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Synthesis of Antimicrobial Agents. I. Synthesis and Antimicrobial Activities of Thiazoloquinoline Derivatives[1)]

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A series of substituted thiazolo[4,5-*g*]-, [5,4-*g*]-, [4,5-*h*]- and [5,4-*h*]quinoline carboxylic acids has been prepared by the following two methods with the aim of providing new antimicrobial drugs. One of the synthetic methods has been carried out through successive steps of condensation of aminobenzothiazole with diethyl ethoxymethylenemalonate, Gould-Jacobs reaction, N-alkylation and hydrolysis. The other is thiazole ring cyclization of *ortho*-aminated mercaptoquinoline. These compounds prepared in this work were evaluated for antimicrobial activities *in vitro*. 9-Chloro-8-ethyl-5,8-dihydro-5-oxothiazolo-[4,5-*g*]quinoline-6-carboxylic acid (**28b**) showed the highest activity.

Keywords——antimicrobial activity; thiazoloquinoline; 3-carboxy-4-pyridone; nitrobenzothiazole; ring-cyclization

Nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) and piromidic acid (8-ethyl-5,8-dihydro-5-oxo-2-pyrrolidinopyrido[2,3-*d*]pyrimidine-6-carboxylic acid) have antimicrobial activities especially against gram-negative bacilli and consequently have been clinically used in the treatment of urinary tract infections. Both compounds have 3-carboxy-4-pyridone moiety in common. Therefore, many compounds having this partial structure were synthesized for new drug research.

In the course of our studies on the synthesis of antimicrobial agents, our interest was focussed on thiazoloquinoline carboxylic acids. Thiazolo[5,4-*f*]- and [4,5-*f*]quinolines were already reported by Dohmori[3)] and Nagano,[4)] respectively. The present paper is concerned with the synthesis of thiazolo[4,5-*g*]-, [5,4-*g*]-, [4,5-*h*]- and [5,4-*h*]quinoline derivatives possessing the remaining four ring systems, and their antimicrobial activities.

Two methods are anticipated to be suitable for synthesizing the thiazoloquinoline derivatives; one is the condensation of an aminobenzothiazole with ethyl ethoxymethylenemalonate (EMME) followed by pyridine ring cyclization of the resulted condensate (method A), and the other is thiazole ring cyclization of an *ortho*-aminated mercaptoquinoline (method B).

1) This work was presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, 1978.
2) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
3) R. Dohmori, S. Kadoya, I. Takamura, and N. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **24**, 130 (1976).
4) Y. Nagano, M. Murakami, and F. Miyamoto, Japan Kokai 73-61500 (1973) [*Chem. Abstr.* **80**, 59929 (1974)].

Synthesis of Aminobenzothiazoles

In method A, thermal cyclization of the condensates of 5- and 6-aminobenzothiazoles with EMME afforded thiazolo[4,5-*f*]-[4] and [5,4-*f*]quinolines,[3] respectively. This kind of cyclization is liable to give angular type products. In our studies to obtain linear type products, thiazolo[4,5-*g*]- and [5,4-*g*]quinolines, 4-substituted 5-amino- and 7-substituted 6-aminobenzothiazoles were used as the starting materials which were synthesized according to the processes shown in Chart 1.

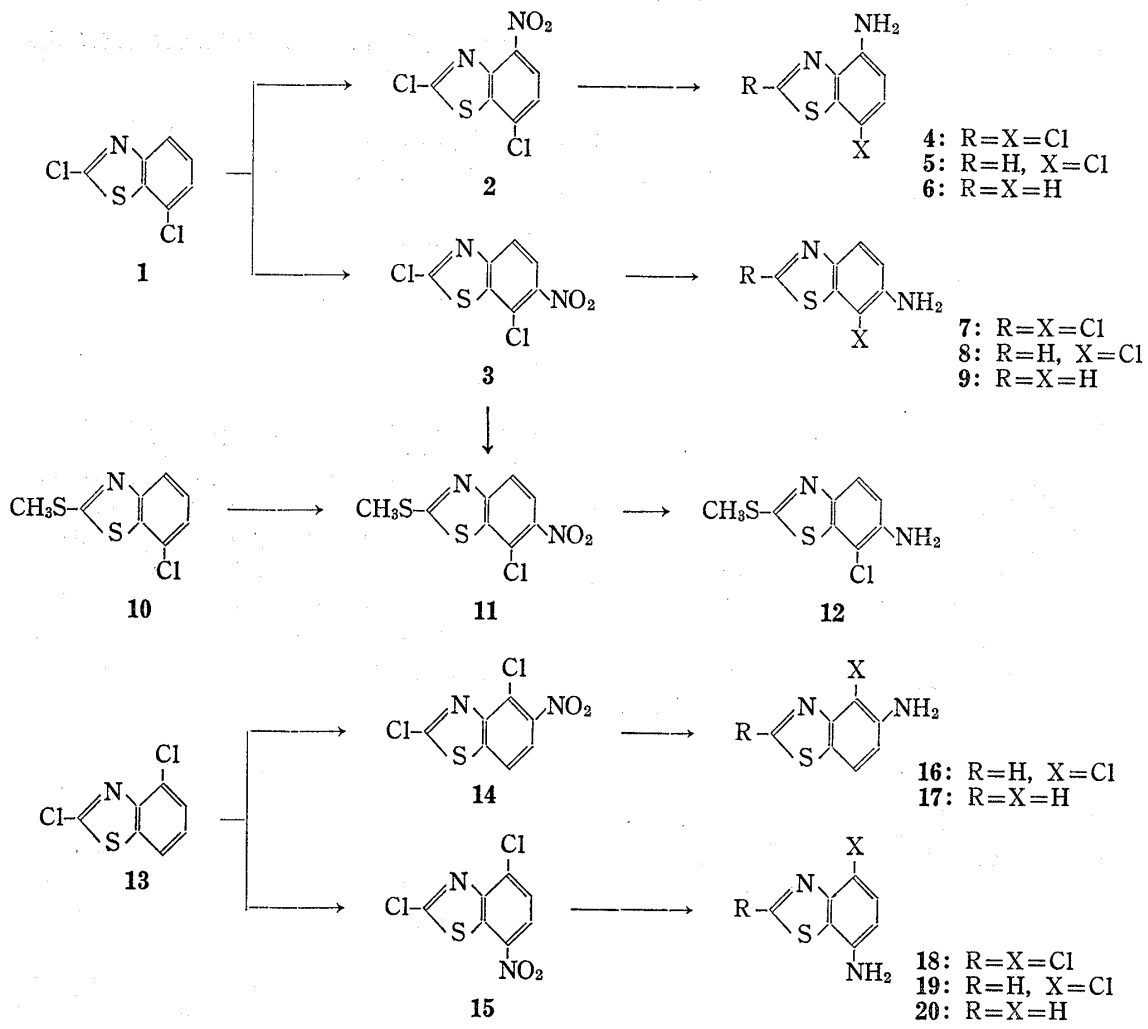


Chart 1

2,7-Dichlorobenzothiazole (**1**) was nitrated with conc. HNO_3 in conc. H_2SO_4 to afford a mixture of the two nitro derivatives in approximately equal ratio. Both derivatives were purified by recrystallization and column chromatography to give 2,7-dichloro-4-nitrobenzothiazole (**2**), mp 104—106°, and 2,7-dichloro-6-nitrobenzothiazole (**3**), mp 174—176°. The nuclear magnetic resonance (NMR) spectra of these nitro derivatives showed *ortho*-coupling quartet, so nitro groups are substituted at the 4- and the 6-position. Reduction of **3** with red phosphorus and hydroiodic acid gave known 6-aminobenzothiazole (**9**). Therefore, the other is the 4-nitro derivative (**2**).

The nitro groups of **2** and **3** were reduced to the amino groups by three methods; Fe in HCl, and red phosphorus in HI under mild conditions accompanying dechlorination on the thiazole ring, and under drastic conditions accompanying dechlorination on both the thiazole and the benzene rings, to give 2,7-dichloro-4-aminobenzothiazole (**4**), 7-chloro-4-aminobenzo-

thiazole (**5**) and 4-aminobenzothiazole (**6**) from **2**, and 2,7-dichloro-6-aminobenzothiazole (**7**), 7-chloro-6-aminobenzothiazole (**8**) and 6-aminobenzothiazole (**9**) from **3**, respectively.

Nitration of 7-chloro-2-methylmercaptobenzothiazole (**10**) with conc. HNO_3 in conc. H_2SO_4 gave exclussively 7-chloro-2-methylmercapto-6-nitrobenzothiazole (**11**). Its structure was confirmed by mixed melting point test with the reaction product of **3** with sodium methylmercaptide. Compound **11** was reduced to 6-amino-7-chloro-2-methylmercaptobenzothiazole (**12**) with Fe and HCl.

2,4-Dichlorobenzothiazole (**13**) was nitrated with fum. HNO_3 in conc. H_2SO_4 to yield a mixture of the two nitrated derivatives, which were separated by recrystallization and column chromatography to give 2,4-dichloro-5-nitrobenzothiazole (**14**), mp 167—168°, and 2,4-dichloro-7-nitrobenzothiazole (**15**), mp 116—117°. The positions of the nitro groups were determined by deriving **14** and **15** to known 5-amino- (**17**) and 7-aminobenzothiazole (**20**) by reduction with red phosphorus and HI under drastic condition.

4-Chloro-5-aminobenzothiazole (**16**) was obtained by reducing **14** with red phosphorus and HI under mild conditions. Compound **15** was reduced to 7-amino-2,4-dichlorobenzothiazole (**18**) by Fe and HCl, and to 7-amino-4-chlorobenzothiazole (**19**) by red phosphorus and HI under mild conditions.

Thiazolo[4,5-*g*]quinolines

Aminobenzothiazoles **7**, **8** and **12** were used for the synthesis of the 9-substituted thiazolo-[4,5-*g*]quinoline derivatives by method A as shown in Chart 2. Heating **7**, **8** and **12** with EMME in EtOH gave the condensates, **25a**, **25b** and **25d**, respectively. Thermal cyclization of these condensates (**25a**, **25b** and **25d**) in Dowtherm A afforded thiazolo[4,5-*g*]quinoline (**26a**, **26b** and **26d**). The desired N-ethyl derivative, **27b**, was exclusively obtained from the reaction of **26b** with ethyl iodide in the presence of K_2CO_3 in dimethylformamide (DMF). However, from **26d** were derived desired **27d** together with the O-ethyl derivative (**27d'**). The structure of **27d'** was confirmed by converting **26d** with $POCl_3$ to the chlorinated derivative (**29**) followed by treating with NaOEt. On the contrary, ethylation of **26a** afforded only the O-ethyl derivative (**27e'**) in which the chlorine atom at the 2-position was replaced with dimethylamine arising from DMF. The structure of **27e'** was confirmed by obtaining **27e'** from **27d'** by oxidation of the methylmercapto group to the methylsulfonyl, followed by replacement of the latter with a dimethylamino group.

The N-ethyl esters, **27b** and **27d** thus obtained, were hydrolyzed by HCl in aqueous AcOH to the corresponding carboxylic acids, **28b** and **28d**, respectively.

Compound **27d** was oxidized with $KMnO_4$ to the methylsulfonyl derivative (**30**), treatment of which with pyrrolidine, followed by hydrolysis gave the acid (**32**), *via* the ester (**31**).

The 9-unsubstituted thiazolo[4,5-*g*]quinoline derivatives were synthesized according to method B as shown in Chart 3. The 7-chloro-6-nitro derivative (**41**)[5] was reduced by Fe and AcOH to give the amino derivative (**42**). Compound **42** was heated with KOH in aqueous MeOH saturated with H_2S and the intermediate thus obtained was heated in HCOOH to afford the desired acid (**43**) in 15.4% yield from **42**.

Thiazolo[5,4-*g*]quinolines

According to method A as shown in Chart 2, condensation of **16** with EMME gave **33b**, which afforded the ester (**34b**) by heating in boiling Dowtherm A. Ethylation of **34b** in the usual manner afforded only 5.7% of the N-ethyl derivative (**35b**), which was hydrolyzed in HCl–AcOH to give the acid (**36b**). One of the reasons of the low yield in the ethylation may be due to the steric hindrance of the chlorine atom at the 4-position.

5) N. Barton, A.F. Crowther, W. Hepworth, D.N. Richardson, and G.W. Driver, Brit. Patent, 830832 (1960) [*Chem. Abstr.*, **55**, 7442 (1961)].

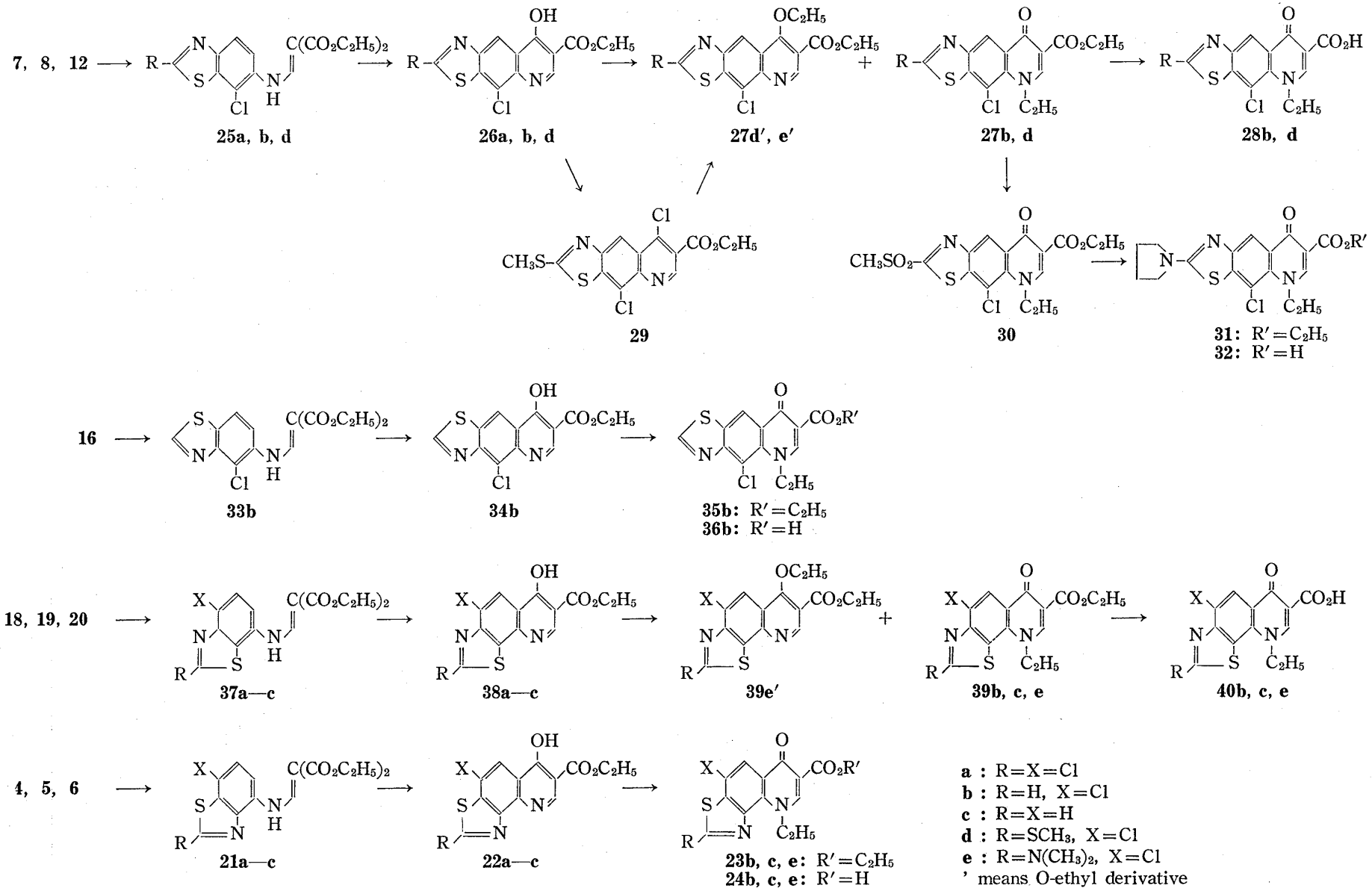


Chart 2

Other derivatives of this series were synthesized according to method B as shown in Chart 3. To synthesize the 6-chloro-7-nitroquinoline derivative (**48**), 3-nitro-4-chloroaniline (**44**) was used as a starting material. Compound **44** was heated with EMME to give the condensate (**45**), which was cyclized in Dowtherm A to afford a mixture of **46** and **47** in approximately equal ratio. Because of being unable to be purified due to their insolubility, both were converted to the N-ethyl derivatives (**48** and **49**), which were separated by column chromatography. The structure of desired **48** was confirmed by the NMR spectrum which exhibited three singlets assignable to aromatic protons. After reduction of **48**, the amino derivative (**50**) was heated with carbon disulfide resulting in thiazole ring cyclization to give the 2-mercapto derivative (**51**), which was methylated without further purification to the acid (**52**) in poor yield from **50**. The acid (**52**) was oxidized with $KMnO_4$ to the methylsulfonyl derivative (**53**), which was treated with pyrrolidine to afford the 2-pyrrolidino derivative (**54**).

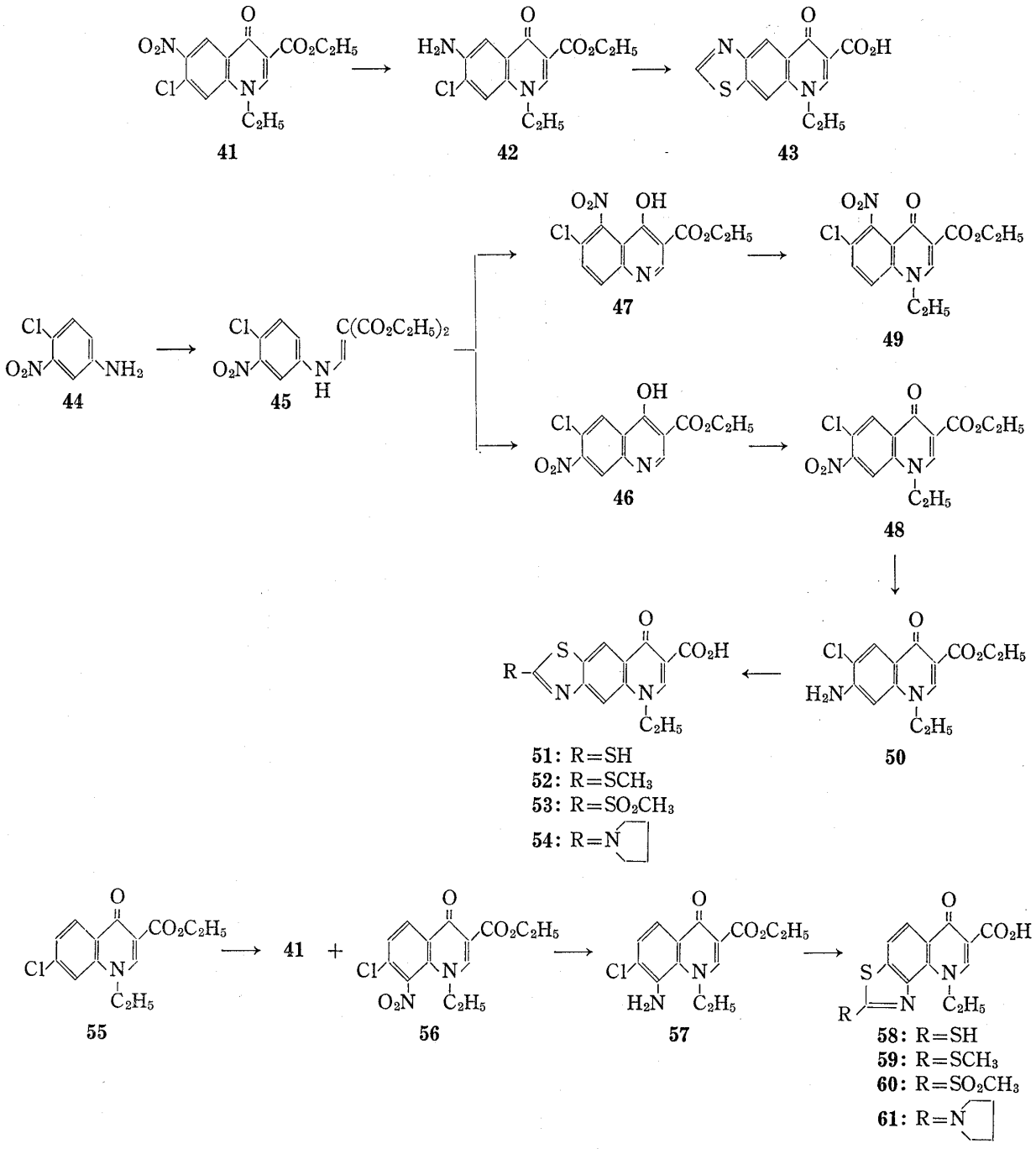


Chart 3

Thiazolo[4,5-*h*]quinolines

The derivatives possessing this ring system were synthesized according to method A (see Chart 2). Aminobenzothiazoles used in this case were **19**, **20** and **18**. In the case of **19** and **20**, successive condensation, cyclization, ethylation and hydrolysis in a manner similar to those for the preparation of **28b** and **28d** afforded the acids, **40b** and **40c** *via* **37b,c**, **38b,c** and **39b,c**, respectively. Condensation of **18** with EMME, followed by cyclization of the condensate (**37a**) afforded the thiazolo[4,5-*h*]quinoline (**38a**) which was allowed to react with ethyl iodide to give a mixture of the O-ethyl (**39e'**) and the N-ethyl (**39e**) derivatives, accompanying the exchange of the chlorine atom at the 2-position with dimethylamine arising from DMF. Compound **39e** was hydrolyzed to the acid (**40e**). The yields in the N-ethylation of **38a**, **38b** and **38c** were low in general.

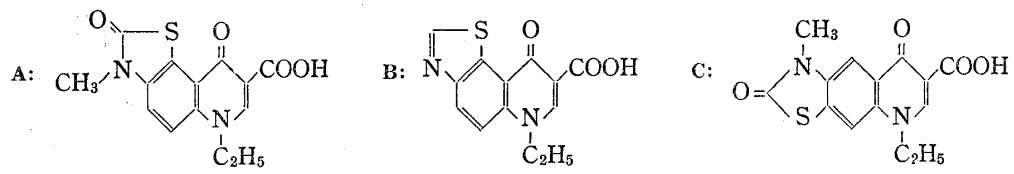
Thiazolo[5,4-*h*]quinolines

This kind of derivatives were synthesized by method A and B. Aminobenzothiazoles used in method A were **4**, **5** and **6** (see Chart 2). From these aminobenzothiazoles, the acids **24e**, **24b** and **24c** were synthesized by the usual way described above. The chlorine atom at the 2-position of **22a** was replaced by the dimethylamino group when **22a** was applied to ethylation in DMF. As was distinct from the case of thiazolo[4,5-*h*]quinoline derivatives, ethylation of the cyclized products, **22a**, **22b** and **22c** afforded the corresponding N-ethyl derivatives, **23e**, **23b** and **23c**, in high yields.

Thiazolo[5,4-*h*]quinolones were also synthesized according to method B (see Chart 3). Nitration of ethyl 7-chloro-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (**55**)[5] afforded a mixture of the 6-nitro derivative (**41**) and the 8-nitro one (**56**). The nitro group in **56** must be situated in the 8-position because its NMR spectrum showed *ortho* coupling quartet. Reduction of **56** with Fe in AcOH afforded the amino derivative (**57**), which was applied to thiazole ring cyclization. Treatment of **57** with carbon disulfide and Na in methylcarbitol

Table I. Antimicrobial Activities (MIC, μg/ml)

Type	Compd. No.	*Staph. aureus*	*E. coli*	*Sh. flexneri*	*Pr. mirabilis*	*Ps. aeruginosa*
[4, 5-*g*]	**28b**	6.25	1.56	1.56	0.39	>100
	28d	>100	>100	>100	>100	>100
	32	6.25	>100	>100	>100	>100
	43	>100	12.5	3.13	1.56	>100
[5, 4-*g*]	**36b**	>100	>100	>100	>100	>100
	52	>100	>100	>100	>100	>100
	54	>100	>100	>100	>100	>100
[4, 5-*h*]	**40e**	>100	>100	>100	>100	>100
	40b	>100	25	>100	>100	>100
	40c	>100	25	6.25	50	>100
[5, 4-*h*]	**24e**	6.25	>100	>100	>100	>100
	24c	>100	12.5	3.13	3.13	>100
	59	>100	>100	>100	>100	>100
	61	>100	>100	>100	>100	>100
	A[7]	3.13	<0.2	<0.2	<0.2	50
	B[3]	>100	50	12.5	6.25	>100
	C[8]	>100	>100	>100	>100	>100
	Nalidixic acid	>100	3.13	6.25	6.25	>100



followed by methylation with methyl iodide gave the thiazolo[5,4-*h*]quinoline derivative (**59**). Compound **59** was oxidized with $KMnO_4$ to **60**, which was treated with pyrrolidine to give the 2-pyrrolidino derivative (**61**).

All carboxylic acids prepared in this work were tested for their antimicrobial activities *in vitro* and these data are listed in Table I as minimum inhibitory concentration (MIC, μg/ml). MICs were measured by the serial agar dilution method.[6] Among them, **28b** exhibited high activities against four pathogens tested except for *Ps.* aeruginosa. We have reported that the thiazolone derivative (**A**)[7] showed far higher activity than the thiazole (**B**)[3] in a series of [5,4-*f*] type thiazoloquinolines. With respect to [4,5-*g*] type compounds, however, the thiazolone (**C**)[8] exhibited no sufficient activity, whereas the thiazole (**28b**) possesses excellent activity against tested bacteria. These results suggest that the activities of the condensed quinoline carboxylic acids are closely affected by the bulkiness of substituents and the condensing position of the fused ring.

Experimental

All melting points are uncorrected. NMR spectra were recorded on a Hitachi Perkin Elmer R-20B NMR spectrometer using tetramethylsilane as an internal standard.

Nitration of 2,7-Dichlorobenzothiazole (1)——To a solution of **I** (20.0 g) in conc.H_2SO_4 (50 ml) was added dropwise a mixture of conc.HNO_3 (d, 1.42, 10.0 g) and conc.H_2SO_4 (7 g) below 5°. After stirring the reaction mixture at room temperature for 2 hr, it was poured onto ice and the precipitate was filtered. The dried crude products were applied onto a silica-gel column and eluted with light petroleum–benzene (10: 1) and subsequently with benzene. The former eluate was evaporated to dryness and the residue was crystallized from benzene–light petroleum to afford 2,7-dichloro-6-nitrobenzothiazole (3) (4.8 g), mp 174—176° (NMR in $CDCl_3$ (δ); 7.92 (1H, d, J=9 Hz), 8.18 (1H, d, J=9 Hz)). From the latter eluate, 2,7-dichloro-4-nitrobenzothiazole (2) (5.7 g), mp 104—106° (NMR in $CDCl_3$ (δ); 7.55 (1H, d, J=9 Hz), 8.23 (1H, d, J=9 Hz)) was obtained by crystallization of the residue from light petroleum-benzene.

Nitration of 7-Chloro-2-methylmercaptobenzothiazole (10)——To a solution of **10** (17.5 g) in conc.H_2SO_4 (100 ml) was added dropwise a mixture of conc.HNO_3 (d, 1.42, 12.0 g) and conc. H_2SO_4 (12.4 g) keeping the reaction temperature below 12°. After stirring of the reaction mixture for 3 hr at 10—20°, it was poured onto ice and the resulting precipitate was collected by filtration. Crystallization of the crude product (1.61 g, 76.0%) from EtOH gave light yellow needles, 7-chloro-2-methylmercapto-6-nitrobenzothiazole (**11**), mp 171—172°.

7-Chloro-2-methylmercapto-6-nitrobenzothiazole (11)——Compound **3** (300 mg) was added to 20% aqueous solution of CH_3SNa, and the mixture was stirred at room temperature for 2 hr. The precipitate formed was filtered and recrystallized from $CHCl_3$–EtOH to give light yellow needles (**11**) (111 mg, 35.4%), mp 169—171° (undepressed on admixture with a sample prepared by nitration of **10**).

Nitration of 2,4-Dichlorobenzothiazole (13)——Compound **13** (47.0 g) was dissolved in conc.H_2SO_4 (130 ml) and to the cooled solution was added dropwise a mixture of fum.HNO_3 (30 ml) and conc.H_2SO_4 (20 ml) below 10°. The reaction mixture was stirred for 4 hr at room temperature, and poured onto ice. The products were extracted with $CHCl_3$, and the extract was washed with H_2O, dried over Na_2SO_4 and

Table II

Product	Reaction time (hr)	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4	2			*a*)						
7	3	72.9	132—133	$C_7H_4Cl_2N_2S$	38.37	1.84	12.79	38.22	1.92	12.83
12	3	82.4	97—98	*a*)						
18	2	94.2	190 (dec.)	$C_7H_4Cl_2N_2S$	38.37	1.84	12.79	38.53	1.79	12.75

a) Structures of the aminobenzothiazoles were confirmed as their condensates in the next step.

6) MIC Committee of Japan Society of Chemotherapy, *Chemotherapy*, **22**, 1126 (1974).
7) S. Kadoya, N. Suzuki, I. Takamura, and R. Dohmori, *Chem. Pharm. Bull.* (Tokyo), **24**, 147 (1976).
8) N. Suzuki, S. Kadoya, and R. Dohmori, *Chem. Pharm. Bull.* (Tokyo), **24**, 1050 (1976).

concentrated *in vacuo*. On standing at room temperature, the precipitated 2,4-dichloro-7-nitrobenzothiazole (**15**) (4.2 g) was collected by filtration. The filtrate was concentrated to dryness, and the residue dissolved in light petroleum was chromatographed on silica-gel using light petroleum–benzene (10: 1) and subsequently benzene as eluents. From the former eluate, **15** (11.8 g), mp 116—118° (NMR in $CDCl_3$ (δ); 7.72 (1H, d, J=9 Hz), 8.39 (1H, d, J=9 Hz)), was also obtained, and from the latter, 2,4-dichloro-5-nitrobenzothiazole (**14**) (5.0 g), mp 167—168°.

Reduction of Nitrobenzothiazoles by Fe and HCl——To a suspension of nitrobenzothiazole (0.1 mol) in H_2O (350 ml) and conc.HCl (17.5 ml) was added portionwise Fe powder (17.5 g) with stirring keeping the temperature at 80—100°. The mixture was continued to stir and heat at the same temperature for 2—3 hr. $CHCl_3$ was added to the mixture and the insoluble materials were removed by filtration. The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The product thus obtained was crystallized from aqueous EtOH (Table II).

Reduction of Nitrobenzothiazoles by Red Phosphorus and HI——a) Dichloronitrobenzothiazole was added to a mixture of red phosphorus (1.0—1.5 time weight), H_2O (4—5 times volume), AcOH (4—5 times volume) and 58% HI (10—15 times volume), and the mixture was gently heated to reflux for 1—2 hr. To the reaction mixture was added H_2O and refluxing was continued for further 1 hr. The insoluble material was removed by filtration and the filtrate was made alkaline. The precipitate formed was purified by column chromatography and crystallization. Structures of aminobenzothiazoles containing one chlorine atom on the benzene ring thus obtained were confirmed as these condensates (**25b**, **33b**, **37b** and **21b**) in the next step.

b) Dichloronitrobenzothiazole was applied to the reaction in a manner similar to those described in a) except that the reaction mixture was vigorously refluxed for 4 hr. Purification of the crude products by crystallization and column chromatography afforded 4-amino- (**6**, mp 89—92°),[9] 5-amino- (**17**, mp 70—73°),[10] 6-amino (**9**, mp 82—84°)[10] and 7-amino- (**20**, mp 122—124°)[10] benzothiazoles.

Condensation of Aminobenzothiazoles with EMME——To aminobenzothiazole dissolved in EtOH was added equimolar weight of EMME and the solution was heated at 80° with stirring for 1—2 hr. The resulted precipitate on cooling was filtered and crystallized from suitable solvent (Table III).

Table III

Product	Yield (%)	mp (°C)	Recryst. Solvent	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
21a	65.8	142—143	$CHCl_3$–EtOH–ether	$C_{15}H_{14}Cl_2N_2O_4S$	46.28	3.62	7.20	45.87	3.67	7.11
21b	85.5	178—179	EtOH	$C_{15}H_{15}ClN_2O_4S$	50.77	4.26	7.90	50.96	4.10	8.03
21c	93.8	166—168	EtOH	$C_{15}H_{16}N_2O_4S$	56.23	5.03	8.75	56.47	5.07	8.67
25a	86.4	148—150	benzene light petr.	$C_{15}H_{14}Cl_2N_2O_4S$	46.28	3.62	7.20	46.11	3.72	7.23
25b	95.4	166—167	$CHCl_3$–EtOH	$C_{15}H_{15}ClN_2O_4S$	50.77	4.26	7.90	51.22	4.24	7.98
25d	77.9	167—168	EtOH	$C_{16}H_{17}ClN_2O_4S_2$	47.93	4.28	6.99	47.82	4.30	7.13
33b	88.6	184—186	EtOH	$C_{15}H_{15}ClN_2O_4S$	50.77	4.26	7.90	50.63	4.21	8.05
37a	84.5	129—130	EtOH	$C_{15}H_{14}Cl_2N_2O_4S$	46.28	3.62	7.20	46.45	3.53	7.41
37b	78.7	137—139	EtOH	$C_{15}H_{15}ClN_2O_4S$	50.77	4.26	7.90	50.66	4.25	8.08
37c	93.8	92—93	EtOH	$C_{15}H_{16}N_2O_4S$	56.23	5.03	8.75	55.94	4.98	8.62

Pyridine Ring Cyclization of the Condensates——To boiling Dowtherm A (10—30 times volume) was added a condensate and the mixture was heated at 250° for 10—30 min. After cooling, the precipitate was filtered and crystallized from DMF to give thiazoloquinoline (Table IV).

Ethylation of the Cyclization Products——A mixture of a cyclization product, K_2CO_3 (1.5—3.0 mol ar equivalent) and EtI (2.0—4.0 mol ar equivalent) in DMF was heated at 100—120° with stirring. After evaporation of the solvent, the residue was treated with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and the solvent was removed. The crude product was purified by silica-gel chromatography followed by crystallization from $CHCl_3$–EtOH (Table V).

9) H. Erlenmeyer and H. Ueberwasser, *Helv. Chim. Acta*, 23, 328 (1940).
10) T. Nishizawa, *Yakugaku Zasshi*, 62, 47 (1942).

TABLE IV

Product	Reaction Time (min)	Yield (%)	mp (C°)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
22a	30	78.2	303—305	$C_{13}H_8Cl_2N_2O_3S$	45.49	2.35	8.16	45.43	2.37	8.21
22b	10			*a*)						
22c	10	77.2	270—271	$C_{13}H_{10}N_2O_3S$	56.92	3.67	10.22	56.65	3.76	10.43
26a	15	85.2	>300	$C_{13}H_8Cl_2N_2O_3S$	45.49	2.35	8.16	45.26	2.69	8.21
26b	10	60.3	>300	$C_{13}H_9ClN_2O_3S$	50.57	2.94	9.08	50.53	2.98	9.18
26d	12	85.7	305—310	$C_{14}H_{11}ClN_2O_3S_2$	47.39	3.13	7.90	47.50	3.22	8.16
34b	15	81.1	>300	$C_{13}H_9ClN_2O_3S$	50.57	2.94	9.08	50.48	2.99	9.28
38a	15	85.7	>300	$C_{13}H_8Cl_2N_2O_3S$	45.49	2.35	8.16	45.77	2.41	8.48
38b	15	100	>300	$C_{13}H_9ClN_2O_3S$	50.57	2.94	9.08	50.74	2.97	9.20
38c	15	93.0	295(dec.)	$C_{13}H_{10}N_2O_3S$	56.92	3.67	10.22	56.66	3.79	10.53

a) Structure of the product was confirmed as its N-ethyl derivative in the next step.

TABLE V

Product	Reaction time(hr)	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
23e	2	77.9	241—243	$C_{17}H_{18}ClN_3O_3S$			*b*)			
23b	3	73.7[a)]	256—258	$C_{15}H_{13}ClN_2O_3S$	53.49	3.89	8.32	53.43	4.04	8.24
23c	2	79.2	163—164	$C_{15}H_{14}N_2O_3S$	59.58	4.67	9.27	59.41	4.62	9.19
27e'	2	21.0	178—180	$C_{17}H_{18}ClN_3O_3S$			*b*)			
27b	3	63.7	199	$C_{15}H_{13}ClN_2O_3S$			*b*)			
27d	1.5	61.7	164—166	$C_{16}H_{15}ClN_2O_3S_2$	50.19	3.95	7.32	50.02	4.15	7.53
27d'	1.5	33.0	151—153	$C_{16}H_{15}ClN_2O_3S_2$	50.19	3.95	7.32	49.99	4.00	7.27
35b	2	5.7	199—201	$C_{15}H_{13}ClN_2O_3S$	53.49	3.89	8.32	53.22	3.76	8.34
39e	3	40.3	240—241	$C_{17}H_{18}ClN_3O_3S$	53.75	4.78	11.06	54.16	4.84	11.17
39e'	3	26.4	237—239	$C_{17}H_{18}ClN_3O_3S$			*b*)			
39b	2	23.6		$C_{15}H_{13}ClN_2O_3S$			*b*)			
39c	2	28.6	244—246	$C_{15}H_{14}N_2O_3S$	59.58	4.67	9.27	59.27	4.62	9.39

a) Total yield of cyclization and ethylation.
b) Structure of the product was confirmed as its acid in the next step.

TABLE VI

Product	Reaction time(hr)	Yield (%)	mp (°C)	Recryst. Solvent	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
24e	1	57.0	>300	(A)	$C_{15}H_{14}ClN_3O_3S$	51.21	4.11	11.94	51.26	4.08	11.97
24b	2	79.7	>300	(A)	$C_{13}H_9ClN_2O_3S$	50.57	2.94	9.08	50.78	3.21	9.55
24c	1	42.1	>300	(A)	$C_{13}H_{10}N_2O_3S$	56.92	3.67	10.22	56.09	3.62	10.11
28b	2	65.0	>300	(A)	$C_{13}H_9ClN_2O_3S$	50.57	2.94	9.08	50.63	3.00	9.17
28d	2	38.6	>300	(A)	$C_{14}H_{11}ClN_2O_3S_2$	47.39	3.13	7.90	47.60	3.39	8.00
32	1.5	40.2	>300	(A)	$C_{17}H_{17}ClN_3O_3S$	54.04	4.27	11.12	54.26	4.33	11.59
36b	45	56.0	276—278	(B)	$C_{13}H_9ClN_2O_3S$	50.57	2.94	9.08	50.33	3.12	9.37
40e	2	64.0	>300	(A)	$C_{15}H_{14}ClN_3O_3S$	51.21	4.11	11.94	51.27	4.08	12.33
40b	1	58.5	>300	(B)	$C_{13}H_9ClN_2O_3S$	50.57	2.94	9.08	50.39	2.90	9.38
40c	2	58.2	>300	(A)	$C_{13}H_{10}N_2O_3S$	56.92	3.67	10.22	57.22	3.77	10.43

(A); DMF. (B); DMF–EtOH.

Hydrolysis of N-Ethylated Esters——Ester was dissolved in 1 N HCl–85% AcOH (10—20 times volume), and the solution was gently refluxed for a few hours. To the reaction mixture was added H_2O and the precipitate was collected and crystallized from DMF or a mixture of DMF and EtOH (Table VI).

Ethyl 5,9-Dichloro-2-methylmercaptothiazolo[4,5-*g*]quinoline-6-carboxylate (29)——A mixture of **26d** (3.0 g) in $POCl_3$ (20 ml) and DMF (4 ml) was heated at 80—90° for 1 hr and poured into ice-water. The product was extracted with $CHCl_3$ and crystallized from EtOH to give **29** (2.3 g, 73%), mp 166—168°. *Anal.* Calcd. for $C_{14}H_{10}Cl_2N_2O_2S_2$: C, 45.11; H, 2.70; N, 7.51. Found: C, 45.42; H, 2.87; N, 7.33.

Ethyl 9-Chloro-5-ethoxy-2-methylmercaptothiazolo[4,5-*g*]quinoline-6-carboxylate (27d′)——Compound **29** (746 mg) was added to NaOEt solution (50 mg of Na in 10 ml of EtOH) and the suspension was stirred at room temperature for 3 hr and then at 40—50° for 1 hr. The precipitate was collected and crystallized from EtOH to afford **27d′** (257 mg, 33.6%), mp 151—153°, which agreed with the authentic sample obtained by ethylation of **26d.**

Ethyl 9-Chloro-2-dimethylamino-5-ethoxythiazolo[4,5-*g*]quinoline-6-carboxylate (27e′)——To a suspension of **27d′** (3.1 g) in AcOH (40 ml) was added dropwise an aqueous solution of $KMnO_4$ (4.5 g) at 45—50°. The solution was stirred for 30 min and treated with $NaHSO_3$. The precipitate was collected and crystallized from benzene–EtOH to give the corresponding methylsulfonyl derivative (2.36 g, 70.0%), mp 158—159°. *Anal.* Calcd. for $C_{16}H_{15}ClN_2O_5S_2$: C, 46.32; H, 3.64; N, 6.75. Found: C, 46.40; H, 3.66; N, 6.58.

To a solution of the above compound (200 mg) in DMF (5 ml) was added a mixture of 40% dimethylamine (1 ml) and EtOH (5 ml). The solution was stirred for 3 hr at 100°. The precipitate formed was collected and crystallized from $CHCl_3$–EtOH to give **27e′** (145 mg, 80.1%), mp 180—181°. *Anal.* Calcd. for $C_{17}H_{18}ClN_3O_3S$: C, 53.75; H, 4.78; N, 11.06. Found: C, 53.85; H, 4.76; N, 11.05.

8-Ethyl-5,8-dihydro-5-oxo-2-pyrrolidinothiazolo[4,5-*g*]quinoline-6-carboxylic Acid (31)——To a suspension of **27d** (420 mg) in AcOH (5 ml) was added an aqueous solution of $KMnO_4$ (1.0 g) at 30—40°. The solution was stirred for 1 hr and treated with $NaHSO_3$. The precipitate was collected and crystallized from $CHCl_3$–EtOH to give the corresponding methylsulfonyl derivative (**30**) (215 mg, 47.3%), mp 213—215°. *Anal.* Calcd. for $C_{16}H_{15}ClN_2O_5S_2$: C, 46.32; H, 3.64; N, 6.75. Found: C, 46.15; H, 3.70; N, 6.85.

Compound **30** (174 mg) was heated with pyrrolidine (52 mg) in EtOH (10 ml) for 1.5 hr. The precipitate was collected and crystallized from $CHCl_3$–EtOH to give the corresponding pyrrolidino derivative (**31**) (141 mg, 83.9%), mp 269—270°. *Anal.* Calcd. for $C_{16}H_{15}ClN_2O_5S_2$: C, 55.22; H, 4.97; N, 10.35. Found: C, 56.03; H, 4.95; N, 10.21.

8-Ethyl-5,8-dihydro-5-oxothiazolo[4,5-*g*]quinoline-6-carboxylic Acid (43)——A mixture of **41** (8.0 g) and powdered Fe (15 g) in AcOH (300 ml) was heated at 80° for 1 hr with vigorous stirring. The insoluble material was removed off and the filtrate was concentrated. To the brown oily residue was added H_2O. The insoluble amino derivative (**42**) was collected and crystallized from $CHCl_3$–MeOH to give light yellow needles (6.5 g, 89.5%), mp 167—170°. *Anal.* Calcd. for $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; N, 9.61. Found: C, 56.48; H, 4.97; N, 9.76.

Compound **42** (20.0 g) in MeOH was added to a solution of KOH (1.6 g) in H_2O (3 ml) and MeOH (30 ml) saturated with H_2S, and the mixture was heated to reflux for 1 hr. After evaporation of MeOH, the resulted aqueous solution was acidified with AcOH and the precipitate was filtered, which was heated to reflux in HCOOH (20 ml) for 5 hr. After cooling, the needles resulted were collected and crystallized from DMF to give **43** (287 mg, 15.4%), mp>300°. *Anal.* Calcd. for $C_{13}H_{10}N_2O_3S$: C, 56.92; H, 3.67; N, 10.22. Found: C, 56.97; H, 3.77; N, 10.19. NMR in CF_3COOH (δ); 1.87 (3H, t), 5.08 (2H, q), 9.29, 9.65, 9.73 and 10.42 (each 1H, s).

2-Substituted 5-Ethyl-5,8-dihydro-8-oxothiazolo[5,4-*g*]quinoline-7-carboxylic Acids (52 and 54)——Heating a mixture of **44** (51.8 g) and EMME (71.3 g) afforded the condensate (**45**) (95.5 g, 92.8%), 50 g of which was heated in boiling Dowtherm A (250 ml) for 30 min. Upon cooling to room temperature, the mixture resulted in appearance of deposit (35 g) as a mixture of the two products (**46** and **47**), which was treated with K_2CO_3 (74 g) and EtI (91 g) in DMF (250 ml) with stirring at 110—120° for 3 hr. DMF was evaporated to dryness *in vacuo*, and the residue was extracted with $CHCl_3$. The products were separated by silica-gel chromatography to afford 13.4 g of **49**, mp 186—188°, (NMR in CF_3COOH (δ): 8.56 (2H, s), 9.69 (1H, s)), and 15.0 g of **48**, mp 184—186°, (NMR in CF_3COOH (δ); 8.89 (1H, s), 9.06 (1H, s), 9.69 (1H, s)). *Anal.* Calcd. for $C_{14}H_{13}ClN_2O_5$: C, 51.78; H, 4.03; N, 8.63. Found: C, 51.30; H, 4.02; N, 8.58.

To a solution of **48** (8.0 g) in AcOH (300 ml) was added powdered Fe (15 g) portionwise with stirring keeping the temperature at 85—90°. After the mixture was stirred for 1.5 hr, the insoluble materials were removed. The filtrate was concentrated and poured into ice-water. The precipitate was collected and crystallized from DMF to afford the amino derivative (**50**) (6.6 g, 90.9%), mp>300°. *Anal.* Calcd. for $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; N, 9.51. Found: C, 56.97; H, 5.13; N, 9.58.

A mixture of **50** (1.0 g), Na (230 mg) and CS_2 (1.0 ml) in methylcarbitol was heated at 160° for 6 hr. The solution was poured into H_2O and acidified with HCl. The precipitate formed was filtered and added to a mixture of NaOH (500 mg) and MeI (1.0 ml) in H_2O (20 ml). The solution was stirred at 100° for 30 min, and acidified with HCl. The precipitate was collected and crystallized from DMF to afford **52** (160 mg, 14.8%), mp>300°. *Anal.* Calcd. for $C_{14}H_{12}N_2O_3S_2$: C, 52.48; H, 3.78; N, 8.75. Found: C, 52.66; H, 3.78; N, 8.32.

To a suspension of **52** (500 mg) in AcOH (15 ml) was added dropwise an aqueous solution of $KMnO_4$ (1.5 g). After stirring of the solution at room temperature for 2 hr, it was treated with $NaHSO_3$. The insoluble **53** was collected and heated in a mixture of pyrrolidine (0.5 ml) and DMF (3 ml) at 120—130° for 1 hr. The solvent was distilled off and the residue was crystallized from DMF to afford 30 mg (5.5%) of the 2-pyrrolidino derivative (**54**), mp 300°. *Anal.* Calcd. for $C_{17}H_{17}N_3O_3S \cdot 1/2\ H_2O$: C, 57.97; H, 5.15; N, 11.92. Found: C, 57.23; H, 4.83; N, 11.76.

2-Substituted 4-Ethyl-4,7-dihydro-7-oxothiazolo[5,4-*h*]quinoline-6-carboxylic Acids (59 and 61)——To a solution of **55** (10.5 g) in conc.H_2SO_4 (60 ml) was added dropwise the mixed acids of fum.HNO_3 (6 ml) and conc.H_2SO_4 (6 ml), and the reaction mixture was stirred for 4 hr at room temperature and then for 30 min at 40°. The solution was poured into ice-water and the products were extracted with $CHCl_3$. Chromatographic separation of the mixture with elution by benzene–$CHCl_3$ afforded **41** (6.7 g, 55.0%) and desired **56** (3.7 g, 30.4%) (NMR in CF_3COOH (δ); 8.94 (1H, d, J=9 Hz), 8.17 (1H, d, J=9 Hz)).

Compound **56** (4.0 g) was dissolved in AcOH (150 ml) at 80—90°, and powdered Fe (7.5 g) was added portionwise to the solution. After the reaction mixture was heated at the same temperature for 1.5 hr, EtOH (100 ml) was added to it, and the insoluble materials were removed. Evaporation of the solvents and crystallization of the residue by $CHCl_3$–EtOH afforded **57** (2.8 g, 77.7%), mp>300°. *Anal.* Calcd. for $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; N, 9.51. Found: C, 57.08; H, 4.99; N, 9.52.

Na (460 mg) was dissolved in methylcarbitol (12 ml), and to the solution were added **57** (1.17 g) and CS_2 (2 ml). The reaction mixture was gently refluxed for 6.5 hr and then poured into H_2O (20 ml). NaOH (1 g) and MeI (1.0 ml) were added to the solution and stirring was continued at 30—40° for 1 hr. After the solution was acidified with HCl, the precipitate formed was collected and crystallized from DMF to afford **59**, mp>300°. *Anal.* Calcd. for $C_{14}H_{12}N_2O_3S_2$: C, 52.48; H, 3.78; N, 8.75. Found: C, 52.37; H, 3.82; N, 8.60.

To a suspension of **59** (90 mg) in AcOH (3 ml) was added an aqueous solution of $KMnO_4$ (300 mg) and the mixture was stirred for 1 hr at room temperature. After the mixture was treated with $NaHSO_3$, the precipitate was filtered. Without further purification the crude methylsulfonyl derivative (**60**) was dissolved in a solution of DMF (1.0 ml), EtOH (0.5 ml) and pyrrolidine (0.1 ml), and stirred at 100—110° for 1 hr. The precipitate was collected and crystallized from DMF to give 25 mg (26.0%) of **61**, mp>300°. *Anal.* Calcd. for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24. Found: C, 58.21; H, 5.05; N, 11.86.

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