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Synthesis of Antimicrobial Agents. IV.[1] Synthesis and Antimicrobial Activities of Imidazo[4,5-*b*][1,8]naphthyridine Derivatives

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As part of a search for new antimicrobial agents, some 3,5-disubstituted 5,8-dihydro-8-oxoimidazo and triazolo[4,5-*b*][1,8]naphthyridine-7-carboxylic acids and related compounds, which contain a new ring system, were prepared. The reactions of 6-amino-7-alkylamino-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine derivatives (**3**, **7**, **11**, **12** and **35**) with acid, acetic anhydride, ethyl orthoformate and ethylxanthate afforded several imidazo[4,5-*b*][1,8]naphthyridine derivatives. Treatment of the diamines (**11** and **12**) with sodium nitrite gave the triazolo[4,5-*b*][1,8]naphthyridine derivatives (**15** and **16**). Reaction of the 7-acetylamino-4-hydroxy-1,8-naphthyridine-3-carboxylate (**17**) with 1,2-bromochloroethane gave different products (**24** and **27**), depending upon the reaction conditions. 3-Methyl-5-vinyl-5,8-dihydro-8-oxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylic acid (**38**) was prepared by successive chloroethylation, nitration, chlorination, substitution with methylamine, reduction of the nitro group, imidazole cyclization and elimination of hydrogen chloride with simultaneous hydrolysis of the ester group.

Some compounds obtained in this work showed activity nearly equal to that of pipemidic acid, but were slightly less active against *Ps. aeruginosa*.

Keywords——antimicrobial activity; imidazo[4,5-*b*][1,8]naphthyridine; triazolo[4,5-*b*][1,8]naphthyridine; imidazo[1,2,3-*i*,*j*][1,8]naphthyridine; 3-carboxy-4-pyridone moiety; imidazole cyclization; 6,7-diamino[1,8]naphthyridine

In our previous paper,[1] it was reported that 8-ethyl-5,8-dihydro-5-oxothiazolo[5,4-*b*][1,8]naphthyridine-6-carboxylic acid (B) exhibited higher antimicrobial activities than the corresponding quinoline compound (A)[3] against the bacteria tested. Therefore, our attention was directed to the synthesis of its analogs, the imidazo and triazolo naphthyridine derivatives (C).

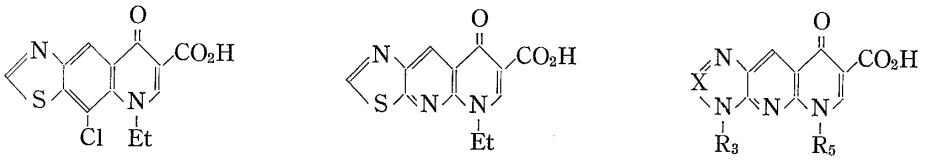

Fig. 1.

For the synthesis of imidazo[4,5-*b*][1,8]naphthyridine derivatives, having a new ring system, 6,7-disubstituted 1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates (**1**) and (**2**)[4] were chosen as starting materials. Treatment of **2** with aqueous methylamine in EtOH at 60° for 30 min, which caused simultaneous amidation of the ester group, gave the methylamide (**3**). Heating **3** in acetic anhydride gave the imidazo[4,5-*b*][1,8]naphthyridine (**4**) as needles in 83% yield. Its nuclear magnetic resonance (NMR) spectrum (CF_3COOH) exhibited a singlet signal (3H) at 4.32 ppm due to the 2-methyl group of the imidazole ring. Compound

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

(**4**) was hydrolyzed to the corresponding acid (**5**) with $NaNO_2$ in H_2SO_4 in 36% yield. The 3-aryl-imidazo[4,5-*b*][1,8]naphthyridine derivative (**9**) was synthesized from **1** *via* **6**, **7** and **8**. After hydrogenation of **6**[4] with PtO_2, the resulting diamino derivative (**7**) was heated in 98% formic acid to give the 3-*p*-chlorophenylimidazo[4,5-*b*][1,8]naphthyridine derivative (**8**), which was hydrolyzed to the desired acid **9** by heating with a mixture of conc. HCl–90% AcOH (1:11).

Next, compound (**2**) was hydrolyzed in the same manner as **8** to give the corresponding acid (**10**). Reaction of **10** with a large excess of primary amines afforded the 7-alkylamino-3-carboxylic acids (**11** and **12**), which were heated with ethyl orthoformate in DMF, resulting in imidazole ring cyclization to give the imidazo[4,5-*b*][1,8]naphthyridine derivatives **13** and **14**, respectively.

For the synthesis of triazolo[4,5-*b*][1,8]naphthyridine derivatives (**15** and **16**) in which the imidazole nucleus in **13** and **14** was replaced by a triazole nucleus, the diamino acids **11** and **12** were treated with $NaNO_2$ in 80% H_2SO_4 with cooling. The structures of **15** and **16** thus obtained were confirmed by the similarity of the absorption patterns in their infrared (IR) spectra to those of **13** and **14**, and by their mass spectra and elemental analysis data (Chart 1).

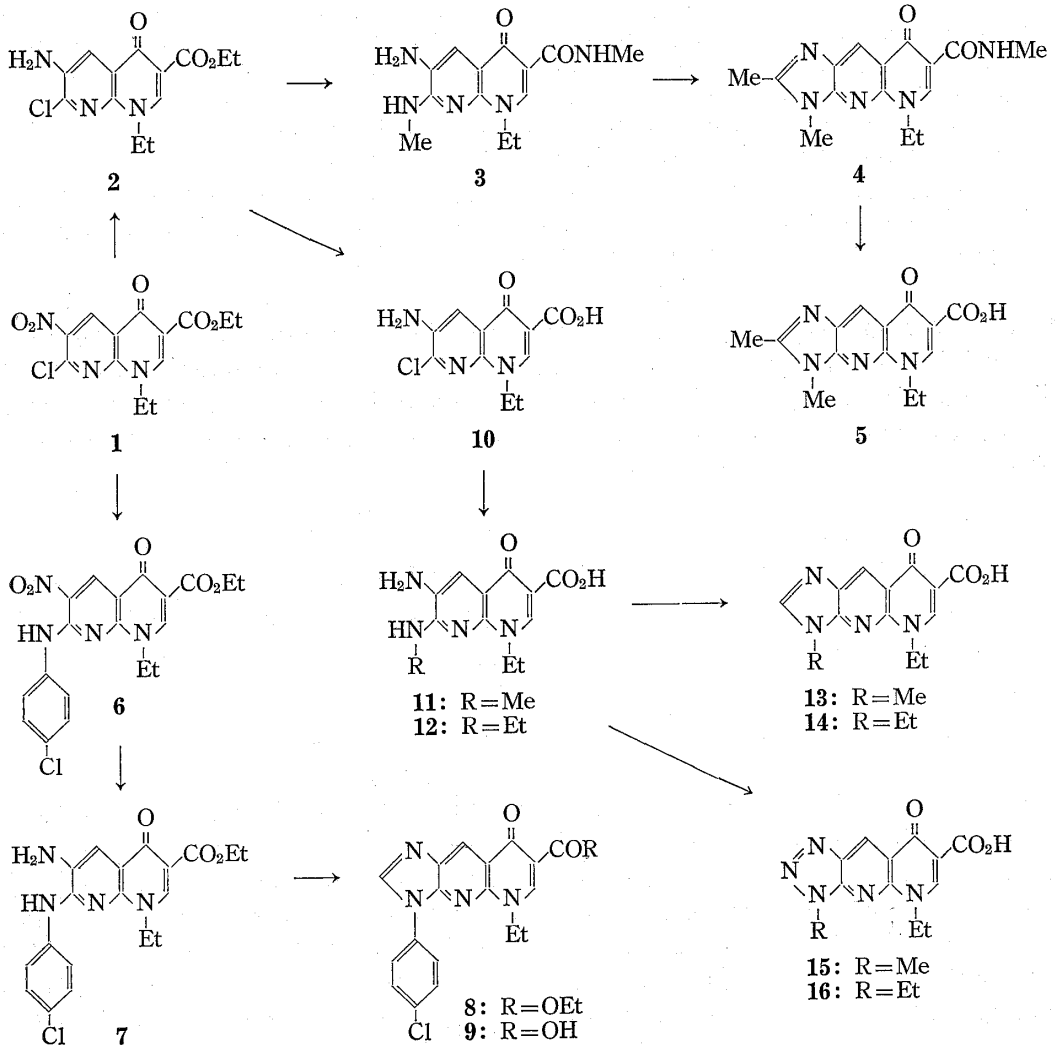

Chart 1

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

In the case of 1-alkyl-7-piperazinyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids, Minami *et al.*[5] reported that the *in vitro* activity of the N-vinyl derivative is similar to that of the N-ethyl derivative and, furthermore, that the N-vinyl compounds are better as regards systemic activity. Since the compound (**13**) obtained above showed good antibacterial activity, we attempted to synthesize the corresponding 3-methyl-5-vinyl-5,8-dihydro-8-oxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylic acid (**38**) to examine the equivalence of the N-vinyl and N-ethyl moieties (Chart 2).

Hydroxyethylation of **17** with ethylene bromohydrin in the presence of potassium carbonate in DMF followed by hydrolysis of the resulting 1-hydroxyethyl ester (**18**) with sodium hydroxide solution gave the corresponding acid (**19**). Nitration of **19** with conc. HNO_3 in conc. H_2SO_4 yielded the mononitro derivative (**20**) as a sole product, which was found to have a molecular weight of 277 and empirical formula of $C_{11}H_7N_3O_6$ by mass spectrometry and elemental analysis. The NMR spectrum showed signals of two ring protons as singlets and four protons due to the ethylene group (N–CH_2–CH_2–N) as a multiplet. These spectral data suggested that imidazole cyclization had occurred at the same time. The structure of the nitration product was determined to be 9-nitro-1,4,5,6,7,8-hexahydro-1,8-dioxoimidazo[1,2,3-*i*,*j*][1,8]naphthyridine-2-carboxylic acid (**20**). Reaction of **20** with ethyl iodide in the prescence of potassium carbonate in DMF afforded the corresponding ethyl ester (**21**). Reaction of **20** with thionyl chloride at 50—60° and successive treatment with anhyd. EtOH gave the dichloro ester (**22**), which was subsequently converted to the corresponding carboxylic acid (**23**) by acid hydrolysis.

Chloroethylation of **17** with 1,2-bromochloroethane in the presence of potassium carbonate in DMF gave two products, depending upon the reaction conditions. Firstly, heating **17** at 110—120° for 5 hr gave colorless needles as a sole product in 42% yield. Its NMR spectrum (CF_3COOH) showed four protons at 5.64 ppm as a singlet signal which was assignable to the protons of the ethylene group (N–CH_2–CH_2–N). The elemental analysis data and mass spectrum indicated the molecular formula $C_{15}H_{15}N_3O_4$ (M^+ m/e=301). Based on the above spectral data, it was concluded to be an imidazole-cyclized product, ethyl 8-acetylimino-1,4,5,6,7,8-hexahydro-1-oxoimidazo[1,2,3-*i*,*j*][1,8]naphthyridine-2-carboxylate (**24**). It was converted into the corresponding 8-imino acid (**26**) by acid hydrolysis and to the 8-oxo acid (**25**) by hydrolysis in NaOH solution. The latter was identical with an authentic sample prepared by the method of Minami *et al.*[6] Secondly, the compound **17** was heated at 60—65° for 40 min. Colorless crystals thus obtained, mp 111—113°, showed the empirical formula $C_{15}H_{14}ClN_3O_4$ on elemetal analysis and mass spectroscopy. Its NMR spectrum (CF_3COOH) showed two pairs of broad triplets at 4.18 and 5.28 assignable to the chloroethyl group. Based on the above spectral and analytical data, this compound was confirmed to be ethyl 7-acetylamino-1-chloroethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**27**). Treatment of **27** with sodium ethoxide in dioxane at room temperature overnight gave the 1-vinyl-7-amino acid (**28**) in 24% yield. Nitration of **28** with conc. HNO_3 in conc. H_2SO_4 at 70—80° afforded the devinylated product (**29**), which was identical with an authentic sample prepared by the method of Carboni.[7] Nitration of **27** with conc. HNO_3 in conc. H_2SO_4 at 80—85° gave exclusively ethyl 1-chloroethyl-7-hydroxy-6-nitro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**30**). Heating **30** with a mixture of phosphoryl chloride and DMF at 60—70° in order to prevent replacement of the nitro group with a chlorine atom gave the 6-nitro-7-chloro ester (**31**), successive reduction of which with iron powder in acetic acid afforded the 6-amino ester (**32**). To eliminate hydrogen chloride and simultaneously hydrolyze the ester group,

5) S. Minami, J. Matsumoto, M. Shimizu and Y. Takabe (Dainippon Pharm), DOS 2362552 (20. 6. 74); *Chem. Abstr.*, **81**, 105562 (1974). Dainippon Pharm., Belg. Pat. 821481 (25. 4. 75).
6) S. Mishio, T. Hirose, A. Minamida, J. Matsumoto and S. Minami, Abstracts of Papers, 95th Annual Meeting of the Pharmaceutical Society of Japan, April, 1976, 120.
7) S. Carboni, A. Da. Settimo, P.L. Ferrarini and I. Tonetti, *Gazz. Chim. Ital.*, **101**, 129 (1971).

32 was treated with sodium methoxide under mild reaction conditions, giving the acid (33). The NMR spectrum of this acid indicated the absence of the vinyl group and showed a singlet signal at 4.48 ppm due to the methyl group and a pair of broad triplet signals at 4.19 and 5.29 ppm assignable to the chloroethyl group. In mass spectrometry, the most characteristic fragment ion, *m/e* 217 (M^+-CO_2, $-CH_2Cl$), indicates the presence of the chloroethyl group.

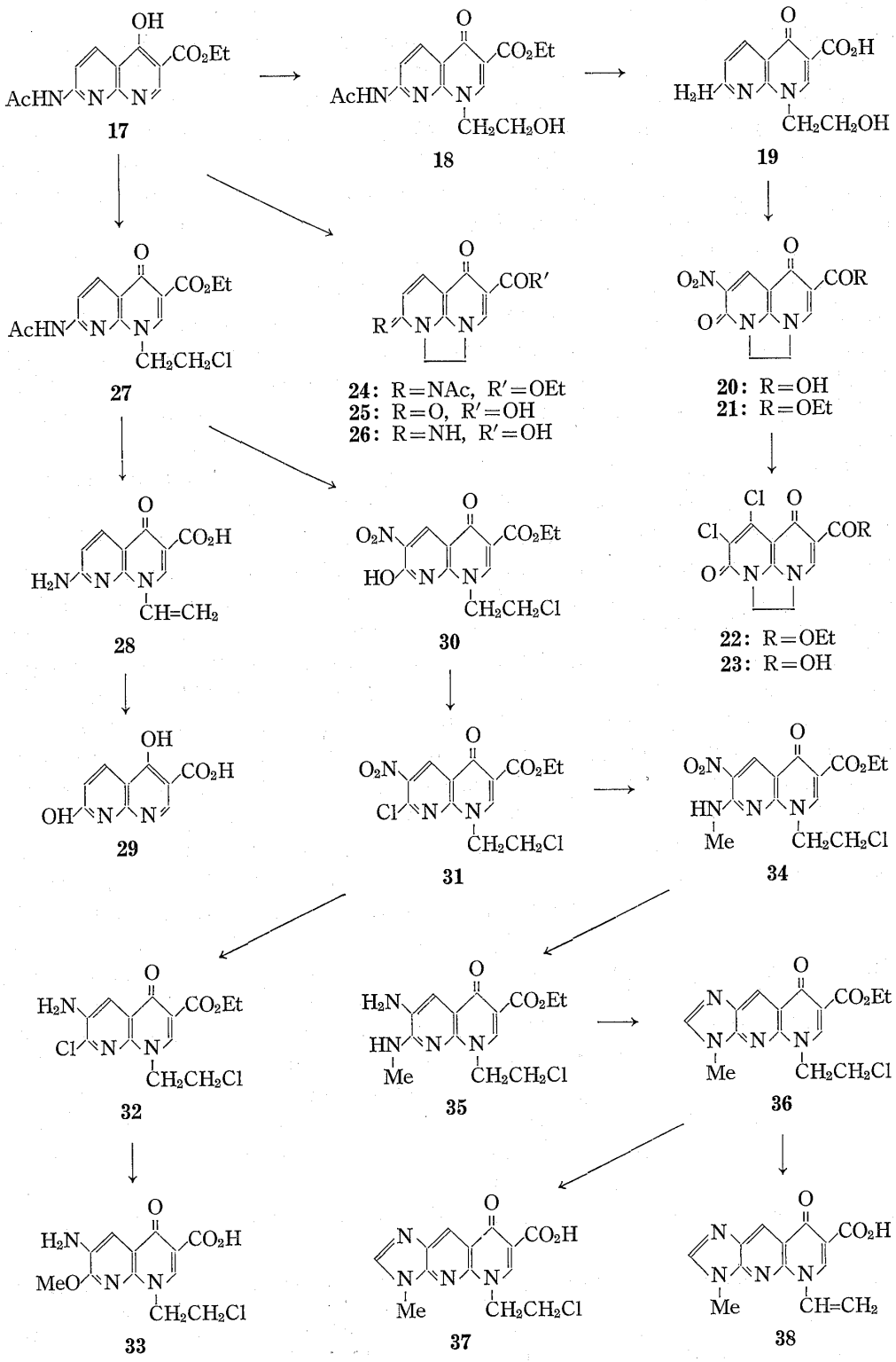

Chart 2

Based on these spectral data, **33** was unexpectedly concluded to be 6-amino-1-chloroethyl-7-methoxy-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

Reaction of **31** with aqueous methylamine in EtOH at room temperature for 30 min afforded **34** quantitatively. After reduction of **34** with iron powder in acetic acid, the diamino ester (**35**) obtained was heated with ethyl orthoformate in DMF, resulting in imidazole ring cyclization to give the imidazo[4,5-*b*][1,8]naphthyridine derivative (**36**), which was hydrolyzed with acid to the corresponding acid (**37**). On treatment with sodium methoxide in dioxane at room temperature, the compound (**36**) underwent elimination of hydrogen chloride accompanied by simultaneous hydrolysis of the ester group to give the desired 5-vinyl-imidazo-[4,5-*b*][1,8]naphthyridine-7-acid (**38**) in 35% yield.

Refluxing of **11** with potassium ethylxanthate in EtOH resulted in imidazole ring closure to afford the 2-mercapto-imidazo[4,5-*b*][1,8]naphthyridine derivative (**39**) in 58% yield. Reaction of **39** with methyl iodide in an alkaline medium at room temperature gave the 2-methylthio-7-acid (**40**). It was evident that the product was not the N-methly but the S-methyl derivative, since it was oxidized by potassium permanganate in acetic acid to give the 2-hydroxy-6-acid (**41**). Alkylation of **41** with methyl iodide in DMF in the presence of potassium carbonate gave the 1,3-dimethyl-6-acid (**42**) which was converted into the corresponding methyl ester (**46**), *via* its acid chloride. In part III of this series,[1] we reported that the reaction of 8-ethyl-2-methylthio-5,8-dihydro-5-oxothiazolo[5,4-*b*][1,8]naphthyridine-6-carboxylic acid with dimethyl sulfate in DMF gave the 2-dimethylamino and the 3-methyl-2-oxo derivatives. We applied this reaction to the imidazo[4,5-*b*][1,8]naphthyridine derivative. The 2-methylthio-6-acid (**40**) was heated with dimethyl sulfate in DMF at 130—140° for 30 hr, and the mixture obtained showed two spots on TLC. One of the components was presumed to be unchanged **40** from its *Rf* value on TLC. The products were difficult to separate from each other, because both of them were sparingly soluble in various organic solvents. Therefore the mixture was converted into the corresponding esters (**44** and **45**) and they were then purified by silica gel chromatography. The compound (**44**) provided

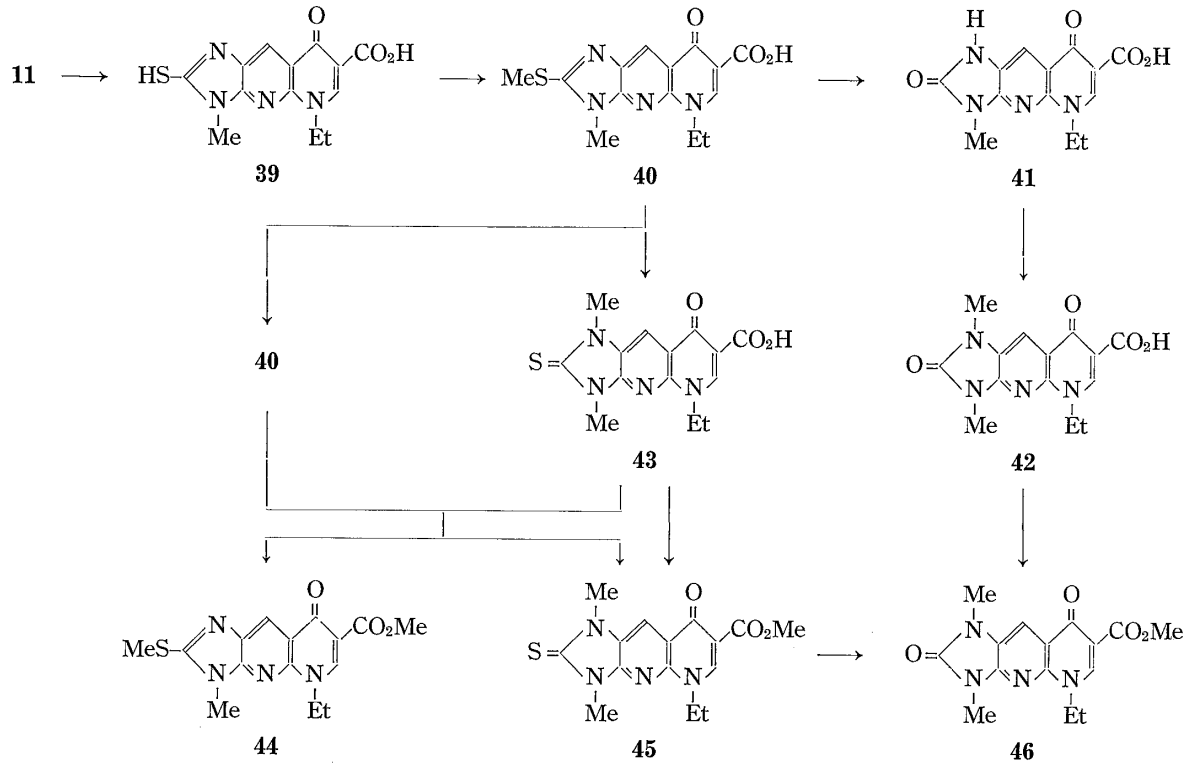

Chart 3

the starting material (**40**) on hydrolysis. The main product **45** was hydrolyzed with acid to the corresponding acid (**43**). From the empirical formula, $C_{14}H_{14}N_4O_3S$, it was assumed to be the 1,3-dimethyl-2-thioxo acid. Heating **45** with mercuric acetate in DMF at 130° for 3 hr afforded the 2-oxo derivative (**46**) in 84% yield; this was identical with the product obtained by esterification of **42**. Therefore the structure of the product obtained from the reaction of **40** with dimethyl sulfate was determined to be 5-ethyl-1,3-dimethyl-1,2,5,8-tetrahydro-8-oxo-2-thioxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylic acid (**43**) (Chart 3).

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

Compd. No.	R_5	R_3	X	Organism: *Staphylococcus aureus* 209p	*Escherichia coli* NIHJ	*Shigella flexneri* 2a 5503	*Proteus mirabilis* 1287	*Pseudomonas aeruginosa* 2063
13	Et	Me	CH	25	6.25	3.13	1.56	100
14	Et	Et	CH	25	3.13	3.13	3.13	>100
38	$CH=CH_2$	Me	CH	100	0.78	3.13	3.13	100
15	Et	Me	N	12.5	3.13	1.56	1.56	>100
16	Et	Et	N	12.5	6.25	3.13	1.56	>100
Pipemidic Acid				25	3.13	0.78	3.13	50
Compound B				3.13	0.2	0.39	0.2	50

The *in vitro* antibacterial activities of the imidazo and triazolo[4,5-*b*][1,8]naphthyridine derivatives obtained above were tested by the serial agar dilution method.[8] The minimum inhibitory concentrations (MIC, μg/ml) are listed in Table I. Among them, **13**, **14**, **15**, **16** and **38** exhibited activities similar to those of the related drug, pipemidic acid, against the five pathogens tested, but none of the others showed significant activities. The replacement of the thiazole ring in compound B with an imidazole ring caused a decrease of the activity. The triazolo naphthyridine derivatives (**15** and **16**) were found to have activities similar to those of the corresponding imidazo naphthyridine derivatives (**13** and **14**). The N-vinyl (**38**) and the N-ethyl (**13**) compounds appear to be equivalent in the case of the imidazo[4,5-*b*]-[1,8]naphthyridine derivatives. Substitution with bulky groups at the 2 and 3 positions and the formation of 1,3-disubstituted-2-thioxo and oxo derivatives appear to decrease the activity. These results are quite similar to those observed in the series of thiazolo[4,5-*g*]-quinoline and thiazolo[5,4-*b*][1,8]naphthyridine derivatives.

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 tetramethyl silane as an internal standard. Abbreviations: s=singlet, d=doublet, t=triplet, and m=multiplet. Mass spectra were run on a Hitachi RMU-6D mass spectrometer.

6-Amino-1-ethyl-7-methylamino-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxymethylamide (3)——A mixture of **2** (2.0 g) and 30% aq. methylamine (10 ml) in EtOH (30 ml) was stirred at 60° for 30 min. After cooling, the deposited solid was recrystallized from MeOH to give **3** (1.77 g, 95%) as needles, mp above 300°. *Anal.* Calcd for $C_{13}H_{17}N_5O_2$: C, 56.71; H, 6.23; N, 25.44. Found: C, 56.37; H, 6.05; N, 25.06.

2,3-Dimethyl-5-ethyl-5,8-dihydro-8-oxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxymethylamide (4)——A suspension of **3** (200 mg) in acetic anhydride (3 ml) was heated under reflux for 3 hr. The reaction mixture was evaporated to dryness *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extracts were subjected to chromatography on silica gel. The fraction eluted with $CHCl_3$ gave **4** (180 mg, 83%) as needles,

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

mp above 300°. NMR (CF_3COOH) ppm: 3.24 (3H, s), 3.22 (3H, s), 4.32 (3H, s), 9.58 (1H, s), 9.62 (1H, s). *Anal.* Calcd for $C_{15}H_{17}N_5O_2$: C, 60.18; H, 5.73; N, 23.40. Found: C, 59.78; H, 5.70; N, 23.00.

2,3-Dimethyl-5-ethyl-5,8-dihydro-8-oxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylic Acid (5)—A mixture of **4** (144 mg) and $NaNO_2$ (78 mg) in conc. H_2SO_4 (2 ml) was heated at 80—100° for 5 hr. The reaction mixture was poured onto crushed ice and neutralized with $NaHCO_3$. The deposited solid was recrystallized from DMF–MeOH to give **5** (49 mg, 36%) as pale yellow needles, mp above 300°. *Anal.* Calcd for $C_{14}H_{17}N_5O_2$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.41; H, 4.99; N, 19.57.

Ethyl 3-*p*-Chlorophenyl-5-ethyl-5,8-dihydro-8-oxoimidazo[4,5-b][1,8]naphthyridine-7-carboxylate (8)——A solution of **6** (2.0 g) in DMF (20 ml) and EtOH (30 ml) was hydrogenated with PtO_2 (0.2 g) at atmospheric pressure for 3 hr. After removal of the catalyst by filtration, the filtrate was concentrated to give the crude diamine (**7**). This diamine, without further purification. was heated under reflux with formic acid (30 ml) for 5 hr. After cooling, insoluble material was removed by filtration and the filtrate was concentrated. Water was added to the residue and the resulting precipitate was collected. Recrystallization from $CHCl_3$–EtOH gave **8** (0.74 g, 39%) as colorless needles, mp 262—264°. *Anal.* Calcd for $C_{20}H_{17}ClN_4O_3$: C, 60.53; H, 4.32; N, 14.12; Found: C, 60.10; H, 4.25; N, 14.37.

Hydrolysis of 8——A mixture of **8** (300 mg) in conc. HCl-90% AcOH (1: 11) (3 ml) was heated under reflux for 1 hr. The solid obtained on addition of water was recrystallized from DMF to give **9** (146 mg, 52%) as needles, mp above 300°. *Anal.* Calcd for $C_{18}H_{13}ClN_4O_3$: C, 58.62; H, 3.55; N, 15.19. Found: C, 58.29; H, 3.99; N, 15.45.

6-Amino-7-chloro-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (10)——A suspension of **2** (0.80 g) in conc. HCl–90% AcOH (1: 11) (8 ml) was stirred at 100° for 5 hr. After removal of the solvent, the residue was crystallized from DMF to give **10** (0.53 g, 73%) as needles, mp above 300°. *Anal.* Calcd for $C_{11}H_{10}ClN_3O_3$: C, 49.36; H, 3.77; N, 15.70. Found: C, 49.21; H, 3.82; N, 15.59.

7-Alkylamino-6-amino-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (11, 12)——i) A mixture of **10** (1.0 g) and 40% aq. methylamine (20 ml) in EtOH (20 ml) was heated at 90—100° in a sealed tube for 5 hr. After cooling, a small quantity of insoluble material was removed by filtration, and the filtrate was concentrated. The solid obtained was recrystallized from DMF–EtOH to give **11** (0.82 g, 83%) as pale brown needles, mp above 300°. *Anal.* Calcd for $C_{12}H_{14}N_4O_3$: C, 54.95; H, 5.38; N, 21.36. Found: C, 55.14; H, 5.68; N, 21.40.

ii) The compound **12** was obtained in 75% yield by the reaction of **10** with 70% aq. ethylamine as described above, mp above 300°. *Anal.* Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.58; H, 5.77; N, 20.68.

3-Alkyl-5-ethyl-5,8-dihydro-8-oxoimidazo[5,4-*b*][1,8]naphthyridine-7-carboxylic Acid (13, 14)——i) A mixture of **11** (120 mg) and ethyl orthoformate (1 ml) in DMF (2 ml) was heated under reflux for 15 hr with stirring. After cooling, the deposited solid was recrystallized from DMF to give **13** (57 mg, 46%) as colorless needles, mp above 300°. *Anal.* Calcd for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.17; H, 4.61; N, 20.12.

ii) Compound **14** was prepared in 87% yield by the reaction of **12** with ethyl orthoformate in a similar manner, mp above 300°. *Anal.* Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.72; H, 5.03; N, 19.57.

3-Alkyl-5-ethyl-5,8-dihydro-8-oxotriazolo[5,4-*b*][1,8]naphthyridine-7-carboxylic Acid (15, 16)——i) $NaNO_2$ (0.25 g) was added to a suspension of **11** (0.50 g) in 80% H_2SO_4 (10 ml) under ice-water cooling, with stirring. The reaction mixture was stirred at this temperature for 3 hr and then for 2 hr at room temperature. The solid deposited on addition of ice-water was recrystallized from DMF to give **15** (0.37 g, 71%) as needles, mp 275—295°. MS (*m/e*): 273 (M^+), 229. *Anal.* Calcd for $C_{12}H_{11}N_5O_3$: C, 52.74; H, 4.06; N, 25.63. Found: C, 53.15; H, 4.17; N, 25.83.

ii) In a manner similar to that described above, the reaction of **12** and $NaNO_2$ gave **16** in a yield of 86%, mp 272—275°. *Anal.* Calcd for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found: C, 53.95; H, 4.51; N, 24.22.

Ethyl 7-Acetylamino-1-hydroxyethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (18) and Hydrolysis of the Ester——A mixture of **17** (27.5 g), K_2CO_3 (41 g) and ethylenebromohydrin (14 g) in DMF (300 ml) was heated at 110—120° for 4 hr with stirring. After removal of the solvent by evaporation, the residue was treated with $CHCl_3$. The $CHCl_3$ extract was washed with water and the solvent was removed. The crude product was recrystallized from $CHCl_3$–EtOH to give **18** (6.5 g) as colorless prisms, mp 263—265°. *Anal.* Calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.11; H, 5.58; N, 12.87.

The materials insoluble in the $CHCl_3$ and aqueous layers were hydrolyzed with 10% NaOH solution and acidified with dil. HCl. The precipitate deposited was collected and crystallized from DMF–EtOH to afford **19** (12.7 g) as colorless needles, mp above 300°. *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.88; H, 4.50; N, 16.45.

9-Nitro-1,4,5,6,7,8-hexahydro-1,8-dioxoimidazo[1,2,3-*i,j*][1,8]naphthyridine-2-carboxylic Acid (20)——Conc. HNO_3 (d 1.42, 21 g) was added dropwise to a solution of **19** (20.9 g) in conc. H_2SO_4 (210 ml) and the reaction mixture was stirred at 80—85° for 1 hr. The solution was poured onto ice and the resulting precipitate was collected by filtration. Recrystallization of the crude product **20** (16.9 g, 77%) from DMF–

EtOH gave light yellow needles, mp above 300°. MS *m/e*: 277 (M^+). NMR (CF_3COOH) ppm: 9.36 (1H, s), 9.29 (1H, s), 4.7—5.4 (4H, m, $-N-CH_2-CH_2-N-$). *Anal.* Calcd for $C_{11}H_7N_3O_6$: C, 47.66; H, 2.55; N, 15.16. Found: C, 47.72; H, 2.79; N, 15.50.

Ethyl 9-Nitro-1,4,5,6,7,8-hexahydro-1,8-dioxoimidazo[1,2,3-*i*,*j*][1,8]naphthyridine-2-carboxylate (21)——A mixture of **20** (590 mg), K_2CO_3 (828 mg) and EtI (624 mg) in DMF (5 ml) was heated at 100—110° for 6 hr with stirring, then concentrated. After addition of water to the residue, the resulting solid was collected and recrystallized from DMF–EtOH to afford **21** (370 mg, 57%) as yellow needles, mp 295—297°. MS (*m/e*): 305 (M^+), 233. *Anal.* Calcd for $C_{13}H_{11}N_3O_6 \cdot H_2O$: C, 48.30; H, 4.05; N, 13.00. Found: C, 48.03; H, 3.82; N, 12.88.

Ethyl 9,10-Dichloro-1,4,5,6,7,8-hexahydro-1,8-dioxoimidazo[1,2,3-*i*,*j*][1,8]naphthyridine-2-carboxylate (22)——A suspension of **20** (14.0 g) in $SOCl_2$ (70 ml) was stirred at 40—50° for 3 hr, then the reaction mixture was poured into anhyd. EtOH. After concentration of the mixture, the residue was washed with water and crystallized from DMF to give **22** (1.9 g, 11%) as needles, mp above 300°. NMR (CF_3COOH) ppm: 9.24 (1H, s, C–2H). *Anal.* Calcd for $C_{13}H_{10}Cl_2N_2O_4$: C, 47.44; H, 3.03; N, 8.51. Found: C, 47.46; H, 3.23; N, 8.57.

9,10-Dichloro-1,4,5,6,7,8-hexahydro-1,8-dioxoimidazo[1,2,3-*i*,*j*][1,8]naphthyridine-2-carboxylic Acid (23)——A mixture of **22** (1.0 g) in conc. HCl–90% AcOH (1:11) (9 ml) was stirred at 100° for 1 hr. The solid deposited on cooling was recrystallized from DMF to give **23** (0.7 g, 77%) as yellow needles, mp above 300°. *Anal.* Calcd for $C_{11}H_6Cl_2N_2O_4$: C, 43.88; H, 2.01; N, 9.31. Found: C, 43.97; H, 2.28; N, 9.67.

Ethyl 8-Acetylimino-1,4,5,6,7,8-hexahydro-1-oxoimidazo[1,2,3-*i*,*j*][1,8]naphthyridine-2-carboxylate (24)——A mixture of **17** (35.0 g), 1,2-bromochloroethane (27.0 g) and K_2CO_3 (35.0 g) in DMF (350 ml) was stirred at 110—120° for 5 hr. After concentration, the reaction mixture was treated with water and filtered. The remaining solid was recrystallized from EtOH to give **17** (16.1 g, 42%) as colorless needles, mp 222—223°. MS *m/e*: 301 (M^+). NMR (CF_3COOH) ppm: 9.81 (1H, s), 9.34 (2H, s), 5.63 (4H, s), 4.79 (2H, q), 2.68 (1H, s), 1.59 (3H, t). *Anal.* Calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.68; H, 5.03; N, 13.81.

Ethyl 7-Acetylamino-1-chloroethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (27)——A mixture of **17** (50.0 g), 1,2-bromochloroethane (28.5 g) and powdered K_2CO_3 (26.0 g) in DMF (400 ml) was stirred at 60—65° for 40 min. The reaction mixture was poured into water and extracted with $CHCl_3$. The extract was washed with water and concentrated *in vacuo* to leave crude **27** (30.4 g, 49%). Recrystallization from $CHCl_3$–EtOH gave **27**, mp 111—113°. NMR (CF_3COOH): 9.57 (1H, s), 9.06 (2H, q), 5.28 (2H, bt), 4.18 (2H, bt), 2.59 (3H, s), 4.78 (2H, q), 1.60 (3H, t). *Anal.* Calcd for $C_{15}H_{16}ClN_3O_4$: C, 53.34; H, 4.78; N, 12.44. Found: C, 53.52; H, 4.63; N, 12.56.

1,4,5,6,7,8-Hexahydro-1,8-dioxoimidazo[1,2,3-*i*,*j*][1,8]naphthyridine-2-carboxylic Acid (25)——i) A suspension of **27** (1.5 g) in 10% NaOH (24 ml) and EtOH (10 ml) was heated under reflux and concentrated. The solid deposited on acidification with dil. HCl was recrystallized from DMF to give **25** (0.5 g, 49%) as yellow needles, mp above 300°, this compound was identical with the sample obtained by Minami *et al.*

ii) Compound **25** was prepared in 65% yield by the reaction of **24** with 10% NaOH in a manner similar to that described above.

1,4,5,6,7,8-Hexahydro-8-imino-1-oxoimidazo[1,2,3-*i*,*j*][1,8]naphthyridine-2-carboxylic Acid (26)——A mixture of **24** (0.50 g) in 20% HCl (6 ml) was heated under reflux for 3 hr. The reaction mixture, after neutralization with K_2CO_3 followed by acidification with AcOH, was concentrated. The solid deposited was recrystallized from DMF to give **26** (0.10 g, 26%) as colorless needles, mp above 300°. *Anal.* Calcd for $C_{11}H_9N_3O_3 \cdot 1/4 \cdot H_2O$: C, 56.05; H, 4.06; N, 17.83. Found: C, 56.19; H, 4.43; N, 17.71.

7-Amino-1-vinyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (28)——NaOEt solution (4.0 g of Na and 300 ml of anhyd. EtOH) was added to a suspension of **27** (9.3 g) in dioxane (50 ml) and the mixture was stirred at room temperature overnight. After removal of the solvent, water was added to the residue and undissolved materials were removed by filtration. The solid deposited on acidification was washed with water and recrystallized from DMF to give **28** (1.6 g, 25%) as needles, mp above 300°. NMR (CF_3COOH) ppm: 9.23 (1H, s), 8.52 (2H, d), 7.18 (2H, d), 7.82 (1H, q, N–C<u>H</u>=CH_2), 5.7—6.1 (2H, m, N–CH=C<u>H</u>$_2$). *Anal.* Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 56.84; H, 3.93; N, 17.84.

Nitration of 28——Conc. HNO_3 (1.5 g) was added dropwise to a solution of **28** (1.5 g) in conc. H_2SO_4 (15 ml). After stirring the reaction mixture at 70—80° for 2 hr, it was poured onto ice and the resulting precipitate was collected by filtration. Crystallization of the crude product from DMF gave **29** (0.85 g, 63%) as light yellow needles, mp above 300°; this compound was identical with an authentic sample. MS *m/e*: 206 (M^+). NMR (CF_3COOH) ppm: 8.57 (1H, d), 7.15 (1H, d), 9.28 (1H, s).

Ethyl 1-Chloroethyl-7-hydroxy-6-nitro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (30)——Conc. HNO_3 (d 1.42, 15 g) was added dropwise to a solution of **27** (15.2 g) in conc. H_2SO_4 (150 ml), keeping the reaction temperature at 80—85°. After stirring the reaction mixture for 1 hr at the same temperature, it was poured onto ice and the solid deposited was recrystallized from $CHCl_3$–EtOH to give **30** (10.0 g, 65%) as pale yellow needles, mp 275—285°. NMR (CF_3COOH) ppm: 9.51 (1H, s), 9.76 (1H, s), 5.22 (2H, bs), 4.15 (2H, bs). *Anal.* Calcd for $C_{13}H_{12}ClN_3O_6$: C, 45.69; H, 3.54; N, 12.30. Found: C, 45.83; H, 3.53; N, 12.84.

Ethyl 7-Chloro-1-chloroethyl-6-nitro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (31)——A mixture of **30** (3.8 g), $POCl_3$ (25 ml) and DMF (5 ml) was stirred at 60—70° for 1 hr. After cooling, the reaction mixture was poured into ice-water and the solid deposited was recrystallized from $CHCl_3$–EtOH to give **31** (3.3 g, 82%), mp 130—132°. *Anal.* Calcd for $C_{13}H_{11}Cl_2N_3O_5$: C, 43.35; H, 3.08; N, 11.67. Found: C, 43.16; H, 3.09; N, 11.82.

Ethyl 1-Chloroethyl-7-methylamino-6-nitro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (34)——A mixture of **31** (2.0 g) and 30% aq. methylamine (3 ml) in EtOH (20 ml) was stirred at room temperature for 0.5 hr. The solid deposited on cooling was recrystallized from EtOH to give **34** (quantitatively) as yellow needles, mp 239—242°. *Anal.* Calcd for $C_{14}H_{15}ClN_4O_5$: C, 47.40; H, 4.26; N, 15.79. Found: C, 47.64; H, 4.25; N, 16.11.

Ethyl 6-Amino-7-chloro-1-chloroethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (32)——A mixture of **31** (3.3 g) and Fe powder (7.0 g) in AcOH (100 ml) was gently warmed on a water bath, until a vigorous reaction began. When the initial reaction had slowed down, the mixture was heated at 80° for 1 hr, then concentrated. Water was added to the residue and the resulting solid was recrystallized from $CHCl_3$–EtOH to give **32** (2.5 g, 84%), mp above 250°. *Anal.* Calcd for $C_{13}H_{13}Cl_2N_3O_3$: C, 47.29; H, 3.97; N, 12.73. Found: C, 47.04; H, 3.96; N, 12.84.

6-Amino-1-chloroethyl-7-methoxy-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (33)——Compound **32** (660 mg) in NaOMe solution (160 mg of Na and 15 ml of anhyd. MeOH) was stirred at room temperature overnight. Water was added to the reaction mixture and a small quantity of insoluble material was removed by filtration, then the filtrate was acidified with dil. HCl. The product deposited was recrystallized from DMF–EtOH to give **33** (360 mg, 60%) as needles, mp above 300°. MS *m/e*: 299, 297, 255, 261, 204, 217. NMR (CF_3COOH) ppm: 9.48 (1H, s), 8.92 (1H, s), 5.29 (2H, bt), 4.19 (2H, bt), 4.48 (3H, s). *Anal.* Calcd for $C_{12}H_{12}ClN_3O_4$: C, 48.41; H, 4.06; N, 14.12. Found: C, 48.61; H, 4.01; N, 14.44.

Ethyl 5-Chloroethyl-3-methyl-5,8-dihydro-8-oxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylate (36)——Fe powder (6.0 g) was added portionwise to a solution of **34** (3.3 g) in acetic acid (100 ml) with stirring, keeping the temperature at 80—85°. The mixture was stirred and kept at the same temperature for 1 hr, then the insoluble material was removed by filtration and the filtrate was concentrated. H_2O was added to the residue and the deposited crude **35** (mp 156—160° decomp.) was collected. A mixture of crude **35** and ethyl orthoformate (8 ml) in DMF (5 ml) was heated under reflux for 3 hr. The solid deposited on cooling was recrystallized from DMF to give **36** (1.4 g, 36%) as pale yellow needles, mp 258—262°. NMR (CF_3COOH) ppm: 10.00 (1H, s), 9.82 (1H, s), 9.74 (1H, s), 4.22 (3H, s), 5.50 (2H, bt), 4.21 (2H, bt), 4.76 (2H, q), 1.57 (3H, t). *Anal.* Calcd for $C_{15}H_{15}ClN_4O_3$: C, 53.82; H, 4.52; N, 16.74. Found: C, 53.87; H, 4.52; N, 17.03.

5-Chloroethyl-3-methyl-5,8-dihydro-8-oxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylic Acid (37)——Compound **36** (780 mg) was heated to reflux in conc. HCl–90% AcOH (1:11) (6 ml) for 3 hr. After removal of the solvent, the residue was washed with H_2O and recrystallized from DMF to give **37** (550 mg, 76%) as pale yellow needles, mp above 300°. *Anal.* Calcd for $C_{13}H_{11}ClN_4O_3$: C, 50.91; H, 3.62; N, 18.27. Found: C, 50.94; H, 3.69; N, 18.49.

3-Methyl-5-vinyl-5,8-dihydro-8-oxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylic Acid (38)——NaOMe solution (690 mg of Na and 15 ml of MeOH) was added to a suspension of **36** (495 mg) in absolute dioxane (8 ml) and the mixture was stirred at room temperature for 25 hr. The reaction mixture was poured into H_2O and acidified. Recrystallization of the resulting solid from DMF gave **38** (141 mg, 35%) as pale yellow needles, mp above 300°. NMR (CF_3COOH) ppm: 9.80 (1H, s), 9.63 (2H, s), 4.32 (3H, s), 8.02 (1H, N–C<u>H</u>=CH_2), 5.6—6.1 (2H, N–CH=C<u>H</u>$_2$). *Anal.* Calcd for $C_{13}H_{10}N_4O_3$: C, 57.77; H, 3.73; N, 20.71. Found: C, 57.74; H, 3.85; N, 21.09.

5-Ethyl-2-mercapto-3-methyl-5,8-dihydro-8-oxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylic Acid (39)——A solution of ethylxanthate was prepared by dissolving KOH (225 mg) in H_2O (1.3 ml) and EtOH (25 ml) followed by addition of CS_2 (1 ml) with shaking. To this solution, **11** (655 mg) was added and the mixture was heated under reflux for 5 hr, then the solvent was removed by filtration. A small amount of H_2O was added to the residue and it was acidified with dil. HCl. The solid obtained was recrystallized from DMF to give **39** (438 mg 58%) as pale brown needles, mp above 300°. NMR (CF_3COOH) ppm: 9.59 (1H, s), 8.78 (1H, s), 4.04 (3H, s), 5.22 (2H, q), 1.87 (3H, t). *Anal.* Calcd for $C_{13}H_{12}N_4O_3S$: C, 51.30; H, 3.98; N, 18.41. Found: C, 51.45; H, 4.11; N, 18.45.

5-Ethyl-2-methylmercapto-3-methyl-5,8-dihydro-8-oxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylic Acid (40)——MeI (2 ml) was added to a solution of **39** (445 mg) in EtOH (2 ml) and H_2O (10 ml) containing KOH (252 mg). The reaction mixture was stirred at room temperature for 12 hr. A large amount of water was added to the reaction mixture to dissolve the resulting potassium salts and a small quantity of insoluble material was removed by filtration. The clear filtrate was acidified with dil. HCl. The separated solid was recrystallized from DMF to give **40** (431 mg, 93%) as colorless needles, mp above 300°. *Anal.* Calcd for $C_{14}H_{14}N_4O_3S$: C, 52.82; H, 4.43; N, 17.60. Found: C, 52.79; H, 4.57; N, 17.14.

5-Ethyl-3-methyl-1,2,5,8-tetrahydro-2,8-dioxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylic Acid (41)——A suspension of **40** (500 mg) in AcOH (15 ml) was treated dropwise with 8% $KMnO_4$ solution (5 ml) at room temperature. After stirring for 1.5 hr, the suspension was treated with $NaHSO_3$. The remaining

solid was recrystallized from DMF to give **41** (151 mg, 33%) as needles, mp above 300°. *Anal.* Calcd for $C_{13}H_{12}N_4O_4$: C, 54.10; H, 4.20; N, 19.44. Found: C, 53.81; H, 4.45; N, 19.81.

5-Ethyl-1,3-dimethyl-1,2,5,8-tetrahydro-2,8-dioxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylic Acid (42)——A mixture of **41** (0.22 g) MeI (1.14 g) and K_2CO_3 (0.55 g) in DMF (20 ml) was stirred at 100° for 2 hr. After concentration, the reaction mixture was treated with water and filtered. Recrystallization from AcOEt gave **42** (0.17 g, 73%) as colorless needles, mp above 300°. *Anal.* Calcd for $C_{14}H_{14}N_4O_4$: C, 55.62; H, 4.67; N, 18.54. Found: C, 55.55; H, 4.83; N, 18.60.

Methyl 5-Ethyl-1,3-dimethyl-1,2,5,8-tetrahydro-2,8-dioxoimidazo[5,4-*b*][1,8]naphthyridine-7-carboxylate (46)——A suspension of **42** (31 mg) in $SOCl_2$ (1 ml) was stirred at room temperature for 1 hr. The reaction mixture was poured into anhyd. MeOH. After stirring for 10 min, the suspension was concentrated and the residue was washed with water. Recrystallization from EtOH gave **46** (17 mg, 53%) as colorless needles, mp 261—262°. *Anal.* Calcd for $C_{15}H_{16}N_4O_4$: C, 56.95; H, 5.10; N, 17.71. Found: C, 56.72; H, 4.96; N, 17.65.

Methyl 5-Ethyl-1,3-dimethyl-1,2,5,8-tetrahydro-5-oxo-2-thioxoimidazo[4,5-*b*][1,8]naphthyridine-7-carboxylate (45)——A mixture of **40** (318 mg) and dimethyl sulfate (630 mg) in DMF (3 ml) was stirred at 130—140° for 30 hr and cooled. The resulting precipitate was colleced, washed with ether and dried to give a mixture (254 mg) of **40** and **43**. The product (250 mg) was added to a mixture of K_2CO_3 (500 mg) and MeI (300 mg) in DMF (10 ml), and the reaction mixture was stirred for 3 hr at 100°, then filtered. The filtrate was concentrated to dryness and the residue was extracted with $CHCl_3$. Concentration of the dried extract gave a mixture of **44** and **45**. The mixture was chromatographed on a silica gel column. Elution with benzene–AcOEt (5:1) gave **45** (127 mg) as colorless needles, mp above 300°. *Anal.* Calcd for $C_{15}H_{16}N_4O_3S$: C, 54.20; H, 4.85; N, 16.86. Found: C, 54.16; H, 4.94; N, 16,83.

Hydrolysis of Ester 45——A suspension of **45** (50 mg) in conc. HCl–90% AcOH (1:11) (3 ml) was stirred at 100° for 2.5 hr. The solid deposited on addition of water was recrystallized from DMF to give **43** (35 mg, 73%) as needles, mp above 300°. *Anal.* Calcd for $C_{14}H_{14}N_4O_3S$: C, 52.82; H, 4.43; N, 17.60. Found: C, 52.52; H, 4.61; N, 17.40.

Conversion of the 2-Thioxo Derivative (45) to the 2-Oxo Derivative (46)——A mixture of **45** (50 mg) and mercuric acetate (150 mg) in DMF (3 ml) was stirred at 130° for 3 hr. After cooling, insoluble material was removed by filtration and the filtrate was concentrated. The residue was extracted with $CHCl_3$ and the extract was evaporated to dryness. Recrystallization from EtOH gave **46** (40 mg, 84%) as colorless needles. The product was identical (IR spectrum) with an authentic sample obtained from **42**.

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