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Synthesis of Antimicrobial Agents. III.[1] Synthesis and Antimicrobial Activities of Thiazolo[5,4-*b*]naphthyridine Derivatives

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In order to search for new antimicrobial agents, a number of 2-substituted 8-ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic acid and their related compounds which consist of a new ring system were prepared.

Reactions of the 6-amino-1-ethyl-7-mercapto-1,4-dihydro-4-oxonaphthyridine-3-carboxylic acid (**2**) with acid, acid anhydride, acid chloride and ethylxanthate afforded several thiazolo[5,4-*b*]naphthyridine derivatives. Refluxing ethyl 7-chloro-1-ethyl-6-nitro-1,4-dihydro-4-oxonaphthyridine-3-carboxylate (**16**) with KSCN in acetic acid gave directly the thiazole cyclization product **19**. Reaction of 8-ethyl-2-methylthio-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic acid (**11**) with dimethyl sulfate gave various products (**13b**, **25** and **26**) depending upon its reaction conditions.

Some compounds obtained in this work exhibited high activities against gram-negative and gram-positive bacteria *in vitro*.

Keywords——antimicrobial activity; thiazolo[5,4-*b*]naphthyridine; 3-carboxy-4-pyridone moiety; thiazole-cyclization; thiazolium salt; 6-amino-7-mercaptonaphthyridine; 7-chloro-6-nitronaphthyridine

In part I[3] of this series, we reported that 8-ethyl-9-chloro-5,8-dihydro-5-oxothiazolo[4,5-*g*]quinoline-6-carboxylic acid (A, X=Cl) showed high antibacterial activities against gram-negative bacteria and also moderate activities against some gram-positive bacteria. This finding prompted us to synthesize thiazolo[5,4-*b*]naphthyridine derivatives (B) which were expected to show better absorption from gastrointestinal tract than that of A.

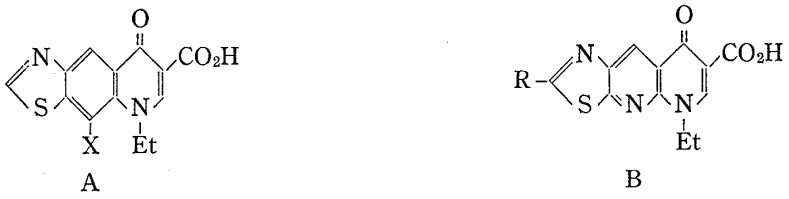


Fig. 1

For the synthesis of thiazolo[5,4-*b*]naphthyridine derivatives which consist of a new ring system, ethyl 6-amino-7-chloro-1-ethyl-1,4-dihydro-4-oxonaphthyridine-3-carboxylate(**1**)[1] was chosen as a starting material. Treatment of **1** with aqueous sodium hydrosulfide afforded the 6-amino-7-mercapto carboxylic acid **2**. Using **2** containing bifunctional groups, we synthesized various 2-substituted thiazolo[5,4-*b*]naphthyridine derivatives as shown in the following Chart 1.

Refluxing **2** with 98% formic acid (or ethyl orthoformate) gave colorless needles in good yield. Its nuclear magnetic resonance (NMR) spectrum (CF_3COOH) exhibited a singlet signal at 10.20 ppm which was assignable to the proton of the 2 position in the thiazole ring. Its ultraviolet (UV) spectrum revealed a maximum at 354 mμ was quite different from those of substituted naphthyridines. From those spectroscopic data and elemental analysis, this

1) Part II: N. Suzuki, M. Kato, and R. Dohmori, *Yakugaku Zasshi*, **99**, 155 (1979).
2) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
3) Part I: N. Suzuki, Y. Tanaka, and R. Dohmori, *Chem. Pharm. Bull.* (Tokyo), 27, 1 (1979).

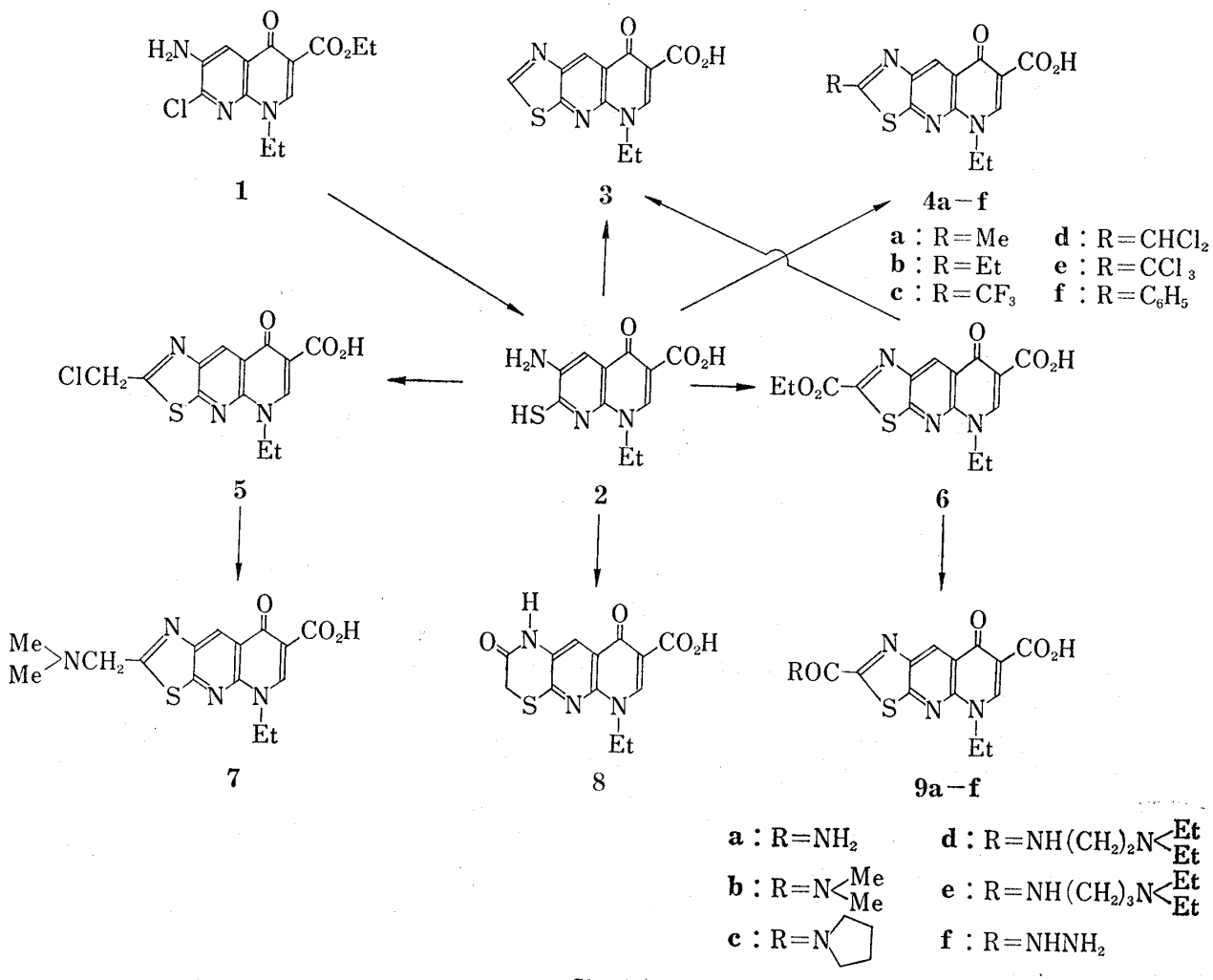


Chart 1

compound was determined to be a cyclized product, 8-ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]-naphthyridine-6-carboxylic acid (**3**). In a similar procedure, reaction of **2** with benzoyl chloride gave the 2-phenyl derivative **4f**.

In the cases of reactions of **2** with acetic anhydride, propionyl chloride, trifluoroacetic anhydride, dichloroacetyl chloride, trichloroacetyl chloride, chloroacetyl chloride and ethyl oxalyl chloride, the reaction mixture was warmed at 50° for 0.5—1 hr and then concentrated. Refluxing the reaction intermediates in dimethylformamide (DMF) afforded the corresponding cyclized products (**4a—e**, **5**, **6**) (Table II). The structures of **4a—f** were confirmed by the resemblance of the absorption patterns in their infrared (IR) spectra to that of **3** and by elemental analysis. The structure of the product **5** which was obtained from **2** and chloroacetyl chloride was established as follows. Compound **5** reacted readily with dimethylamine to give the 2-dimethylaminomethyl derivative **7**. On the other hand **2** was converted with ethyl bromoacetate into the lactam derivative **8**, the IR spectrum of which showed an absorption band at 1670 cm^{-1} (lactam C=O) supporting the presence of a lactam group resulted from ring closure. Since it was different from **5** in the physical properties, **5** was concluded to be 2-chloromethyl thiazolo[5,4-*b*]naphthyridine-6-carboxylic acid. Compound **6** was treated with amines and hydrazine to give the 2-carbamoyl-6-acids **9a—e** and the 2-hydrazinocarbonyl-6-acid **9f**, respectively (Table III). Reaction of **6** with sodium hydroxide or ammonia in aqueous ethanol and DMF afforded the decarboxylated product **3** which was identical with the sample obtained by reaction of **2** with formic acid. From the results of these reactions, **6** was concluded as 2-ethoxycarbonyl-8-ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic acid.

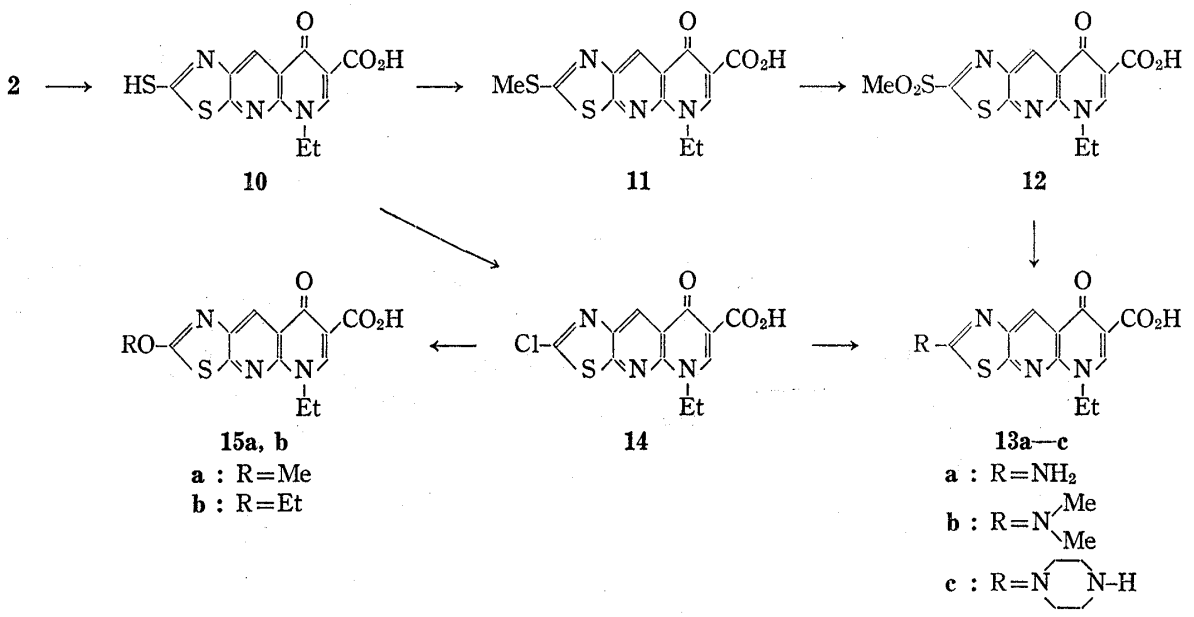


Chart 2

Synthetic routes for the 2-amino, the N-substituted amino and the alkoxy derivatives were shown in Chart 2.

Treatment of **2** with potassium ethylxanthate in ethanol resulted in ring closure to afford 2-mercapto-thiazolo[5,4-*b*]naphthyridine derivative (**10**) in good yield. Alkylation of **10** with methyl iodide in alkaline medium at room temperature gave the 2-methylthio-6-acid **11**. It is evident that the product was not N-methyl but S-methyl derivative, from the fact that it was oxidized with potassium permanganate to give the methylsulfonyl-6-acid **12**. Heating **12** with ammonia, dimethylamine and piperazine gave the corresponding 2-amino derivatives **13a—c**. Treatment of **10** with sulfuryl chloride at room temperature afforded the 2-chloro-6-acid **14**. Compounds **13a—c** were also prepared from **14** with amines. The structure of **13a** obtained here was shown to be identical with the compound by another synthetic route described later. Reaction of **14** with sodium alkoxide gave the 2-alkoxy derivatives **15a, b.**

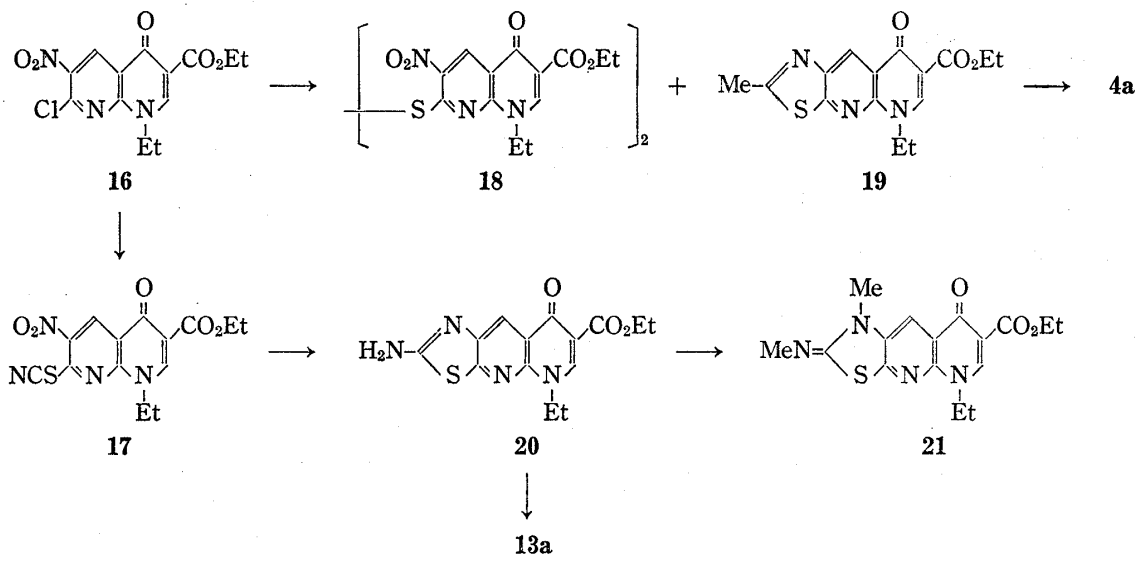


Chart 3

In the case of reaction of 6-nitro-7-chloro derivative **16**[1] with potassium thiocyanate in glacial acetic acid, various products were formed depending upon its reaction temperature. Reaction of **16** under the mild conditions (70—80°) afforded quantitatively the 6-nitro-7-

thiocyanate ester **17** which displayed on a characteristic band at 2180 cm^{-1} due to the SCN streching in the IR spectrum. On the other hand, when **16** was heated with potassium thiocyanate in acetic acid under gentle refluxing until the spots of starting material and **17** disappeared on thin-layer chromatography (TLC), an anomalous reaction occurred. The products obtained by this reaction were purified by recrystallization and column chromatography. The structure of the minor product (mp above 300°) which was insoluble in alkaline medium was elucidated as the disulfide **18** by elemental analysis. The NMR spectrum of the main product exhibited a singlet signal (3H) at 3.27 ppm due to the 2-methyl group of the thiazole ring. It was converted into the corresponding acid **4a** which was identical with an authentic sample prepared from the reaction of the amino thiol **2** with acetic anhydride. Therefore the structure of the main product was determined to be ethyl 8-ethyl-2-methyl-5, 8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylate (**19**). It is much interesting that **16** afforded **19** by one step reaction.

Formation of **19** from **16** will be explained as followes. The intermediate **17** was converted to the corresponding 6-nitro-7-mercapto derivative by hydrolysis, which partly afforded the above disulfide **18** by oxidation, and subsequent reduction of the nitro group occurred to give 6-amino-7-mercapto derivative, then cyclization by acetic acid led to the final product **19**.

Compound **17** was cyclized to ethyl 2-amino-8-ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]-naphthyridine-6-carboxylate (**20**) by reduction with iron powder and acetic acid, which was subsequently converted to the corresponding carboxylic acid (**13a**) by acid hydrolysis. It was identical with the product obtained by the reaction of the 2-methylsulfonyl derivative **12** with ammonia. Alkylation of the ester **20** with methyl iodide in DMF in the presence of potassium carbonate gave the 2-methylimino derivative **21**. Since **21** was different from the 2-dimethylamino ester **22** described below in the physical properties, it was proved that the methylation of **20** took place at 2-amino and thiazole ring nitrogen (Chart 3).

Recently we reported that 8-ethoxycarbonyl-6,9-dihydro-3-methyl-2-methylthio-9-oxothiazolo[5,4-*f*]quinolinium methylsulfate, showing that the methylthio group is convertible

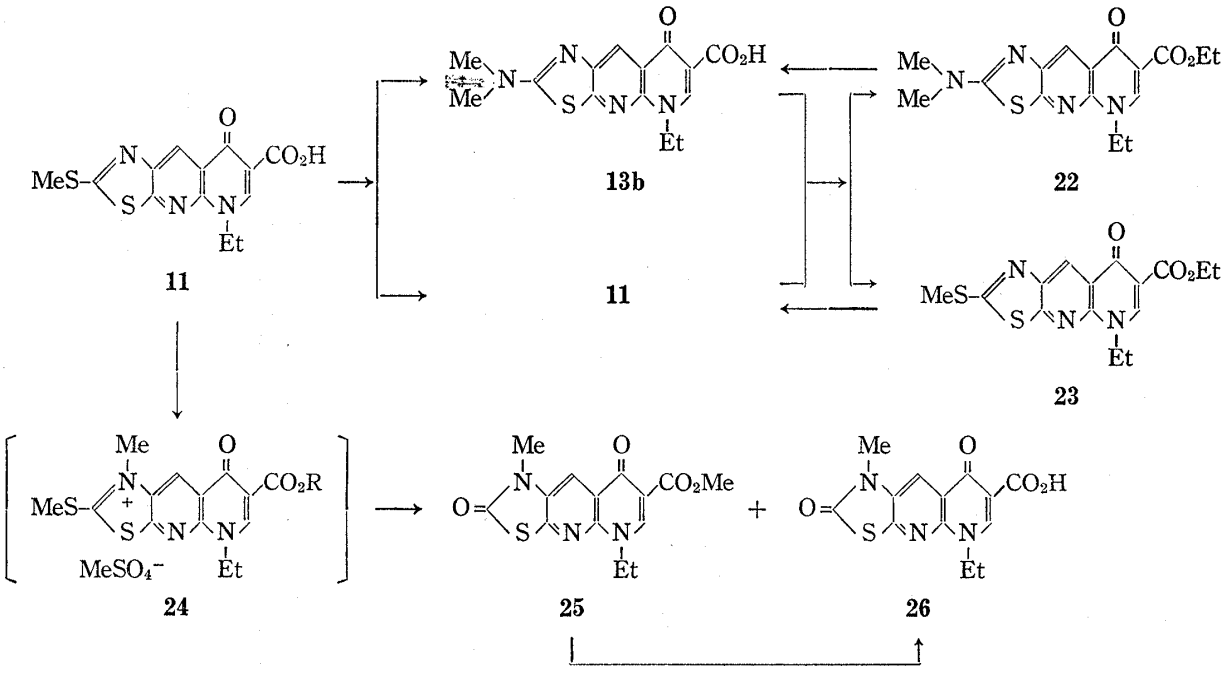


Chart 4

4) N. Suzuki, S. Kadoya, and R. Dohmori, *Chem. Pharm. Bull.* (Tokyo), **24**, 1050 (1976).

into the 2-oxo group.[4] We applied this reaction to the synthesis of the thiazolo[5,4-*b*]naphthyridine derivatives. Reaction of **11** with dimethyl sulfate gave various products depending upon its reaction condition.

At first the compound **11** was heated with dimethyl sulfate in DMF at 120° for 30 hr and the mixture obtained showed two spots on TLC. One of the components was presumed by *Rf*-value of TLC to be unchanged **11**. The products were difficult to separate from each other, because they were sparingly soluble in various organic solvents. Therefore the mixture was converted, *via* its acid chloride, into the corresponding esters (**22**, **23**) and they were separated by silica gel chromatography. The compound **23** (mp 222—224°) changed to the starting material (**11**) by hydrolysis. Another compound was hydrolyzed with acid to the corresponding acid. The NMR spectrum of this acid indicates the presence of a dimethylamino group and absence of methylmercapto group, so its structure was presumed to be **13b**. Its IR spectrum was identical with that of an authentic sample prepared from 2-methylsulfonyl derivative (**12**) with dimethylamine. The substitution reaction of the 2-methylmercapto group of the thiazole ring to dimethylamino group under the above reaction conditions is of interest. Secondly, the compound **11** was heated at 140—150° for 40 hr with dimethyl sulfate without solvent. The resulting precipitate was collected and washed with water. The water-insoluble material revealed the formula of $C_{14}H_{13}N_3O_4S$ from its elemental analysis. Furthermore the IR spectrum showed maxima at 1680 cm^{-1} (C=O) and 1665 cm^{-1} (C=O). The relatively low frequency at 1665 cm^{-1} was attributable to the amide carbonyl group. The NMR spectrum (CF_3COOH) showed two singlet signals at 4.23 and 3.78 ppm assignable to methyl groups. From the above spectral data, it was concluded to be methyl 8-ethyl-3-methyl-2,3,5,8-tetrahydro-2,5-dioxothiazolo[5,4-*b*]naphthyridine-6-carboxylate (**25**).

On the other hand, treatment of the aqueous layer containing the thiazolium salt **24** with aqueous sodium hydroxide at room temperature, liberating methyl mercaptane, produced the Na-salt of the 2-oxo-acid **26**. The product was identical with **26** obtained by hydrolysis of the above ester **25** (Chart 4).

The *in vitro* antibacterial activity of thiazolo[5,4-*b*]naphthyridine derivatives obtained in this work was tested by the serial dilution method.[5] The minimum inhibitory concentrations of several active derivatives are illustrated in Table I and none of the others showed

Table I. Antibacterial Activity (M.I.C. mcg/ml)

Compd. No.	Organism				
	Staphylococcus aureus 209P	*Escherichia coli* NIHJ	*Shigella flexneri* 2a 5503	*Proteus mirabilis* 1287	*Pseudomonas aeruginosa* 2063
3	3.13	0.2	0.39	0.2	50
4a	50	25	25	3.13	>100
4b	>100	>100	>100	25	>100
4c	100	50	25	12.5	>100
4e	>100	>100	100	50	>100
5	>100	>100	100	50	>100
6	>100	>100	>100	50	>100
10	>100	>100	12.5	12.5	>100
11	>100	>100	>100	6.3	>100
12	>100	>100	>100	50	>100
13b	12.5	>100	>100	>100	>100
14	12.5	12.5	6.25	6.25	>100
Compd. A (X=H)	100	12.5	3.13	1.56	>100
Compd. A (X=Cl)	6.25	1.56	1.56	0.39	>100

5) MIC Committee of Japan Society of Chemotherapy, *Chemotherapy*, **22**, 1126 (1974).

significant activities against all of the bacteria listed. The activity of these compounds was markedly varied with the substituent at the 2 position of the thiazole ring. The substitution with a bulky group appears to decrease the activity. 8-Ethyl-5,8-dihydro-5-oxothiazolo-[5,4-*b*]naphthyridine-6-carboxylic acid (**3**) unsubstituted on the thiazole ring exhibited the highest activity in this series against gram-negative bacteria including *Pseudomonas aeruginosa*. This result is quite similar to that observed in the series of thiazolo[4,5-*g*]quinoline derivatives.[3] Compound **3** was also showed more potent activity than those of the corresponding quinoline derivative (A, X=H) and its chloro analog (A, X=Cl).

Experimental

All melting points were uncorrected. IR spectra were measured with discs in potassium bromide, using a Hitachi EPI 285 IR spectrophotometer. NMR spectra were recorded on a Hitachi Perkin Elmer R-20B NMR spectrometer using tetramethylsilane as an internal standard. Abbreviation: s=singlet, d=doublet, t=triplet and m=multiplet. Mass spectra were run on a Hitachi Mass spectrometer Model RMU-6D.

6-Amino-1-ethyl-7-mercapto-1,4-dihydro-4-oxonaphthyridine-3-carboxylic Acid (**2**)——A suspension of **1**[1] (10.0 g) and NaSH hydrate (5.0 g) in water (50 ml) was stirred at 90—100° for 5 hr. The solid separated on acidification, was recrystallized from DMF to give **2** (7.4 g, 83%) as yellow powder, mp above 300°. *Anal.* Calcd. for $C_{11}H_{11}N_3O_3S$: C, 49.80; H, 4.18; N, 15.84. Found: C, 49.52; H, 4.31; N, 15.58.

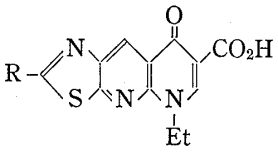
8-Ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic Acid (**3**)——i) A suspension of **2** (6.0 g) in 98% HCOOH (60 ml) was heated to reflux for 5 hr. After cooling, separated crystals (5.2 g, 94%) were recrystallized from DMF to give **3** as colorless needles, mp above 300°. NMR (CF_3COOH) ppm: 10.20 (1H, s), 9.77 (1H, s), 9.93 (1H, s), 5.24 (2H, q), 1.85 (3H, t). UV λ_{max}^{EtOH} mμ: 354, 272, 236.

ii) A suspension of **6** (0.14 g) in 10% NaOH (4 ml) and EtOH (2 ml) was heated to reflux for 1 hr. The separated solid on acidification was recrystallized from DMF to give **3** (0.052 g, 43%), mp above 300°, identical with the sample obtained above.

iii) A mixture of **6** (0.10 g), conc. -NH_4OH (5 ml), EtOH (3 ml) and DMF (2 ml) was refluxed for 1 hr. A small amount of insoluble materials was removed by filtration and filtrate was concentrated *in vacuo*. Recrystallization of the residue from DMF to give **3** (0.023 g, 29%) as colorless needles, mp above 300°, identical with the sample obtained above.

2-Substituted 8-Ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic Acid (4a—f, 5 and 6)——i) To a stirred suspension of **2** (0.40 g) in CCl_4 (2 ml) a solution of EtO_2CCOCl (1 ml) in CCl_4 (2 ml) was added at room temperature. After stirring for 0.5 hr, the reaction mixture was warmed at 50° for 0.5 hr. The excess reagent and the solvent were removed *in vacuo* to give an intermediate of this reaction, which was heated to reflux in DMF for 5 min. After cooling, separated crystals were collected. Recrystallization from DMF gave **6** (0.39 g, 75%) as pale yellow needles. mp 280—286°.

Table II. 2-Substituted Thiazolo[5,4-*b*]naphthyridine-6-carboxylic Acid



Compd. No.	R	Reagent	mp[a] (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
3	H	HCOOH	>300	94	$C_{12}H_9N_3O_3S$	52.35	3.30	15.26	52.15	3.50	15.34
4a	Me	$(CH_3CO)_2O$	>300	63	$C_{13}H_{11}N_3O_3S$	53.94	3.83	14.52	54.20	4.02	14.64
4b	Et	EtCOCl	261—264	54	$C_{14}H_{13}N_3O_3S$	55.43	4.32	13.85	55.43	4.42	14.16
4c	F_3C	$(CF_3CO)_2O$	263 (dec.)	28	$C_{13}H_8F_3N_3O_3S$	45.48	2.35	12.24	45.23	2.51	12.21
4d	Cl_2HC	$Cl_2HCCOCl$	245—249	60	$C_{13}H_9Cl_2N_3O_3S$	43.59	2.53	11.73	43.73	2.59	12.03
4e	Cl_3C	Cl_3CCOCl	259—261	7	$C_{13}H_8Cl_3N_3O_3S$	39.76	2.05	10.70	39.98	2.21	11.07
4f	H_5C_6	H_5C_6COCl	>300	65	$C_{18}H_{13}N_3O_3S$	61.53	3.73	11.96	61.57	3.80	11.92
5	ClH_2C	ClH_2CCOCl	285—288	69	$C_{13}H_{10}ClN_3O_3S$	48.26	3.11	12.98	48.37	3.15	13.35
6	EtO_2C	EtO_2CCOCl	280—286	75	$C_{15}H_{13}N_7O_5S$	51.87	3.77	12.10	51.69	3.73	12.24

a) All compounds were recrystallized from DMF.

ii) In a manner similar to that described above, the reaction of **2** with acetic anhydride, propionyl chloride, trifluoroacetic anhydride, dichloroacetyl chloride trichloroacetyl chloride or chloroacetyl chloride gave **4a—f** and **5**, respectively. Details are summarized in Table II.

2-Dimethylaminomethyl-8-ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic Acid (7)——A mixture of **5** (80 mg) and 40% aq. dimethylamine (0.5 ml) in EtOH (5 ml) was heated at 100° in a sealed tube for 15 min. The excess reagent and the solvent were evaporated and the solid separated was recrystallized from DMF to give **7** (34 mg, 42%) as pale yellow needles, mp 260—267° (dec.). *Anal.* Calcd. for $C_{15}H_{16}N_4O_3S$: C, 54.20; H, 4.85; N, 16.86. Found: C, 54.09; H, 5.01; N, 16.82.

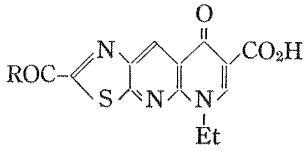
9-Ethyl-3,4,6,9-tetrahydro-3,6-dioxo-2*H*-thiazino[2,3-*b*]naphthyridine-7-carboxylic Acid (8)——A mixture of **2** (0.2 g), ethyl bromoacetate (0.3 g) and DMF (5 ml) was heated at 120—130° for 0.5 hr. After cooling, the deposited solid was collected, washed and dried. Recrystallization from DMF gave **8** (0.13 g, 58%) as colorless needles, mp above 300°. *Anal.* Calcd. for $C_{13}H_{11}N_3O_4S$: C, 51.14; H, 3.63; N, 13.76. Found: C, 50.90; H, 3.66; N, 13.85. IR (cm^{-1}) KBr: 1670 (lactam C=O), 1703 (COOH).

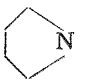
Amidation of 2-Ethoxycarbonyl Derivative (6) giving 2-Carbamoyl and 2-(N-Substituted)carbamoyl Derivatives (9a—f) (Table II)——i) A mixture of **6** (0.20 g) and 8% NH_3–EtOH (4 ml) in DMF (2 ml) was heated in a sealed tube at 100—110° for 5 hr. The deposited solid on cooling was recrystallized from DMF to give **9a** (0.10 g, 55%) as colorless needles, mp above 300°.

ii) A mixture of **6** (0.15 g) and 40% aq. diethylamine (2 ml) in DMF–EtOH (1 : 1) (6 ml) was refluxed for 5 min and concentrated. The residue was recrystallized from DMF to give **9b** (0.09 g, 86%) as pale yellow needles, mp above 300°.

iii) The compounds **9c—f** were prepared in a manner similar to that described above. Yields of the products and their analytical data are recorded in Table III.

Table III. 2-Carbamoyl and 2-N-Substituted Carbamoyl-Thiazolo[5,4-*b*]-naphthyridine-6-Carboxylic Acids



Compd. No.	R	mp[a] (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
9a	H_2N	>300	55	$C_{13}H_{10}N_4O_4S$	49.05	3.17	17.60	48.91	3.22	17.26
9b	Me_2N	>300	86	$C_{15}H_{14}N_4O_4S$	52.01	4.07	16.18	51.60	4.12	16.25
9c		295—300	60	$C_{17}H_{16}N_4O_4S$	54.83	4.33	15.05	54.46	4.67	14.89
9d	$Et_2N(CH_2)_2HN$	>300	36	$C_{19}H_{23}N_5O_4S$	54.66	5.55	16.78	54.48	5.60	16.41
9e	$Et_2N(CH_2)_3HN$	241—243	35	$C_{20}H_{25}N_5O_4S$	55.67	5.84	16.23	55.55	5.76	16.17
9f	H_2NHN	>300	31	$C_{13}H_{11}N_5O_4S$	46.84	3.33	21.01	46.67	3.16	20.83

a) All compounds were recrystallized from DMF.

8-Ethyl-2-mercapto-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic Acid (10)——A solution of ethylxanthate was prepared by dissolving KOH (225 mg) in H_2O (2 ml) and EtOH (25 ml) and by subsequent addition of CS_2 (2 ml) with shaking. To this solution, **2** (633 mg) was added and the mixture was heated under reflux for 4 hr. After being heated, the reaction mixture was filtered and the filtrate was acidified with AcOH. The solid obtained was recrystallized from DMF to give **10** (463 mg; 62%) as yellow needles, mp above 300°. *Anal.* Calcd. for $C_{12}H_9N_3O_3S_2 \cdot H_2O$: C, 44.99; H, 3.46; N, 13.11. Found: C, 45.43; H, 2.94; N, 13.17.

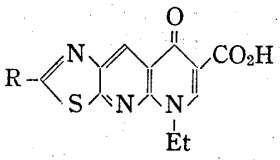
8-Ethyl-2-methylthio-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic Acid (11)——To a solution of **10** (0.45 g) in 50% EtOH (4 ml) containing KOH (0.25 g) was added MeI (1.0 g). The reaction mixture was stirred at room temperature for 2.5 hr. Water was added to the reaction mixture and a small amount of insoluble materials were removed by filtration and the filtrate was acidified with dil. HCl. The product deposited was recrystallized from DMF to give **11** (0.33 g, 70%) as colorless needles, mp 284—285°. *Anal.* Calcd. for $C_{13}H_{11}N_3O_3S_2$: C, 48.58; H, 3.45; N, 13.08. Found: C, 48.60; H, 3.41; N, 13.08.

8-Ethyl-2-methylsulfonyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic Acid (12)——To a suspension of **11** (3.0 g) in AcOH (150 ml) was added dropwise 7.5% aq. $KMnO_4$ solution (36 ml) with stirring at 20—30°. The suspension was further stirred at the same temperature for 2 hr, and then treated with $NaHSO_3$. Water was added to the suspension and the product deposited was recrystallized from DMF–EtOH to give **12** (2.8 g, 85%) as pale yellow needles, mp 290° (dec.). *Anal.* Calcd. for $C_{13}H_{11}N_3O_5S_2$: C, 44.18; H, 3.14; N, 11.89. Found: C, 44.38; H, 3.30; N, 12.25.

2-Amino and 2-Alkylamino-8-ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic Acids (13a—c) (Table IV)——i) A solution of **12** (42 mg) and 30% aq. dimethylamine (1 ml) in EtOH (3 ml) was refluxed for 2 hr. After cooling, the solvent was removed and the resulting crystals were recrystallized from DMF to give **13b** (17 mg, 45%) as orange needles, mp above 300°.

ii) Reaction of **12** with NH_3–EtOH or piperazine in a similar manner gave **13a** or **13c**, respectively. Yields of the products and their analytical data are recorded in Table IV. The compound **13b** was prepared in 43% yield by the reaction of **14** with aq. dimethylamine in a manner similar to that described above.

Table IV. 2-Amino and 2-Alkylamino-thiazolo[5,4-*b*]naphthyridine-6-carboxylic Acids



Compd. No.	R	mp[a] (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
13a	H_2N	>300	57	$C_{12}H_{10}N_4O_3S$	49.68	3.47	19.30	49.25	3.54	19.21
13b	Me_2N	>300	45	$C_{14}H_{14}N_4O_3S$	52.82	4.43	17.60	52.47	4.49	17.23
13c	HN N	>300	29	$C_{16}H_{17}N_5O_3S$	53.47	4.77	19.49	53.20	4.80	19.25

a) All compounds were recrystallized from DMF.

2-Chloro-8-ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic Acid (14)——A suspension of **10** (1.0 g) in SO_2Cl_2 (5 ml) was stirred at room temperature for 2 hr. The reaction mixture was poured onto ice, and the solid deposited was recrystallized from DMF to give **14** (0.47 g, 46%) as yellow needles, mp 280—290°. NMR (CF_3COOH) ppm: 9.41 (1H, s), 9.47 (1H, s). MS (*m/e*): 309 (M^+). *Anal.* Calcd. for $C_{12}H_8ClN_3O_3S$: C, 46.53; H, 2.60; N, 13.57. Found: C, 46.17; H, 2.62; N, 13.70.

2-Alkoxy-8-ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylic Acids (15a, b)——i) A mixture of **14** (0.10 g) in NaOEt solution (0.05 g of Na, 5 ml of EtOH) was refluxed for 3 hr and evaporated *in vacuo*. Water was added to the residue and a small quantity of insoluble materials was removed by filtlation, and the filtrate was acidified with dil. HCl. The product deposited was recrystallized from DMF to give **15b** (0.065 g, 66%) as needles, mp 248—250°. *Anal.* Calcd. for $C_{14}H_{13}N_3O_4S$: C, 52.65; H, 4.10; N, 13.16. Found: C, 52.59; H, 4.15; N, 13.88.

ii) In a similar manner as described above, the reaction of **14** and NaOMe gave **15a** in a yield of 58%, mp above 300°. *Anal.* Calcd. for $C_{13}H_{11}N_3O_4S$: C, 51.14; H, 3.63; N, 13.76. Found: C, 51.35; H, 3.55; N, 13.51.

Reaction of 16 with KSCN in AcOH——i) A mixture of **16** (3.0 g) and KSCN (2.4 g) in AcOH (40 ml) was stirred at 70—80° for 4.5 hr. The reaction mixture was evaporated to dryness under diminished pressure and the residue was extracted with $CHCl_3$. Concentration of the dried extract gave needles (quantitatively). Recrystallization from DMF–EtOH gave ethyl 1-ethyl-6-nitro-7-thiocyanato-1,4-dihydro-4-oxonaphthyridine-3-carboxylate (**17**) as yellow needles, mp 186—188°. IR (cm^{-1}) KBr: 2180 (SCN). *Anal.* Calcd. for $C_{14}H_{12}N_4O_5S$: C, 48.27; H, 3.47; N, 16.09. Found: C, 48.31; H, 3.53; N, 16.01.

ii) A mixture of **16** (1.0 g) and KSCN (1.6 g) in AcOH (10 ml) was refluxed for 2.5 hr. After cooling, separated crystals were collected. Recrystallization from DMF–MeOH gave disulfide (**18**) (0.062 g) as needles, mp above 300°. *Anal.* Calcd. for $C_{26}H_{24}O_{10}N_6S_2$: C, 48.40; H, 3.75; N, 13.04. Found: C, 48.04; H, 3.74; N, 12.87. The filtrate was evaporated to dryness and the residue was extracted with $CHCl_3$. The $CHCl_3$ extracts were subjected to chromatography on silica gel. The fraction eluted by benzene–AcOEt (2:1) gave ethyl 8-ethyl-2-methyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylate (**19**) (0.23 g, 23%) as colorless needles, mp 204—207°. NMR (CF_3COOH) ppm: 3.28 (3H, s), 9.65 (1H, s), 9.67 (1H, s),

5.20 (2H, q, N-$\underline{CH_2}CH_3$), 4.75 (2H, q, COO$\underline{CH_2}CH_3$), 1.80 (3H, t, N-$CH_2\underline{CH_3}$), 1.58 (3H, t, COO$CH_2\underline{CH_3}$), *Anal.* Calcd. for $C_{15}H_{15}N_3O_3S$: C, 56.76; H, 4.76; N, 13.24. Found: C, 56.63; H, 4.74; N, 13.42.

Hydrolysis of 19——A mixture of **19** (65 mg) in conc. HCl–90% AcOH (1: 11) (2 ml) was refluxed for 2 hr and the solid obtained on addition of water, was recrystallized from DMF to give **4a** (36 mg, 61%) as needles, mp above 300°. This product was identical with an authentic sample obtained from **2**.

Ethyl 2-Amino-8-ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*]naphthyridine-6-carboxylate (20)——A mixture of **17** (3.4 g), Fe powder (10 g) and AcOH (60 ml) was stirred at 70—80° for 0.5 hr. The reaction mixture was filtered and filtrate was concentrated. After addition of water to the residue, the deposited solid was collected and recrystallized from DMF to afford pale yellow needles of **20** (2.5 g, 79%), mp above 300°. *Anal.* Calcd. for $C_{14}H_{14}O_3N_4S$: C, 52.82; H, 4.43; N, 17.50. Found: C, 52.47; H, 4.51; N, 17.30.

Hydrolysis of 20——A mixture of **20** (0.40 g) in conc. HCl–90% AcOH (1: 11) (10 ml) was refluxed for 2 hr. The solid obtained, on addition of water, was recrystallized from DMF to give **13a** (0.12 g, 32%) as pale yellow needles, mp above 300°. *Anal.* Calcd. for $C_{12}H_{10}N_4O_3S$: C, 49.65; H, 3.47; N, 19.30. Found: C, 49.15; H, 3.54; N, 19.09.

This product was identical with an authentic sample obtained from **12**.

Methylation of 20——A mixture of **20** (0.95 g), MeI (1.0 g) and K_2CO_3 (1.7 g) in DMF (30 ml) was stirred at 100° for 2 hr. The reaction mixture was concentrated and the crude products were chromatographed on silica gel. The fraction eluted by benzene–AcOEt (1: 1) gave **21** (0.31 g, 12%) as pale yellow needles, mp 186—188°. *Anal.* Calcd. for $C_{16}H_{18}N_4O_3S$: C, 55.47; H, 5.24; N, 16.18. Found: C, 55.71; H, 5.23; N, 15.96.

Reaction of 11 with Dimethyl Sulfate——i) A mixture of **11** (0.64 g) and dimethyl sulfate (1.0 g) in DMF (20 ml) was stirred at 120° for 30 hr. After cooling, the resulting precipitate was collected, washed with ether and dried to give a mixture (0.44 g) of **13b** and the starting material. This mixture in $SOCl_2$ (5 ml) was stirred at room temperature for 1 hr and then poured into absolute EtOH. EtOH was removed *in vacuo* and addition of a small amount of water to the residue gave a mixture of **22** and **23** which was purified by silicagel chromatography. Eluate from benzene–AcOEt (7: 3) afforded colorless needles of the ester (**23**), mp 222—224°. *Anal.* Calcd. for $C_{15}H_{15}N_3O_3S_2$: C, 51.56; H, 4.33; N, 12.03. Found: C, 51.21; H, 4.35; N, 12.11. A mixture of **23** (0.064 g) in conc. HCl–90% AcOH (1: 11) (2 ml) was refluxed for 2 hr and the solid obtained on addition of water, was recrystallized from DMF to give **11** (0.030 g) as needles. This product was identical in IR spectrum with the starting material.

Eluate from AcOEt gave crystalline mass of the ester (**22**) (0.013 g). This ester without further purification, was hydrolyzed in conc. HCl–90% AcOH (1: 11) (2 ml) at 100° for 1 hr. The solid obtained was recrystallized from DMF to give **13b** (0.009 g), which was identical with the sample obtained from the reaction of **12** with dimethylamine.

ii) A mixture of **11** (0.48 g) and dimethyl sulfate (1 ml) was stirred at 140—160° for 50 hr. The solid obtained, on addition of water, was recrystallized from DMF to give methyl 8-ethyl-3-methyl-2,3,5,8-tetrahydro-2,5-dioxothiazolo[5,4-*b*]naphthyridine-6-carboxylate (**25**) as colorless needles. Yield 0.21 g (44%), mp above 300°. NMR (CF_3COOH) ppm: 3.78 (3H, s, COO$\underline{CH_3}$), 4.23 (3H, s, N-$\underline{CH_3}$), 8.47 (1H, s), 9.42 (1H, s), 5.11 (2H, q, N-$\underline{CH_2}CH_3$), 1.75 (3H, t, N-$CH_2\underline{CH_3}$). *Anal.* Calcd. for $C_{14}H_{13}N_3O_4S$: C, 52.65; H, 4.10; N, 13.16. Found: C, 52.64; H, 4.16; N, 13.48.

The filtrate was made basic with aq. NaOH. This reaction mixture was allowed to stand at room temperature overnight and acidified with AcOH. The crystalline mass was recrystallized from DMF–EtOH to give 8-ethyl-3-methyl-2,3,5,8-tetrahydro-2,5-dioxothiazolo[5,4-*b*]naphthyridine-6-carboxylic acid (**26**) (0.12 g, 26%), mp above 300°. *Anal.* Calcd. for $C_{13}H_{11}N_3O_4S$: C, 51.14; H, 3.63; N, 13.76. Found: C, 51.21; H, 3.75; N, 13.80.

Hydrolysis of Ester 25——A solution of **25** (0.10 g) in conc. HCl–90% AcOH (1: 11) (4 ml) was stirred at 100° for 1 hr. The solid separated, on addition of water, was recrystallized from DMF to give **26** (0.067 g, 70%) as colorless needles, mp above 300°, which was identical with the sample obtained above.

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