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Pyridonecarboxylic Acids as Antibacterial Agents. V.[1] Synthesis of 1-Vinyl-1,4-dihydro-4-oxo-1,8- and 1,6-naphthyridine-3-carboxylic Acids[2]

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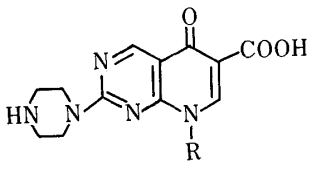
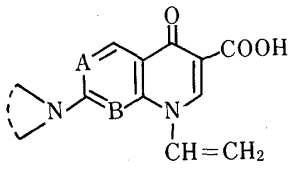
A series of 7-substituted 1,4-dihydro-4-oxo-1-vinyl-1,8- and 1,6-naphthyridine-3-carboxylic acids (**5a**—**e** and **13a**—**c**) was prepared. During the preparation of **5a**, unexpected compounds (**4**, **7** and **8**) were also obtained. Structural elucidation of these compounds was achieved on the basis of chemical and spectral (ultraviolet, mass and proton nuclear magnetic resonance) data. The structure–antibacterial activity relationships are discussed.

Keywords——1,8-naphthyridine; 1,6-naphthyridine; imidazo[1,2,3-*ij*][1,8]naphthyridine; pyridonecarboxylic acid; synthesis; NOE experiment; antibacterial activity; structure–activity relationship

Our previous study[4] on structure–antibacterial activity relationships (SARs) of a series of pyrido[2,3-*d*]pyrimidine derivatives (I) showed that the introduction of a vinyl group into position 8 caused an increase in activity, particularly against Gram-negative bacteria. The present study was undertaken to determine whether a similar relationship holds in case of the 1,8- and 1,6-naphthyridine analogues (IIa and IIb) having the vinyl group at position 1. Several by-products were obtained during the preparation of IIa and their structures were elucidated.



Ia: R=Et
Ib: R=CH=CH$_2$



IIa: A=CH, B=N
IIb: A=N, B=CH

Chart 1

Chemistry

Ethyl 7-chloro-1,4-dihydro-1-(2-hydroxyethyl)-4-oxo-1,8-naphthyridine-3-carboxylate (**1**)[5] was treated with thionyl chloride to give the 1-(2-chloroethyl) analogue **2**. Displacement reaction of **2** with either an *N*-substituted piperazine or pyrrolidine in ethanol took place smoothly to give the corresponding ethyl 7-substituted 1-(2-chloroethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates (**3a**—**e**) in good to excellent yields. It was expected that treatment of **3** with a strong base would permit the elimination of hydrogen chloride from the *N*-(chloroethyl) group of **3** in preference to the substitution at the methylene carbon bearing the chloro group. In fact, treatment of **3a** with 10% sodium hydroxide in ethanol produced the 7-(1-piperazinyl)-1-vinyl derivative **5a** in an excellent yield. On the other hand, when **3a** was

treated with a weak base such as potassium carbonate, ring closure of its ethylene group occurred across the N^1 and N^8 atoms with concomitant cleavage of the 7-piperazinyl group and resulted in the formation of the imidazo[1,2,3-*ij*][1,8]naphthyridine derivative **4** in a quantitative yield. The other vinyl analogues **5b—e** were similarly prepared by treatment of the corresponding *N*-(chloroethyl) compounds **3b—e** with 10% sodium hydroxide. The assigned structures of these products were confirmed by spectral analysis.

When 1-bromo-2-chloroethane was allowed to react with ethyl 7-chloro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**6**)[5] in order to prepare **2** in a one-step process, compounds **7** and **8** were unexpectedly formed in 5 and 25% yields, respectively, besides the desired compound **2** in 40% yield. The structures of these by-products were assigned on the

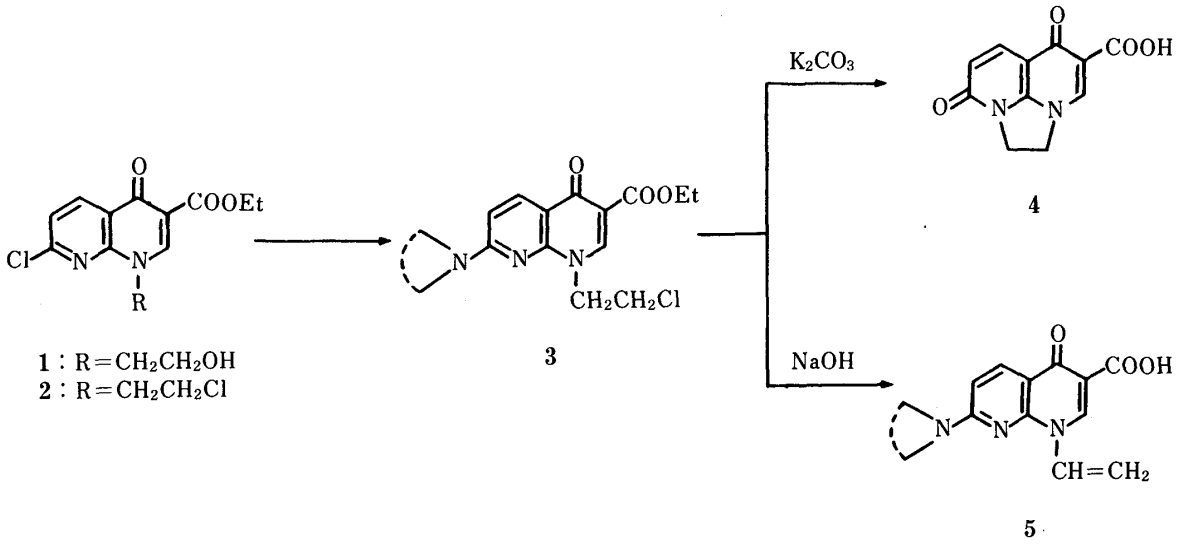


Chart 2

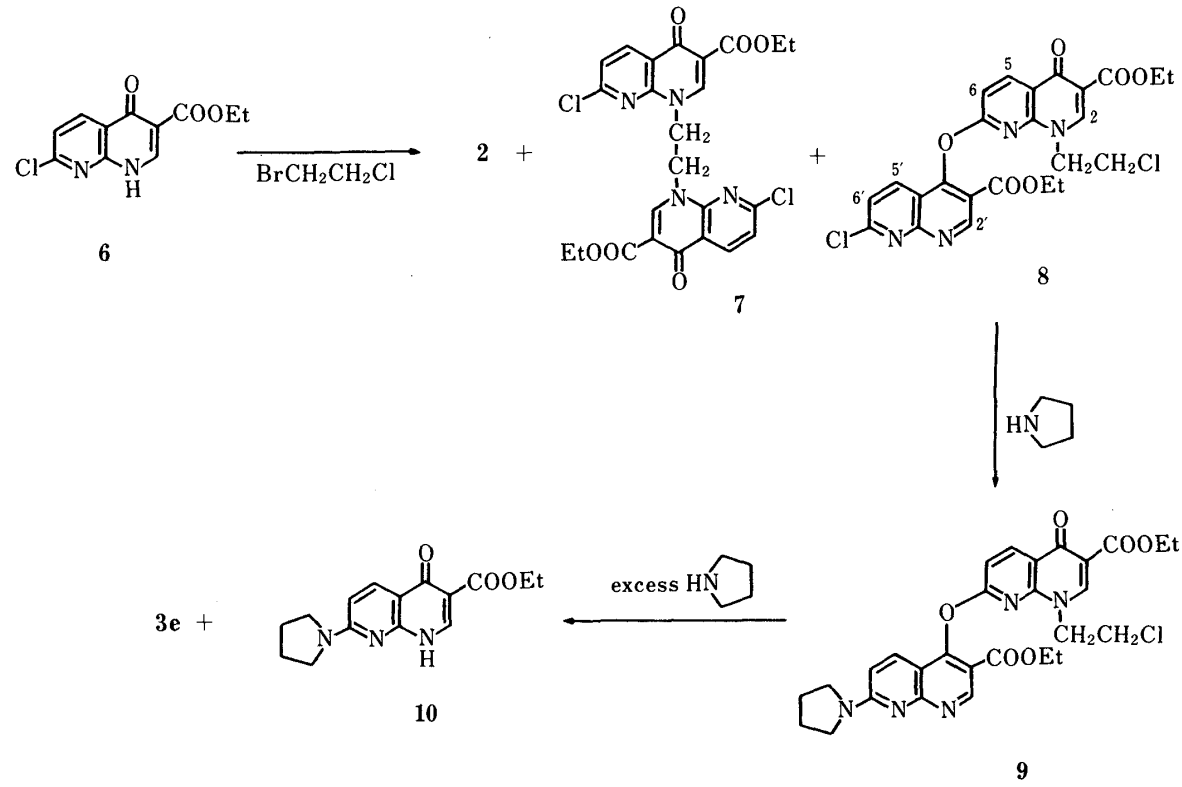
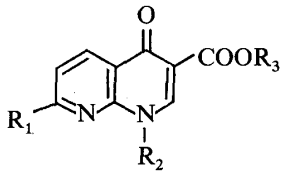


Chart 3

TABLE I. 1,7-Disubstituted 1,4-Dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids and Their Esters



Compd. No.	R_1	R_2	R_3	Yield (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found)			
							C	H	Cl	N
3a	EtOOCN N	CH_2CH_2Cl	Et	85	174—175 (AcOEt)	$C_{20}H_{25}ClN_4O_5$	54.98 (54.83	5.77 5.86	8.12 8.21	12.83 12.71)
3b	MeN N	CH_2CH_2Cl	Et	75	125—127 (Me_2CO–*n*-Hexane)	$C_{18}H_{23}ClN_4O_3$	57.06 (57.01	6.11 5.88	9.36 9.21	14.79 14.77)
3c	$PhCH_2N$ N	CH_2CH_2Cl	Et	92	123—124 (AcOEt–*n*-Hexane)	$C_{24}H_{27}ClN_4O_3$	63.36 (63.46	5.98 5.96	7.79 7.97	12.32 12.24)
3d	AcN N	CH_2CH_2Cl	Et	77	169—170 (MeCN)	$C_{19}H_{23}ClN_4O_4$	56.09 (56.26	5.70 5.93	8.72 8.85	13.77 13.88)
3e	N	CH_2CH_2Cl	Et	72	200—201 (MeCN)	$C_{17}H_{20}ClN_3O_3$	58.37 (58.54	5.76 5.79	10.14 10.32	12.01 12.18)
5a	HN N	$CH=CH_2$	H	81	266—268 (DMF)	$C_{15}H_{16}N_4O_3$	59.99 (60.07	5.37 5.53	— —	18.66 18.62)
5b	MeN N	$CH=CH_2$	H	75	238—239 (EtOH)	$C_{16}H_{18}N_4O_3$	61.13 (61.36	5.77 5.59	— —	17.83 18.04)
5c	$PhCH_2N$ N	$CH=CH_2$	H	85	203—205 (AcOEt)	$C_{22}H_{22}N_4O_3$	67.67 (67.50	5.68 5.51	— —	14.35 14.15)
5d	AcN N	$CH=CH_2$	H	80	261—262 (DMF)	$C_{17}H_{18}N_4O_4$	59.64 (59.79	5.30 5.20	— —	16.37 16.41)
5e	N	$CH=CH_2$	H	69	>300 (DMF)	$C_{15}H_{15}N_3O_3$	63.15 (63.08	5.30 5.13	— —	14.73 14.81)

basis of spectral (proton nuclear magnetic resonance (^{1}H-NMR), ultraviolet (UV) and mass) and chemical evidence. Thus, the mass spectra (MS) and elemental analysis of **7** and **8** revealed their molecular formulae to be both $C_{24}H_{20}Cl_2N_4O_6$. The ^{1}H-NMR spectrum of **7** (Table II) showed the presence of three aromatic protons, being indicative of a symmetrical structure for **7**. Furthermore, the symmetrical feature is strongly supported by the appearance of a fragment peak of $1/2\,M^+$ at m/z 265 in the MS of **7**. The UV spectrum of **7** was practically the same as that of ethyl 7-chloro-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate[5] having a pyridone chromophore (Fig. 1). These data were fully in accord with the assigned structure **7**, 1,2-bis(7-chloro-3-ethoxycarbonyl-1,4-dihydro-4-oxo-1,8-naphthyridin-1-yl)ethane.

In the ^{1}H-NMR spectrum of **8**, an nuclear Overhauser effect (NOE) (19% enhancement of the intensity) of the signal of C_2-H at δ 8.71 was observed upon irradiation at δ 4.76 (signal due to the *N*-methylene protons). The singlet at δ 9.04 was assigned to $C_{2'}$-H on the pyridinol ring because of its appearance at lower field than δ 8.71 for C_2-H on the pyridone ring.[5] The presence of both pyridone and pyridinol moieties in **8** was supported by its UV spectrum (Fig. 1). Treatment of **8** with 2 mol eq of pyrrolidine in chloroform gave a 92% yield of **9**. Further treatment of **9** with an excess of pyrrolidine gave **3e** and ethyl 1,4-

TABLE II. ^{1}H-NMR Data for Compounds **2**, **7**, **8** and **9**

Compd. No.	Solvent	Chemical shift, δ (J, Hz)						
		C_2-H	$C_{2'}$-H	C_5-H	$C_{5'}$-H	C_6-H	$C_{6'}$-H	$-CH_2CH_2-$
2	$CDCl_3$	8.66 (s)	—	8.73 (d, J=8)	—	7.40 (d, J=8)	—	4.00, 4.70 (each t, J=6)
7	CF_3COOD	9.85 (s)	—	9.04 (d, J=8)	—	7.98 (d, J=8)	—	4.76 (s)
8	$CDCl_3$	8.71 (s)	9.04 (s)	8.74 (d, J=8)	8.99 (d, J=8.5)	7.48 (d, J=8)	7.88 (d, J=8.5)	4.04, 4.76 (each t, J=5.5)
9	$CDCl_3$	8.70 (s)	8.90 (s)	8.90 (d, J=8)	8.45 (d, J=8.5)	8.06 (d, J=8)	6.52 (d, J=8.5)	4.04, 4.78 (each t, J=5)

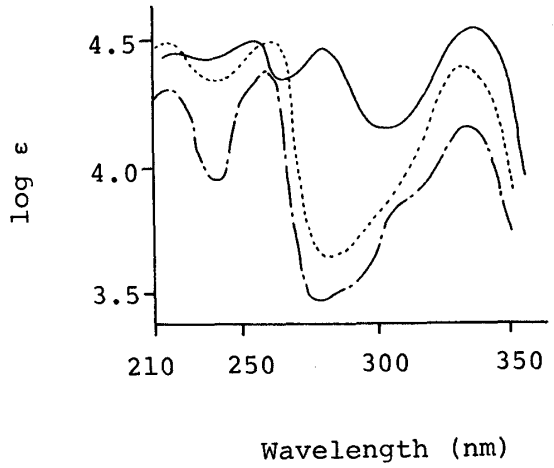
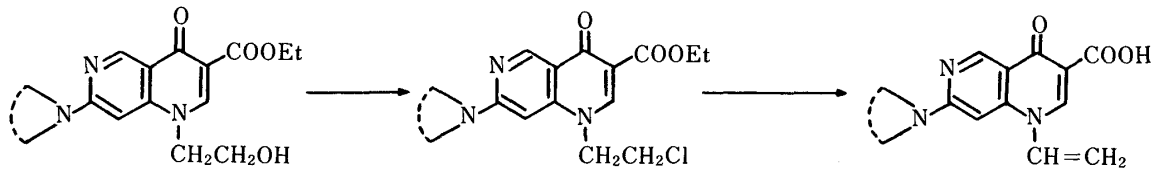


Fig. 1. UV Spectra of Compounds **7** (----) and **8** (——), and Ethyl 7-Chloro-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (—·—)



11 **12** **13**

Chart 4

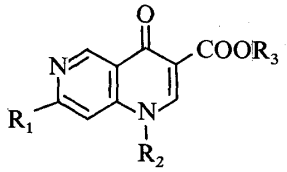
dihydro-4-oxo-7-(1-pyrrolidinyl)-1,8-naphthyridine-3-carboxylate (**10**) in 18 and 52% yields, respectively. Compounds **3e** and **10** were identical with authentic specimens. These spectral and chemical findings permit assignment of the structure of **8** as ethyl 1-(2-chloroethyl)-7-7′-chloro-3′-ethoxycarbonyl-1′,8′-naphthyridine-4′-oxy-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate.

1,4-Dihydro-4-oxo-7-(4-substituted 1-piperazinyl)-1-vinyl-1,6-naphthyridine-3-carboxylic acids (**13a—c**) were analogously prepared by chlorination of 1-(2-hydroxyethyl)-1,6-naphthyridines **11a—c**[5] with thionyl chloride, followed by treatment of 1-(2-chloroethyl)-1,6-naphthyridines **12a—c** with 5% potassium hydroxide (Chart 4).

Structure–Activity Relationships

The *in vitro* antibacterial activities (minimal inhibitory concentrations, MICs) of the 1-vinyl-1,8- and 1,6-naphthyridine derivatives (**5a—e** and **13a—c**) are given in Table IV, which includes the MICs of their 1-ethyl counterparts,[5] pipemidic acid (Ia) and its vinyl analogue

TABLE III. 1,7-Disubstituted 1,4-Dihydro-4-oxo-1,6-naphthyridine-3-carboxylic Acids and Their Esters



Compd. No.	R_1	R_2	R_3	Yield (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found)			
							C	H	Cl	N
12a	EtOOC	CH_2CH_2Cl	Et	78	205—208 (EtOH)	$C_{20}H_{25}ClN_4O_5$	54.98 (54.73	5.77 5.50	8.12 8.45	12.82 12.76)
12b	Me	CH_2CH_2Cl	Et	56	218—219 (MeCN)	$C_{18}H_{23}ClN_4O_3$	57.06 (57.18	6.12 6.17	9.36 9.71	14.79 14.84)
12c	$PhCH_2$	CH_2CH_2Cl	Et	47	210—212 (MeCN)	$C_{24}H_{27}ClN_4O_3$	63.36 (63.17	5.98 5.96	7.79 7.79	12.32 12.04)
13a	HCl·HN	$CH=CH_2$	H	65	248—249 (H_2O)	$C_{15}H_{16}N_4O_3 \cdot HCl$	53.50 (53.66	5.09 5.13	10.53 10.35	16.46 16.57)
13b	Me	$CH=CH_2$	H	69	229—230 (EtOH)	$C_{16}H_{18}N_4O_3$	61.13 (61.15	5.77 5.62	— —	17.83 17.59)
13c	$PhCH_2$	$CH=CH_2$	H	96	206—208 (EtOH)	$C_{22}H_{22}N_4O_3$	67.67 (67.79	5.68 5.65	— —	14.35 14.65)

TABLE IV. *In Vitro* Antibacterial Activity

Compound No.	Minimum inhibitory concentration (μg/ml)		
	S. aureus TERAJIMA	*E. coli* K-12	*P. aeruginosa* TSUCHIJIMA
5a	100 (30)[a]	1 (3)	10 (10)
5b	>100 (100)	1 (1)	10 (30)
5c	10 (10)	3 (1)	>100 (>100)
5d	>100 (100)	3 (10)	100 (>100)
5e	10 (10)	1 (1)	30 (>100)
13a	>100 (>100)	3 (3)	30 (30)
13b	100 (30)	3 (3)	30 (100)
13c	10 (3)	1 (1)	100 (100)
Ib	>100 (30)	3 (1)	3 (10)

a) Figures in parentheses represent MICs of the corresponding 1-ethyl derivatives.

(Ib)[4] for comparison.

The vinyl compounds **5** and **13** exhibit enhanced activity against Gram-negative bacteria (*Escherichia coli* K-12 and *Pseudomonas aeruginosa* TSUCHIJIMA) compared with the 1-ethyl congeners, whereas they tend to show lower activity against Gram-positive *Staphylococcus aureus* TERAJIMA. The 1,8-naphthyridine derivatives (**5**) are generally more active than the corresponding 1,6-naphthyridine analogues (**13**), particularly against Gram-negative bacteria. The intermediate ethyl esters (**3**, **11** and **12**) and the by-products (**4**, **7**, **8** and **9**) are practically inactive.

The present study thus demonstrates a similarity in SARs between the 1-vinylnaphthyridine derivatives and the corresponding 8-vinylpyrido[2,3-*d*]pyrimidine analogues discussed

in our previous paper.[4]

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 215 spectrometer. UV spectra were measured in EtOH on a Shimadzu MPS-5000 spectrometer. NMR spectra were recorded on a Varian A-60 or HA-100D in a $CDCl_3$ solution, unless otherwise specified, with tetramethylsilane as an internal standard. MS were determined with a Hitachi RMU-6L spectrometer. Organic extracts were dried over anhydrous $MgSO_4$.

Ethyl 7-Chloro-1-(2-chloroethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (2)——A mixture of ethyl 7-chloro-1,4-dihydro-1-(2-hydroxyethyl)-4-oxo-1,8-naphthyridine-3-carboxylate (**1**)[5] (3.9 g, 13 mmol) and thionyl chloride ($SOCl_2$) (1.45 ml, 20 mmol) in dry $CHCl_3$ (50 ml) was refluxed for 2 h with stirring. The mixture was cooled and poured into ice-water, and the $CHCl_3$ layer was washed successively with saturated $NaHCO_3$ solution and water. The $CHCl_3$ solution was dried, and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel using $CHCl_3$ as an eluent to give **2** (2.88 g, 70%), which was recrystallized from EtOH as pale yellow needles, mp 148—149 °C. *Anal.* Calcd for $C_{13}H_{12}Cl_2N_2O_3$: C, 49.54; H, 3.84; Cl, 22.50; N, 8.89. Found: C, 49.56; H, 3.65; Cl, 22.80; N, 8.59. IR ν_{max}^{KBr} cm^{-1}: 1670, 1640. NMR (60 MHz) δ: 4.00 (2H, t, J=6 Hz, $NCH_2\underline{CH_2}Cl$), 4.70 (2H, t, J=6 Hz, $N\underline{CH_2}CH_2Cl$), 7.40 (1H, d, J=8 Hz, C_6-H), 8.66 (1H, s, C_2-H), 8.73 (1H, d, J=8 Hz, C_5-H).

Ethyl 7-Substituted 1-(2-Chloroethyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (3a—e)——General Procedure: A mixture of **2** (6 mmol), an appropriate amine (18 mmol), and EtOH (50 ml) was refluxed for 1—3 h. After removal of the solvent and the excess amine, the resulting residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried, and concentrated to dryness *in vacuo*. The residual solid was recrystallized from an appropriate solvent to give **3a—e** (Table I).

1,2,3,6,9,10-Hexahydro-6,9-dioxoimidazo[1,2,3-*ij*][1,8]naphthyridine-5-carboxylic Acid (4)——To a solution of **3a** (4.37 g, 10 mmol) in EtOH (50 ml) was added aqueous 10% K_2CO_3 (100 mmol) and the mixture was refluxed for 2 h. The EtOH was distilled off *in vacuo* and the residual aqueous solution was acidified with AcOH. The precipitate was collected, washed with water, and recrystallized from dimethylformamide (DMF) to give **4** (2.25 g, 97%) as pale yellow needles, mp >300 °C. *Anal.* Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.07. Found: C, 56.86; H, 3.52; N, 12.28. IR ν_{max}^{KBr} cm^{-1}: 1710, 1670. NMR (60 MHz, DMSO-d_6) δ: 4.2—4.8 (4H, m), 6.47 (1H, d, J=8 Hz, C_6-H), 7.98 (1H, d, J=8 Hz, C_5-H), 8.90 (1H, s, C_2-H). EIMS *m/z*: 232 (M^+), 188 ($M^+ - CO_2$).

7-Substituted 1,4-Dihydro-4-oxo-1-vinyl-1,8-naphthyridine-3-carboxylic Acids (5a—e)——General Procedure: To a solution of **3** (10 mmol) in EtOH (50 ml) was added aqueous 10% NaOH (100 mmol) and the mixture was refluxed for 1—2 h. The EtOH was distilled off *in vacuo*. The residual aqueous solution was acidified with AcOH. The precipitate was collected, washed with water, and recrystallized from an appropriate solvent to give **5a—e** (Table I).

Reaction of Ethyl 7-Chloro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (6)[5] with 1-Bromo-2-chloroethane——1-Bromo-2-chloroethane (8.65 g, 30 mmol) was added to a mixture of **6** (5.05 g, 20 mmol) and anhydrous K_2CO_3 (4.10 g, 30 mmol) in DMF (60 ml) with stirring at 60 °C. The mixture was heated at 60—70 °C for 2 h and then filtered. The filtrate was concentrated to dryness *in vacuo*. The resulting residue was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to dryness. The residue was chromatographed on silica gel with a $CHCl_3$–MeOH mixture (50 : 1, v/v) to give **2** (2.50 g, 40%), ethyl 1-(2-chloroethyl)-7-7′-chloro-3′-ethoxycarbonyl-1′,8′-naphthyridine-4′-oxy-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**8**) (0.66 g, 25%) and 1,2-bis(7-chloro-3-ethoxycarbonyl-1,4-dihydro-4-oxo-1,8-naphthyridin-1-yl)ethane (**7**) (0.10 g, 5%). **7**: mp 283—286 °C (EtOH), colorless needles. *Anal.* Calcd for $C_{24}H_{20}Cl_2N_4O_6 \cdot 1/2\,H_2O$: C, 53.54; H, 3.92; Cl, 13.12; N, 10.37. Found: C, 53.54; H, 3.62; Cl, 13.29; N, 10.30. IR ν_{max}^{KBr} cm^{-1}: 1725, 1700. EIMS *m/z*: 530 (M^+), 458 ($M^+ - CO_2C_2H_5$), 386 ($M^+ - 2CO_2C_2H_5$), 265 (1/2 M^+). **8**: mp 246—248 °C (MeCN), colorless needles. *Anal.* Calcd for $C_{24}H_{20}Cl_2N_4O_6$: C, 54.25; H, 3.79; Cl, 13.35; N, 10.55. Found: C, 54.09; H, 3.72; Cl, 13.45; N, 10.57. IR ν_{max}^{KBr} cm^{-1}: 1730, 1700. EIMS *m/z*: 530 (M^+), 458 ($M^+ - CO_2C_2H_5$), 386 ($M^+ - 2CO_2C_2H_5$). ^{1}H-NMR data for **7** and **8** are given in Table II.

Ethyl 1-(2-Chloroethyl)-7-7′-(1-pyrrolidinyl)-3′-ethoxycarbonyl-1′,8′-naphthyridine-4′-oxy-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (9)——A mixture of **8** (2.65 g, 5 mmol) and pyrrolidine (0.92 ml, 11 mmol) in $CHCl_3$ (40 ml) was stirred overnight at room temperature. The mixutre was washed with water, dried, and concentrated to dryness. The residual solid was recrystallized from AcOEt to give **9** (2.60 g, 92%) as colorless needles, mp 138—140 °C. *Anal.* Calcd for $C_{28}H_{28}ClN_5O_6 \cdot 1/2\,H_2O$: C, 58.48; H, 5.08, Cl, 6.17; N, 12.18. Found: C, 58.40; H, 4.78; Cl, 6.46; N, 12.23. IR ν_{max}^{KBr} cm^{-1}: 1725, 1700. ^{1}H-NMR: See Table II.

Reaction of 9 with an Excess of Pyrrolidine——A mixture of **9** (1.30 g, 2.3 mmol) and pyrrolidine (0.96 ml, 11.5 mmol) in $CHCl_3$ (30 ml) was refluxed for 10 h. After the mixture had cooled, the precipitate was collected and recrystallized from DMF to give ethyl 1,4-dihydro-4-oxo-7-(1-pyrrolidinyl)-1,8-naphthyridine-3-carboxylate (**10**) (0.34 g, 52%). The filtrate was concentrated to dryness. The resulting solid was recrystallized from MeCN to give **3e** (0.14 g, 18%), which was identical with an authentic specimen (mp and IR). **10**: mp >300 °C (DMF), pale yellow needles. *Anal.* Calcd for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.61; H, 5.87; N, 14.67. IR ν_{max}^{KBr} cm^{-1}:

1680, 1620.

Ethyl 7-Substituted 1-(2-Chloroethyl)-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylate (12a—c)——General Procedure: A mixture of ethyl 7-substituted 1-(2-hydroxyethyl)-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylate (**11a—c**)[5] (2 mmol) and $SOCl_2$ (0.22 ml, 3 mmol) in dry $CHCl_3$ (30 ml) was refluxed for 1—3 h. After evaporation of the solvent and the excess $SOCl_2$, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried, and concentrated to dryness. The residual solid was recrystallized from an appropriate solvent to give **12a—c** (Table III).

7-Substituted 1,4-Dihydro-4-oxo-1-vinyl-1,6-naphthyridine-3-carboxylic Acids (13a—c)——General Procedure: A suspension of the ester **12a—c** (10 mmol) in aqueous 5% KOH (10 ml) was heated at 100 °C for 30 min, then cooled. The alkaline solution was adjusted to pH 4 with 5% HCl. The precipitate was collected, washed with water, and recrystallized from an appropriate solvent to give **13a—c** (Table III).

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References and Notes

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