, mp 147—149° (from $CHCl_3$–MeOH). *Anal.* Calcd. for $C_{10}H_{10}O_3N_2S$: C, 50.41; H, 4.23; N, 11.76. Found: C, 50.45; H, 4.19; N, 11.61.

General Procedure of 3-Substituted 6-Amino-2,3-dihydro-2-oxobenzothiazoles (16q—s, 24, *cf.* Table I)——conc. HCl (20.0 g) was added dropwise to a stirred mixture of 6-nitro compound (0.1 mol), Fe powder (54.0 g) in water (360 ml) and EtOH (30 ml). The mixture was stirred at 90—100° for 2.5 hr, and EtOH (500 ml) was added. After stirring for 1 hr at the same temperature, the hot mixture was filtered and concentrated. The separated crystals were collected and dried. Recrystallization from an appropriate solvent gave the pure product as colorless crystals. Yield, 34—69%.

General Procedure of N-(Benzothiazolyl)aminomethylenemalonate Derivatives (17q—s, 25, *cf.* Table I)——A mixture of 6-amino compound (**16q, r** or **24**) (0.05 mol), diethyl ethoxymethylenemalonate (10.8 g) in Dow therm A (50 ml) was stirred at 90—100° for 3 hr and allowed to stand overnight at room temperature. The resulting precipitate was collected, washed with ether and recrystallized from an appropriate solvent to give the colorless product. Yield, 72—96%.

Table I. 6-Amino- and N-Substituted 6-Aminobenzothiazole Derivatives



Compd. No.	Substituents X	R	R′	mp (°C)	Appearance	Recrystn. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
16q	O	Me	H	188—189 (decomp.)	needles	AcOEt	$C_8H_8ON_2S$	53.31 (53.32)	4.47 (4.49)	15.55 (15.37)
24	S	Me	H	150—154	needles[a]	EtOH	$C_8H_8N_2S_2$	48.94 (49.28)	4.11 (4.09)	14.27 (14.56)
16r	O	Et	H	130—132	needles	Benzene	$C_9H_{10}ON_2S$	55.64 (55.60)	5.19 (5.13)	14.42 (14.15)
16s	O	Pr	H	77—80	needles	petr. ether–ether	$C_{10}H_{12}ON_2S$	57.66 (57.65)	5.81 (5.82)	13.45 (13.35)
17q	O	Me	BECV[b]	153—154	powder	MeOH	$C_{16}H_{18}O_5N_2S$	54.84 (54.61)	5.18 (5.14)	7.92 (7.81)
25	S	Me	BECV	223—226	needles[c]	$CHCl_3$–MeOH	$C_{16}H_{18}O_4N_2S_2$	52.44 (52.43)	4.95 (4.77)	7.64 (7.98)
17r	O	Et	BECV	124—127	needles	EtOH–ether	$C_{17}H_{20}O_5N_2S$	56.02 (56.28)	5.53 (5.59)	7.68 (7.50)
17s	O	Pr	BECV	94—96	powder	—	$C_{18}H_{22}O_5N_2S$	57.12 (56.99)	5.85 (5.74)	7.40 (7.18)

a) yellow needles
b) BECV=–CH=C(COOEt)$_2$
c) pale yellow needles

In the case of **16s**, the product did not precipitate from the reaction mixture after cooling. Then the reaction mixture was diluted with petro. ether and chromatographed on Al_2O_3 column. Dowtherm A was eluted with petro. ether and the product (**17s**) was obtained from the fraction eluted with benzene. Yield, 64%.

Cyclization of Diethyl N-(2,3-Dihydro-3-methyl-2-oxobenzothiazolyl)aminomethylenemalonate——A mixture of **17q** (2.05 g) in Dowtherm A (25 ml) was refluxed for 5 min. After cooling, the resulting precipitate was collected, washed with ether and dried to give a mixture (1.86 g; 86%) of **18q** and **19q** in 1: 1 ratio, mp> 300°. *Anal.* Calcd. for $C_{14}H_{12}O_4N_2S$: C, 55.25; H, 3.29; N, 2.21. Found: C, 55.68; H, 3.01; N, 2.58. The product above obtained showed two spots on TLC (Rf^2=0.45 and 0.68) and its NMR spectrum was shown in Fig. 1. The product (1.52 g) was added to a mixture of K_2CO_3 (4.14 g), EtI (4.65 g) in DMF (60 ml), and the reaction mixture was stirred for 2 hr at 90° and filtered. The filtrate was concentrated to dryness and the residue was extracted with $CHCl_3$. Concentration of the dried extract gave a mixture (0.93 g; 56%) of **3a** and **20**. The mixture was fractionated by the preparative TLC using $CHCl_3$-MeOH (10: 1). From the earlier fraction showed Rf^1=0.59, **3a** (125 mg) was obtained as needles, mp 259—262° (from MeOH). *Anal.* Calcd. for $C_{16}H_{16}O_4N_2S$: C, 57.81; H, 4.85; N, 8.43. Found: C, 57.88; H, 4.87; N, 8.27. NMR (CF_3-COOH) δ: 9.41 (1H, s, 7-H), 8.44 and 8.22 (each 1H, d, 4 and 5-H), 3.87 (3H, s, N–CH_3), 1.86 and 1.59 (each 3H, t, N–$CH_2\underline{CH_3}$ and O–$CH_2\underline{CH_3}$), 4.77 and 5.03 (each 2H, q, O–CH_2– and N–CH_2–). Mass Spectrum *m/e*: 332 (M^+), 287, 260, 231, 223, 185, 184, 149. These data were identical with those of a sample obtained from **1a**.

From the second fraction showed Rf^1 0.66, **20** (147 mg) was obtained as needles, mp 243—245° (from AcOEt–EtOH). *Anal.* Calcd. for $C_{16}H_{16}O_4N_2S$: C, 57.81; H, 4.85; N, 8.43. Found: 57.60; H, 4.71; N, 8.70. NMR (CF_3COOH) δ: 9.34 (1H, s, 7-H), 8.52 and 8.42 (each 1H, s, 4- and 9-H), 3.83 (3H, s, N–CH_3), 1.56 and 1.42 (each 3H, t, N–$CH_2\underline{CH_3}$ and O–$CH_2\underline{CH_3}$), 4.98 and 4.73 (each 2H, q, N–CH_2– and O–CH_2–). Mass Spectrum *m/e*: 332 (M^+), 287, 260, 245, 231, 203, 185, 184, 149.

8-Ethyl-2,3,5,8-tetrahydro-3-methyl-2,5-dioxothiazolo[4,5-*g*]quinoline-6-carboxylic Acid (21)——A suspension of **20** (0.111 g) in conc. HCl–90% AcOH (1: 11) (2 ml) was stirred at 100° for 2 hr. After evaporation of the solvent, the residue was crystallized from DMF–MeOH to give **21** (0.067 g; 66%) as pale yellow needles, mp 305° (decomp.). *Anal.* Calcd. for $C_{14}H_{12}O_4N_2S$: C, 55.25; H, 3.98; N, 9.21. Found: C, 55.05; H, 4.48; N, 9.58.

Cyclization of 17r, s——**17r** and **17s** were cyclized in a similar manner described in the case of **17q**. Each product was detected by TLC and NMR spectra to be a mixture of an angular quinoline derivative and a linear one.

Cyclization Products of **17r**: Yield 82%. mp>300°. *Anal.* Calcd. for $C_{15}H_{14}O_4N_2S$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.32; H, 4.64; N, 8.54. It showed two spots on TLC (Rf^1=0.52 and 0.59). NMR (CF_3COOH) δ: 8.18 and 8.36 (each d, 4-H and 5-H of **18r**), 8.38 and 8.45 (each s, 4-H and 9-H of **19r**), 1.3—1.8 (m, N-CH_2-$C\underline{H}_3$ and O-CH_2-$C\underline{H}_3$ of **18r** and **19r**), 4.2—5.0 (m, N-$C\underline{H}_2$-CH_3 and O-$C\underline{H}_2$-CH_3 of **18r** and **19r**) and 9.3—9.5 (broad s, 7-H of **18r** and **19r**). The intensity of the absorption signals due to the aromatic protons of **18r** and **19r** was observed in about 1: 1 ratio.

Cyclization Products of **17s**: Yield 78%. mp>300°. *Anal.* Calcd. for $C_{16}H_{16}O_4N_2S$: C, 57.80; H, 4.85; N, 8.43. Found: C, 58.02; H, 4.55; N, 8.03. It showed two spots on TLC (Rf^1=0.56 and 0.65). NMR (CF_3COOH) δ: 8.15 and 8.35 (each d, 4-H and 5-H of **18s**), 8.36 and 8.43 (each s, 4-H and 9-H of **19s**), 1.11 and 1.14 (each t, N-CH_2-$C\underline{H}_3$ of **18s** and **19s**), 1.6 (t, O-CH_2-$C\underline{H}_3$ of **18s** and **19s**), 2.0—2.1 (m, N-CH_2-$C\underline{H}_2$-CH_3 of **18s** and **19s**), 4.5—5.0 (m, N-$C\underline{H}_2$-CH_2-CH_3 and O-$C\underline{H}_2$-CH_3 of **18s** and **19s**), and 9.3—9.4 (broad s, 7-H of **18s** and **19s**). The intensity of the absorption signals due to the aromatic protons of **18s** and **19s** was observed in about 1: 1 ratio.

2,3-Dihydro-3-methyl-6-nitro-2-thioxobenzothiazole (23)——A mixture of **12** (22.6 g), Me_2SO_4 (26 g) in benzene (100 ml) was refluxed for 3 hr. After cooling, the precipitated quaternary salt was collected and dissolved in water (280 ml). H_2S was bubbled into the solution for 2.5 hr and the mixture was allowed to stand for 2 days. The product was collected and recrystallized from DMF–MeOH to give **23** (9.80 g; 61%) as pale yellow needles, mp 197—202°. *Anal.* Calcd. for $C_8H_6O_2N_2S_2$: C, 42.47; H, 2.67; N, 12.38. Found: C, 42.74; H, 2.60; N, 12.61.

Cyclization of Diethyl N-(2,3-Dihydro-3-methyl-2-thioxobenzothiazolyl)aminomethylenemalonate (25)——The compound, **25** (2.00 g), was refluxed for 15 min in Dowtherm A (20 ml). A mixture was obtained as a pale yellow precipitate (1.66 g; 95%), mp>300°. *Anal.* Calcd. for $C_{14}H_{12}O_3N_2S_2$: C, 52.50; H, 3.78; N, 8.74. Found: C, 52.09; H, 3.98; N, 8.58. It showed one spot on TLC (Rf^2=0.42). NMR (CF_3COOH) δ: 8.21 and 8.39 (each d, 4-H and 5-H of **26**), 8.30 and 8.38 (each s, 4-H and 9-H of **27**), 1.60 (t, O-CH_2-$C\underline{H}_3$ of **26** and **27**), 4.55—4.95 (m, O-$C\underline{H}_2$-CH_3 of **26** and **27**), 4.05 and 4.11 (each s, N-$C\underline{H}_3$ of **27** and **26**) and 9.30—9.45 (broad s, 7-H of **26** and **27**). The intensity of absorption signals due to the aromatic protons of **26** and **27** was observed in about 4: 1 ratio. The mixture (1.28 g) above obtained, K_2CO_3 (2.21 g), EtI (3.1 g), and DMF (40 ml) was stirred for 2 hr at 90—100°. After evaporation of the solvent, the residue was extracted with $CHCl_3$. The crude product obtained from the extract was recrystallized three times from DMF to give ethyl 6-ethyl-2,3,6,9-tetrahydro-3-methyl-9-oxo-2-thioxothiazolo[5,4-*f*]quinoline-8-carboxylate, **28** (0.27 g) as yellow needles, which was identified by comparing its IR spectrum with that of an authentic sample.[1] From the mother liquor, pure N-ethyl linear compound could not be obtained.

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