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Synthetic Antibacterials. V.[1] 7-Substituted 1-Ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids

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The reaction of nalidixic acid (**1**) with thionyl chloride afforded 1-ethyl-1,4-dihydro-4-oxo-7-trichloromethyl-1,8-naphthyridine-3-carboxylic acid (**2**) in high yield. Several 7-N-substituted carbamoyl- (**3**—**47**) and 7-(5-substituted benzimidazol-2-yl)-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids (**48**—**52**) were prepared by treatment of **2** with appropriate amine and *o*-phenylenediamine, respectively. Alkaline treatment of **2** provided unexpected 7-hydroxy derivative (**54**), while the action of conc. sulfuric acid gave 3,7-dicarboxylic acids (**53**). The *in vitro* antibacterial activity and structural requirements of these compounds for broad spectrum activity were also discussed.

Since the lead of nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) (**1**)[3] as a clinically useful antibacterial agent against Gram-negative bacteria, considerable attention has been directed toward the synthesis of various heterocycles having 1-alkyl-3-carboxy-4-pyridone moiety.[4a–d] Previously, we have also synthesized a number of 1,8-naphthyridine and pyrido[2,3-*d*]pyrimidine derivatives containing the 4-pyridone ring and examined their antibacterial activity.[1,5a–c] In particular, some compounds with a 5-nitro-2-furylvinyl group which can be considered as an electron-withdrawing group, at the position 7 of 1,8-naphthyridine as well as the position 2 of pyrido[2,3-*d*]pyrimidine exhibited significant *in vitro* broad spectrum activity including *Pseudomonas aeruginosa*. In addition to the presence of pyridone moiety, these results suggested that certain electron-withdrawing group may be also necessary for broad spectrum activity. On the basis of this prediction, we carried out the preliminary investigation on 1-ethyl-1,4-dihydro-4-oxo-7-trichloromethyl-1,8-naphthyridine-3-carboxylic acid (**2**)[6] as a possible candidate and found that this compound possesses potent activity against a wide range of bacteria. These findings prompted us to investigate systematic synthesis of 1,8-naphthyridine derivatives with electron-withdrawing groups at the 7-position. This paper is concerned with the synthesis and antibacterial profiles of **2** and several other 7-substituted 1,8-naphthyridines derived from **2**.

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1) Part IV: S. Nishigaki, K. Ogiwara, S. Fukazawa, M. Ichiba, N. Mizushima, and F. Yoneda, *J. Med. Chem.*, **15**, 731 (1972).
2) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo, 160, Japan.*
3) G.Y. Lesher, E.J. Froelich, M.D. Gruett, J.H. Bailey, and R.P. Brundage, *J. Med. Pharm. Chem.*, **5**, 1063 (1962).
4) *a*) S. Minami, T. Shono, and J. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 1482 (1971); *b*) S. Minami, T. Shono, and J. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 1426 (1971); *c*) H. Nakao, M. Fukushima, H. Yanagisawa, and S. Sugawara, *Chem. Pharm. Bull.* (Tokyo), **22**, 1864 (1974); *d*) J. Matsumoto and S. Minami, *J. Med. Chem.*, **18**, 74 (1975).
5) *a*) S. Nishigaki, F. Yoneda, K. Ogiwara, T. Naito, R. Dohmori, S. Kadoya, Y. Tanaka, and I. Takamura, *Chem. Pharm. Bull.* (Tokyo), **17**, 1827 (1969); *b*) S. Nishigaki, K. Ogiwara, K. Senga, S. Fukazawa, Y. Machida, and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **18**, 1385 (1970); *c*) S. Nishigaki, N. Mizushima, F. Yoneda, and H. Takahashi, *J. Med. Chem.*, **14**, 638 (1971).
6) This compound has been claimed in the patent without description of melting point and synthetic procedure: U.S. Patent, 3590036 (1971).

In the present work, the key compound **2**[6] was prepared in high yield by the reaction of **1**[3] with thionyl chloride under comparatively mild condition. The structure of **2** was assigned on the basis of its spectral data and elemental analysis. The Beilstein test of **2** indicated the presence of chlorine atom in the molecule. The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) of **2** exhibited a broad band at δ 14.00 (1H, COOH), a singret at δ 9.11 (1H, H-2), a pair of doublets at δ 8.98 (1H, $J_{5,6}$=7 Hz) and δ 8.21 (1H, $J_{5,6}$=7 Hz), a qualtet at δ 4.72 (2H, NCH_2CH_3) and a triplet at δ 1.80 (3H, NCH_2CH_3), while a singlet of methyl protons at the 7-position of **1** could not be observed. Furthermore, the mass spectrum revealed a parent ion (*m/e* 334), M+2, M+4, and M+6 ions, which suggested the presence of three chlorine atoms in the molecule. The elemental analysis (C, H, and N) of **2** indicated good agreement with the proposed structure. The structure of **2** was finally substantiated by its catalytic hydrogenation over palladium-carbon to **1**. The successful conversion of **1** into **2** by thionyl chloride should be noted as relatively unique exhaustive halogenation,[7] since most of trihalogenomethylpyridines have been prepared by the action of elemental halogens.[8]

During the course of exhaustive halogenation, the formation of 1-ethyl-1,4-dihydro-4-oxo-7-trichloromethyl-1,8-naphthyridine-3-carboxylic acid chloride (**2'**) was detected by the IR spectrum.[9] This acid chloride was extremely unstable and underwent hydrolysis to afford **2**. Therefore, its purification was unsuccessful. Obviously, **2'** can be regarded as a precursor of **2**.

The trichloromethyl-1,8-naphthyridine (**2**) has strong reactivity and served as an useful intermediate for several nucleophilic reaction. For example, treatment of **2** with various primary or secondary amines provided the corresponding 7-N-substituted carbamoyl-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**3**—**47**) (Table I). The use of *o*-phenylenediamines furnished 7-(benzimidazol-2-yl)-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids (**48**—**52**) (Table II).

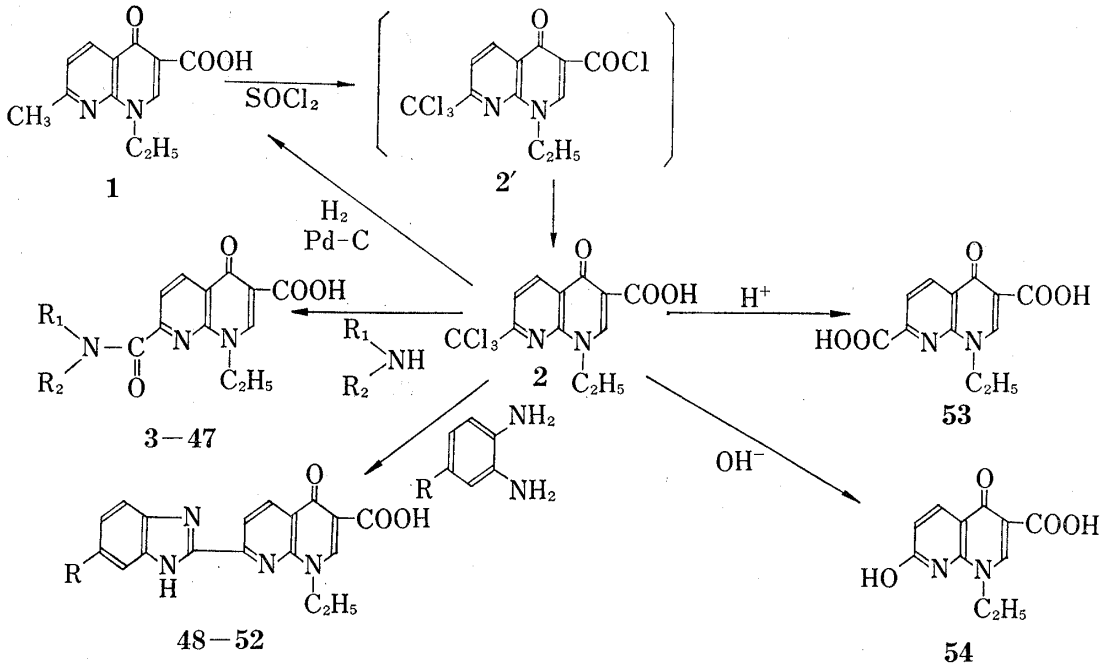
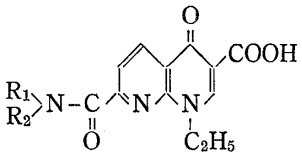
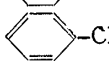
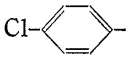
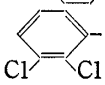
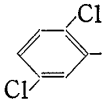
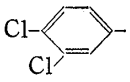
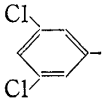
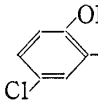
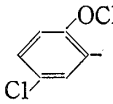


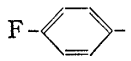
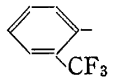
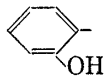
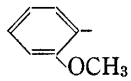
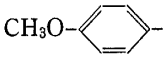
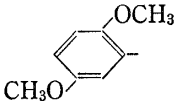
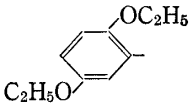
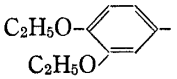
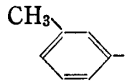
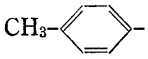
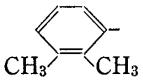
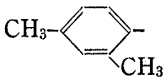
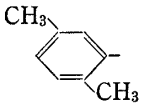
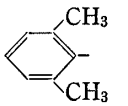
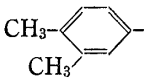
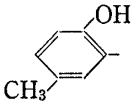
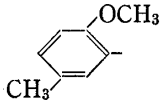
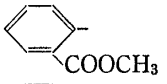
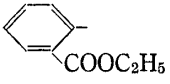
Chart 1

7) Only one paper has been reported regarding the exhaustive halogenation of picolines by thionyl chloride: R. Graf and F. Zettl, *J. Prakt. Chem.*, **147**, 188 (1936).
8) E. Klingsberg, "The Chemistry of Heterocyclic Compounds, Pyridine and Its Derivatives," ed by A. Weissberger, Interscience Publishers, Part 2, 1961, p. 299. Literatures are cited therein.
9) The IR spectrum revealed a carbonyl stretching band at 1780 cm^{-1}.

TABLE I. 7-N-Substituted Carbamoyl-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids



Compd. No.	R_1	R_2	Method	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
3	CH_3	H	A	303—305	70	DMF	$C_{13}H_{13}O_4N_3$	56.72 (57.01)	4.76 (4.87)	15.27 (15.50)
4	C_2H_5	H	A	276—278	60	DMF	$C_{14}H_{15}O_4N_3$	58.12 (58.03)	5.23 (4.96)	14.53 (14.71)
5	n-C_3H_7	H	A	143—145	65	DMF	$C_{15}H_{17}O_4N_3$	59.39 (59.24)	5.65 (5.92)	13.86 (13.75)
6	iso-C_3H_7	H	A	293—295	80	DMF	$C_{15}H_{17}O_4N_3$	59.39 (59.43)	5.65 (5.66)	13.86 (14.09)
7	C_2H_5–CH(CH$_3$)–	H	B	267—269	70	DMF	$C_{16}H_{19}O_4N_3$	60.55 (60.45)	6.04 (6.31)	13.24 (13.27)
8	$HOCH_2CH_2$–	H	C	267—269	96	EtOH	$C_{14}H_{15}O_5N_3$	55.08 (54.81)	4.95 (5.23)	13.76 (13.92)
9	$CH_3NCH_2CH_2$–(CH$_3$)	H	C	258—259	93	EtOH	$C_{16}H_{20}O_4N_4$	57.82 (57.59)	6.06 (6.18)	16.86 (16.73)
10		H	B	241—242	70	DMF	$C_{18}H_{21}O_4N_3$	62.96 (62.93)	6.16 (6.34)	12.24 (12.44)
11		H	B	187—189	68	DMF	$C_{19}H_{17}O_4N_3$	64.95 (65.22)	4.88 (5.08)	11.96 (11.68)
12	$-CH_2CH_2CH_2CH_2-$		B	275—276	50	DMF	$C_{16}H_{17}O_4N_3$	60.94 (60.65)	5.43 (5.52)	13.33 (13.58)
13	$-CH_2CH_2OCH_2CH_2-$		B	253—255	50	DMF	$C_{16}H_{17}O_5N_3$	58.00 (57.98)	5.17 (5.08)	12.68 (12.74)
14		H	B	>300	90	DMF	$C_{18}H_{15}O_4N_3$	64.09 (64.33)	4.48 (4.46)	12.46 (12.39)
15		H	B	>300	78	DMF	$C_{18}H_{14}O_4N_3Cl$	58.14 (58.43)	3.77 (3.59)	11.30 (11.30)
16		H	B	295—298	90	DMF	$C_{18}H_{14}O_4N_3Cl$	58.14 (57.86)	3.77 (3.90)	11.30 (11.09)
17		H	B	>300	72	DMF	$C_{18}H_{13}O_4N_3Cl_2$	53.20 (53.25)	3.20 (2.96)	10.34 (10.30)
18		H	B	>300	75	DMF	$C_{18}H_{13}O_4N_3Cl_2$	53.20 (53.48)	3.20 (3.43)	10.34 (10.63)
19		H	B	>300	93	DMF	$C_{18}H_{13}O_4N_3Cl_2$	53.20 (53.22)	3.20 (3.47)	10.34 (10.11)
20		H	B	>300	80	DMF	$C_{18}H_{13}O_4N_3Cl_2$	53.20 (53.30)	3.20 (3.44)	10.34 (10.36)
21		H	B	>300	62	DMF	$C_{18}H_{14}O_5N_3Cl$	55.74 (55.77)	3.61 (3.61)	10.84 (11.10)
22		H	B	>300	50	DMF	$C_{19}H_{16}O_5N_3Cl$	56.79 (56.65)	3.99 (3.79)	10.46 (10.62)
23		H	B	>300	60	DMF	$C_{19}H_{16}O_4N_3Cl$	59.14 (59.04)	4.15 (4.30)	10.89 (10.60)

Compd. No.	R_1	R_2	Method	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
24		H	B	>300	68	DMF	$C_{18}H_{14}O_4N_3F$	60.84 (60.58)	3.94 (4.22)	11.83 (11.97)
25		H	B	>300	72	DMF	$C_{18}H_{14}O_4N_3F$	60.84 (60.68)	3.94 (4.01)	11.83 (11.84)
26		H	B	>300	70	DMF	$C_{19}H_{14}O_4N_3F_3$	56.30 (56.29)	3.46 (3.55)	10.37 (10.37)
27		H	B	>300	82	DMF	$C_{18}H_{15}O_5N_3$	61.19 (61.07)	4.28 (4.33)	11.89 (11.70)
28		H	B	295—298	59	DMF	$C_{19}H_{17}O_5N_3$	62.12 (62.34)	4.66 (4.54)	11.44 (11.29)
29		H	B	>300	60	DMF	$C_{19}H_{17}O_5N_3$	62.12 (62.18)	4.66 (4.80)	11.44 (11.43)
30		H	B	>300	65	DMF	$C_{20}H_{19}O_6N_3$	60.45 (60.45)	4.82 (5.04)	10.58 (10.87)
31		H	B	273—274	95	DMF	$C_{22}H_{23}O_6N_3$	62.16 (62.09)	5.45 (5.56)	9.88 (9.82)
32		H	B	261—262	82	DMF	$C_{22}H_{23}O_6N_3$	62.16 (62.39)	5.45 (5.53)	9.88 (10.12)
33		H	B	>300	80	DMF	$C_{19}H_{17}O_4N_3$	64.95 (64.78)	4.88 (4.84)	11.96 (11.67)
34		H	B	>300	74	DMF	$C_{19}H_{17}O_4N_3$	64.95 (64.96)	4.88 (4.80)	11.96 (11.99)
35		H	B	>300	65	DMF	$C_{20}H_{19}O_4N_3$	65.74 (66.02)	5.24 (5.27)	11.50 (11.32)
36		H	B	>300	70	DMF	$C_{20}H_{19}O_4N_3$	65.74 (65.70)	5.24 (5.20)	11.50 (11.76)
37		H	B	>300	73	DMF	$C_{20}H_{19}O_4N_3$	65.74 (65.89)	5.24 (5.45)	11.50 (11.27)
38		H	B	>300	60	DMF	$C_{20}H_{19}O_4N_3$	65.74 (65.79)	5.24 (5.35)	11.50 (11.61)
39		H	B	>300	75	DMF	$C_{20}H_{19}O_4N_3$	65.74 (65.63)	5.24 (5.02)	11.50 (11.50)
40		H	B	293—295	83	DMF	$C_{19}H_{17}O_5N_3$	62.12 (62.34)	4.66 (4.96)	11.44 (11.41)
41		H	B	295—298	62	DMF	$C_{20}H_{19}O_5N_3$	62.98 (62.90)	5.02 (5.00)	11.02 (11.29)
42		H	B	279—281	70	DMF	$C_{20}H_{17}O_6N_3$	60.75 (60.84)	4.33 (4.39)	10.63 (10.54)
43		H	B	>300	68	DMF	$C_{21}H_{19}O_6N_3$	61.61 (61.65)	4.68 (4.55)	10.27 (10.01)

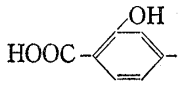
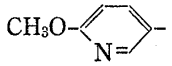
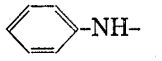
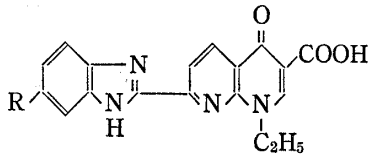
Compd. No.	R_1	R_2	Method	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
44		H	B	>300	50	DMF	$C_{19}H_{15}O_7N_3$	57.43 (57.36)	3.81 (3.87)	10.58 (10.60)
45		H	B	>300	65	DMF	$C_{15}H_{12}O_4N_4S$	52.33 (52.08)	3.49 (3.25)	16.28 (15.99)
46		H	B	>300	60	DMF	$C_{18}H_{16}O_5N_4$	58.69 (58.66)	4.38 (4.58)	15.21 (15.32)
47		H	B	262—265	80	DMF	$C_{18}H_{16}O_4N_4$	61.36 (61.34)	4.58 (4.65)	15.90 (15.81)

TABLE II. 7-(5-Substituted benzimidazol-2-yl)-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids



Compd. No.	R	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
48	H	>300	95	DMF	$C_{18}H_{14}O_3N_4$	64.66	4.22	16.76	64.82	4.24	16.98
49	Cl	>300	82	DMF	$C_{18}H_{13}O_3N_4Cl$	58.61	3.53	15.20	58.65	3.49	15.31
50	CH_3	>300	80	DMF	$C_{19}H_{16}O_3N_4$	65.51	4.63	16.08	65.23	4.60	15.86
51	CH_3O	>300	65	DMF	$C_{19}H_{16}O_4N_4$	62.63	4.43	15.38	62.81	4.45	15.12
52	NO_2	>300	50	DMF	$C_{18}H_{13}O_5N_5$	56.99	3.46	18.46	56.94	3.58	18.49

TABLE III. *In Visro* Antibacterial Activity of **2**

Strain	MIC, μg/ml[a] Compd. **2**	Compd. **1**
Escherichia coli Kauffman O-1	6.25	3.13
Klebsiella pneumoniae ATCC 10031	6.25	3.13
Proteus vulgaris	100	12.5
Pseudomonas aeruginosa	>100	>100
Salmonella typhi H901W (S57)	25	6.25
Salmonella enteritidis (S64)	1.56	1.56
Shigella flexneri 2a1675 (Ewing 10)	12.5	3.13
Shigella sonnei II 37148 (Ewing 34)	12.5	3.13
Bacillus megatherium 10778	6.25	25
Bacillus subtilis ATCC 6633	6.25	6.25
Micrococcus flavus ATCC 10240	25	>100
Staphylococcus aureus FDA 209P	12.5	100
Staphylococcus aureus (Shimanishi)	12.5	100
Staphylococcus aureus (Onuma)	25	100
Mycobacterium 607	50	>100
Mycobacterium phlei	50	>100

a) Minimum inhibitory concentration (MIC) is the lowest concentration of the compound that prevents visible growth after 48 hr of incubation at 37°.

TABLE IV. *In Vitro* Antibacterial Activity

Compd. No.	MIC, μg/ml[a]				
	Escherichia coli 0111	*Shigella dysenteriae* (Hanabusa)	*Staphylococcus aureus* (Terajima)	*Streptococcue disgalactiae* 9926	*Streptococcus pyogenes* G-36
3	>100	>100	50	100	>100
4	>100	>100	100	100	100
5	>100	>100	100	100	100
6	>100	>100	100	>100	>100
7	>100	>100	100	100	100
8	>100	>100	100	>100	>100
9	>100	>100	>100	>100	>100
10	>100	>100	50	50	50
11	>100	>100	>100	>100	>100
14	>100	>100	50	100	>100
15	>100	>100	100	100	100
16	>100	>100	3.2	6.3	6.3
17	>100	>100	12.5	6.3	12.5
18	>100	>100	100	100	100
19	>100	>100	≦1.6	3.2	≦1.6
20	>100	>100	≦1.6	3.2	3.2
21	>100	100	100	100	100
22	>100	>100	100	100	100
23	>100	>100	>100	>100	>100
24	>100	>100	100	>100	>100
25	>100	>100	100	100	>100
26	>100	>100	50	25	25
27	>100	>100	100	>100	100
28	>100	>100	100	>100	>100
29	>100	>100	>100	>100	>100
30	>100	>100	>100	>100	>100
31	>100	>100	>100	100	100
32	>100	>100	>100	100	100
33	>100	>100	100	100	100
34	>100	>100	100	100	100
35	>100	>100	100	100	>100
36	>100	>100	100	100	100
37	>100	>100	100	100	100
38	>100	>100	100	100	100
39	>100	>100	100	50	50
40	>100	>100	100	100	100
41	>100	>100	100	>100	>100
42	>100	>100	25	12.5	12.5
43	>100	>100	100	100	100
44	>100	>100	3.2	12.5	12.5
45	>100	>100	100	100	100
46	>100	>100	100	100	100
47	>100	>100	100	100	100
48	>100	>100	100	100	100
49	>100	>100	3.2	12.5	12.5
1	≦1.6	≦1.6	>100	>100	>100
—[b]	100	3.2	6.3	3.2	3.2

a) Minimum inhibitory concentration (MIC) is the lowest concentration of the compound that prevents visible growth after 48 hr of incubation at 37°.
b) sulfadimethoxin

Treatment of **2** with concentrated sulfuric acid at 60° gave the expected 1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3,7-dicarboxylic acid (**53**).[10] On the other hand, it is interesting to note that heating of **2** with aqueous ethanolic sodium hydroxide led to 1-ethyl-1,4-dihydro-7-hydroxy-4-oxo-1,8-naphthyridine-3-carboxylic acid (**54**)[10] in good yield. There seems to be no previous instances in the literature for the conversion of trihalogenomethyl group into hydroxy group. It has generally been known that trihalogenomethyl groups underwent hydrolysis to carboxy group in such a case.[11]

Screening Results

As shown in Table III, compound (**2**) has been found to be active *in vitro* against both Gram-negative and Gram-positive bacteria except *Pseudomonas aeruginosa* and *Proteus vulgaris*, and to display similar potency with that of **1** against Gram-negative bacteria. The additional compounds prepared in this study were also screened for *in vitro* antibacterial activity against *Escherichia coli* 0111, *Shigella dysenteriae* Hanabusa, *Staphyococcus aureus* Terajima, *Streptococcus disgalactiae* 9926 and *Streptococcus pyogenes* G-36, and the results are surmmarized in Table IV. Several compounds (**16**, **17**, **19**, **20**, **42**, **44**, and **49**) possessed antibacterial activity against Gram-positive bacteria, however, none of the compounds exhibited activity against Gram-negative bacteria as anticipated from the spectrum of **1**. Among them, **19** and **20** displayed significant activity against tested Gram-positive bacteria. Although the structural requirements of these compounds for broad spectrum activity have not been fully investigated at this time, it seems apparent from these results that a strong electron-withdrawing group such as trichloromethyl or 5-nitro-2-furylvinyl group is preferred to N-substituted carbamoyl or benzimidazol-2-yl group. Namely, the contribution of latter two groups as an electron-withdrawing group is much smaller than that of the former.

Experimental[12]

1-Ethyl-1,4-dihydro-4-oxo-7-trichloromethyl-1,8-naphthyridine-3-carboxylic Acid (**2**)——To 23.2 g (0.01 mole) of well dried nalidixic acid (**1**)[3] was added dropwise 50 ml of $SOCl_2$ and the mixture was heated at 60° for 30 min. The excess $SOCl_2$ was removed *in vacuo* and the residue was extracted with boiling benzene (250 ml × 10). The benzene extracts were combined and kept at room temperature overnight to separate the decomposed material. The benzene filtrate was evaporated to 50 ml *in vacuo* and the separated solid was filtered. Recrystallization from EtOH afforded 30 g (90%) of pure product (**2**), mp 195—198°. *Anal.* Calcd. for $C_{12}H_9O_3N_2Cl_3$: C, 42.92; H, 2.68; N, 8.35. Found: C, 43.13; H, 2.67; N, 8.24.

Reduction of 2——A solution of 0.34 g (0.001 mole) of **2** in 30 ml of EtOH containing 0.07 g of 10% palladium-carbon was hydrogenated at room temperature under an atmospheric pressure. Hydrogenation was stopped when the theoretical volume (67 ml) of hydrogen was consumed. The solution was filtered and evaporated to dryness to give 0.21 g (90%) of product (**1**) which is identical in all respects with the authentic sample of **1**.[3]

7-N-Substituted Carbamoyl-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids (**3**—**47**). **General Procedures**——Method A: A suspension of **2** (0.003 mole) in 50 ml of appropriate saturated ethanolic amine was heated at 90° for 9 hr in sealed tube. After the reaction mixture was cooled to room temperature, the precipitated solid was filtered and recrystallized from dimethylformamide (DMF) to give an analytically pure product.

Method B: A mixture of **2** (0.003 mole) and appropriate amine (0.006 mole) was placed at room temperature for 5 min. The precipitated solid was collected and washed with a small amount of MeOH. Recrystallization from EtOH afforded an analytically pure product.

Method C: A mixture of **2** (0.003 mole) and an equimolar amount of appropriate amine was heated in 7 ml of pyridine at 80° for 3—24 hr. After cooling the reaction mixture, the precipitated solid was filtered, washed with MeOH and recrystallized from DMF to give an analytically pure product.

10) See patent in footnote 7.
11) S. Cohen, E. Thom, and A. Bendich, *J. Org. Chem.*, **27**, 3545 (1962).
12) Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR and NMR spectra were recorded on a Japan Spectroscopic Co., Ltd., Model IR-E spectrometer and Japan Electron Optics Lab. Co., Ltd., Model JNM-C-60-H spectrometer, respectively.

7-(5-Substituted benzimidazol-2-yl)-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids (48—52). General Procedure——A mixture of **2** (0.003 mole) and appropriate 3-substituted *o*-phenylenediamine (0.003 mole) in 8 ml of pyridine was heated at 80° for 3—5 hr. After the reaction mixture was cooled, the precipitated solid was collected. The filtrate was diluted with MeOH and the precipitated solid was again filtered to give second crop. These crystals were combined and recrystallized from DMF to give pure product.

1-Ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3,7-dicarboxylic Acid (53)——A mixture of 1 g (0.003 mole) of **2** and 5 ml of conc. H_2SO_4 was heated at 80° for 3 hr. After cooling, the solution was diluted with H_2O. The precipitated solid was collected and recrystallized from EtOH to give 0.4 g (50%) of pure product (**53**) which is identical in all respects with the authentic sample.[10]

1-Ethyl-1,4-dihydro-7-hydroxy-4-oxo-1,8-naphthyridine-3-carboxylic Acid (54)——To a solution of 1.7 g (0.005 mole) of **2** in 15 ml of EtOH was added 2.5 g of NaOH in 15 ml of H_2O. The mixture was refluxed for 45 min and acidified with AcOH. The precipitated solid was collected and recrystallized from EtOH to provide 0.82 g (70%) of pure product (**54**) which is identical in all respects with the authentic sample.[10]