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Synthesis of Antimicrobial Agents. V.[1] Synthesis and Antimicrobial Activities of Some Heterocyclic Condensed 1,8-Naphthyridine Derivatives

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In order to search for compounds with higher activity than thiazolo[5,4-*b*], imidazo-[4,5-*b*] and triazolo[4,5-*b*][1,8]naphthyridine derivatives against *Ps. aeruginosa*, we synthesized some heterocyclic condensed 1,8-naphthyridine derivatives by using bifunctional 6,7-disubstituted 1,8-naphthyridine as a starting material.

Thiadiazolo[5,4-*b*] and oxazolo[5,4-*b*][1,8]naphthyridine derivatives (3) and (5) were prepared by hydrolysis of the 6-amino-7-chloro-3-ester (1) with sodium hydroxide or sodium hydrosulfide, followed by cyclization with acetic anhydride or sodium nitrite.

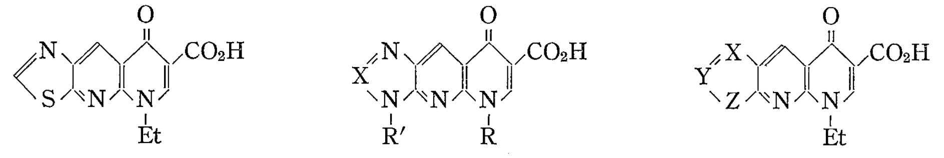
Pyrazolo[3,4-*b*] and isothiazolo[5,4-*b*][1,8]naphthyridine derivatives (12) and (14) were synthesized by ring cyclization of the 7-chloro-6-formyl-3-ester (10) with methyl hydrazine or ethanolic ammonia in the presence of sulfur, followed by hydrolysis.

Thieno and furo[2,3-*b*][1,8]naphthyridine derivatives (20) and (31) were prepared through a series of reaction steps, *e.g.* diazotization, reduction of the nitrile ester (7) or (24), ring cyclization by means of ethyl mercaptoacetate or ethyl bromomalonate, hydrolysis and decarboxylation.

The compounds obtained were tested for antimicrobial activities *in vitro*. 8-Ethyl-5,8-dihydro-5-oxothieno[2,3-*b*][1,8]naphthyridine-6-carboxylic acid (20) exhibited the highest activities among these compounds against many gram-negative bacteria, including *Ps. aeruginosa*, and against gram-positive bacteria.

Keywords——antimicrobial activity; thiadiazolo[5,4-*b*][1,8]naphthyridine; oxazolo-[5,4-*b*][1,8]naphthyridine; pyrazolo[3,4-*b*][1,8]naphthyridine; isothiazolo[5,4-*b*][1,8]-naphthyridine; thieno[2,3-*b*][1,8]naphthyridine; furo[2,3-*b*][1,8]naphthyridine; 3-carboxy-4-pyridone moiety

In previous papers[1,3] of this series, we reported that thiazolo[5,4-*b*][1,8]naphthyridine (A), 3,5-disubstituted imidazo ($X{=}CH$) and triazolo[4,5-*b*][1,8]naphthyridines ($X{=}N$) (B) showed high antimicrobial activities against gram-negative and gram- positive bacteria *in vitro*.



A B C

Fig. 1

As a part of our medicinal chemical studies on 1,8-naphthyridines, we synthesized oxazolo-[5,4-*b*], thiadiazolo[5,4-*b*], isothiazolo[5,4-*b*], pyrazolo[3,4-*b*], thieno[2,3-*b*] and furo[2,3-*b*][1,8]-naphthyridines (C) to evaluate their antimicrobial activities. The results are reported herein.

The reaction of 6-amino-1-ethyl-7-mercapto-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (2)[3] with sodium nitrite in 5% hydrochloric acid under cooling gave yellow needles in good yield. The structure of this compound was confirmed to be 8-ethyl-5,8-dihydro-5-oxothiadiazolo[5,4-*b*][1,8]naphthyridine-6-carboxylic acid (3) by infrared (IR) spectroscopy; its

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1) Part IV: N, Suzuki, Y. Tanaka, and R. Dohmori, *Chem. Pharm. Bull.*, **28**, 235 (1980).
2) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo, 132, Japan.*
3) Part III: N. Suzuki and R. Dohmori, *Chem. Pharm. Bull.*, **27**, 410 (1979).

absorption patterns resemble those of the thiazolo[5,4-*b*][1,8]naphthyridine derivative (A). Further confirmation was obtained by nuclear magnetic resonance (NMR) spectroscopy. Treatment of the 6-amino-7-chloro-3-ester (**1**)[4] with 10% sodium hydroxide gave the 7-hydroxy-3-acid (**4**) which was then converted into the oxazolo[5,4-*b*][1,8]naphthyridine derivative (**5**) by heating with acetic anhydride. However, reaction of **4** with 98% formic acid, ethyl orthoformate or with sodium nitrite in 80% sulfuric acid gave no cyclized product (**6**) (Chart 1).

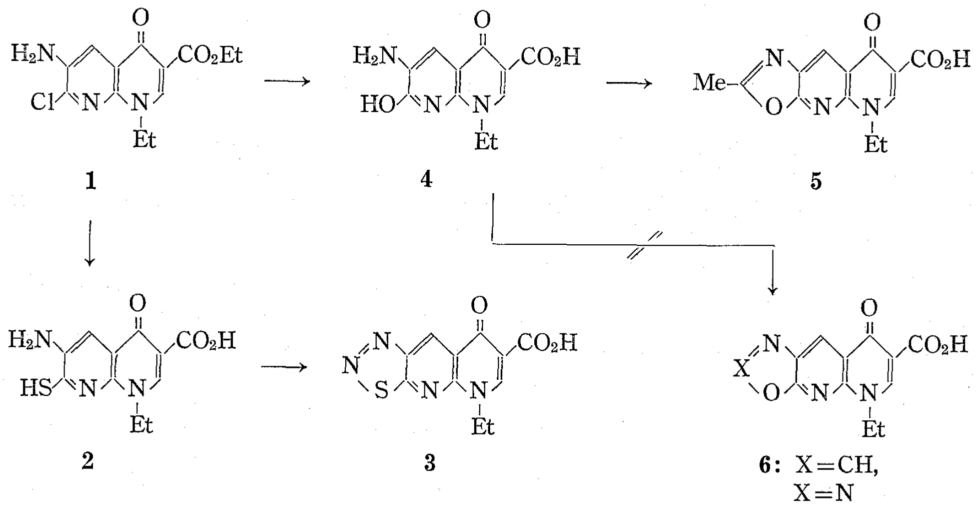

Chart 1

For the synthesis of pyrazolo[3,4-*b*] and isothiazolo[5,4-*b*][1,8]naphthyridine derivatives in which the nitrogen atom is replaced by a carbon atom at position 3 of compound B and **3**, the 6-amino-7-chloro-3-ester (**1**)[4] was chosen as a starting material. The 6-cyano-3-ester (**7**) was prepared from **1** by treatment with sodium nitrite in trifluoroacetic acid followed by potassium cyanide in the presence of cuprous ions. Reaction of **7** with methylhydrazine in EtOH at 70—75° gave the pyrazolo[3,4-*b*][1,8]naphthyridine derivative (**8**) which was easily convertible into the corresponding acid (**9**) by hydrolysis. Treatment of the 6-cyano-3-ester (**7**) with stannous chloride and dry hydrogen chloride in dry ethyl ether, followed by hydrolysis, gave the 6-formyl-3-ester (**10**) in 25% yield. Treatment of **10** with methylhydrazine gave the pyrazolo[3,4-*b*][1,8]naphthyridine (**11**) in 41% yield, and this was subsequently converted to the corresponding acid (**12**) by acid hydrolysis.

Heating **10** at 80—90° with 2% ethanolic ammonia in the presence of powdered sulfur in a sealed tube afforded a 37% yield of the isothiazolo[5,4-*b*][1,8]naphthyridine (**13**), which was then converted into the acid (**14**) by acid hydrolysis (Chart 2).

The thieno[2,3-*b*][1,8]naphthyridine derivatives were prepared as shown in Chart 3. Reaction of the 6-cyano-3-ester (**7**) with ethyl thioglycolate in EtOH in the presence of sodium carbonate gave the thieno[2,3-*b*][1,8]naphthyridine (**15**). Similarly, treatment of **10** with ethyl thioglycolate afforded the thieno[2,3-*b*][1,8]naphthyridine (**16**), which is unsubstituted at the 3 position of the thiophene ring, in good yield. Hydrolysis of the diester (**16**) with 10% sodium hydroxide at 100° afforded the dicarboxylic acid (**17**). On the other hand, treatment of **16** with ethanolic potassium hydroxide at 40° for 30 min or with HCl–AcOH at 100° gave the mono ester (**18**). This ester (**18**) was decarboxylated at 200° in quinoline in the presence of copper powder to give the ester (**19**) which was converted into the acid (**20**) by acid hydrolysis. The structure of **20** was confirmed by its IR spectrum, which resembles that of A, by elemental analysis, and furthermore by its NMR spectrum (CF_3COOH), which showed two doublets ($J=6$ Hz) at 8.15 and 7.80 ppm. If the partial hydrolysis and decarboxylation of the diester (**16**) took

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4) Part II: N. Suzuki, M. Kato, and R. Dohmori, *Yakugaku Zasshi*, 99, 155 (1979).

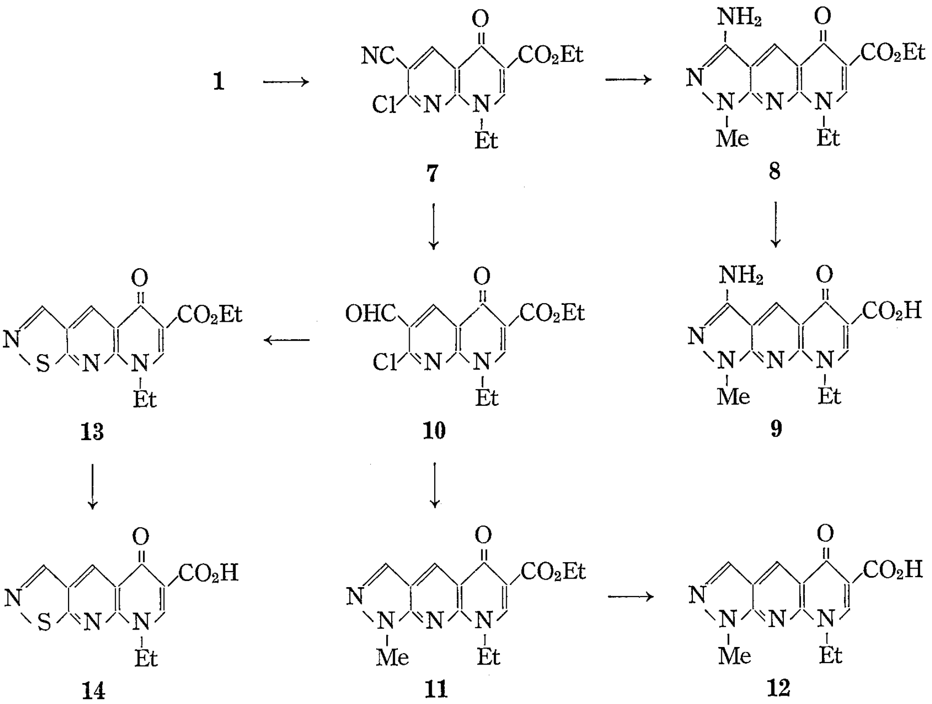

Chart 2

place at position 6, the coupling constant of the protons at positions 6 and 7 of the final product should be much larger.[5] Based on the above spectral data, this compound was concluded to be 8-ethyl-5,8-dihydro-5-oxothieno[2,3-*b*][1,8]naphthyridine-6-carboxylic acid (**20**) (Chart 3).

A synthetic route to furo[2,3-*b*][1,8]naphthyridine, which is a new ring system, is shown in Chart 4. Reaction of ethyl 1-ethyl-7-hydroxy-6-nitro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**21**)[4] with ethyl iodide in sulfolane in the presence of potassium carbonate gave the O-ethylated product (**22**) in good yield. Compound (**22**) was reduced with Fe powder and acetic acid to give the 6-amino-3-ester (**23**). The 6-cyano-3-ester (**24**) was prepared by displacement of the NH_2 group in **23** with CN^- *via* the diazo compound. The 6-formyl-3-ester (**25**)

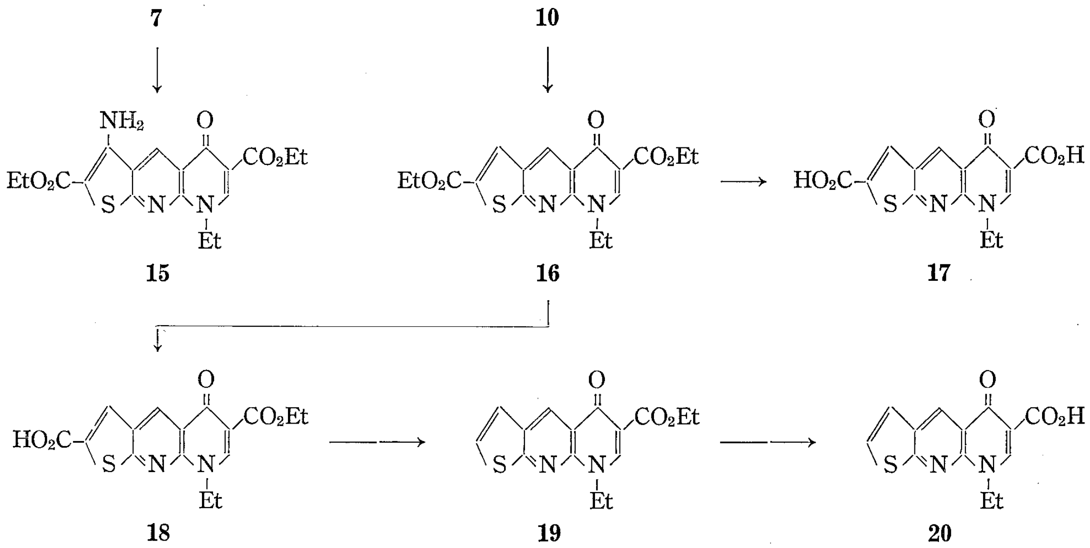

Chart 3

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5) M. Martin-Smith, S.T. Rend, and S. Stornhell, *Tetrahedron Lett.*, **1965**, 2393; S. Carboni, A. Da. Settimo, D. Bertini, P.L. Ferrarini, O. Livi, and I. Tonetti, *Farm. Ed. Sci.*, **28**, 134 (1973).

was prepared according to the procedure described by Staskun *et al.*[6] Reduction of the 6-cyano-3-ester (**24**) with moist Raney nickel at 70° in formic acid gave a mixture which showed two spots on TLC. The products were purified by silica gel column chromatography. The NMR spectrum (CF_3COOH) of the main product eluted by $CHCl_3$ exhibited a singlet signal (1H) at 10.38 ppm which was assignable to the proton of the aldehyde group. Its IR spectrum showed an absorption band at 1680 cm^{-1}, supporting the presence of an aldehyde group. Based on these spectroscopic data and the results of elemental analysis, this compound was concluded to be 7-ethoxy-1-ethyl-6-formyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**25**). The NMR spectrum (CF_3COOH) of the minor product eluted by $CHCl_3$–EtOH (10:1) exhibited a singlet signal (2H) 5.13 ppm due to the methylene of the hydroxymethyl group at position 6. On the basis of the above data, the mass spectrum and elemental analysis data, the structure of the minor product was concluded to be 7-ethoxy-1-ethyl-6-hydroxymethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**26**). Treatment of **25** with aluminum chloride in dichloromethane at room temperature afforded the 6-formyl-7-hydroxy-3-ester (**27**). Diethyl 8-ethyl-5,8-dihydro-5-oxofuro[2,3-*b*][1,8]naphthyridine-2,6-dicarboxylate (**28**) was prepared by the method of Tanaka for benzofuran synthesis.[7] Heating **27** with ethyl bromomalonate in sulfolane in the presence of anhydrous potassium carbonate gave **28** in 40% yield. The diester (**28**) was hydrolyzed in HCl–AcOH to give the monoester (**30**) in a similar manner to the synthesis of **18** from **16**. On the other hand, alkaline hydrolysis of the diester

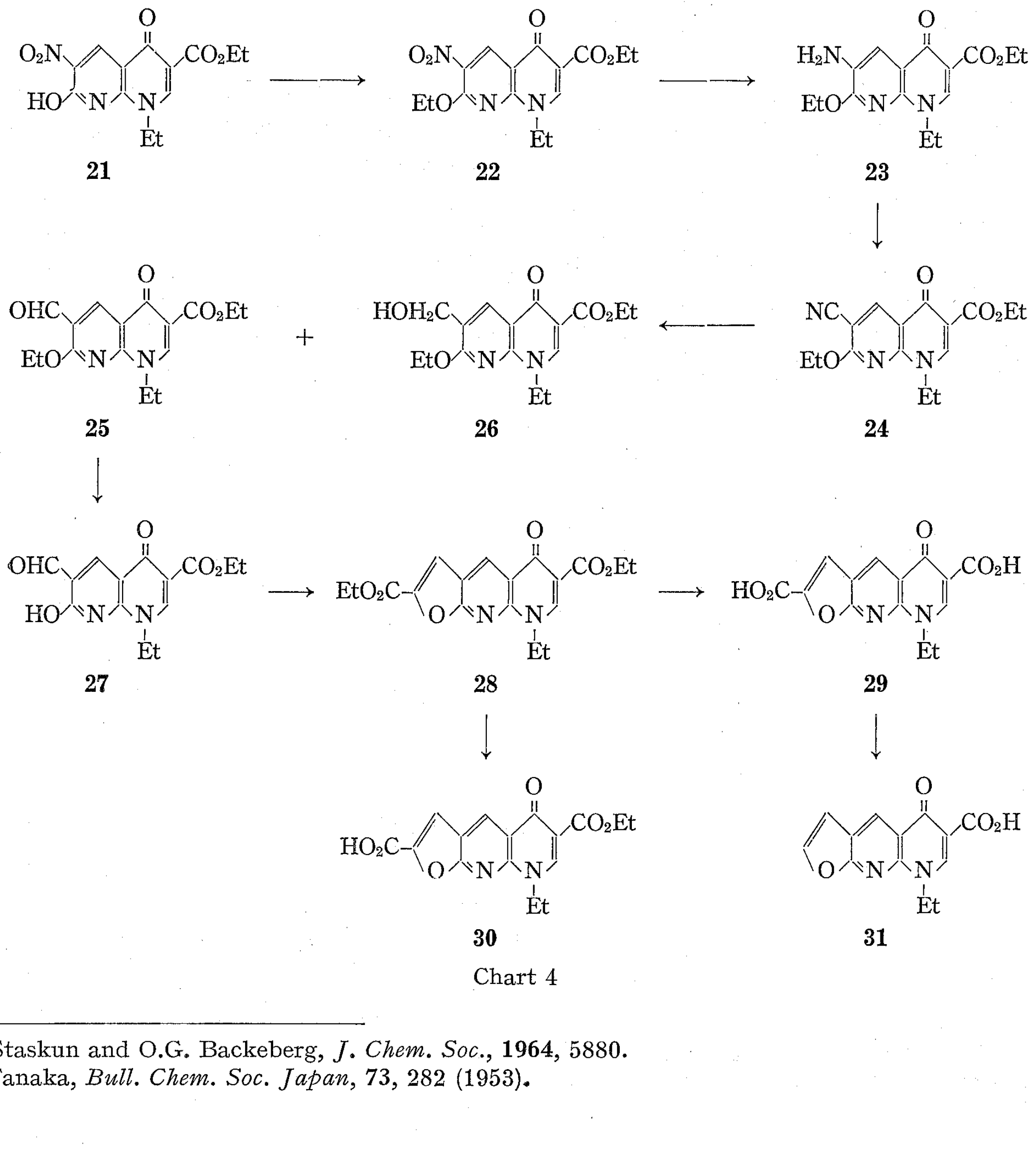

Chart 4

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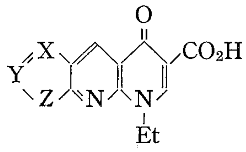
[6] B. Staskun and O.G. Backeberg, *J. Chem. Soc.*, **1964**, 5880.
[7] S. Tanaka, *Bull. Chem. Soc. Japan*, 73, 282 (1953).

(**28**) afforded the corresponding dicarboxylic acid (**29**). The 2,6-dicarboxylic acid (**29**) was partially decarboxylated at 190° in sulfolane with copper powder, yielding the monocarboxylic acid (**31**). It was considered that the product was not the 2-carboxylic acid, but was the 6-carboxylic acid, since the decarboxylation of pyridine and quinoline-3-carboxylic acids generally requires more vigorous conditions.[8] Furthermore, its NMR spectrum (CF_3COOH) showed two doublet signals at 8.28 and 7.35 ppm ($J=2$ Hz) assignable to the protons of the 2 and 3 positions in the furan ring.[9] Therefore the structure of the decarboxylated product was concluded to be 8-ethyl-5,8-dihydro-5-oxofuro[2,3-*b*][1,8]naphthyridine-6-carboxylic acid (**31**).

All carboxylic acids prepared in this work were tested for antimicrobial activities *in vitro* by the serial dilution method.[10] The minimum inhibitory concentrations of several active derivatives are illustrated in Table I; none of the others showed significant activities against any of the bacteria listed. Some compounds obtained in this work showed higher activities than the related drug, pipemidic acid. The nature of the heterocyclic ring condensed at the 6,7 positions of the 1,8-naphthyridine carboxylic acid significantly affected the antibacterial activity. Among the compounds with a five-membered heterocyclic ring in the 6,7 position of the 1,8-naphthyridine system, 8-ethyl-5,8-dihydro-5-oxothieno[2,3-*b*][1,8]naphthyridine-6-carboxylic acid (**20**) exhibited the highest activity against many gram-negative bacteria, including *Ps. aeruginosa*, and against gram-positive bacteria. It is interesting that the replacement of the nitrogen atom at position 3 of compound A with a carbon atom caused enhancement of the activity against *Ps. aeruginosa*.

TABLE I. Antibacterial Activities (M.I.C. mcg/ml)

Compd. No.				Organism				
	X	Y	Z	*Staphylococcus aureus* 209P	*Escherichia coli* NIHJ	*Shigella flexneri* 2a 5503	*Proteus mirabilis* 1287	*Pseudomonas aeruginosa* 2063
5	N	C–Me	O	25	1.56	1.56	3.13	>100
3	N	N	S	12.5	3.13	0.39	0.39	>100
14	CH	N	S	12.5	0.78	3.13	3.13	100
12	CH	N	N–Me	12.5	1.56	6.25	6.25	100
20	CH	CH	S	1.56	0.2	0.39	0.78	12.5
31	CH	CH	O	6.25	0.39	0.78	0.78	25
Compound A	N	CH	S	3.13	0.2	0.39	0.2	50
Compound B	N	CH	N–Me	25	6.25	3.13	1.56	100
	N	N	N–Me	12.5	3.13	1.56	1.56	>100
Pipemidic acid				25	3.13	0.78	3.13	50

Experimental

All melting points are uncorrected. IR spectra were measured in potassium bromide discs, 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. Abbreviations: s=singlet, d=doublet, t=triplet, q=qualtet. Mass spectra were run on a Hitachi RMU-6D mass spectrometer.

8-Ethyl-5,8-dihydro-5-oxothiadiazolo[5,4-*b*][1,8]naphthyridine-6-carboxylic Acid (3)——A solution of $NaNO_2$ (3.3 g) in H_2O (20 ml) was added with stirring to a suspension of **2** (6.5 g) in 5% HCl (350 ml) at 5°.

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

9) K. Tori and T. Nakagawa, *J. Phys. Chem.*, **68**, 3163 (1964); G.S. Reddy and J.H. Goldstein, *J. Am. Chem. Soc.*, **84**, 583 (1962).

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

After 2.5 hr, the precipitated solid was collected by filtration, washed with water, and dried. It was recrystallized from DMF to afford **3** (5.5 g, 84%), mp 230—250° (NMR (CF_3COOH) ppm: 9.89 (1H, s), 10.45 (1H, s), 5.21 (2H, q), 1.81 (3H, t). *Anal.* Calcd for $C_{11}H_8N_4O_3S$: C, 47.82; H, 2.92; N, 20.28. Found: C, 47.68; H, 2.96; N, 20.08.

6-Amino-1-ethyl-7-hydroxy-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (4)——A mixture of **1** (800 mg) in 10% NaOH (10 ml) was refluxed for 11 hr. The solid that separated on acidification was recrystallized from DMF to give **4** (390 mg, 60%) as a pale brown powder, mp above 300°. *Anal.* Calcd for $C_{11}H_{11}N_3O_4\cdot 1/2H_2O$: C, 52.80; H, 4.84; N, 16.79. Found: C, 52.79; H, 4.77; N, 16.43.

8-Ethyl-2-methyl-5,8-dihydro-5-oxooxazolo[5,4-*b*][1,8]naphthyridine-6-carboxylic Acid (5)——A suspension of **4** (390 mg) in acetic anhydride (6 ml) was heated under reflux for 3 hr. After cooling, the deposited solid was collected, washed and dried. Recrystallization from DMF gave **5** (339 mg, 68%) as pale brown needles, mp above 300°. *Anal.* Calcd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.32; H, 4.17; N, 15.56.

Ethyl 7-Chloro-6-cyano-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (7)——A solution of **1** (1.48 g) in 50% CF_3COOH (20 ml) was diazotized at −5° with a solution of $NaNO_2$ (0.5 g) in H_2O (2 ml). The diazotized solution was added slowly to a solution of cupric sulfate monohydrate (0.54 g) and potassium cyanide (1.17 g) in H_2O (10 ml) with vigorous stirring, which was continued for 1 hr afterwards. The reaction mixture was heated at 40° for 30 min. After cooling, the products were extracted with $CHCl_3$. Silica gel chromatographic separation of the mixture, eluting with $CHCl_3$, afforded **7** (0.53 g, 35%) as colorless needles, mp 243°. IR (KBr) cm^{-1}: 2230 (CN). *Anal.* Calcd for $C_{14}H_{12}ClN_3O_3$: C, 54.99; H, 3.96; N, 13.74. Found: C, 54.59; H, 4.01; N, 13.49.

Ethyl 3-Amino-8-ethyl-1-methyl-5,8-dihydro-5-oxopyrazolo[3,4-*b*][1,8]naphthyridine-6-carboxylate (8)——A stirred solution of **7** (306 mg, 1 mmol) in absolute EtOH (10 mg) was treated dropwise with methyl hydrazine (92 mg, 2 mmol) and the resulting suspension was heated at 70—75° for 1 hr. The reaction mixture was cooled and filtered to give **8** (243 mg, 77%). Recrystallization from DMF gave orange needles, mp above 300°. IR (KBr) cm^{-1}: 3300, 3440 (NH_2), 1715 (CO_2Et). *Anal.* Calcd for $C_{15}H_{17}N_5O_3$: C, 57.13; H, 5.44; N, 22.21. Found: C, 56.79; H, 5.40; N, 22.55.

3-Amino-8-ethyl-1-methyl-5,8-dihydro-5-oxopyrazolo[3,4-*b*][1,8]naphthyridine-6-carboxylic Acid (9)——A solution of **7** (194 mg) in conc. HCl–90% AcOH (1 : 11) (2 ml) was stirred at 110° for 2 hr. The separated solid was recrystallized from DMF to give **9** (124 mg, 70%) as an orange powder, mp above 300°. *Anal.* Calcd for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found: C, 54.00; H, 5.07; N, 24.74.

Ethyl 7-Chloro-1-ethyl-6-formyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (10)——Dry hydrogen chloride was passed into a mixture of anhydrous Et_2O (20 ml) and anhydrous stannous chloride (2.6 g) until the latter had dissolved. A $CHCl_3$ solution of **7** (0.71 g) was then added with stirring until the solid product first formed had changed to a viscous yellow oil (2 days). The Et_2O was decanted off and the oil was taken up in a little water then warmed at 50° for 30 min. The resulting precipitate was collected by filtration. The crude products were chromatographed on silica gel. The fraction eluted with $CHCl_3$ gave **10** (0.78 g, 25%) as colorless needles, mp 171—173°. IR (KBr) cm^{-1}: 1715 (CO_2Et), 1685 (CHO). *Anal.* Calcd for $C_{14}H_{13}ClN_2O_4$: C, 54.46; H, 4.24; N, 9.08. Found: C, 54.92; H, 4.24; N, 9.65.

Ethyl 8-Ethyl-1-methyl-5,8-dihydro-5-oxopyrazolo[3,4-*b*][1,8]naphthyridine-6-carboxylate (11)——A mixture of **10** (30 mg) and methyl hydrazine (10 mg) in EtOH (3 ml) was heated at 70—80° for 30 min. After cooling, the separated precipitate was recrystallized from EtOH to give **11** (12 mg, 41%) as needles, mp 215—217°. IR (KBr) cm^{-1}: 1680 (CO_2Et). *Anal.* Calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 59.61; H, 5.31; N, 18.47.

8-Ethyl-1-methyl-5,8-dihydro-5-oxopyrazolo[3,4-*b*][1,8]naphthyridine-6-carboxylic Acid (12)——A solution of **11** in conc. HCl–90% AcOH (1 : 11) (5 ml) was heated under reflux for 4 hr. Water was added to the reaction mixture and the resulting solid was recrystallized from DMF to give **12** (98 mg, 72%) as pale yellow plates, mp above 300°. NMR (CF_3COOH) ppm: 9.90 (1H, s), 9.81 (1H, s), 8.94 (1H, s), 4.48 (3H, s), 5.25 (2H, q), 1.88 (3H, t). *Anal.* Calcd for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.24; H, 4.47; N, 20.76.

Ethyl 8-Ethyl-5,8-dihydro-5-oxoisothiazolo[5,4-*b*][1,8]naphthyridine-6-carboxylate (13)——A mixture of **10** (50 mg) and sulfur (10 mg) in 2% ethanolic ammonia (10 ml) was heated at 80—90° for 2 hr. The reaction mixture was concentrated and the crude products were chromatographed on silica gel. The fraction eluted with benzene–$CHCl_3$ (1 : 1) gave **13** (18 mg, 37%) as pale yellow needles, mp 260—263°. *Anal.* Calcd for $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85. Found: C, 55.53; H, 4.32; N, 13.83.

8-Ethyl-5,8-dihydro-5-oxoisothiazolo[5,4-*b*][1,8]naphthyridine-6-carboxylic Acid (14)——A mixture of **13** (110 mg) in conc. HCl–90% AcOH (1 : 11) (2 ml) was heated under reflux for 5 hr. A small amount of insoluble material was filtered off and the filtrate was poured into water. The separated crystals were recrystallized from DMF to give **14** (76 mg, 76%) as pale yellow needles, mp 289—290°. NMR (CF_3COOH) ppm: 10.09 (1H, s), 9.69 (1H, s), 5.76 (2H, q), 1.85 (3H, t). *Anal.* Calcd for $C_{12}H_9N_3O_3S$: C, 52.35; H, 3.30; N, 15.26. Found: C, 52.52; H, 3.36; N, 15.53.

Diethyl 3-Amino-8-ethyl-5,8-dihydro-5-oxothieno[2,3-*b*][1,8]naphthyridine-2,6-dicarboxylate (15)——A mixture of **7** (306 mg), anhydrous sodium carbonate (91 mg) and ethyl thioglycolate (132 mg) in EtOH (30 ml) was heated under reflux for 4.5 hr. The solid that deposited on cooling was recrystallized from DMF to give **15** (337 mg, 87%) as yellow needles, mp above 300°. *Anal.* Calcd for $C_{18}H_{19}N_3O_5S$: C, 55.51; H, 4.92; N, 10.79. Found: C, 55.73; H, 4.91; N, 11.12.

Diethyl 8-Ethyl-5,8-dihydro-5-oxothieno[2,3-*b*][1,8]naphthyridine-2,6-dicarboxylate (16)——A mixture of **10** (500 mg), anhydrous sodium carbonate (2.0 g) and ethyl thioglycolate (250 mg) in EtOH (40 ml) was heated under reflux for 2 hr. The reaction mixture was concentrated and extracted with $CHCl_3$. The residue, after removal of the solvent, was crystallized from EtOH to give **16** (580 mg, 96%) as needles, mp 198—200°. IR (KBr) cm^{-1}: 1720, 1680 (CO_2Et). NMR ($CDCl_3$) ppm: 9.26 (1H, s), 8.73 (1H, s), 8.14 (1H, s) and three ethyl groups. *Anal.* Calcd for $C_{18}H_{18}N_2O_5S$: C, 57.74; H, 4.85; N, 7.48. Found: C, 57.90; H, 4.73; N, 7.46.

6-Ethoxycarbonyl-8-ethyl-5,8-dihydro-5-oxothieno[2,3-*b*][1,8]naphthyridine-2-carboxylic Acid (18)——a) A mixture of **16** (160 mg) in conc. HCl–90% AcOH (1: 11) (3 ml) was heated under reflux for 2 hr. The solid that separated on addition of water was recrystallized from DMF to give **18** (140 mg, 95%) as pale yellow needles, mp 297—300°. NMR (CF_3COOH) ppm: 9.80 (1H, s), 9.76 (1H, s), 8.59 (1H, s), 5.26 (2H, q, N-$C\underline{H}_2CH_3$), 4.73 (2H, q, $CO_2C\underline{H}_2CH_3$), 1.87 (3H, t), 1.61 (3H, t). *Anal.* Calcd for $C_{16}H_{14}N_2O_5S$: C, 55.48; H, 4.08; N, 8.09. Found: C, 55.47; H, 4.04; N, 8.28.

b) A suspension of **16** (800 mg) and potassium hydroxide (600 mg) in EtOH (30 ml) was stirred at room temperature for 15 min and then at 40° for 5 min. After acidifying the mixture with dilute HCl, the solvent was distilled off, and the precipitates were collected, washed with water then recrystallized from EtOH to give **18** (610 mg, 82%) as needles; this material was identical with the sample obtained above.

Ethyl 8-Ethyl-5,8-dihydro-5-oxothieno[2,3-*b*][1,8]naphthyridine-6-carboxylate (19)——A mixture of **18** (780 mg) and copper powder (100 mg) in quinoline (20 ml) was heated with stirring at 200° for 10 min until the evolution of carbon dioxide ceased. The filtered solution was combined with $CHCl_3$ and washed three times with 5% HCl and with water. The crystals obtained on removal of the solvent from the dried $CHCl_3$ extract were recrystallized from EtOH to give **19** (240 mg, 35%), mp 225—227°. NMR ($CDCl_3$) ppm: 9.18 (1H, s), 8.27 (1H, s), 7.60 (1H, d), 7.42 (1H, d), 4.2—4.8 (4H, $C\underline{H}_2CH_3 \times 2$), 1.3—1.7 (6H, $CH_2C\underline{H}_3 \times 2$). *Anal.* Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.58; H, 4.67; N, 9.27. Found: C, 59.51; H, 4.95; N, 9.19.

8-Ethyl-5,8-dihydro-5-oxothieno[2,3-*b*][1,8]naphthyridine-6-carboxylic Acid (20)——A solution of **19** (140 mg) in conc. HCl–90% AcOH (1: 11) (2 ml) was stirred at 100° for 2 hr. The solid that separated on cooling was recrystallized from DMF to give **20** (106 mg, 84%) as pale yellow needles, mp 295—297°. NMR (CF_3COOH) ppm: 9.75 (1H, s), 9.55 (1H, s), 8.15 (1H, d), 7.80 (1H, d), 5.30 (2H, q, N-$C\underline{H}_2CH_3$), 1.90 (3H, t, N-$CH_2C\underline{H}_3$). *Anal.* Calcd for $C_{13}H_{10}N_2O_3S$: C, 56.92; H, 3.67; N, 10.22. Found: C, 57.20; H, 3.67; N, 10.08.

8-Ethyl-5,8-dihydro-5-oxothieno[2,3-*b*][1,8]naphthyridine-2,6-dicarboxylic Acid (17)——A suspension of **16** (420 mg) in 10% KOH (10 ml) and EtOH (10 ml) was heated under reflux for 7 hr. The mixture was acidified with dilute HCl and the solvent was distilled off, then the precipitates were collected, washed with water and recrystallized from DMF to give **17** (334 mg, 94%) as pale orange needles, mp above 300°. *Anal.* Calcd for $C_{14}H_{10}N_2O_5S$: C, 52.82; H, 3.17; N, 8.80. Found: C, 52.82; H, 3.43; N, 9.26.

Ethyl 7-Ethoxy-1-ethyl-6-nitro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (22)——A mixture of **21** (5.0 g), K_2CO_3 (10.0 g) and EtI (10.0 g) in sulfolane (100 ml) was stirred at 120° for 3 hr. Water was added to the reaction mixture and the resulting precipitate was collected. Recrystallization from EtOH gave **22** (4.8 g 87%) as yellow needles, mp 184—185°. *Anal.* Calcd for $C_{15}H_{17}N_3O_6$: C, 53.73; H, 5.11; N, 12.52. Found: C, 53.59; H, 5.14; N, 13.03.

Ethyl 6-Amino-7-ethoxy-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (23)——A mixture of **22** (4.7 g) and powdered Fe (5.0 g) in AcOH (100 ml) was heated at 80—90° for 1 hr with vigorous stirring. The insoluble material was removed and the filtrate was concentrated. H_2O was added to the brown oily residue. The insoluble amino derivative (**23**) was collected and crystallized from EtOH to give pale yellow needles (4.0 g, 94%), mp 249—253°. IR (KBr) cm^{-1}: 3460, 3310 (NH_2). *Anal.* Calcd for $C_{15}H_{19}N_3O_4$: C, 59.00; H, 6.27; N, 13.76. Found: C, 59.33; H, 6.32; N, 13.84.

Ethyl 6-Cyano-7-ethoxy-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (24)——A solution of **23** (15.25 g) in conc. HCl (23 ml) and water (33 ml) was diazotized at 0° with a solution of $NaNO_2$ (4.5 g) in H_2O (15 ml). The diazotized solution was added to a solution of cupric sulfate (47.0 g, hydrate) and potassium cyanide (27.5 g) in H_2O (38 ml) with vigorous stirring during the addition and for 1 hr afterwards. Chloroform was added to the reaction mixture and the whole was warmed at 40—50° for 1 hr. After cooling, a small quantity of insoluble material was removed by filtration, and the filtrate was washed with water. The crystals obtained on removal of the solvent from the dried $CHCl_3$ extract were recrystallized from EtOH to give **24** (13.0 g, 82%) as colorless needles, mp 175—180°. IR (KBr) cm^{-1}: 2245 (CN), 1700 (CO_2Et). *Anal.* Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.44; N, 13.33. Found: C, 60.40; H, 5.62; N, 13.34.

Ethyl 7-Ethoxy-1-ethyl-6-formyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (25) and Ethyl 7-Ethoxy-1-ethyl-6-hydroxymethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (26)——A mixture of **24** (1.70 g), Raney alloy (50: 50, 2.0 g) and 80% by volume of aqueous formic acid (17 ml) was heated at 70°, with stirring, for 20 min, then poured into ice-water. After neutralization of the solution with $NaHCO_3$, the products were extracted with $CHCl_3$. Concentration of the dried extract gave a mixture of **25** and **26**

which was purified by silica gel chromatography. Elution with $CHCl_3$ afforded colorless needles of the ester **25** (0.85 g, 48%), mp 199—202°. IR (KBr) cm^{-1}: 1680 (CHO), 1715 (CO_2Et). NMR ($CDCl_3$) ppm: 10.38 (1H, s, CHO), 9.10 (1H, s), 8.48 (1H, s), 4.1—4.7 (6H, $C\underline{H}_2CH_3 \times 3$), 1.2—1.7 (9H, $CH_2C\underline{H}_3 \times 3$). *Anal.* Calcd for $C_{16}H_{18}N_2O_5 \cdot 1/2H_2O$: C, 58.71; H, 5.85; N, 8.56. Found: C, 59.07; H, 5.71; N, 8.73. The eluate with $CHCl_3$–EtOH (10: 1) gave a crystalline mass of the ester **26** (0.21 g), mp 200—202°. NMR (CF_3COOH) ppm: 9.33 (1H, s), 8.90 (1H, s), 5.13 (2H, s), 4.5—5.1 ($C\underline{H}_2CH_3 \times 2$), 1.3—1.9 ($CH_2C\underline{H}_3 \times 2$). MS *m/e*: 320 ($M^+$). *Anal.* Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.75. Found: 59.57; H, 6.35; N, 8.89.

Ethyl 1-Ethyl-6-formyl-7-hydroxy-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (27)——A solution of **25** (0.80 g) in CH_2Cl_2 (8 ml), was added dropwise to a suspension of aluminum chloride (1.90 g) in CH_2Cl_2 (15 ml). After stirring at room temperature for 3 hr, the reaction mixture was poured into ice-water and the product was extracted with $CHCl_3$. The residue, after removal of the solvent, was crystallized from EtOH to give **27** (0.44 g, 61%) as needles, mp 232—235°. *Anal.* Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 41.86; N, 9.64. Found: C, 57.91; H, 4.90; N, 9.83.

Diethyl 8-Ethyl-5,8-dihydro-5-oxofuro[2,3-*b*][1,8]naphthyridine-2,6-dicarboxylate (28)——A mixture of **27** (3.6 g), ethyl bromomalonate (7.1 g) and anhydrous potassium carbonate (5.5 g) in sulfolane (25 ml) was heated at 100—110° for 1 hr and then at 140—150° for 30 min with stirring. After cooling, $CHCl_3$ was added to the reaction mixture and the insoluble materials were removed by filtration. The $CHCl_3$ layer was washed with H_2O, then dried over Na_2SO_4. Removal of the solvent and crystallization of the residue from Et_2O afforded **28** (1.75 g, 40%), mp 212—213°. NMR ($CDCl_3$) ppm: 9.24 (1H, s), 8.73 (1H, s), 7.71 (1H, s), 4.2—4.8 (6H, $C\underline{H}_2CH_3 \times 3$), 1.3—1.7 (9H, $CH_2C\underline{H}_3 \times 3$). *Anal.* Calcd for $C_{18}H_{18}N_2O_6$: C, 58.85; H, 5.21; N, 7.62. Found: C, 59.10; H, 5.15; N, 7.40.

6-Ethoxycarbonyl-8-ethyl-5,8-dihydro-5-oxofuro[2,3-*b*][1,8]naphthyridine-2-carboxylic Acid (30)——A suspension of **28** (150 mg) in conc. HCl–90% AcOH (1: 11) (3 ml) was stirred at 100° for 2 hr. After removal of the solvent, the residue was crystallized from $CHCl_3$–EtOH to give **30** (97 mg, 70%) as colorless needles, mp 285—290°. *Anal.* Calcd for $C_{16}H_{14}N_2O_6 \cdot 1/4H_2O$: C, 57.40; H, 4.37; N, 8.37. Found: C, 57.48; H, 4.31; N, 8.48.

8-Ethyl-5,8-dihydro-5-oxofuro[2,3-*b*][1,8]naphthyridine-2,8-dicarboxylic Acid (29)——A mixture of **28** (700 mg), 10% potassium hydroxide (15 ml) and EtOH (10 ml) was heated under reflux for 30 min on a steam bath. After removal of EtOH, the residue was cooled and acidified with dilute HCl. The resulting precipitate was crystallized from DMF–EtOH to give **29** (571 mg, 80%) as colorless needles, mp above 300°. *Anal.* Calcd for $C_{14}H_{10}N_2O_6 \cdot 1/2H_2O$: C, 54.02; H, 3.89; N, 9.00. Found: C, 54.13; H, 3.76; N, 9.43.

8-Ethyl-5,8-dihydro-5-oxofuro[2,3-*b*][1,8]naphthyridine-6-carboxylic Acid (31)——A mixture of **29** (560 mg) with copper powder (100 mg) in sulfolane (14 ml) was heated at 190° for 25 min. After the addition of $CHCl_3$, the cooled and filtered solution was washed ten times with water. The residue obtained from the extract was crystallized from $CHCl_3$–EtOH to give **31** (213 mg, 45%) as needles, mp 265—268°. IR (KBr) cm^{-1}: 1720 (CO_2H). NMR (CF_3COOH) ppm: 9.70 (1H, s), 9.45 (1H, s), 8.28 (1H, d), 7.35 (1H, d), 5.28 (2H, q, $C\underline{H}_2CH_3$), 1.58 (3H, t, $CH_2C\underline{H}_3$). *Anal.* Calcd for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.90; N, 10.85. Found: C, 60.30; H, 3.97; N, 10.98.

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