[Chem. Pharm. Bull. 32(12)4914—4922(1984)]

Synthesis of Antimicrobial Agents. VI.[1] Studies on the Synthesis of Furo[3,2-*b*][1,8]naphthyridine Derivatives[2]

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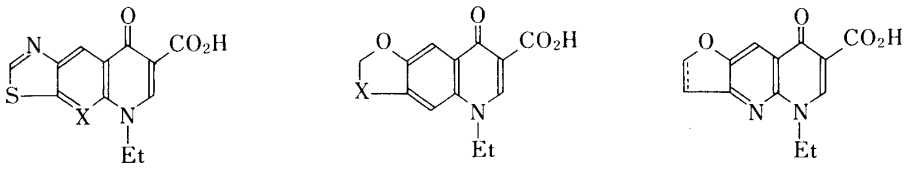
(Received March 24, 1984)

As a part of our search for new antibacterial agents, 5-ethyl-8-oxo-5,8-dihydrofuro[3,2-*b*]-[1,8]naphthyridine-7-carboxylic acid and its 2,3-dihydrofuro derivative, the 4-aza analogue of droxacin, were synthesized and their antibacterial activities were tested. Both compounds exhibited high antibacterial activities and a broad antibacterial spectrum. In an attempt to find a suitable method for industrial-scale synthesis of these compounds, several methods for the furan ring cyclization of 6,7-disubstituted 1,8-naphthyridine-3-carboxylate derivatives were compared.

Keywords——furo[3,2-*b*][1,8]naphthyridine; furan ring cyclization; Gould–Jacobs reaction; ylide; decarboxylation; enamine; antibactetial activity

In the previous papers,[1,3,4] we reported the synthesis and antibacterial activities of 1,8-naphthyridine derivatives fused linearly with five-membered heterocyclic rings (thiazolo[5,4-*b*]-,[3] imidazo[4,5-*b*]-,[4] triazolo[4,5-*b*]-,[4] oxazolo[5,4-*b*]-,[1] thiadiazolo[5,4-*b*]-,[1] isothiazolo-[5,4-*b*]-,[1] pyrazolo[3,4-*b*]-,[1] thieno[2,3-*b*]-,[1] and furo[2,3-*b*]-[1] [1,8]naphthyridines). Among these derivatives, 5-ethyl-8-oxo-5,8-dihydrothiazolo[5,4-*b*][1,8]naphthyridine-7-carboxylic acid (A) exhibited higher antibacterial activity *in vitro* against Gram-positive and -negative pathogens than the corresponding quinoline derivative (B). However, compound A was less potent in antibacterial activity than oxolinic acid (C) and was not very active against *Pseudomonas aeruginosa*.

As part of a series of studies on the synthesis of antibacterial agents, we synthesized 5-ethyl-8-oxo-5,8-dihydrofuro[3,2-*b*][1,8]naphthyridine-7-carboxylic acid (E) and its 2,3-dihydrofuro derivative (F), which were designed on the basis that oxygen is directly bound to the 6-position of the quinoline ring in both highly active oxolinic acid (C) and droxacin (D). Among the 5-membered heterocyclic ring-fused 1,8-naphthyridine derivatives described above, compounds E and F were the most potent in terms of antibacterial activity against Gram-positive and -negative pathogens including *Pseudomonas aeruginosa*.



A : X=N
B : X=CH

C : X=O (oxolinic acid)
D : X=CH_2 (droxacin)

E : 2–3 double bond
F : 2–3 single bond

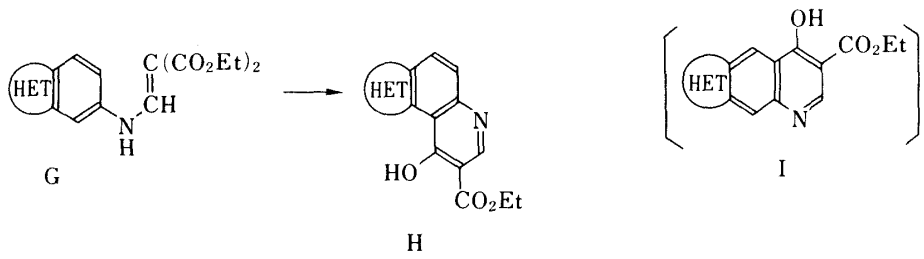
Chart 1

The present paper is mainly concerned with the synthesis of compound E by furan ring

cyclization of 6,7-disubstituted 1,8-naphthyridine-3-carboxylate derivatives.

Chemistry

Thermal cyclization of the condensation product (G) of a bicyclic aromatic amine and diethyl ethoxymethylenemalonate (EMME) is known to give an angular-type product H and not a linear-type product I in the Gould-Jacobs reaction.[5,6] However, when HET in



HET: heterocyclic ring

Chart 2

compound G is an alicyclic ring, the linear-type compound I is obtained as a main product.[5] Consequently, we first investigated 2,3-dihydrofuro[3,2-*b*]pyridine **2** as a starting material for the synthesis of E.

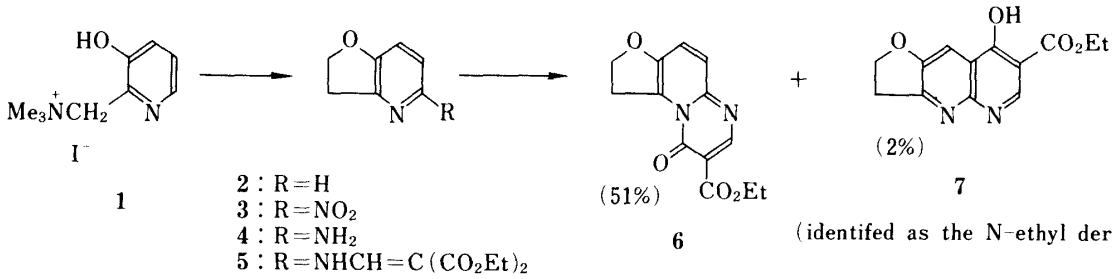


Chart 3

As shown in Chart 3, the condensation product **5**, which was synthesized successively from **1** *via* **2**, **3** and **4**, was heated in Dowtherm to give the angular-type compound **6** in a yield of 51%, while the yield of the desired linear-type compound **7** obtained simultaneously was only 2%.

Synthesis of Key Intermediates

Subsequently we examined various methods for the furan ring cyclization of 6,7-disubstituted 1,8-naphthyridine-3-carboxylates. As shown in Chart 4, the key intermediates **12**, **14**, **15** and **16** were synthesized from 3-ethoxy-2-picoline **8**.

The product **13** was obtained successively from **8** *via* **9**, **10**, **11** and **12**. All the steps proceeded in good yield. Oxidation of the methyl group of **13** to a formyl group was achieved by the use of SeO_2 in high-boiling-point solvents (sulfolane, *etc.*) or without a solvent at 150—200 °C. The ethyl moiety of the ethoxy group at the 6-position of **13** and **15** was eliminated by treatment with $AlCl_3$ to give **14** and **16**, respectively.

Synthesis of the Target Compounds

Firstly, the reaction of salicylaldehyde with dimethylsulfoxonium methylide to give 3-

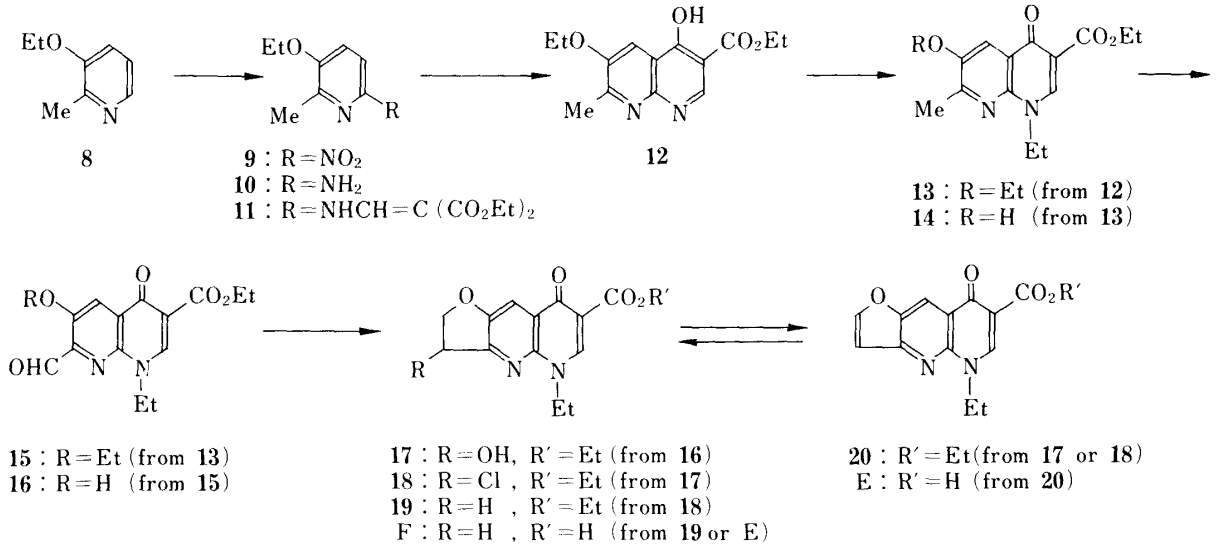


Chart 4

hydroxy-2,3-dihydrobenzofuran[7] was applied to the synthesis of compound E.

The 3-hydroxy-2,3-dihydrofuro derivative **17** was obtained in a low yield by treating the key intermediate **16** with dimethylsulfoxonium methylide under a nitrogen atmosphere. Dehydration of **17** by heating in dimethylsulfoxide (DMSO) gave **20**, which was hydrolyzed with HCl to afford the desired compound E. Compound **20** was also obtained by treating **17** with thionyl chloride and then with 1,8-diazabicyclo[5.4.0]-7-undecene. The intermediate **18** was catalytically hydrogenated in the presence of Pd–C to give the dihydrofuro ester **19**, which was hydrolyzed to the dihydrofuro derivative F. Compound F was alternatively obtained by catalytic hydrogenation of E in the presence of Pd–C at an initial pressure of 4 atom. Thus the target compounds E and F were obtained. However, the method is unsuitable for mass production because of its low yield and the requirement for anhydrous conditions in the step from **16** to **17**.

Tanaka[8] reported a synthesis of benzofuran-2-carboxylic acids by condensation of *o*-hydroxybenzaldehydes with ethyl bromomalonate in the presence of K_2CO_3. By applying this method to the intermediate **16**, the tricarboxylate **21** was obtained in a moderate yield, and treatment of **21** with K_2CO_3 in aqueous EtOH gave the dicarboxylic acid **22**. Selective decarboxylation of **22** to E was effected by heating in *N*, *N*-dimethylformamide (DMF), *N*, *N*-dimethylacetamide (DMAc) or quinoline in the presence of Cu powder, cuprous or cupric

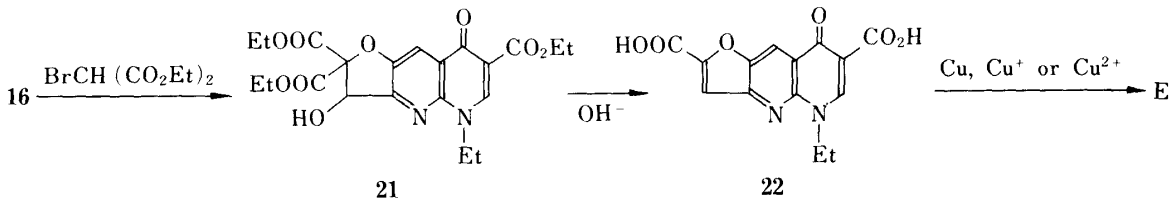


Chart 5

salts. However, in this method, contamination by colored decomposed products in the crude compound E could not be neglected, and further purification was required.

Condensation of **15** with malonic acid in pyridine containing a secondary amine (pyrrolidine, piperidine, *etc.*) afforded an *E*-form of the acrylic acid derivative **23**. Addition reaction of **23** with bromine gave the dibromo derivative **24** in a high yield.

Dehydrobromination and decarboxylation occurred simultaneously on treatment of **24** with a base ($NaHCO_3$, K_2CO_3 *etc.*) to afford the *Z*-form of the 2-bromovinyl derivative **25**. The *E*-form of **23** and the *Z*-form of **25** were assigned on the basis of a comparison of the coupling constants of the vinyl proton in the nuclear magnetic resonance (NMR) spectra; the *J* values are 13 and 7 Hz, respectively.

The ethyl moiety of the ethoxy group at the 6-position of **25** was eliminated by $AlCl_3$ treatment in the usual way to give **26**, which was converted to **20**, the ethyl ester of E, by heating under mild basic conditions.

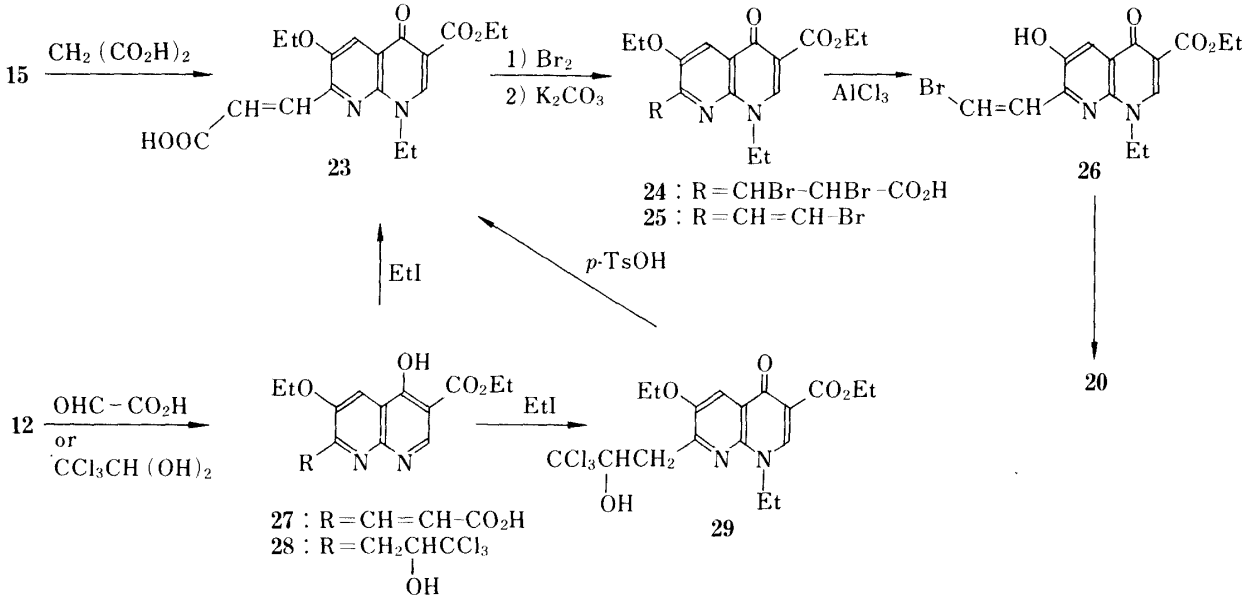


Chart 6

Compound **23** was also synthesized from **12** without the SeO_2-oxidation process. One route is the condensation of **12** with glyoxylic acid, followed by N-ethylation of **27**. The other is N-ethylation of **28**, obtained by the condensation of **12** with chloral hydrate, followed by treatment of **29** with *p*-TsOH.

Rufer *et al.*[9] reported that the reaction of nalidixic acid with *tert*-butyl dimethylaminal gave the corresponding 7-(2-dimethylaminovinyl) derivative in 90% yield. Since an enamino group is considered to be equivalent to a formylmethyl group, we applied this method to the synthesis of the desired compound E. Compound **30**, obtained from **14** by O-benzylation, was treated with DMF–diethylacetal (DMFDEA) in hexamethylphosphoramide (HMPA), or DMFDEA in DMF in the presence of dimethylamine to give the intended intermediate **31** in a high yield. Compound **31** was converted to the acetal **32** by heating in EtOH in the presence of 47% HBr. Compound E was obtained by treating the acetal **32** with conc. H_2SO_4 at room temperature, or heating the enamine **31** in a mixture of polyphosphoric acid and 85% phosphoric acid.

This enamine method could be applied to the mass production of E on the basis of the high yield in each step and the ease of purification.

Antibacterial Activities

Furo[3,2-*b*][1,8]naphthyridine derivatives (E and F) prepared in this work were tested for *in vitro* antibacterial activities.[10] Droxacin (D) was chosen as the reference compound. The results are shown in Table I in terms of the minimum inhibitory concentration (MIC, μg/ml) of the compounds, as determined by the serial agar dilution method. The furo[3,2-*b*]-

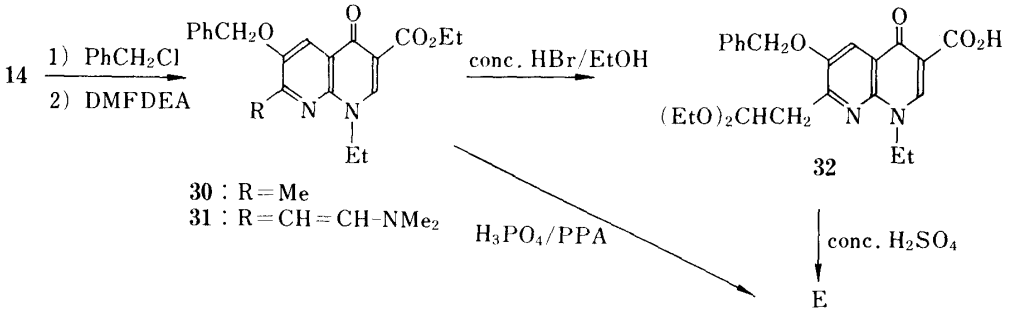


Chart 7

TABLE I. Antibacterial Activities (MIC, μg/ml)

Organisms	Compound		
	E	F	D
E. coli, NIHJ	<0.2	<0.2	<0.2
Pr. vulgaris, 3167	<0.2	<0.2	<0.2
K. pneumoniae, Type I	1.56	0.78	3.13
Ent. cloacae, 12001	0.39	<0.2	0.78
Ser. marcescens, 13014	0.39	<0.2	0.39
Ps. aeruginosa, 2063	3.13	6.25	25
S. aureus, 209 p	3.13	3.13	6.25

[1,8]naphthyridine derivatives (E and F) showed higher activities than the furo[2,3-*g*]-quinoline derivative (D).

Experimental

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

2,3-Dihydrofuro[3,2-*b*]pyridine (2)——A solution of (3-hydroxy-2-pyridyl)methyltrimethylammonium iodide (**1**) (5.9 g) in DMSO (20 ml) was added dropwise to a solution of dimethylsulfoxonium methylide in DMSO (25 ml) prepared from trimethylsulfoxonium iodide (4.5 g) and 50% NaH (2.0 g) in oil. The reaction mixture was stirred at room temperature for 2 h, poured into ice-water, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, and then extracted with 10% HCl. The aqueous layer was basified with 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and concentrated to dryness. The oily residue solidified on standing, and was purified by sublimation to give **2** (1.4 g, 58%), mp 55 °C. *Anal.* Calcd for C_7H_7NO: C, 69.40; H, 5.83; N, 11.57. Found: C, 69.19; H, 5.80; N, 11.31. ^{1}H-NMR ($CDCl_3$) δ: 3.30, 4.63 (each 2H, t, J=9.0 Hz), 7.00 (2H, d, J=3.0 Hz), 8.06 (1H, t, J=7.0 Hz).

5-Nitro-2,3-dihydrofuro[3,2-*b*]pyridine (3)——A mixture of fum. HNO_3 (3 ml) and conc. H_2SO_4 (3 ml) was added dropwise to a solution of **2** (4.0 g) in conc. H_2SO_4 (20 ml) below 5 °C. The reaction mixture was stirred at the same temperature for 30 min, poured into ice-water, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from a mixture of $CHCl_3$ and isopropyl ether to give **3** (3.8 g, 69%), mp 155.5 °C. *Anal.* Calcd for $C_7H_6N_2O_3$: C, 50.60; H, 3.64; N, 16.87. Found: C, 50.31; H, 3.63; N, 16.64. ^{1}H-NMR ($CDCl_3$) δ: 3.43 (2H, t, J=9.5 Hz), 4.85 (2H, t, J=9.5 Hz), 7.14 (1H, d, J=9.0 Hz), 8.10 (1H, d, J=9.0 Hz).

5-Amino-2,3-dihydrofuro[3,2-*b*]pyridine (4)——A solution of **3** (3.0 g) in MeOH (40 ml) was catalytically hydrogenated in the presence of 5% Pd–C (500 mg) at atmospheric pressure. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was recrystallized from a mixture of MeOH and isopropyl ether to give **4** (2.3 g, 93%) as needles, mp 126 °C. *Anal.* Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.56; H, 6.14; N, 20.66. ^{1}H-NMR ($CDCl_3$) δ: 3.16 (2H, t, J=9.0 Hz), 4.15 (1H, br s), 4.54 (2H, t, J=9.0 Hz), 6.22 (1H, d, J=8.5 Hz), 6.85 (1H, d, J=8.5 Hz).

Diethyl (2,3-Dihydrofuro[3,2*b*]pyridin-5-yl)aminomethylenemalonate (5)——A mixture of **4** (1.5 g) and EMME (2.8 g) was heated at 100 °C for 15 min. After the mixture had cooled, EtOH generated was evaporated off *in vacuo* and the residue was triturated with isopropyl ether. The insoluble product was collected by filtration and recrystallized from *n*-hexane to give **5** (3.3 g, 91%), mp 103 °C. *Anal.* Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.14. Found: C, 58.52; H, 5.99; N, 9.02.

Ethyl 1,2-Dihydro-9-oxo-9*H*-furo[3,2-*b*]pyrimido[2,1-*f*]pyridine-8-carboxylate (6) and Ethyl 5-Ethyl-8-oxo-2,3,5,8-tetrahydrofuro[3,2-*b*][1,8]naphthyridine-7-carboxylate (19)——A solution of **5** (2.0 g) in Dowtherm (20 ml) was refluxed for 15 min. After the mixture had cooled, ether (50 ml) was added and insoluble materials were separated by filtration. The filtrate was concentrated and the residue was triturated with *n*-hexane (100 ml). The resulting precipitate was collected and purified by silica-gel column chromatography using $CHCl_3$ as an eluent to give **6** (0.86 g, 51%), mp 166—167 °C (dec.). *Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.87; H, 4.71; N, 10.77. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (3H, t, J=8.0 Hz), 4.35 (2H, q, J=8.0 Hz), 4.32, 4.47 (each 2H, t, J=8.0 Hz), 7.53 (2H, s), 8.67 (1H, s).

A mixture of the insoluble materials obtained above, K_2CO_3 (300 mg) and ethyl iodide (150 mg) in DMF (15 ml) was heated at 90—100 °C for 30 min. The solvent was evaporated off and the residue was partitioned between $CHCl_3$ and water. The separated $CHCl_3$ layer was washed with water, dried and concentrated to dryness. The residue was purified by silica-gel column chromatography using $CHCl_3$ as an eluent to afford the N^5-ethyl derivative of **7** (40 mg, 2%), which was identical with **19** obtained from **18**.

3-Ethoxy-6-nitro-2-picoline (9)——3-Ethoxy-2-picoline (**8**) (70 g) was dissolved in conc. H_2SO_4 (280 ml) under ice-cooling. A mixture of fum. HNO_3 (42 ml) and conc. H_2SO_4 (50 ml) was added dropwise to the solution at 0—3 °C, and the whole was stirred at the same temperature for 30 min. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and concentrated to dryness to give **9** (85 g, 91%), mp 80—82 °C. *Anal.* Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.53; H, 5.47; N, 15.21.

6-Amino-3-ethoxy-2-picoline (10)——A suspension of **9** (18.2 g) in EtOH (300 ml) was catalytically reduced in the presence of 5% Pd–C (2 g) at atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated to dryness *in vacuo*. The residue was recrystallized from benzene to give **10** (13.8 g, 91%), 98—99 °C. *Anal.* Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.36; H, 8.04; N, 18.27.

Diethyl (3-Ethoxy-2-methylpyridin-6-yl)aminomethylenemalonate (11)——A solution of **10** (10.6 g) and EMME (15.9 g) in EtOH (30 ml) was heated under reflux for 1 h. After the mixture had cooled, isopropyl ether was added and the precipitate was recrystallized from EtOH to give **11** (19.0 g, 85%), mp 137—138 °C. *Anal.* Calcd for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.96. Found: C, 59.92; H, 6.71; N, 8.63.

Ethyl 6-Ethoxy-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (12)——A solution of **11** (16.1 g) in Dowtherm (160 ml) was heated under reflux for 1 h. After the mixture had cooled to room temperature, the precipitate was collected by filtration and recrystallized from DMF to give **12** (11.8 g, 85%), mp 279—282 °C (dec.). *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.67; H, 5.98; N, 9.97.

Ethyl 6-Ethoxy-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (13)——A mixture of **12** (11.0 g) and K_2CO_3 (6.6 g) in DMF (110 ml) was heated at 90—100 °C for 10 min, then ethyl iodide (7.5 g) was added and the reaction mixture was heated at the same temperature for 1 h. Insoluble materials were filtered off, and the filtrate was concentrated to dryness *in vacuo*. The residue was taken up in $CHCl_3$ and water, and the separated $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from EtOH to give **13** (10.5 g, 87%), mp 163—164 °C. *Anal.* Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 62.93; H, 6.59; N, 9.36.

Ethyl 6-Ethoxy-1-ethyl-7-formyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (15)——Selenium oxide (22.0 g) was added portionwise to a solution of **13** (30.4 g) in sulfolane (100 ml) at 140—145 °C with vigorous stirring. The reaction mixture was heated at the same temperature for 5 h. After the mixture had cooled to 40 °C, $CHCl_3$ was added and insoluble materials were filtered off. The filtrate was washed with 3% Na_2CO_3 and water, then dried over Na_2SO_4 and the solvent was evaporated off *in vacuo*. The residue was triturated with isopropyl alcohol, and the insoluble product was collected by filtration and recrystallized from EtOH to give **15** (22.0 g, 69%), mp 169—170 °C. *Anal.* Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.58; H, 5.44; N, 8.91.

Ethyl 1-Ethyl-6-hydroxy-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (14)——A solution of **13** (26.5 g) in CH_2Cl_2 (200 ml) was slowly added to a suspension of pulverized $AlCl_3$ (58 g) in CH_2Cl_2 (500 ml) at room temperature during 1.5 h. The reaction mixture was stirred at the same temperature overnight, and poured into ice-water. The resulting precipitate was collected and recrystallized from EtOH–$CHCl_3$ to give **14** (21.4 g, 89%), mp 184—185 °C. *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.88; H, 6.04; N, 10.19. ^{1}H-NMR ($CDCl_3$) δ: 1.51, 1.53 (each 3H, t, J=7.5 Hz), 2.67 (3H, s), 4.49, 4.57 (each 2H, q, J=7.5 Hz), 8.70 (1H, s), 9.05 (1H, s).

Ethyl 1-Ethyl-7-formyl-6-hydroxy-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (16)——A solution of **15** (25.0 g) in CH_2Cl_2 (200 ml) was slowly added dropwise to a suspension of $AlCl_3$ (53 g) in CH_2Cl_2 (500 ml) at room temperature during 2 h. Stirring was continued for an additional 3 h. Ice-water was added to the reaction mixture and

the separated aqueous layer was extracted with $CHCl_3$. The organic layers were combined, washed with water, dried over Na_2SO_4, and concentrated to dryness. The residue was recrystallized from EtOH to give **16** (18.5 g, 81%), mp 243—245 °C. *Anal.* Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 58.04; H, 4.82; N, 9.57.

Ethyl 5-Ethyl-3-hydroxy-8-oxo-2,3,5,8-tetrahydrofuro[3,2-*b*][1,8]naphthyridine-7-carboxylate (17)——Trimethylsulfoxonium iodide (1.59 g) was added with stirring to a suspension of 50% NaH (342 mg) in anhydrous DMSO (12 ml) at room temperature over a 30 min period under a nitrogen atmosphere. A solution of **16** (1.74 g) in anhydrous DMSO (20 ml) was added to the mixture, and stirring was continued at the same temperature for 1 h. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and concentrated to dryness *in vacuo* to give **17** (1.2 g), which was used in the next reaction without further purification.

Ethyl 3-Chloro-5-ethyl-8-oxo-2,3,5,8-tetrahydrofuro[3,2-*b*][1,8]naphthyridine-7-carboxylate (18)——Thionyl chloride (100 mg) was added to a solution of crude **17** (280 mg) in anhydrous $CHCl_3$ (5 ml) below 10 °C. The mixture was stirred at room temperature for 40 min, then poured into ice-water, neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and concentrated to dryness to give crude **18** (300 mg), which was used in the next reaction without further purification.

Triethyl 5-Ethyl-3-hydroxy-8-oxo-2,3,5,8-tetrahydrofuro[3,2-*b*][1,8]naphthyridine-2,2,7-tricarboxylate (21)——A mixture of **16** (6.0 g), diethyl bromomalonate (5.6 g) and K_2CO_3 (4.5 g) in methyl ethyl ketone (300 ml) was heated under reflux for 9 h. Insoluble materials were filtered off and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by silica-gel column chromatography using $CHCl_3$ as an eluent to give **21** (6.1 g, 66%), mp 193 °C. *Anal.* Calcd for $C_{21}H_{24}N_2O_9$: C, 56.24; H, 5.39; N, 6.25. Found: C, 55.80; H, 5.32; N, 6.21.

5-Ethyl-8-oxo-5,8-dihydrofuro[3,2-*b*][1,8]naphthyridine-2,7-dicarboxylic Acid (22)——A mixture of **21** (1.2 g) and K_2CO_3 (0.48 g) in aqueous EtOH (4 ml of water and 14 ml of EtOH) was heated under reflux for 30 min. Then 2 N NaOH was added to the reaction mixture and the whole was heated under reflux for an additional 30 min. The solution was acidified with HCl and the resulting precipitate was collected and recrystallized from DMF to give **22** (0.52 g, 64%), mp >300 °C. *Anal.* Calcd for $C_{14}H_{10}N_2O_6$: C, 55.63; H, 3.34; N, 9.27. Found: C, 55.91; H, 3.24; N, 9.35.

3-(6-Ethoxy-3-ethoxycarbonyl-4-hydroxy-1,8-naphthyridin-7-yl)acrylic Acid (27)——A mixture of **12** (2.76 g) and glyoxylic acid monohydrate (1.5 g) in AcOH (20 ml) and CF_3COOH (10 ml) was heated at 90—95 °C for 2 h with stirring. The solvents were evaporated off and the residue was triturated with EtOH. The insoluble material was collected and washed with EtOH to give **27** (2.62 g, 79%), mp >300 °C. *Anal.* Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.64; H, 4.89; N, 8.28.

Ethyl 6-Ethoxy-4-hydroxy-7-(2-hydroxy-3,3,3-trichloropropyl)-1,8-naphthyridine-3-carboxylate (28)——A mixture of **12** (13.0 g) and chloral hydrate (8 ml) in AcOH (120 ml) was heated at 120—130 °C for 7 h. After the mixture had cooled, the precipitate was collected and washed with EtOH to give **28** (17.5 g, 87%), mp 245—246 °C. *Anal.* Calcd for $C_{16}H_{17}Cl_3N_2O_5$: C, 45.35; H, 4.05; N, 6.61. Found: C, 44.90; H, 4.02; N, 6.35.

Ethyl 6-Ethoxy-1-ethyl-7-(2-hydroxy-3,3,3-trichloropropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (29)——A mixture of **28** (38.0 g), K_2CO_3 (22.0 g) and EtI (25.0 g) in DMF (200 ml) was heated at 90—100 °C for 1.5 h. Insoluble materials were filtered off and the filtrate was concentrated to dryness. The residue was triturated with ether and the precipitate was collected by filtration to give **29** (31.0 g, 77%), mp 179—181 °C. *Anal.* Calcd for $C_{18}H_{21}Cl_3N_2O_5$: C, 47.85; H, 4.69; N, 6.20. Found: C, 47.92; H, 4.68; N, 6.33.

3-(6-Ethoxy-3-ethoxycarbonyl-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridin-7-yl)acrylic Acid (23)——a) From **15**: A mixture of **15** (15.9 g), malonic acid (5.7 g) and pyrrolidine (1 ml) in pyridine (100 ml) was stirred at 90—100 °C for 3 h. The reaction mixture was poured into ice-water and acidified with HCl. The precipitate was collected by filtration, washed with water and dried *in vacuo* to give **23** (14.8 g, 82%), mp 285—286 °C. *Anal.* Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.78. Found: C, 59.54; H, 5.57; N, 7.83. ^{1}H-NMR (DMSO-d_6) δ: 1.31, 1.43, 1.46 (each 3H, t, CH_2CH_3), 4.22, 4.22, 4.38 (each 2H, q, CH_2CH_3), 6.92, 7.86 (each 1H, d, J=13 Hz, –CH=CH–), 7.94 (1H, s, 5-H), 8.70 (1H, s, 2-H).

b) From **27**: A mixture of **27** (2.0 g), K_2CO_3 (2.5 g) and EtI (1.0 g) in sulfolane (5 ml) and water (20 ml) was heated under reflux for 2 h. Insoluble materials were filtered off, then the filtrate was washed with $CHCl_3$. The aqueous layer was acidified with HCl and the resulting precipitate was collected, washed with water and dried *in vacuo* to give **23** (1.75 g, 81%), mp 285—286 °C.

c) From **29**: A mixture of **29** (10.0 g), *p*-toluenesulfonic acid (3.0 g), acetic acid (2 ml) and acetic anhydride (2 ml) was stirred at 130—135 °C for 6 h. After being cooled, the reaction mixture was poured into ice-water. The resulting precipitate was collected by filtration and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4 and concentrated to dryness. The residue was triturated with ether and the insoluble material was collected to give **23** (6.40 g, 80%), mp 285—286 °C.

Ethyl 2,3-Dibromo-3-(6-ethoxy-3-ethoxycarbonyl-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridin-7-yl)propionate (24)——Bromine (18.0 g) in AcOH (100 ml) was added dropwise to a solution of **23** (26.2 g) in AcOH (260 ml) at 90—100 °C. The reaction mixture was stirred at the same temperature for 4 h, and the solvent was evaporated off *in vacuo*. The residue was mixed with $CHCl_3$ and water. The separated $CHCl_3$ layer was washed with water, dried over Na_2SO_4

and concentrated to dryness. The residue was triturated with ether and the insoluble material was collected by filtration to give **24** (35.0 g, 91%), mp 141—143 °C. *Anal.* Calcd for $C_{18}H_{20}Br_2N_2O_6$: C, 41.56; H, 3.88; N, 5.39. Found: C, 41.37; H, 3.90; N, 5.56.

Ethyl 7-(2-Bromovinyl)-6-ethoxy-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (25)——A mixture of **24** (34.0 g) and Na_2CO_3 (20.0 g) in acetone (500 ml) was heated under reflux for 6 h. Insoluble materials were filtered off and the filtrate was concentrated to dryness. The residue was dissolved in $CHCl_3$. The solution was washed with water, dried over Na_2SO_4 and concentrated to dryness. The residue was triturated with ether and the insoluble material was collected by filtration to give **25** (20.8 g, 81%), mp 142—144 °C. *Anal.* Calcd for $C_{17}H_{19}N_2O_4$: C, 51.65; H, 4.84; N, 7.09. Found: C, 51.77; H, 4.91; N, 7.05. ^{1}H-NMR (DMSO-d_6) δ: 1.28, 1.38, 1.40 (each 3H, t, $CH_2\underline{CH}_3$), 4.21, 4.21, 4.52 (each 2H, q, $\underline{CH}_2CH_3$), 7.12, 7.58 (each 1H, d, J=7 Hz, –CH=CH–), 7.90 (1H, s, 5-H), 8.62 (1H, s, 2-H).

Ethyl 7-(2-Bromovinyl)-1-ethyl-6-hydroxy-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (26)——Compound **25** (20.0 g) in CH_2Cl_2 (100 ml) was added dropwise to a suspension of pulverized $AlCl_3$ (40 g) in CH_2Cl_2 (300 ml) at room temperature for 1 h. The mixture was stirred at the same temperature overnight. The reaction mixture was poured into ice-water and the precipitate was collected, washed with water and dried *in vacuo* to give **26** (16.0 g, 86%), mp 235—238 °C. *Anal.* Calcd for $C_{15}H_{15}BrN_2O_4$: C, 49.06; H, 4.12; N, 7.63. Found: C, 49.21; H, 3.98; N, 7.56.

Ethyl 6-Benzyloxy-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-7-carboxylate (30)——A mixture of **14** (17.7 g), benzyl chloride (9.0 g) and K_2CO_3 (16.0 g) in *N*,*N*-dimethylacetamide (150 ml) was stirred at 110 °C for 30 min.

Insoluble materials were filtered off and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$ and the $CHCl_3$ solution was washed with water, dried over Na_2SO_4 and concentrated to dryness. The residue was triturated with ether and the precipitate was collected to give **30** (23.0 g, 98%), mp 192 °C. *Anal.* Calcd for $C_{21}H_{22}N_2O_4$: C, 68.83; H, 6.05; N, 7.65. Found: C, 69.05; H, 6.01; N, 7.76.

Ethyl 6-Benzyloxy-7-(2-dimethylaminovinyl)-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (31)——a) A mixture of **30** (15.0 g) and DMFDEA (11.0 g) in HMPA (100 ml) was heated at 140 °C for 11 h. The solvent was evaporated off *in vacuo* and the residue was triturated with ether and AcOEt. The precipitate was collected by filtration and washed with ether to give **31** (16.5 g, 95%). b) A mixture of **30** (3.5 g) and DMFDEA (2 g) in DMF containing excess dimethylamine was heated at 120—130 °C for 3 h. The solution was evaporated to dryness and the residue was triturated with ether.

The precipitate (**31**) (4 g, almost quant.) obtained was pure enough to use for the next step. A sample for analysis was recrystallized from $CHCl_3$–isopropyl ether to give yellow fine needles, mp 158 °C. *Anal.* Calcd for $C_{24}H_{28}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.63; H, 6.31; N, 10.03.

6-Benzyloxy-7-(2,2-diethoxyethyl)-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid (32)——A solution of **31** (200 mg) in 47% HBr (3 drops)–EtOH (10 ml) was heated under reflux for 4 h, then cooled. The precipitate was collected and recrystallized from EtOH to give **32** (140 mg, 67%), mp 201—203 °C. *Anal.* Calcd for $C_{24}H_{28}N_2O_6$: C, 65.38; H, 6.41; N, 6.36. Found: C, 65.74; H, 6.41; N, 6.47.

Ethyl 5-Ethyl-8-oxo-5,8-dihydrofuro[3,2-*b*][1,8]naphthyridine-7-carboxylate (20)——a) By Dehydrochlorination of **18**: 1,8-Diazabicyclo[5.4.0]-7-undecene (3.2 g) was added dropwise to a solution of **18** (3.2 g) in DMF (50 ml) at room temperature. The reaction mixture was stirred at 40—45 °C for 1 h, and then concentrated to dryness. The residue was mixed with $CHCl_3$ and dil. HCl. The separated $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and concentrated to dryness to give **20** (ethyl ester of E) (2.3 g, 80%), mp 192—193 °C. *Anal.* Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.75; H, 5.06; N, 9.76.

b) By Furan Ring Cyclization of **26**: A mixture of **26** (7.34 g) and K_2CO_3 (4.14 g) in DMAc (70 ml) was heated at 100 °C for 1 h. The solvent was evaporated off and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4 and concentrated to dryness to give **20** (4.80 g, 84%), which was identical with the product described above.

5-Ethyl-8-oxo-5,8-dihydrofuro[3,2-*b*][1,8]naphthyridine-7-carboxylic Acid (E)——a) By Hydrolysis of **20**: A solution of **20** (2.86 g) in 1 N HCl–90% AcOH (1 : 11, 30 ml) was heated under reflux for 2 h, then cooled. The precipitate was collected and recrystallized from DMF to give E (1.85 g, 72%), mp >300 °C. *Anal.* Calcd for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 4.26; N, 10.88. Found: C, 60.79; H, 3.90; N, 10.85. ^{1}H-NMR (CF_3COOH) δ: 1.85 (3H, t), 5.30 (2H, q), 7.45 (1H, dd), 8.65 (1H, d), 9.15 (1H, d), 9.70 (1H, s).

b) By Dehydration of **17**: A solution of crude **17** (35 mg) in DMSO (2 ml) was heated at 180—190 °C for 20 h. After removal of the solvent, the crude ester (**20**) was obtained, and was hydrolyzed with HCl–AcOH in the manner described above to give E.

c) By Decarboxylation of **22**: Compound **22** (1.9 g) was added to a suspension of Cu powder (525 mg) in quinoline (20 ml) at 160 °C under a nitrogen atmosphere, and the reaction mixture was heated at 195 °C for 15 min with vigorous stirring, then cooled. Chloroform (200 ml) was added to the mixture and the insoluble materials were filtered off. The filtrate was washed with 5% HCl and water, then dried over Na_2SO_4 and concentrated to dryness. The residue was purified by silica-gel column chromatography using $CHCl_3$–MeOH (97 : 3) as an eluent, and

recrystallized from DMF to give E (1.1 g, 68%), mp >300 °C.

d) By Furan Ring Cyclization of **31**: A mixture of **31** (1.0 g), 85% H_3PO_4 (5 ml) and PPA (10 g) was heated at 140 °C for 8 h, and poured into ice-water. The resulting precipitate was collected by filtration and recrystallized from DMF to give E (0.34 g, 56%), mp >300 °C. After E had been removed by recrystallization, the mother liquor was concentrated to dryness *in vacuo* and the residue gave the ester **20** (0.11 g, 16%), mp 189—192 °C.

e) By Furan Ring Cyclization of **32**: A solution of **32** (2.0 g) in conc. H_2SO_4 (12 ml) was stirred at room temperature for 14 h, and poured into ice-water. The resulting precipitate was collected, washed with water and dried *in vacuo* to give E (1.05 g, 90%), mp >300 °C.

Ethyl 5-Ethyl-8-oxo-2,3,5,8-tetrahydrofuro[3,2-*b*][1,8]naphthyridine-7-carboxylate (19)——A mixture of crude **18** (300 mg) and 5% Pd–C (200 mg) in MeOH (30 ml) was hydrogenated at room temperature under atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated to dryness to give **19** (250 mg, 93%), which was used in the next reaction without further purification.

5-Ethyl-8-oxo-2,3,5,8-tetrahydrofuro[3,2-*b*][1,8]naphthyridine-7-carboxylic Acid (F)——a) By Hydrolysis of **19**: A suspension of crude **19** (240 mg) in 10% NaOH (5 ml) was heated at 100 °C for 1 h with stirring, then cooled. The solution was acidified with 10% HCl and the resulting precipitate was collected and recrystallized from $CHCl_3$–EtOH to give F (155 mg, 71%), mp 292 °C. *Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.77; H, 4.72; N, 10.59.

b) By Catalytic Hydrogenation of E: Compound E (100 mg) dissolved in MeOH (50 ml) was hydrogenated in the presence of 5% Pd–C (100 mg) at an initial pressure of 4 atm. The catalyst was filtered off and the filtrate was concentrated to dryness to give F, which was identical with the product described above.

Acknowledgement The authors wish to thank Dr. Y. Osada and the staff of the Laboratory of Microbiology, and the Analytical Section.

References and Notes

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