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Pyridone-carboxylic Acids as Antibacterial Agents. I. Synthesis and Antibacterial Activity of 1-Alkyl-1,4-dihydro-4-oxo-1,8- and 1,6-naphthyridine-3-carboxylic Acids[1)]

Tohru Hirose, Shinsaku Mishio, Jun-ichi Matsumoto,* and Shinsaku Minami[2)]

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Enoki-cho 33-94, Suita, Osaka 564, Japan

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Condensation of 2-amino-6-chloropyridine (**1**) with diethyl ethoxymethylenemalonate gave the aminomethylenemalonate **2**, which upon thermal cyclization (Gould-Jacobs reaction) afforded ethyl 7-chloro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**3**). Alkylation of **3** produced the 1-alkyl derivative **4**. Substitution of **4** with a cyclic amine gave ethyl 7-substituted 1-alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**5**). The ester **5** was hydrolyzed to the corresponding carboxylic acid **6**. 7-Substituted 1-alkyl-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylic acids (**20**) were also synthesized from 4-amino-2-chloropyridine (**13**) in a similar manner.

The *in vitro* antibacterial activity was enhanced by the presence of a cyclic amine at position 7 on **6** and **20**. In general, the 1,8-naphthyridine **6** was more active than the 1,6-naphthyrdine counterpart **20**. 1-Ethyl-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid (**6e**) (an analog of both pipemidic acid and nalidixic acid) was comparable to pipemidic acid but superior to nalidixic acid in terms of activity *in vitro* against *Pseudomonas aeruginosa*.

Keywords——1,8-naphthyridine; 1,6-naphthyridine; NOE experiment; synthesis; antibacterial activity; structure–activity relationship

Since the finding of nalidixic acid (I),[3)] an orally effective antibacterial, much attention has been directed to studies on its analogs having a 4-pyridone-3-carboxylic acid moiety in view of their potential biological interest.[4)] A number of 1,8-naphthyridine derivatives related structurally to nalidixic acid were synthesized in an attempt to find more potent antibacterial agents.[5)] They have, for example, an alkoxy, acylamino,[5a)] carbamoyl,[5b)] or heteroaromatic group such as a 4-imidazolyl group[5c)] in place of the 7-methyl group in nalidixic acid. A synthesis and the antibacterial activity of the 1,6-naphthyridine analog were also reported.[6)] Previous studies on the pyrido[2,3-*d*]pyrimidine antibacterials,[7)] which led to the finding of piromidic acid (II) and pipemidic acid (III), revealed that the introduction of a cyclic amino group into position 2 (corresponding to position 7 in 1,8-naphthyridines) on the pyrido[2,3-*d*]-pyrimidine ring resulted in enhancement of the antibacterial activity. Therefore, it is of interest to know whether this structure-activity relationship holds for the corresponding 1,8- and 1,6-naphthyridine derivatives.

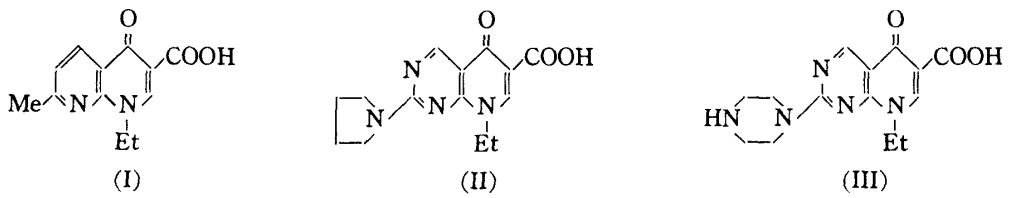


Chart 1

1,8-Naphthyridines

As a synthetic approach to the 1,8-naphthyridines, we employed thermal cyclization (Gould–Jacobs reaction) of diethyl *N*-(6-chloro-2-pyridyl)aminomethylenemalonate (**2**) which was prepared by condensation of 2-amino-6-chloropyridine (**1**) with diethyl ethoxymethylene-

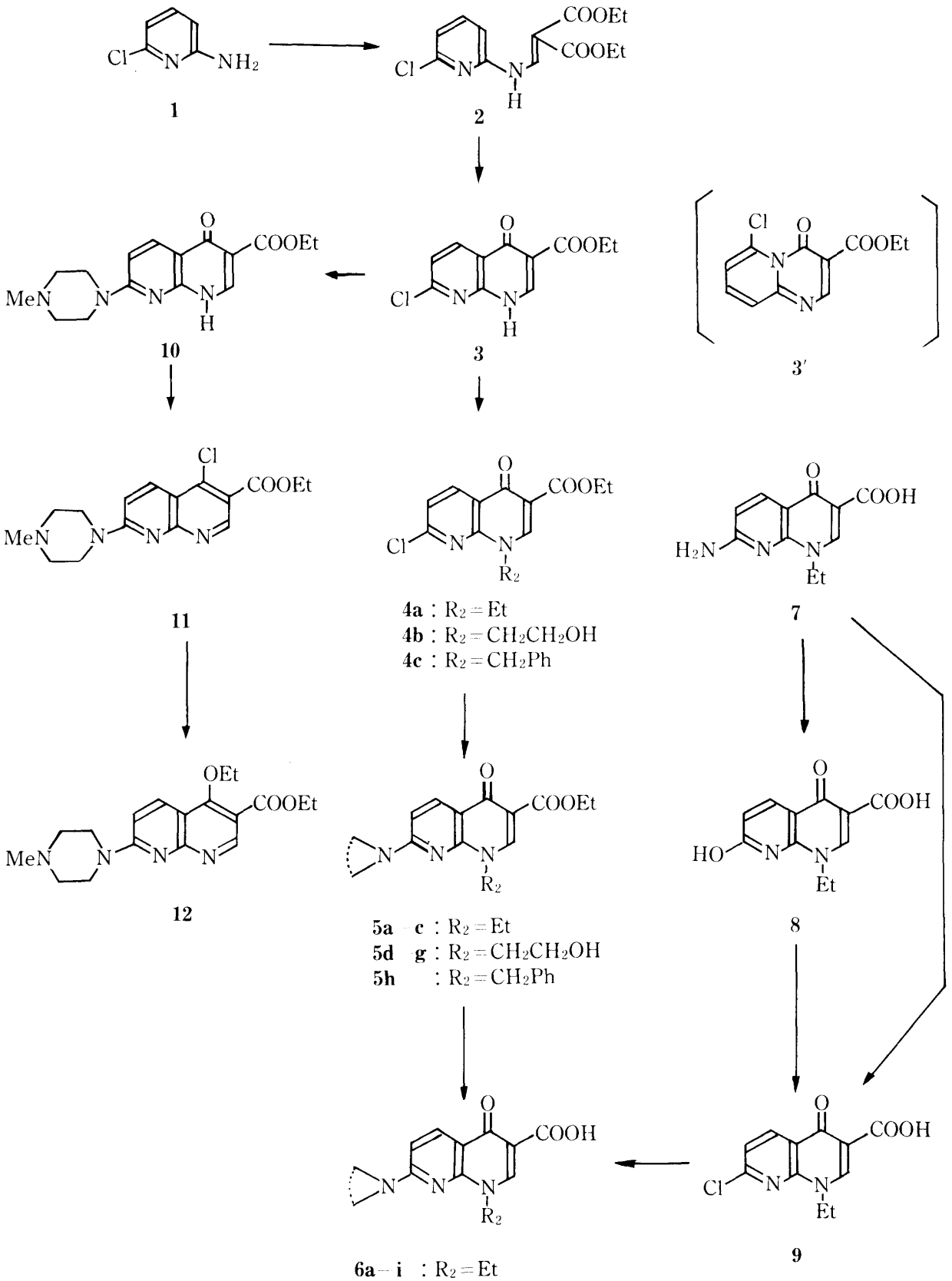


Chart 2

malonate (EMME) by a conventional method. Thermal cyclization of the malonate **2** was carried out in refluxing diphenyl ether to give exclusively ethyl 7-chloro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**3**); a possible isomeric ethyl 6-chloro-4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylate (**3'**), arising from cyclization onto the ring nitrogen atom, could not be detected. The structural assignment of the product **3** was based on the appearance of three 1-proton signals due to aromatic-type protons in its nuclear magnetic resonance (NMR) spectrum. Treatment of **3** with an appropriate alkyl halide gave ethyl 1-alkyl-7-chloro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates (**4a—c**) in good yields. The site of alkylation was clearly shown to be the ring nitrogen atom (the N_1 position), not the oxygen atom at position 4, by the observation of a nuclear Overhauser effect (NOE); upon irradiation of the signal of the methylene protons (adjacent to N_1) of the alkyl group in **4a—c**, the signal intensity of C_2–H increased by 20, 24, and 28%, respectively. A high-field shift of 0.76 ppm for the C_2–H resonance of **5b** (derived from **4a**) was observed as compared with that of the *O*-ethyl counterpart **12**. The C_2–H resonance of **4a—c** appeared at the same region as that of **5b**, supporting the assignment of the site of alkylation as the N_1 position. The ultraviolet (UV) spectrum can differentiate **5b** from **12** as shown in Fig. 1; the UV spectra of **4a—c** (Fig. 2) resemble that of **5b**, indicating the presence of a common chromophore in their molecules and again permitting the assignment of N_1 as the site of alkylation.

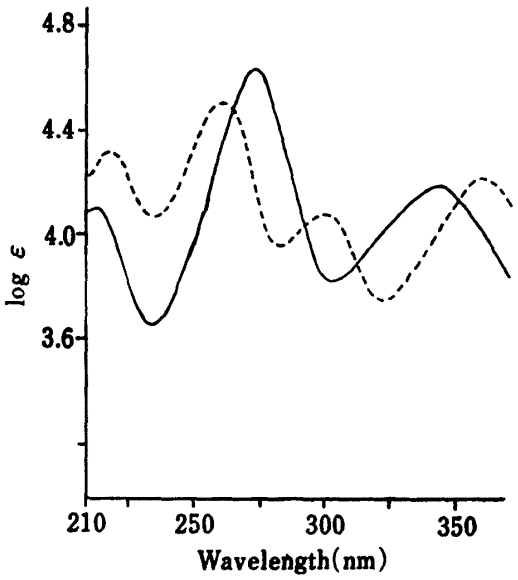


Fig. 1. UV Spectra of Compounds **5b** (—) and **12** (---) in EtOH

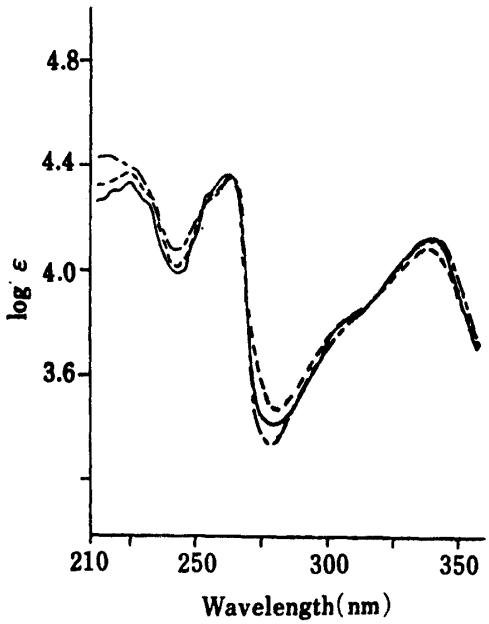


Fig. 2. UV Spectra of Compounds **4a** (—), **4b** (---) and **4c** (-·-) in EtOH

The foregoing compound **12** was prepared by chlorination of ethyl 1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-1,8-naphthyridine-3-carboxylate (**10**) with phosphoryl chloride, followed by treatment of the 4-chloro compound **11** with sodium ethoxide.

Displacement of the chloro group in **4a—c** by an appropriate cyclic amine such as pyrrolidine and piperazine gave ethyl 7-substituted 1-alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates (**5**) in good to excellent yields. Then the ester **5** was hydrolyzed with aqueous sodium hydroxide solution, giving the corresponding carboxylic acids **6**. Compounds **6a—g** where R_2 is an ethyl group were derived alternatively from 7-chloro-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**9**) and a cyclic amine. The intermediate **9** was prepared *via* one step involving the Sandmeyer reaction of the 7-amino compound **7**; an alternate route to **9** from **7**, however, required two steps for hydrolysis and chlorination.[5a]

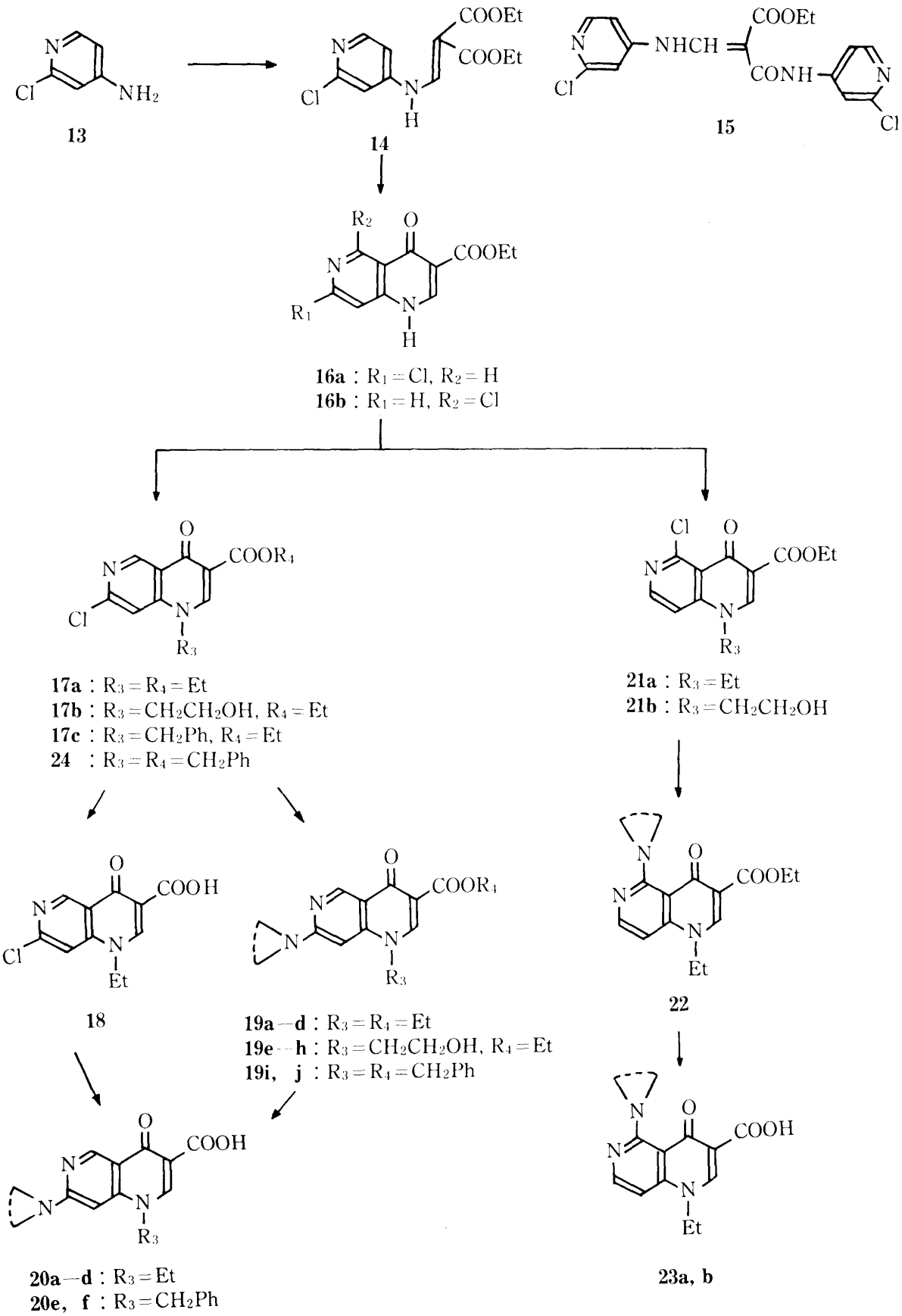
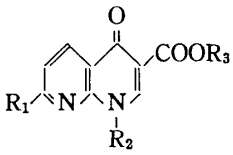
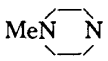
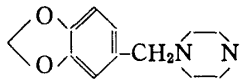
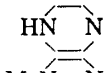
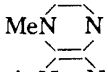
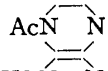
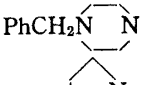
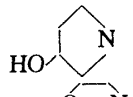
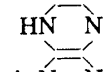
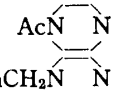
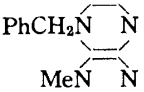
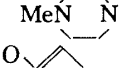
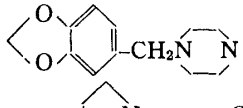
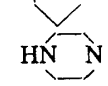
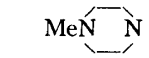
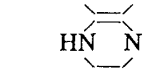
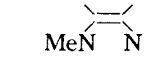
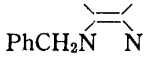


Chart 3

TABLE I. 7-Substituted 1-Alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids and Their Esters

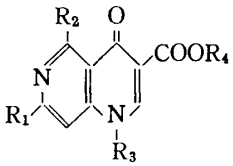


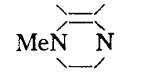
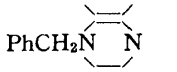
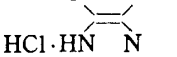
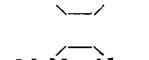
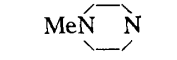
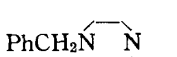
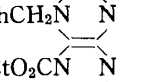
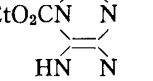
Compd. No.	R_1	R_2	R_3	Yield (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}
4a	Cl	Et	Et	91	164—165 (EtOH)	$C_{13}H_{13}ClN_2O_3$[a]	55.62 (55.76)	4.67 (4.65)	9.98 (10.02)	1680, 1625
4b	Cl	CH_2CH_2OH	Et	85	197—198 (EtOH)	$C_{13}H_{13}ClN_2O_4$[b]	52.62 (52.89)	4.42 (4.65)	9.44 (9.60)	3430, 1710
4c	Cl	CH_2Ph	Et	69	128—130 ($CHCl_3$-Et_2O)	$C_{18}H_{15}ClN_2O_3$[c]	63.07 (62.93)	4.41 (4.47)	8.17 (8.21)	1675, 1620
5a		Et	Et	95	196—198 (AcOEt)	$C_{17}H_{21}N_3O_3$	64.74 (64.69)	6.71 (6.57)	13.33 (13.34)	1665
5b		Et	Et	96	130—131 (*n*-Hexane)	$C_{18}H_{24}N_4O_3$	62.77 (62.76)	7.02 (7.24)	16.27 (16.19)	1720, 1620
5c		Et	Et	72	143—144 (AcOEt)	$C_{25}H_{28}N_4O_5$ · 1/4 H_2O	64.02 (64.03)	6.13 (6.08)	11.95 (11.78)	1720 (sh), 1680, 1620
5b		CH_2CH_2OH	Et	94	199—200 (CH_3CN)	$C_{17}H_{21}N_3O_4$	61.62 (61.37)	6.39 (6.22)	12.68 (12.86)	3400 (br), 1720, 1620
5e		CH_2CH_2OH	Et	87	224—226 (H_2O)	$C_{17}H_{22}N_4O_4$	58.94 (58.97)	6.40 (6.46)	16.18 (16.27)	3320 (br), 1720, 1620
5f		CH_2CH_2OH	Et	83	172—173 (H_2O)	$C_{18}H_{24}N_4O_4$ · 1/4 H_2O	59.24 (59.09)	6.77 (6.88)	15.36 (15.11)	3400 (br), 1710, 1620
5g		CH_2CH_2OH	Et	74	205—206 (DMF)	$C_{19}H_{24}N_4O_5$	58.75 (58.88)	6.23 (6.27)	14.43 (14.45)	3375, 1720 1670
5h		CH_2Ph	Et	93	150—151 (EtOH)	$C_{29}H_{30}N_4O_3$	72.18 (72.22)	6.27 (6.30)	11.61 (11.62)	1670
6a		Et	H	92[d] 97[e]	>300 (DMF)	$C_{15}H_{17}N_3O_3$	62.70 (62.51)	5.96 (5.73)	14.63 (14.53)	1710, 1625
6b		Et	H	86	>300 (DMF)	$C_{15}H_{17}N_3O_4$	59.39 (59.31)	5.65 (5.67)	13.86 (13.97)	3400 (br), 1705, 1620
6c		Et	H	88	288—290 (DMF)	$C_{15}H_{17}N_3O_4$	59.39 (59.51)	5.65 (5.66)	13.86 (13.99)	1700, 1625
6d		Et	H	90	260—262 (DMF)	$C_{16}H_{19}N_3O_3$	63.77 (63.70)	6.36 (6.59)	13.95 (13.98)	1700
6e		Et	H	65	271—272 (H_2O)	$C_{15}H_{18}N_4O_3$	59.59 (59.85)	6.00 (5.97)	18.53 (18.49)	3400 (br), 1710, 1620
6f		Et	H	88	>300 (EtOH)	$C_{17}H_{20}N_4O_4$	59.29 (59.07)	5.85 (6.15)	16.27 (16.53)	1720
6g		Et	H	85	206—207 (EtOH)	$C_{22}H_{24}N_4O_3$	67.33 (67.12)	6.16 (6.33)	14.28 (14.21)	1700, 1620
6h		Et	H	90	233—235 (DMF-H_2O)	$C_{16}H_{20}N_4O_3$	60.74 (60.54)	6.37 (6.39)	17.71 (17.55)	1700
6i		Et	H	82	187—188 (EtOH)	$C_{23}H_{24}N_4O_5$	63.29 (63.24)	5.54 (5.60)	12.84 (12.73)	1710, 1630
6j		CH_2CH_2OH	H	84	>300 (DMF)	$C_{15}H_{17}N_3O_4$	59.39 (59.17)	5.65 (5.67)	13.86 (13.81)	3380, 1670
6k		CH_2CH_2OH	H	88	285—287 (H_2O)	$C_{15}H_{18}N_4O_4$	56.59 (56.31)	5.70 (5.47)	17.60 (17.44)	3325 (br)

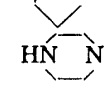
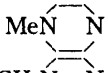
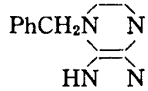
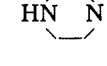
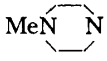
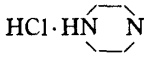
Compd. No.	R_1	R_2	R_3	Yield (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}
6l		CH_2CH_2OH	H	85	264—265 (DMF)	$C_{16}H_{20}N_4O_4$	57.82 (57.90	6.07 6.00	16.86 16.81)	1700, 1620
6m		CH_2Ph	H	83[f]	241—243 (DMF)	$C_{20}H_{20}N_4O_3$	65.92 (65.33	5.53 5.41	15.38 14.87)	1700 (sh), 1620
6n		CH_2Ph	H	80[f]	252—253 (EtOH)	$C_{21}H_{22}N_4O_3$	66.65 (66.70	5.86 5.80	14.81 14.73)	1705, 1620
6o		CH_2Ph	H	80	222—223 ($CHCl_3$–EtOH)	$C_{27}H_{26}N_4O_3$	71.34 (71.61	5.77 5.83	12.33 12.39)	1715

a) *Anal.* Calcd for Cl: 12.63. Found: Cl, 12.92.
b) *Anal.* Calcd for Cl: 11.95. Found: Cl, 12.20.
c) *Anal.* Calcd for Cl: 10.34. Found: Cl, 10.52.
d) Yield based on **9**.
e) Yield based on **5a**.
f) Yield based on **4c**.

TABLE II. 5- or 7-Substituted 1-Alkyl-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylic Acids and Their Esters



Compd. No.	R_1	R_2	R_3	R_4	Yield (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}
17a	Cl	H	Et	Et	66	188—189 (EtOH)	$C_{13}H_{13}ClN_2O_3$[a]	55.62 (55.41	4.67 4.64	9.98 10.29)	1665, 1650
17b	Cl	H	CH_2CH_2OH	Et	56	188—189 (EtOH)	$C_{13}H_{13}ClN_2O_4$[b]	52.62 (52.83	4.42 4.27	9.44 9.47)	3460, 1720 1620
17c	Cl	H	CH_2Ph	Et	9	215—217 (EtOH)	$C_{18}H_{15}ClN_2O_3$[c]	63.08 (63.11	4.41 4.17	8.18 8.26)	1700, 1620
19a		H	Et	Et	98	201—202 (CH_3CN)	$C_{17}H_{21}N_3O_3$	64.74 (64.73	6.71 6.46	13.33 13.23)	1665, 1620
19b		H	Et	Et	95	169—170 (AcOEt)	$C_{17}H_{22}N_4O_3$	61.80 (61.86	6.71 6.70	16.96 16.67)	3200 (br), 1720
19c		H	Et	Et	90	176—177 (AcOEt)	$C_{18}H_{24}N_4O_3$	62.77 (62.76	7.02 7.05	16.27 16.11)	1720 (sh), 1675
19d		H	Et	Et	85	172—173 (CH_3CN)	$C_{24}H_{28}N_4O_3$	68.55 (68.58	6.71 6.79	13.33 13.00)	1720
19e		H	CH_2CH_2OH	Et	95	273—276 (dec.) (H_2O–EtOH)·HCl	$C_{17}H_{22}N_4O_4$[d]	53.33 (53.22	6.05 6.04	14.64 14.60)	3300 (br), 1720
19f		H	CH_2CH_2OH	Et	90	196—197 ($CHCl_3$–AcOEt)	$C_{18}H_{24}N_4O_4 \cdot H_2O$	57.13 (57.21	6.93 6.72	14.81 14.88)	3300 (br), 1720
19g		H	CH_2CH_2OH	Et	76	200—202 (CH_3CN)	$C_{24}H_{28}N_4O_4$	66.03 (65.88	6.47 6.71	12.84 12.84)	3380, 1720 1680
19h		H	CH_2CH_2OH	Et	86	236—237 (EtOH)	$C_{20}H_{26}N_4O_6$	57.40 (57.30	6.26 6.21	13.39 13.44)	3400 (br), 1710
19i		H	CH_2Ph	CH_2Ph	56	163—165 (CH_3CN)	$C_{27}H_{26}N_4O_3$	71.34 (71.64	5.77 5.98	12.33 12.22)	3250 (br), 1725
19j		H	CH_2Ph	CH_2Ph	46	230—231 (AcOEt)	$C_{28}H_{28}N_4O_3$	71.77 (71.67	6.02 5.96	11.96 12.02)	1720, 1690 1630

Compd. No.	R_1	R_2	R_3	R_4	Yield (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}
20a		H	Et	H	98	>300 (DMF)	$C_{15}H_{17}N_3O_3$	62.70 (62.79	5.96 6.05	14.63 14.69)	1700
20b		H	Et	H	98	294—296 (H_2O)	$C_{15}H_{18}N_4O_3$	59.59 (59.36	6.00 5.91	18.53 18.47)	3300 (br), 1620
20c		H	Et	H	85	238—240 (EtOH)	$C_{16}H_{20}N_4O_3$	60.74 (60.43	6.37 6.54	17.71 17.50)	1720
20d		H	Et	H	86	200—201 (EtOH)	$C_{22}H_{24}N_4O_3$	67.33 (67.37	6.16 5.86	14.28 14.17)	1720
20e		H	CH_2Ph	H	70	276—278 (dec.) (CH_3CN)	$C_{20}H_{20}N_4O_3$	65.92 (65.78	5.53 5.46	15.38 15.24)	3400 (br),
20f		H	CH_2Ph	H	58	280—282 (dec.) (CH_3CN)	$C_{21}H_{22}N_4O_3$	66.65 (67.01	5.86 5.90	14.81 14.78)	1720
21a	H	Cl	Et	Et	21	195—197 (EtOH)	$C_{13}H_{13}ClN_2O_3$[e]	55.62 (55.39	4.67 4.54	9.98 9.92)	1720, 1625
21b	H	Cl	CH_2CH_2OH	Et	3	230—232 (EtOH)	$C_{13}H_{13}ClN_2O_4$[f]	52.62 (52.65	4.42 4.56	9.44 9.45)	3480, 1720 1630
22	H		Et	Et	82	168—169 (AcOEt)	$C_{17}H_{22}N_4O_3 \cdot 1/4\ H_2O$	60.97 (61.17	6.77 6.58	16.73 16.76)	3300, 1720 1620
23a	H		Et	H	84[i]	180—181 (EtOH)	$C_{15}H_{17}N_3O_3$	62.70 (62.98	5.96 6.05	14.63 14.85)	1720, 1620
23b	H	HCl· 	Et	H	67	292—294 (EtOH)	$C_{15}H_{18}N_4O_3$[g] ·HCl	53.18 (52.92	5.65 5.70	16.53 16.40)	3450 (br), 1720
24	Cl	H	CH_2Ph	CH_2Ph	6	186—187 (CH_3CN)	$C_{23}H_{17}ClN_2O_3$[h]	68.23 (68.23	4.23 4.41	6.92 6.92)	1720 (sh), 1690, 1640

a) *Anal.* Calcd for Cl: 12.63. Found: Cl, 12.71.
b) *Anal.* Calcd for Cl: 11.95. Found: Cl, 11.93.
c) *Anal.* Calcd for Cl: 10.35. Found: Cl, 10.41.
d) *Anal.* Calcd for Cl: 9.26. Found: Cl, 9.15.
e) *Anal.* Calcd for Cl: 12.63. Found: Cl, 12.35.
f) *Anal.* Calcd for Cl: 11.95. Found: Cl, 11.84.
g) *Anal.* Calcd for Cl: 10.46. Found: Cl, 10.56.
h) *Anal.* Calcd for Cl: 8.76. Found: Cl, 8.94.
i) Yield based on **21a**.

1,6-Naphthyridines

4-Amino-2-chloropyridine (**13**)[8] was treated with a 30% excess of EMME to give diethyl *N*-(2-chloro-4-pyridyl)aminomethylenemalonate (**14**) in 59% yield. The use of an equimolar amount of EMME afforded a by-product which was proved to be the amide **15** on the basis of the elemental analysis and mass and NMR spectra. Thermal cyclization of **14** in refluxing diphenyl ether gave a mixture of ethyl 7- and 5-chloro-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylate (**16a** and **16b**), but they could not be separated because of the close similarity in their physical properties. However, the isomers could be separated as the corresponding 1-alkyl derivatives **17** and **21** after alkylation with an alkyl halide in the presence of potassium carbonate. Alkylation of **16** with benzyl chloride was accompanied by an ester-exchange to form benzyl 1-benzyl-7-chloro-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylate (**24**) as well as the desired ethyl ester **17c**.

The structures of all products were confirmed primarily on the basis of their NMR spectra. Thus, the 7-chloro compounds (**17a**—**c** and **24**) showed a pair of singlets at around δ 9.2 and 7.5 due to C_5–H and C_8–H, respectively, whereas the 5-chloro analogs (**21a** and **21b**) showed two doublets with a coupling constant J=6.0 Hz at δ 8.4 and 7.4 due to C_7–H and C_8–H, respectively. An NOE (28 and 27% enhancement) on the C_2–H signal of **17a** and **17b** was observed

Table III. *In Vitro* Antibacterial Activity[a)]

Compound No.	Minimum inhibitory concentrations, μg/ml		
	S. aureus Terajima	*E. coli* K-12	*P. aeruginosa* Tsuchijima
6a	10	1	>100
6b	10	1	>100
6c	100	3	>100
6d	100	10	100
6e	30	3	10
6f	100	10	>100
6g	10	1	>100
6h	100	1	30
6i	10	1	>100
6j	30	1	>100
6k	>100	100	>100
6l	>100	10	>100
6m	100	3	10
6n	>100	3	30
6o	>100	>100	>100
7	>100	30	100
20a	100	3	100
20b	>100	3	30
20c	30	3	100
20d	3	1	100
20e	100	3	10
20f	100	3	30
23a	>100	>100	>100
23b	>100	>100	>100
I	10	1	>100
II	10	1	>100
III	30	1	10

a) *In vitro* antibacterial tests were carried out by the broth-dilution method using nutrient broth.[9)]

upon irradiation of the signal of the *N*-methylene protons. This finding supports the assigned structure **17**.

The desired 7- and 5-substituted 1-alkyl-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylic acids (**20** and **23**) were derived from **17** and **21**, respectively, by treatment with an appropriate amine followed by alkaline hydrolysis of the intermediates **19** and **22**. Mild hydrolysis of **17a** gave the carboxylic acid **18** with the chloro group intact, in contrast with that of the corresponding 1,8-naphthyridine **4a** which was converted to the 7-hydroxy-carboxylic acid **8** under the same reaction conditions. Treatment of **18** with pyrrolidine gave the 7-(1-pyrrolidinyl) derivative **20a** in quantitative yield.

Structure-activity Relationships

The *in vitro* antibacterial activities of compounds **6**, **7**, **20** and **23** against gram-positive (*Staphylococcus aureus* Terajima) and gram-negative bacteria (*Escherichia coli* K-12 and *Pseudomonas aeruginosa* Tsuchijima) are compiled in Table III; the data for nalidixic acid, piromidic acid, and pipemidic acid are included for comparison.

Replacement of the methyl group at position 7 of nalidixic acid by a pyrrolidinyl group, giving **6a**, produced no change of activity, whereas replacement by an amino group, giving **7**, decreased the activity markedly. Replacement by a piperazinyl group (**6e**) caused an increase in activity against *P. aeruginosa*; in general **6e** shows the same level of activity as pipemidic acid. Introduction of an alkyl or acyl group (**6f**—**i**) into the piperazinyl nitrogen atom of **6e** resulted in a remarkable decrease in activity especially against *P. aeruginosa*. However, *N*-

substitution by a lipophilic group such as in compounds **6g** and **6i** enhanced the activity against *S. aureus*; this is also the case in the corresponding 1,6-naphthyridine derivative (compare **20b** with **20d**).

The 1-hydroxyethyl derivatives (**6j**—**l**) were less active than the corresponding 1-ethyl derivatives (**6a**, **6e** and **6h**), showing essentially no activity against *P. aeruginosa* in particular. The 1-benzyl derivatives (**6m** and **6n**), compared with the 1-ethyl counterparts (**6e** and **6h**), showed decreased activity against gram-positive bacteria, but they retained activity against gram-negative ones.

The 1,6-naphthyridine derivatives, in general, were less active than the corresponding 1,8-naphthyridines. As regards the activity of positional isomers of the substituent on the 1,6-naphthyridine ring, the 7-substituted isomer (**20a** and **20b**) was more potent than the 5-substituted isomer (**23a** and **23b**) which was practically inactive against all the test bacteria.

None of the ethyl esters corresponding to the carboxylic acids prepared in the present study showed antibacterial activity.

The present study on the 1,8- and 1,6-naphthyridines showed that structure–activity relationships associated with variation of the substituent are qualitatively similar to those of the pyrido[2,3-*d*]pyrimidine series reported previously.

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 $CDCl_3$ solution, unless otherwise specified, with tetramethylsilane as an internal standard. Mass spectra were determined with a Hitachi RMU-6L spectrometer. Organic extracts were dried over anhydrous $MgSO_4$.

Diethyl *N*-(6-Chloro-2-pyridyl)aminomethylenemalonate (**2**)——A mixture of 2-amino-6-chloropyridine (**1**) (105 g, 0.82 mol) and diethyl ethoxymethylenemalonate (EMME) (195 g, 0.90 mol) was heated at 100°C for 3 h with stirring. After cooling, the resulting solid was collected and recrystallized from EtOH to give **2** (222 g, 91%) as colorless needles, mp 131.5—132°C. *Anal.* Calcd for $C_{13}H_{15}ClN_2O_4$: C, 52.26; H, 5.06; Cl, 11.87; N, 9.38. Found: C, 52.43; H, 4.99; Cl, 11.89; N, 9.41. IR ν_{max}^{KBr} cm^{-1}: 3250, 1690, 1675. NMR (60 MHz) δ: 9.07 (1H, d, J=13 Hz, -NHC<u>H</u>=C<), 11.18 (1H, d, J=13 Hz, -NHC<u>H</u>=C<).

Ethyl 7-Chloro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**3**)——The malonate **2** (45 g) was added to 15 volumes of refluxing diphenyl ether. The mixture was heated at 250°C for 20 min with stirring, then cooled, and diluted with 10 volumes of *n*-hexane. The resulting precipitates were collected by filtration and washed with $CHCl_3$ to remove the unchanged malonate **2**. The filtrate and washings were combined. The *n*-hexane and $CHCl_3$ were distilled off, and the residual diphenyl ether solution containing the unchanged malonate was heated again under the same conditions as described above. The precipitate together with the original crop of precipitate was recrystallized from DMF to give **3** (18.6 g, 49%) as colorless crystals, mp 287—288°C. *Anal.* Calcd for $C_{11}H_9ClN_2O_3$: C, 52.29; H, 3.59; Cl, 14.03; N, 11.09. Found: C, 52.08; H, 3.43; Cl, 14.29; N, 10.92. IR ν_{max}^{KBr} cm^{-1}: 1715, 1680. NMR (DMSO-d_6, 100 MHz) δ: 7.53 (1H, d, J=8 Hz, C_6–H), 8.47 (1H, s, C_2–H), 8.50 (1H, d, J=8 Hz, C_5–H).

Ethyl 1-Alkyl-7-chloro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates (**4a**—**c**)——General Procedure: An alkyl halide (0.4 mol) was added slowly to a mixture of **3** (25.3 g, 0.1 mol), anhydrous K_2CO_3 (20.7 g, 0.15 mol), and DMF (500 ml) with stirring at 60°C. The mixture was heated at 60—70°C for 2—3 h and filtered. The filtrate was concentrated to dryness, and the resulting residue was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give **4**. Ethyl iodide, 2-bromoethanol and benzyl chloride were used as the alkyl halide for the preparation of **4a**—**c**, respectively. The results are summarized in Table I. **4a**: NMR (60 MHz) δ: 7.36 (1H, d, J=9 Hz, C_6–H), 8.60 (1H, s, C_2–H), 8.70 (1H, d, J=9 Hz, C_5–H). **4b**: NMR (60 MHz) δ: 7.15 (1H, d, J=8 Hz, C_6–H), 8.04 (1H, d, J=8 Hz, C_5–H), 8.62 (1H, s, C_2–H). **4c**: NMR (60 MHz) δ: 5.56 (2H, s, N<u>C</u>$H_2C_6H_5$), 7.36 (1H, d, J=8 Hz, C_6–H), 8.64 (1H, s, C_2–H), 8.68 (1H, d, J=8 Hz, C_5–H).

Ethyl 7-Substituted 1-Alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylates (**5a**—**h**)——General Procedure: A mixture of **4a**—**c** (0.01 mol), an appropriate amine (0.03 mol), and EtOH (70 ml) was refluxed for 3—5 h. After removal of the solvent and excess amine by evaporation, 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 to give **5a**—**h**. In the case of **5e**, the crude product, which was insoluble in $CHCl_3$, was washed with water, and recrystallized from water. The results are summarized in Table I.

7-Substituted 1-Alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids (**6a**—**o**)——General Procedure: a) By Substitution: An appropriate amine (0.03 mol) was added to a suspension of 7-chloro-1-

ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**9**) (2.53 g, 0.01 mol) in acetonitrile (50 ml). The mixture was stirred at 20—25°C for 1—2 h. The resulting precipitates were collected, washed with acetonitrile, and recrystallized to give **6a—g**.

b) By Hydrolysis: A suspension of the ester **5a—h** (0.01 mol) in aqueous 10% NaOH (15 ml) was heated at 100°C until it became clear. After cooling, the alkaline solution was acidified with AcOH, to give precipitates which were collected, washed with water, and recrystallized to give the corresponding acid **6a** and **6h—o**. The results are summarized in Table I.

7-Chloro-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**9**)——A solution of the 7-diazonium chloride [prepared from 7-amino-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid[5a] (**7**) (1.17 g, 5 mmol) in 4 N HCl (30 ml) and $NaNO_2$ (0.38 g, 5.5 mmol) in water (1 ml)] was added dropwise to a stirred solution of cuprous chloride (0.99 g, 10 mmol) in conc. HCl (5 ml) under ice-cooling. After successive stirring at 0—5°C for 30 min, at 20—25°C for 2 h, then at 60°C for 30 min, the mixture was poured into ice-water (200 ml). The precipitates were collected, washed with water, and recrystallized from acetonitrile to give **9** (0.91 g, 71%), mp 249—250°C, which was identical (mixed melting point, TLC, and IR spectrum) with an authentic sample of **9** prepared by Lesher's procedure.[5a]

Ethyl 1,4-Dihydro-4-oxo-7-(4-methyl-1-piperazinyl)-1,8-naphthyridine-3-carboxylate (**10**)——4-Methylpiperazine (2.5 g, 25 mmol) was added to a solution of **3** (1.26 g, 5 mmol) in dimethylformamide (DMF) (30 ml). The mixture was heated at 120°C for 1.5 h and concentrated to dryness under reduced pressure. The resulting 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 EtOH to give **10** (1.42 g, 90%) as yellow needles, mp 248—250°C. *Anal.* Calcd for $C_{16}H_{20}N_4O_3$: C, 60.74; H, 6.37; N, 17.71. Found: C, 60.80; H, 6.05; N, 17.68. IR ν_{max}^{KBr} cm^{-1}: 1710, 1680.

Ethyl 4-Chloro-7-(4-methyl-1-piperazinyl)-1,8-naphthyridine-3-carboxylate (**11**)——A mixture of **10** (1.35 g) and $POCl_3$ (20 ml) was refluxed for 2 h. The excess $POCl_3$ was evaporated off under reduced pressure. The residue was poured onto ice, then the solution was neutralized with aqueous 5% NaOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and concentrated to give **11** (1.02 g, 71%) which was recrystallized from acetonitrile, mp 174—175°C as pale yellow needles. *Anal.* Calcd for $C_{16}H_{19}ClN_4O_2$: C, 57.40; H, 5.72; Cl, 10.59; N, 16.74. Found: C, 57.47; H, 5.49; Cl, 10.44; N, 16.90. IR ν_{max}^{KBr} cm^{-1}: 1720, 1615. NMR (60 MHz) δ: 7.12 (1H, d, J=9.5 Hz, C_6–H), 8.38 (1H, d, J=9.5 Hz, C_5–H), 9.21 (1H, s, C_2–H). UV λ_{max}^{EtOH} nm (log ε): 221 (4.41), 256 (4.46), 302 (4.12), 373 (4.42).

Ethyl 4-Ethoxy-7-(4-methyl-1-piperazinyl)-1,8-naphthyridine-3-carboxylate (**12**)——Sodium ethoxide [prepared from sodium (0.13 g, 5.5 mmol) and dry EtOH (10 ml)] was added to a suspension of **11** (1.67 g, 5 mmol) in dry EtOH (30 ml). The mixture was refluxed for 20 min and the solvent was evaporated off under reduced pressure to leave solids which were taken up in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried, and concentrated to dryness. The resulting solid was recrystallized from *n*-hexane to give **12** (1.15 g, 67%) as orange needles, mp 93—94°C. *Anal.* Calcd for $C_{18}H_{24}N_4O_3$: C, 62.77; H, 7.02; N, 16.27. Found: C, 62.64; H, 7.04; N, 16.00. IR ν_{max}^{KBr} cm^{-1}: 1720, 1620. NMR (60 MHz) δ: 6.99 (1H, d, J=9.5 Hz, C_6–H), 8.28 (1H, d, J=9.5 Hz, C_5–H), 9.21 (1H, s, C_2–H). UV λ_{max}^{EtOH} nm (log ε): 219 (4.32), 261 (4.51), 301 (4.09), 359 (4.22).

Diethyl *N*-(2-Chloro-4-pyridyl)aminomethylenemalonate (**14**)——a) A mixture of 4-amino-2-chloropyridine[8] (**13**) (25.7 g, 0.2 mol) and EMME (56 g, 0.26 mol) was heated at 90°C for 10 h, then cooled.

The resulting precipitates were collected and recrystallized from *n*-hexane to give **14** (35 g, 59%) as colorless prisms, mp 60—62°C. *Anal.* Calcd for $C_{13}H_{15}ClN_2O_4$: C, 52.26; H, 5.06; Cl, 11.87; N, 9.38. Found: C, 52.34; H, 5.07; Cl, 11.71; N, 9.40. NMR (60 MHz) δ: 8.27 (1H, d, J=12.5 Hz, –NHC<u>H</u>=C<), 12.43 (1H, d, J=12.5 Hz, –N<u>H</u>CH=C<).

b) Treatment of an equimolar mixture of **13** and EMME in the same manner as described above afforded crude products, which were chromatographed on silica gel with $CHCl_3$ to give **14** (35%), **15** (6%), and the starting material **13** (14% recovery).

3-[*N*-(2-Chloro-4-pyridyl)amino]-2-ethoxycarbonyl-*N*-(2-chloro-4-pyridyl)acrylamide (**15**) was recrystallized from EtOH as colorless needles, mp 210—211°C. *Anal.* Calcd for $C_{16}H_{14}Cl_2N_4O_3$: C, 50.41; H, 3.70; Cl, 18.60; N, 14.70. Found: C, 50.52; H, 3.73; Cl, 18.74; N, 14.57. IR ν_{max}^{KBr} cm^{-1}: 1680, 1620. NMR (60 MHz) δ: 8.40 (1H, d, J=12.5 Hz, –NHC<u>H</u>=C<), 11.16 (1H, br s, –CON<u>H</u>–), 12.10 (1H, d, J=12.5 Hz, –N<u>H</u>CH=C<). MS *m/e*: 380 (M^+), 253 ($M^+-C_5H_4ClN_2$), 225 ($M^+-C_6H_4ClN_2O$).

Ethyl 7- and 5-Chloro-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylates (**16a and 16b**)——A mixture of **16a** and **16b** was obtained in 57% yield from **14** by the same procedure as described for the preparation of **3**. Attempts to separate the mixture into **16a** and **16b** were unsuccessful. The mixture of **16a** and **16b** gave mp 299—300°C (dec.) as colorless crystals after recrystallization from DMF. *Anal.* Calcd for $C_{11}H_9ClN_2O_3$: C, 52.29; H, 3.59; Cl, 14.03; N, 11.09. Found: C, 52.05; H, 3.28; Cl, 13.78; N, 11.05. IR ν_{max}^{KBr} cm^{-1}: 1700, 1680.

Benzyl and Ethyl 1-Alkyl-7- and 5-Chloro-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylates (**17a—c, 21a, b and 24**)——According to the procedure for the preparation of **4**, the mixture of **16a** and **16b** gave a mixture of **17a—c** and **21a, b**, which was separated by chromatography on silica gel with $CHCl_3$–MeOH (100: 1, v/v) into 7-chloro (**17**) and 5-chloro compounds (**21**). Compound **24** was formed as a by-product

by the reaction with benzyl chloride. The results are summarized in Table II. **17a**: NMR (DMSO-d_6, 100 MHz) δ: 7.93 (1H, s, C_8–H), 8.40 (1H, s, C_2–H), 9.07 (1H, s, C_5–H). **17b**: NMR (DMSO-d_6, 100 MHz) δ: 5.00 (1H, t, J=5.5 Hz, $CH_2CH_2O\underline{H}$), 7.96 (1H, s, C_8–H), 8.60 (1H, s, C_2–H), 9.08 (1H, s, C_5–H). **17c**: NMR (DMSO-d_6, 60 MHz) δ: 5.69 (2H, s, $NC\underline{H}_2C_6H_5$), 7.76 (1H, s, C_8–H), 8.86 (1H, s, C_2–H), 9.08 (1H, s, C_5–H). **21a**: NMR (60 MHz) δ: 7.27 (1H, d, J=6 Hz, C_8–H), 8.35 (1H, s, C_2–H), 8.40 (1H, d, J=6 Hz, C_7–H). **21b**: NMR (DMSO-d_6, 60 MHz) δ: 5.00 (1H, t, J=5.5 Hz, $CH_2CH_2O\underline{H}$), 7.75 (1H, d, J=6 Hz, C_8–H), 8.45 (1H, d, J=6 Hz, C_7–H), 8.52 (1H, s, C_2–H). **24**: NMR (DMSO-d_6, 60 MHz) δ: 5.33 (2H, s, $COOC\underline{H}_2C_6H_5$), 5.70 (2H, s, $NC\underline{H}_2C_6H_5$), 7.78 (1H, s, C_8–H), 8.93 (1H, s, C_2–H), 9.13 (1H, s, C_5–H).

7-Chloro-1-ethyl-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylic Acid (18)——A suspension of **17a** (1.50 g) in aqueous 10% KOH (10 ml) was heated at 90°C for 15 min. After cooling, the solution was acidified with AcOH. The precipitates were collected, washed with water, and recrystallized from acetonitrile to give **18** (1.25 g, 93%), mp 260—262°C as pale yellow needles. *Anal.* Calcd for $C_{11}H_9ClN_2O_3$: C, 52.29; H, 3.59; Cl, 14.03; N, 11.09. Found: C, 52.22; H, 3.54; Cl, 14.26; N, 11.11. IR ν_{max}^{KBr} cm^{-1}: 1720, 1620.

Benzyl and Ethyl 7- and 5-Substituted 1-Alkyl-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylates (19a—j and 22)——According to the procedure for the preparation of **5**, compounds **17a**, **17b**, **21a** and **24** were converted to the corresponding esters **19a—j** and **22**. In the case of **19e**, the crude product, which was insoluble in $CHCl_3$, was washed with EtOH and recrystallized. The results are summarized in Table II.

7- and 5-Substituted 1-Alkyl-1,4-dihydro-4-oxo-1,6-naphthyridine-3-carboxylic Acids (20a—f and 23a, b)——General Procedure: a) By Hydrolysis: Compounds **20a—f** and **23a, b** were obtained from the corresponding esters **19a—d, i, j, 21a** and **22** in the same manner as described for the preparation of **6h—o**.

b) By Substitution: A mixture of **18** (0.51 g, 2 mmol), pyrrolidine (0.75 ml, 6 mmol), and EtOH (25 ml) was refluxed for 4 h, then cooled. The precipitates were collected, washed with EtOH, and recrystallized to give the 7-(1-pyrrolidinyl) derivative **20a** (0.54 g, 95%), which was identical with an authentic sample derived from **19a** by alkaline hydrolysis. Teh results are summarized in Table II.

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