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Synthesis of 1-Substituted 1,4-Dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine Derivatives. II[1,2]

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For screening of antimicrobial agent, a series of 1-substituted 1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acids was synthesized and some of these compounds were converted to the corresponding esters and amides via the acid chloride.

The preceding paper of this series[1] reported that 1-ethyl-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (V) ($R_1=C_2H_5$) had very potent antimicrobial activities against gram-positive and gram-negative bacteria *in vitro*, and attempts were made to synthesize various derivatives of V ($R_1=C_2H_5$) in order to find a new antimicrobial agent.

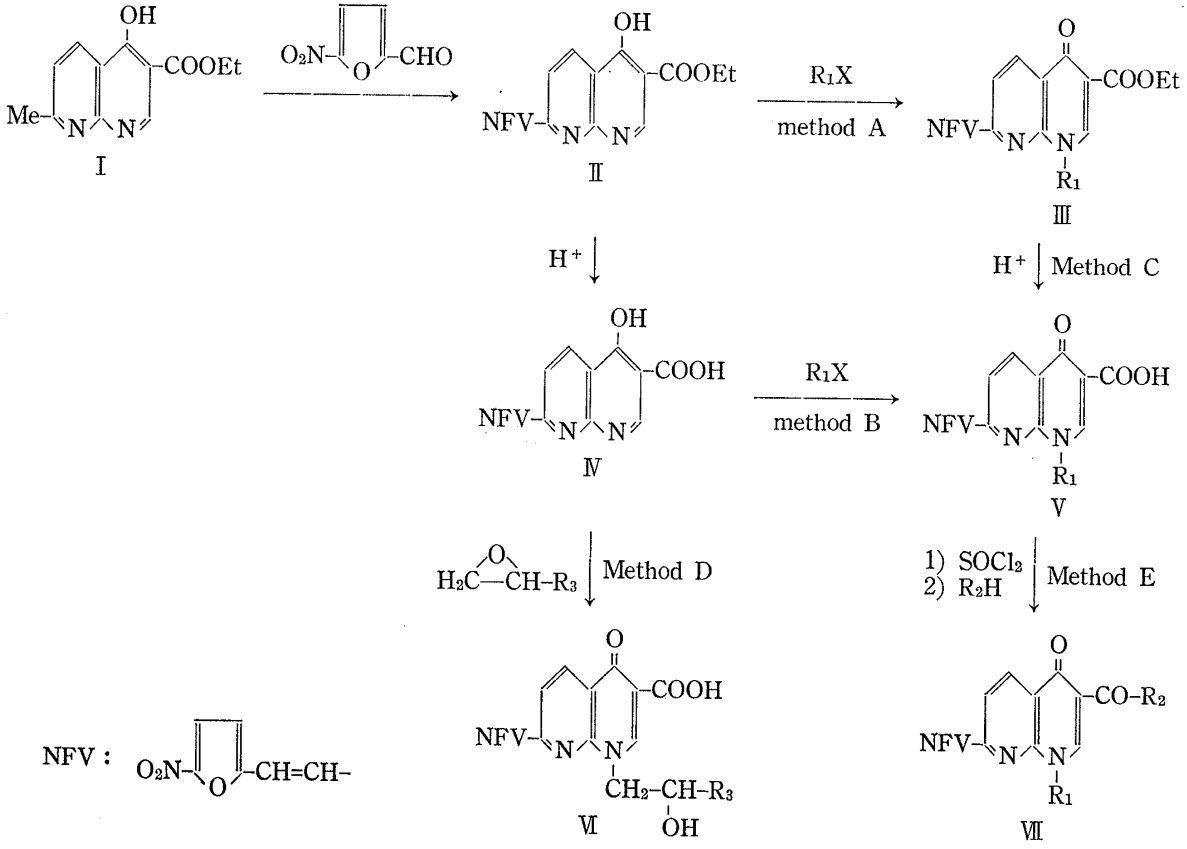
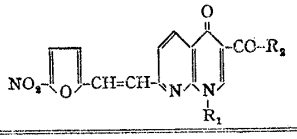


Chart 1

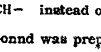
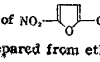
1) Part 1: S. Nishigaki, F. Yoneda, K. Ogiwara, T. Naito, R. Dohmori, S. Kadoya, Y. Tanaka and I. Takamura, *Chem. Pharm. Bull.* (Tokyo), **17**, 1828 (1969).
2) A part of this work was presented at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1968.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*

TABLE I. 1-Substituted 1,4-Dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic Acids and Their Derivatives



Compd. No.	R_1	R_2	mp (°C) (decomp.)	Appearance[a]	Recryst. solvent[b]	Yield (%)	Method[c]	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
1	Me	OH	>300	ne	DMF	63	B	$C_{16}H_{11}O_6N_3$	56.31	3.25	12.31	56.25	3.59	12.53
2	Me	OK	>300	pl	——	95	—[d]	$C_{16}H_{10}O_6N_3K$	50.65	2.66	11.06	50.77	2.92	11.33
3	Pr(n)	OH	277—278	ne	AcOH	71	C	$C_{18}H_{15}O_6N_3$	58.53	4.09	11.38	58.92	4 40	11.41
4	Pr(i)	OH	297—298	ne	AcOH	66	C	$C_{18}H_{15}O_6N_3$	58.53	4.09	11.38	58.66	4.51	11.30
5	CH_2COMe	OH	>300	ne	DMF	88	C	$C_{18}H_{13}O_7N_3$	56.40	3.42	10.96	56.83	3.45	10.93
6	CH_2CO-Ph	OH	>300	ne	DMF	70	B	$C_{23}H_{15}O_7N_3$	61.83	3.69	9.64	62.02	3.39	9.44
7	CH_2COOH	OH	>300	ne	DMSO	83	C	$C_{17}H_{11}O_8N_3$	52.99	2.88	10.90	53.01	3.00	10.89
8	CH_2COOK	OH	>300	ne	——	100	—[d]	$C_{17}H_{10}O_8N_3K\cdot 1\frac{1}{2}H_2O$	45.33	2.90	9.33	45.61	3.10	9.19
9	CH_2COOK	OK	>300	ne	——	100	—[d]	$C_{17}H_9O_8N_3K_2\cdot 2\frac{1}{2}H_2O$	40.31	2.79	8.30	40.21	3.13	8.33
10	CH(Me)–COOH	OH	>300	po	DMSO	83	—[e]	$C_{18}H_{13}O_8N_3\cdot\frac{1}{2}H_2O$	52.95	3.46	10.29	52.55	3.40	10.16
11	CH(Me)–COOEt	OH	204—205	po	$CHCl_3$+EtOH	84	—[e]	$C_{20}H_{17}O_8N_3$	56.21	4.01	9.83	56.33	4.16	10.07
12	CH_2CONH_2	OH	>300	ne	DMSO	68	B	$C_{17}H_{12}O_7N_4\cdot\frac{1}{2}H_2O$	51.90	3.31	14.25	52.32	3.40	14.06
13	CH_2CN	OH	>300	po	DMF	38	B	$C_{17}H_{10}O_6N_4$	55.74	2.75	15.30	55.85	3.18	14.71
14	$CH_2CH{=}CH_2$	OH	277—278	ne	AcOH	69	C	$C_{18}H_{13}O_6N_3$	58.86	3.57	11.44	59.03	3.75	12.03
15	$CH_2CH{=}C(Me)_2$	OH	267—268	ne	DMF	81	B	$C_{20}H_{17}O_6N_3$	60.75	4.34	10.63	60.28	4.40	10.79
16	CH_2-Ph	OH	283—284	ne	DMF	84	C	$C_{22}H_{15}O_6N_3$	63.33	3.62	10.07	62.66	3.68	10.56
17	CH_2-(4-NO_2-Ph)	OH	293—294	ne	DMF	96	C	$C_{22}H_{14}O_8N_4$	57.15	3.05	12.12	57.34	3.62	12.18
18	CH_2CH_2OH	OH	283—284	ne	DMF	60	D	$C_{17}H_{13}O_7N_3$	54.99	3.53	11.32	55.06	3.45	11.25
19	CH_2–CH(OH)–Me	OH	254—255	ne	DMF+MeOH	52	D	$C_{18}H_{15}O_7N_3$	56.10	3.92	10.91	56.04	4.05	10.72
20	CH_2–CH(OH)–CH_2(OH)	OH	230—234	po	DMF+EtOH	32	D	$C_{18}H_{15}O_8N_3\cdot\frac{1}{2}H_2O$	52.69	3.93	10.24	52.56	4.30	9.88
21	CH_2–CH(OH)–CH_2Cl	OH	>300	po	DMF+MeOH	50	D	$C_{18}H_{14}O_7N_3Cl$	51.50	3.36	10.01	52.32	3.73	10.03
22	$CH_2CH_2NEt_2$	OH	222—223	ne	DMF	68	B	$C_{21}H_{22}O_6N_4$	59.15	4.80	13.14	58.91	4.97	12.93
23	$CH_2CH_2NEt_2$	OK	>280	ne	DMSO+H_2O	67	—[d]	$C_{21}H_{21}O_6N_4K\cdot H_2O$	52.27	4.80	11.61	52.46	5.25	11.81
24	$CH_2CH_2NEt_2\cdot HCl$	OH	*ca.* 270	ne	DMF	80	B	$C_{21}H_{23}O_6N_4Cl\cdot\frac{1}{2}H_2O$	53.45	5.13	11.87	53.85	5.32	11.79
25	$CH_2CH_2NEt_2\cdot MeSO_3H$	OH	266—268	ne	DMF	97	—[d]	$C_{22}H_{26}O_9N_4S$	50.57	5.02	10.72	50.76	5.05	10.77
26	$CH_2CH_2NEt_2$	OH	227—229	ne	DMF	99	—[d]	$C_{27}H_{35}O_9N_5S$	53.54	5.83	11.56	53.19	5.91	11.14
	(H)-$NHSO_3H$													
27	$CH_2CH_2\overset{+}{N}Et_2$–Et I^-	OH	258—260	ne	——	91	—[d]	$C_{22}H_{25}O_6N_4I$	46.49	4.43	9.86	46.64	4.71	9.38
	(Me)													
28	$CH_2CH_2\overset{+}{N}Et_2$–Et $\cdot MeSO_4^-$	OH	255—257	ne	——	71	—[d]	$C_{23}H_{29}O_{10}N_4S$	49.99	5.11	10.14	49.67	5.10	10.13
	(Me)													
29	$CH_2CH_2NMe_2\cdot HCl$	OH	>280	po	DMSO	73	B	$C_{19}H_{19}O_6N_4Cl\cdot\frac{1}{2}H_2O$	51.42	4.54	12.62	51.22	4.33	12.01
30	$CH_2CH_2CH_2NMe_2\cdot HCl$	OH	271—273	pr	DMF	50	B	$C_{20}H_{21}O_6N_4Cl\cdot\frac{1}{2}H_2O$	52.46	4.84	12.24	52.69	4.97	11.88
31	CH_2–CH(Me)–$CH_2NEt_2\cdot HCl$	OH	245—247	pr	DMF	72	B	$C_{23}H_{27}O_6N_4Cl\cdot\frac{1}{2}H_2O$	55.25	5.64	11.21	55.01	5.70	11.09
32	$CH_2CH_2NHEt\cdot HCl$[f]	OH	>300	pr	DMF	80	B	$C_{19}H_{19}O_6N_4Cl$	52.48	4.40	12.89	52.37	4.91	12.52
33	CH_2CH_2N(H)$\cdot HCl$	OH	>280	ne	DMSO	92	B	$C_{21}H_{21}O_6N_4Cl\cdot\frac{1}{2}H_2O$	53.68	4.72	11.92	53.66	4.82	11.60
34	CH_2CH_2N(H)	OH	234—236	pr	DMF+MeOH	31	B	$C_{22}H_{22}O_6N_4\cdot H_2O$	57.89	5.30	12.28	58.35	5.25	12.66
35	CH_2CH_2N(H)$\cdot HCl$	OH	>300	pr	DMSO	89	B	$C_{22}H_{23}O_6N_4Cl\cdot H_2O$	53.61	5.11	11.37	53.72	5.17	11.05
36	CH_2CH_2N(H)O$\cdot HCl$	OH	>280	ne	DMF	90	B	$C_{21}H_{21}O_7N_4Cl\cdot\frac{1}{2}H_2O$	51.91	4.56	11.53	51.53	4.98	11.33
37	CH_2CH_2N(H)S$\cdot HCl$	OH	>280	ne	DMSO	83	B	$C_{21}H_{21}O_6N_4SCl\cdot\frac{1}{2}H_2O$	50.25	4.42	11.16	50.22	4.76	11.58
38	H	OMe	>280	po	——	76	—[g]	$C_{16}H_{11}O_6N_3$	56.31	3.25	12.31	55.97	3.52	11.82
39	Me	OMe	275—276	ne	DMF	40	—[h]	$C_{17}H_{13}O_6N_3$	57.47	3.69	11.83	57.40	4.02	11.54
40	Me	OEt	253—254	po	DMF	82	A	$C_{18}H_{15}O_6N_3$	58.53	4.09	11.38	58.37	4.25	11.07
41	Pr(n)	OEt	257—258	ne	$CHCl_3$+MeOH	60	A	$C_{20}H_{19}O_6N_3$	60.45	4.82	10.57	60.31	5.03	10.87
42	Pr(i)	OEt	235—237	ne	$CHCl_3$+MeOH	48	A	$C_{20}H_{19}O_6N_3$	60.45	4.82	10.57	60.09	4.96	10.71
43	CH_2COMe	OEt	287—295	ne	DMF	42	A	$C_{20}H_{17}O_7N_3$	58.39	4.17	10.22	58.47	4.36	10.57
44	CH_2COOH	OEt	>300	ne	DMSO	48	A	$C_{19}H_{15}O_8N_3$	55.20	3.63	10.20	54.65	3.63	10.61
45	CH_2COOEt	OEt	218—220	ne	$CHCl_3$	68	A	$C_{21}H_{19}O_8N_3$	57.10	4.30	9.52	57.27	4.46	9.66
46	CH(Me)–COOEt	OEt	218—219	pr	$CHCl_3$+MeOH	74	A[e]	$C_{22}H_{21}O_8N_3$	58.02	4.65	9.23	57.98	4.53	9.07

47	$CH_2CH=CH_2$	OEt	235—236	pr	$CHCl_3$	36	A	$C_{20}H_{17}O_6N_3$	60.75	4.34	10.63	60.14	4.36	11.04
48	CH_2-Ph	OEt	243—245	ne	$CHCl_3$	40	A	$C_{24}H_{19}O_6N_3$	64.71	4.30	9.43	64.40	4.36	9.72
49	CH_2-Ph-NO_2	OEt	273—275	po	DMF	54	A	$C_{24}H_{18}O_8N_4$	58.77	3.70	11.43	58.73	3.85	11.42
50	$CH_2CH_2N(Et)_2$	OEt	189—190[f]	pr	EtOH	40	A	$C_{23}H_{26}O_6N_4$	60.78	5.77	12.33	60.52	6.16	12.24
51	$CH_2CH_2N(Et)_2\cdot HCl$	OEt	239—240	ne	EtOH+H_2O	40	A	$C_{23}H_{27}O_6N_4Cl\cdot\frac{1}{2}H_2O$	55.25	5.64	11.21	55.30	5.50	11.12
52	$CH_2CH_2N(Me)_2$	OEt	210—212	pr	$CHCl_3$+AcOEt	45	A	$C_{21}H_{22}O_6N_4$	59.15	5.20	13.10	58.69	5.68	12.89
53	$CH_2CH_2N(Me)_2\cdot MeSO_3H$	OEt	236—238	ne	DMF	84	—[d]	$C_{22}H_{26}O_9N_4S$	50.57	5.02	10.72	50.58	5.32	10.92
54	CH_2CH_2N(H)	OEt	211—213	ne	$CHCl_3$	24	A	$C_{24}H_{26}O_6N_4$	61.79	5.62	12.01	61.73	5.76	12.06
55	H	OBu(*n*)	285—286	po	DMF	67	—[g]	$C_{19}H_{17}O_6N_3$	59.53	4.47	10.96	59.70	4.70	11.00
56	Et	OBu(*n*)	204—207[f]	ne	$CHCl_3$+ether	46	E	$C_{21}H_{21}O_6N_3$	61.31	5.15	10.21	61.38	5.31	10.48
57	Et	$OC_{10}H_{21}$(*n*)	177—180[f]	po	acetone	86	E	$C_{27}H_{33}O_6N_3$	65.44	6.71	8.48	65.51	6.73	9.01
58	Et	OCH_2CH_2OH	238—241	ne	DMF	53	E	$C_{19}H_{17}O_7N_3$	57.14	4.29	10.52	57.15	4.30	10.43
59	Et	$OCH_2CH(OH)CH_2OH$	238—241	pr	DMF+H_2O	50	E	$C_{20}H_{19}O_8N_2$	55.94	4.46	9.79	55.75	4.51	9.89
60	Et	$OCH_2CH(O\cdot C(Me)_2\cdot O)CH_2$	175—178	pr	acetone	99	E	$C_{23}H_{23}O_8N_3$	58.84	4.94	8.95	58.44	4.82	8.99
61	Et	OCH_2CH_2Cl	245—248[f]	pr	DMF	51	E	$C_{19}H_{16}O_6N_3Cl$	54.62	3.86	10.06	54.96	4.09	10.44
62	H	$OCH_2CH_2N(Et)_2$	217—220	ne	DMF	46	E	$C_{21}H_{22}O_6N_4$	59.15	5.20	13.14	59.14	5.31	12.92
63	Et	$OCH_2CH_2N(Et)_2$	182—185[f]	ne	MeCN	47	E	$C_{25}H_{26}O_6N_4$	60.78	5.77	12.33	60.70	5.74	12.33
64	CH_2COOEt	OCH_2COOEt	209—210	ne	$CHCl_3$+MeOH	52	—[e]	$C_{23}H_{21}O_{10}N_3$	55.31	4.24	8.41	55.43	4.39	8.95
65	CH(Me)-COOEt	OCH(Me)-COOEt	170—175[f]	ne	acetone	76	—[e]	$C_{25}H_{25}O_{10}N_3$	56.92	4.78	7.97	56.77	4.83	8.22
66	Et	NH_2	>300	po	DMSO	77	E	$C_{17}H_{14}O_5N_4$	57.62	3.98	15.81	57.76	4.20	15.71
67	Et	NHEt	>300	ne	DMF	86	E	$C_{19}H_{18}O_5N_4$	59.68	4.74	14.65	59.52	4.89	14.43
68	Et	NH-Ph	289—290	ne	DMF	62	E	$C_{23}H_{18}O_5N_4$	64.18	4.21	13.02	63.72	4.45	12.90
69	Et	NH-(H)	288—290	ne	DMF	45	E	$C_{23}H_{24}O_5N_4$	63.29	5.54	12.84	62.95	5.68	12.66
70	Et	N(H)O	263—264	ne	DMF	53	E	$C_{21}H_{20}O_6N_4$	59.43	4.75	13.20	59.22	5.19	13.32
71	Et	$N(CH_2CH_2OH)_2$	212—215[f]	ne	DMF+acetone	40	E	$C_{21}H_{22}O_7N_4$	57.01	5.01	12.66	57.55	5.12	12.51
72[j]	$CH_2CH_2N(Et)_2\cdot HCl$	OH	278—281	ne[k]	DMF	43	—[l]	$C_{21}H_{24}O_4N_3Cl$	60.35	5.79	10.06	60.49	5.90	10.22
73[j]	$CH_2CH_2N(Et)_2\cdot HCl$	OEt	236—239	ne[k]	MeOH+ether	32	—[m]	$C_{23}H_{28}O_4N_3Cl\cdot H_2O$	59.54	6.52	9.06	59.55	6.86	8.70

a) ne: yellow needles, pl: yellow plates, po: yellow powder, pr: yellow prisms
b) AcOH: acetic acid, $CHCl_3$: chloroform, DMF: dimethylformamide, DMSO: dimethylsulfoxide, AcOEt: ethyl acetate, EtOH: ethanol, MeOH: methanol, MeCN: acetonitrile, H_2O: water
c) See Chart 1. *d*) salt formation (see Experimental) *e*) See Experimental.
f) 2-Ethylaminoethylchloride was prepared from 2-ethylaminoethanol and thionyl chloride by J. H. Parkkari's method[29] (see Experimental).
g) These compounds were prepared from 5-nitro-2-furaldehyde and methyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (see Experimental) or the corresponding butyl ester (see Experimental). The procedure used here was virtually identical with the method for the synthesis of the corresponding ethyl ester (II).
h) This compound was prepared from No. 38 in a similar manner of method A. *i*) melting point (not decomposing point)
j)  instead of  *k*) colorless crystals *l*) This compound was prepared from No. 73 in a similar manner of method C.
m) This componnd was prepared from ethyl 7-[2-(2-furyl)vinyl]-4-hydroxy-1,8-naphthyridine-3-carboxylate in a similar manner of method A.

The present paper deals with the synthetic method for 1-substituted 1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid, and their corresponding esters and amides. The results of the synthesis of 73 derivatives are summarized in Table I.

Synthesis of these derivatives, based on the results of the preceding work, was carried out as shown in Chart 1. 1-Substituted alkyl derivatives (III and V) were synthesized by N^1-alkylation of ethyl 4-hydroxy-7-[2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridine-3-carboxylate (II) or 4-hydroxy-7-[2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridine-3-carboxylic acid (IV) with alkyl halides in the presence of potassium carbonate (method A and B). Compounds (V) were also prepared by the hydrolysis of ethyl 1-substituted 1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate (III) with a mixture of hydrochloric acid and acetic acid (method C). In the case of 1-hydroxyalkyl derivatives (VI), they were obtained by N^1-alkylation of IV with alkylene oxides (method D). Esters or amides derived from carboxyl groups at 3-position were prepared by converting the corresponding carboxylic acids to the acid chlorides with thionyl chloride, followed by their treatment with alcohols or amines (method

E). In addition, the salts of carboxylic acids or amines (Table I, No. 2, 23, 25, 26 and 53) were prepared in dimethylformamide or dimethyl sulfoxide by treating the corresponding carboxylic acids or amines with alkalis or acids.

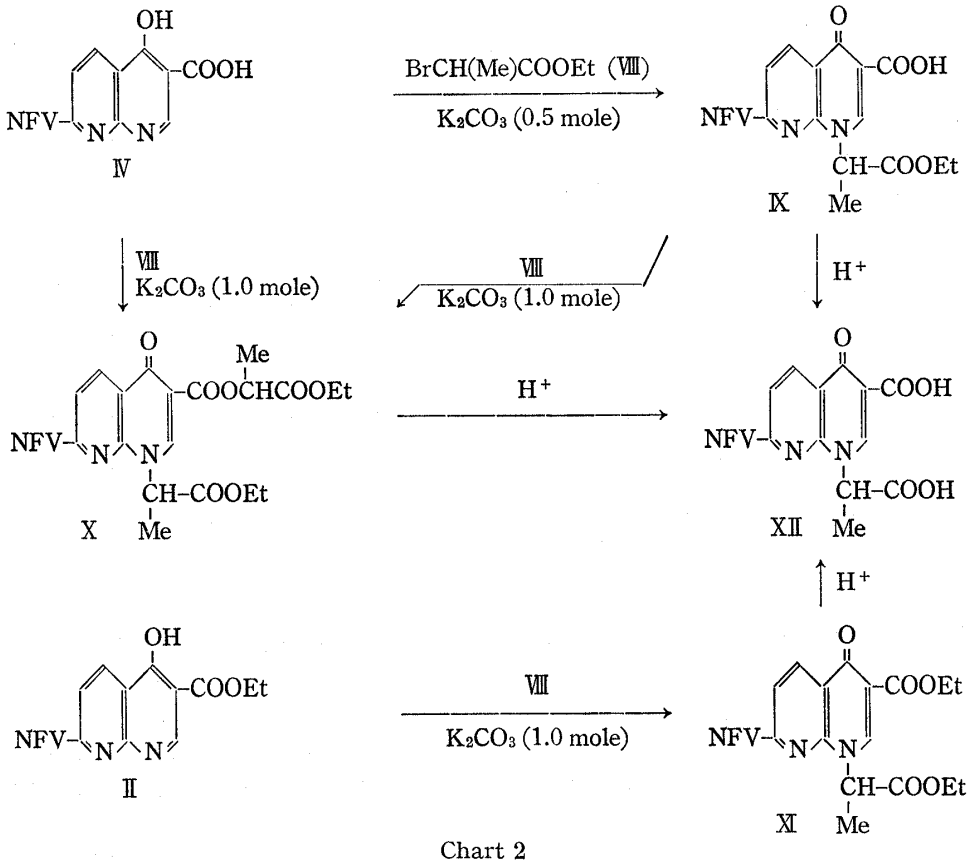


Chart 2

According to method B, IV was alkylated to give usually 1-alkyl derivatives (V), but in the case of treatment of IV with ethoxycarbonylalkyl halides, it was found that not only alkylation at N^1-position but also esterification of carboxyl group at 3-position took place at the same time (See Chart 2). It was concluded from the experiments using ethyl 2-bromopropionate (VIII) that the selectivity of alkylation at N^1-position depended not on the quantity of the reagent (VIII) but on the quantity of potassium carbonate. Treatment of IV with excess VIII in the presence of 1.0 mole of potassium carbonate caused not only N^1-alkylation but also esterification to give 1-ethoxycarbonylethyl 1-(1-ethoxycarbonylethyl)-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate (X) melting at 170—175°, but a similar reaction in the presence of 0.5 mole of potassium carbonate caused only N^1-alkylation to give 1-(1-ethoxycarbonylethyl)-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (IX) decomposing at 204—205°. Further treatment of IX thus obtained with VIII afforded the ester which was identical with X obtained from IV. Hydrolysis of IX and X gave the same compound, 1-(1-carboxyethyl)-1,4-dihydro-7-[2-(5-nitro-2-furyl)-vinyl]-4-oxo-1,8-naphthyridine-3-carobxylic acid (XII) melting above 300°. The ethyl ester (II) was allowed to react with VIII by method A to give ethyl 1-(1-ethoxycarbonylethyl)-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate (XI) decomposing at 218°, which was hydrolyzed to dicarboxylic acid (XII) described above.

The structures of the compounds synthesized in the present work were confirmed by elementary analysis, and from ultraviolet (UV), infrared (IR) and nuclear magnetic resonance (MNR) spectra. The NMR data of some compounds are given in Table II. The double bond combining the furan ring with the naphthyridine ring seemed to be in the *trans* form considering that the coupling constants of two protons lay in the range of 15—16 cps.

Table II. NMR Spectral Data of 1-Substituted 1,4-Dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic Acids[a]

R_1	δ[b] (singlet)	δ (doublet)		J[c]	δ (doublet)		J	δ (doublet)		J
H	9.53	9.06	8.14	8.6	7.53	7.03	4.3	8.00	7.68	15.7
Me	9.62	9.07	8.13	8.6	7.60	7.07	4.4	8.09	7.79	15.5
Et	9.55	9.00	8.07	8.8	7.54	7.00	3.9	7.98	7.73	15.6
Pr(n)	9.57	9.04	8.10	8.9	7.57	7.04	3.8	8.01	7.75	15.9
Pr(i)	9.57	9.08	8.14	8.6	7.57	7.06	4.3	8.02	7.78	15.6
CH_2COOH	9.67	9.04	8.07	8.1	7.53	7.02	3.9	7.96	7.70	15.7
CH_2-C$_6$H$_5$	9.52	9.06	8.11	8.1	7.54	7.03	4.5	8.01	7.76	15.5
$CH_2CH_2N(Et)_2$	9.75	9.07	8.27	8.4	7.57	7.06	3.9	7.89	7.74	16.0
CH(Me)COOH	9.67	9.06	8.07	8.8	7.56	7.06	3.9	7.98	7.71	15.3

a) Measured at 100 Mcps on JNM-4H-100 (Japan Electron Optics Lab. Tokyo Japan) and in 10% solution in CF_3COOH with tetramethylsilane as internal standard.
b) chemical shift in ppm
c) coupling constant in cps

Some structure-activity relationships of the compounds synthesized in the present and preceding work are as follows: (1) Absence of a nitro group in the furan ring results in decreased activity, (2) replacement of -CH=CH- group by -CH(OH)-CH_2- results in a considerable loss of activity, (3) carboxylic acids are generally more active than the corresponding esters or amides, (4) the aminoalkyl or hydroxyalkyl esters are more active than the alkyl esters in the series of carboxylic acid esters, (5) the N^1-methyl derivative is the most active in the N^1-alkyl derivatives, (6) the N^1-ketoalkyl or arylalkyl derivatives are inferior to the lower alkyl, aminoalkyl, hydroxyalkyl and carboxyalkyl derivatives.

Details on the antimicrobial activities will be reported in near future.

Experimental[4]

General Procedure for the Synthesis of Ethyl 1-Substituted-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate (III), Method A——To a stirred suspension of II[1] (3.55 g, 10 mmoles) in dimethylformamide (DMF) (70 ml) were added K_2CO_3 (10—15 mmoles) and alkyl halide (15—20 mmoles). The reaction mixture was heated for 1—15 hr at 80—100° with stirring and concentrated *in vacuo*. After cooling, the resulting precipitate was collected by filtration, washed with H_2O and dried. The crude product was recrystallized from a suitable solvent.

General Procedure for the Synthesis of 1-Substituted-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic Acid (V), Method B——A mixture of IV[1] (3.27 g, 10 mmoles), K_2CO_3 (10—15 mmoles), alkyl halide (15—20 mmoles) and DMF (70 ml) was heated for 6—20 hr at 80—100° with stirring. The reaction mixture was concentrated *in vacuo* and allowed to stand at room temperature. The resulting precipitate was collected by filtration, washed with H_2O and dried. The crude V was recrystallized from a suitable solvent.

Method C——A suspension of III (10 mmoles) in conc. HCl–90% AcOH (1:11) (50 ml) was gently refluxed for 2 hr with stirring. After cooling, the yellow precipitate was collected by filtration, washed with H_2O and dried. The crude product was recrystallized from a suitable solvent.

General Procedure for the Synthesis of 1,4-Dihydro-1-hydroxyalkyl-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic Acid (VI), Method D——IV (3.27 g, 10 mmoles), alkylene oxide (0.1 mole) and DMF (100 ml) were heated in a closed vessel for 10—20 hr at 80—100°. The reaction mixture was concentrated *in vacuo* and added with H_2O. The resulting precipitate was collected and dried. The crude product was recrystallized from a suitable solvent.

4) All melting points were uncorrected.

General Procedure for the Synthesis of Esters or Amides (VII) of 1-Substituted-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic Acid, Method E——V (3 g) was added to thionyl chloride (60 ml) and the mixture was stirred at room temperature for 2 hr. There was added thereto anhydrous ether (60 ml) to precipitate the product completely and the crystals were collected by filtration and washed with anhydrous ether to give the acid chloride of V, which was used for the next step without further purification.

a) Esters: The crude acid chloride was added to a large amount of the corresponding alcohol. The reaction mixture was stirred for 2—4 hr at 25—60° and allowed to stand overnight at room temperature. The precipitate was collected and recrystallized from a suitable solvent.

In the synthesis of the compound (No. 63), the procedure was as follows. To a stirred suspension of the acid chloride in $CHCl_3$ (125 ml) was added dropwise 2-diethylaminoethanol (5 g) in $CHCl_3$ (20 ml) at room temperature and allowed to stand for one hour. The reaction mixture was washed with aqueous $NaHCO_3$ solution and the separated $CHCl_3$ layer was extracted with diluted AcOH. The AcOH extract was neutralized with $NaHCO_3$ (pH 8—9) and re-extracted with $CHCl_3$. The $CHCl_3$ extract was dried and concentrated to dryness. The residue was washed with ether and recrystallized from acetonitrile to give yellow needles (1.8 g).

b) Amides: To a stirred suspension of the acid chloride in DMF (90 ml) was added dropwise the corresponding amine and allowed to stand for 2 hr with stirring. The resulting precipitate was collected by filtration and recrystallized from a suitable solvent.

The compound (No. 66) was prepared as follows. Ammonia gas was bubbled into the hot solution of the acid chloride in DMF (150 ml) for 10 min. After standing for one hour at room temperature, the precipitated crystals were collected and washed with H_2O and dried. The crude product was recrystallized from dimethyl sulfoxide (DMSO) to give yellow powder (1.8 g).

The compound (No. 71) was prepared as follows. The acid chloride obtained above was added to a mixture of bis-(2-hydroxyethyl)amine (6 g) and DMF (150 ml) at room temperature within a period of 30 min with stirring, and the mixture was heated for 4 hr at 60°. The reaction mixture was concentrated *in vacuo*. The resulting residue was treated with H_2O and extracted with $CHCl_3$. Evaporation of $CHCl_3$ afforded the crude product which was recrystallized from DMF–acetone to give the pure product (1.5 g).

Preparation of Carboxylic Acid Salts and Amine Salts——a) Carboxylic Acid Salts: A mixture of V (10 mmoles), K_2CO_3 (0.76 g, 5.5 mmoles), DMSO (170 ml) and H_2O (170 ml) was refluxed for 20 min and a small amount of undissolved material was filtered off. After chilling, the precipitate was collected and washed with H_2O and then with acetone. The potassium salts were dried below 50°.

The compound (No. 9) was prepared in a following manner. To a suspension of the compound (No. 7) (0.40 g) in H_2O (10 ml) was added dropwise aqueous KOH solution and the mixture was adjusted to pH 9.0—9.4. A small amount of undissolved material was filtered off. To the filtrate was added dropwise EtOH (30 ml) with stirring and the resulting precipitate was collected by filtration. The precipitate was dissolved in H_2O and reprecipitated by addition of EtOH. Yield 0.31 g.

b) Amine Salts: To a solution of the amino compound in DMF was added an inorganic or organic acid (1.1 molar equivalent) and the resulting precipitate was collected by filtration and dried *in vacuo*.

Quarternary salts (No. 27 and 28) of the amino compound were also obtained in a similar manner except that acetone was used instead of DMF as the solvent.

1-(1-Ethoxycarbonylethyl)-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic Acid (IX) (No. 11)——IV (0.33 g, 1 mmole), ethyl 2-bromopropionate (0.33 g, 4 mmoles), K_2CO_3 (0.07 g, 0.5 mmole), and DMF (6.5 ml) were heated at 80° for 45 min with stirring. The reaction mixture was diluted with H_2O and acidified with HCl. The solid separated was collected by filtration and washed with H_2O and dried. The crude product was recrystallized from $CHCl_3$–EtOH to give a yellow powder (0.36 g) of IX, mp 204—205° (decomp.).

1-Ethoxycarbonylethyl 1-(1-Ethoxycarbonylethyl)-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate (X) (No. 65)——a) IV (3.27 g, 10 mmoles), ethyl 2-bromopropionate (3.62 g, 20 mmoles), K_2CO_3 (1.38 g, 10 mmoles), and DMF (65 ml) were heated at 80° for 7 hr with stirring. After evaporation of the solvent, the residue was treated with H_2O and acidified with HCl. The solid separated was collected and washed with H_2O and dried. After chromatography in $CHCl_3$ solution over Al_2O_3, the product was recrystallized from acetone to give a yellow powder (4.00 g) of X, mp 170—175°.

b) A mixture of IX (0.85 g, 2 mmoles), ethyl 2-bromopropionate (0.82 g, 6 mmoles), K_2CO_3 (0.28 g, 2 mmoles), and DMF (17 ml) was heated at 80° for one hour with stirring. The reaction mixture was treated as the same manner described above and the product was recrystallized from acetone to give a yellow powder (0.5 g), mp 170—175°, which did not depress the melting point of X. Their IR spectra were identical.

Ethyl 1-(1-Ethoxycarbonylethyl)-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate (XI) (No. 46)——To a suspension of II (3.55 g, 10 mmoles) in DMF (71 ml), ethyl 2-bromopropionate

5) W.E. Parham and L.J. Reed, "Organic Synthesis," Coll. Vol. III, ed. by E.C. Horning, John Wiley & Sons, Inc., New York, N.Y., 1955, p. 395.

(4.01 g, 30 mmoles) and K_2CO_3 (1.38 g, 10 mmoles)were added and the mixture was heated at 80° for 40 min with stirring. The reaction mixture was treated in usual manner. Recrystallization of the crude product from $CHCl_3$–MeOH afforded a yellow powder (4.09 g) of XI, mp 218—219° (decomp.).

1-Carboxyethyl-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic Acid (XII) (No. 10)——a) A suspension of X (0.43 g, 0.81 mmole) in conc. HCl–90% AcOH (1:11) (8.5 ml) was refluxed for 2 hr with stirring. After cooling, the precipitate was collected by filtration and washed with acetone. The crude product was recrystallized from AcOH to give a yellow powder (0.27 g, 83%) of XII, mp>300° (decomp.).

b) The hydrolysis of IX (0.43 g, 1 mmole) was carried out in the similar manner as described above. Recrystallization of the crude product gave a yellow powder (0.30 g, 76%). The melting point and IR spectrum of this substance were identical with those of XII obtained from X.

c) From XI (0.91 g, 2 mmoles), XII (0.68 g, 85%) was obtained by the treatment as described above.

Ethoxycarbonylmethyl 1-Ethoxycarbonylmethyl-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate (No. 64)——A mixture of IV (1.63 g, 5 mmoles), ethyl chloroacetate (1.23 g, 10 mmoles), K_2CO_3 (1.4 g, 10 mmoles) and DMF (25 ml) was heated at 80° for one hour. The reaction mixture was concentrated *in vacuo* and added with H_2O. The resulting dark-brown precipitate was collected and dissolved in $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4 and then passed through an Al_2O_3 column. The solvent was evaporated to dryness and the residue was washed with acetone. Recrystallization from $CHCl_3$–MeOH gave yellow needles (450 mg), mp 209—210° (decomp.).

Dimethyl Ethoxymethylenemalonate——This compound was prepared from dimethyl malonate according to the method[5] described for diethyl malonate. Colorless oil, bp 130° (1—2 mmHg). *Anal.* Calcd. for $C_8H_{12}O_5$: C, 51.10; H, 6.38. Found: C, 50.90; H, 6.47.

Dimethyl N-(6-Methyl-2-pyridyl)aminomethylenemalonate——The reaction was carried out using the technique[6] of Lappin. The crude product was recrystallized from EtOH to give colorless prisms, mp 93—95°. *Anal.* Calcd. for $C_{12}H_{14}O_8N_2$: C, 57.60; H, 5.60; N, 11.20. Found: C, 57.83; H, 5.69; N, 11.44.

Methyl 4-Hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate——This compound was prepared from dimethyl ester instead of diethyl N-(6-methyl-2-pyridyl)aminomethylenemalonate in the manner[6] described by Lappin. Recrystallization from MeOH gave yellow prisms, mp 270—272° (decomp.). *Anal.* Calcd. for $C_{11}H_{10}O_3N_2$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.72; H, 4.41; N, 12.60.

***n*-Butyl 4-Hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate**——A Mixture of 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid (5 g, 24.5 mmoles) and thionyl chloride (50 ml) was stirred at room temperature for 2 hr, and ether (50 ml) was added to the reaction mixture to precipitate the acid chloride. The collected product was added to *n*-butanol (50 ml) and the mixture was stirred at room temperature for 4.5 hr and allowed to stand overnight. After evaporation of the solvent, the residue was washed with dil. alkali and dissolved in AcOH (100 ml). Undissolved material was filtered off, and H_2O (200 ml) was added to the filtrate. The resulting precipitate was collected and recrystallized from DMF to give colorless needles (4 g, 62.8%), mp 234—237°. *Anal.* Calcd. for $C_{14}H_{16}O_3N_2$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.46; H, 6.15; N, 11.22.

2-Ethylaminoethyl Chloride——This compound was prepared according to the procedure described by J.H. Parkkari, *et al.*[7] except that a solution of thionyl chloride in $CHCl_3$ was added dropwise over a period of 3.5 hr. Recrystallization from MeOH–ether gave colorless plates, mp 230—232° (J.H. Parkkari, *et al.* give mp 218—219°). *Anal.* Calcd. for $C_4H_{11}NCl_2$: C, 33.35; H, 7.70; N, 9.73; Cl, 49.23. Found: C, 33.15; H, 7.35; N, 9.63; Cl, 48.84.

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7) J.H. Parkkari, R.A.B. Bannard, and I.W. Coleman, *Can. J. Chem.*, **43**, 3119 (1965).