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Synthetic Antibacterials. VI.[1] 7-[1-Substituted 2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridines

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The starting material, ethyl 7-bromomethyl-4-hydroxy-1,8-naphthyridine-3-carboxylate (**2**), was prepared by the reaction of ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (**1**) with bromine. Condensation of **2** with 5-nitrofurfural afforded ethyl 7-[1-bromo-2-(5-nitro-2-furyl)vinyl]-4-hydroxy-1,8-naphthyridine-3-carboxylate (**3**) which was subsequently hydrolized to give 7-[1-bromo-2-(5-nitro-2-furyl)vinyl]-4-hydroxy-1,8-naphthyridine-3-carboxylic acid (**4**). Alkylation of **4** with alkyl iodide provided 1-alkyl-7-[1-bromo-2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (**5** and **6**). Nucleophilic displacement of bromine in **4**, **5**, and **6** afforded the corresponding 7-[1-alkylamino-2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridine derivative (**7**—**14**). Some members of the series display sufficient antibacterial activity *in vitro* against both Gram-positive and Gram-negative bacteria, however, none of them was active as the model compound, 1-ethyl-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (**15**).

Previous reports[3a,b] from our laboratory described the synthesis and significant antibacterial activity of certain 7-[2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridines. A continuous search for derivatives with better antibacterial potency led us to synthesize a series of 7-[1-substituted 2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridines. The introduction of a proper function into the vinyl group seemed interesting since it has been observed that the antibacterial activity of nitrofurylvinyl heterocycles often varies with the species of incorporated substituent at the conjugated double bond.[4]

Chemistry

Reaction of ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (**1**)[5] with bromine in acetic acid containing sodium acetate afforded ethyl 7-bromomethyl-4-hydroxy-1,8-naphthyridine-3-carboxylate (**2**). The structure of **2** was substantiated by its spectral data and elemental analysis. The nuclear magnetic resonance (NMR) spectrum (CF_3COOH) exhibited a pair of doublets (δ 8.08 and 9.02; J=9 Hz). This fact excluded the possibility of ring bromination. The condensation of **2** with 5-nitrofurfural in acetic acid-sulfuric acid led to ethyl 7-[1-bromo-2-(5-nitro-2-furyl)vinyl]-4-hydroxy-1,8-naphthyridine-3-carboxylate (**3**). The hydrolysis of **3** with acetic acid-hydrochloric acid provided 7-[1-bromo-2-(5-nitro-2-furyl)vinyl]-4-hydroxy-1,8-naphthyridine-3-carboxylic acid (**4**), which was alkylated with alkyl iodide to yield 7-[1-bromo-2-(5-nitro-2-furyl)vinyl]-1-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (**5**) and 7-[1-bromo-2-(5-nitro-2-furyl)vinyl]-1-ethyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (**6**), respectively. The nucleophilic displacement of bromine in **4**, **5** or **6** with

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2) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo, 160, Japan.*
3) *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, N. Mizushima, F. Yoneda, and H. Takahashi, *J. Med. Chem.*, **14**, 638 (1971).
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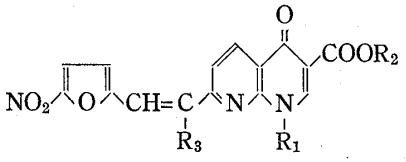
TABLE I. 7-[1-Substituted 2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridines



Compd. No.	R_1	R_2	R_3	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
3	H	C_2H_5	Br	>300	46	EtOH	$C_{17}H_{12}O_6N_3Br$	47.11 (46.85)	2.77 (3.01)	9.70 (9.42)
4	H	H	Br	>300	54	DMF	$C_{15}H_8O_6N_3Br$	44.44 (44.54)	1.97 (1.69)	10.37 (10.25)
5	CH_3	H	Br	>300	52	AcOH	$C_{16}H_{10}O_6N_3Br$	45.82 (45.69)	2.39 (2.56)	10.02 (9.74)
6	C_2H_5	H	Br	249—250	37	EtOH	$C_{17}H_{12}O_6N_3Br$	47.11 (47.37)	2.77 (2.72)	9.70 (9.59)
7	H	H	CH_3NH	>300	28	DMF	$C_{16}H_{12}O_6N_4$	53.93 (54.14)	3.40 (3.27)	15.73 (15.59)
8	H	H	$(CH_3)_2N$	>300	54	EtOH	$C_{17}H_{14}O_6N_4$	55.13 (55.11)	3.81 (3.76)	15.13 (14.90)
9	H	H	$(C_2H_5)_2N$	225—227	40	iso-PrOH	$C_{19}H_{18}O_6N_4$	57.27 (57.35)	4.55 (4.64)	14.07 (13.77)
10	CH_3	H	$(C_2H_5)_2N$	>300	41	iso-PrOH	$C_{20}H_{20}O_6N_4$	58.25 (58.03)	4.89 (5.11)	13.58 (13.40)
11	CH_3	H	piperidyl	>300	40	iso-PrOH	$C_{21}H_{20}O_6N_4$	59.43 (59.71)	4.75 (4.48)	13.20 (13.34)
12	C_2H_5	H	$(CH_3)_2N$	193—195	40	EtOH	$C_{19}H_{18}O_6N_4$	57.28 (57.58)	4.55 (4.34)	14.07 (14.28)
13	C_2H_5	H	$(C_2H_5)_2N$	169—170	56	EtOH	$C_{21}H_{22}O_6N_4$	59.15 (58.89)	5.20 (5.25)	13.14 (12.85)
14	C_2H_5	H	piperidyl	218—219	60	EtOH	$C_{22}H_{22}O_6N_4$	60.27 (60.27)	5.06 (5.15)	12.78 (12.49)

TABLE II. *In Vitro* Antibacterial Activity of 7-[1-Substituted-2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridines

Compd. No.	MIC, μg/ml[a] *Diplococcus pneumoniae* D_p-1	*Streptococcus hemolyticus* A-089	*Staphylococcus aureus* 209P	*Bacillus subtilis* PCI 219	*Staphylococcus enteritidis* 1891	*Staphylococcus pullorum* Chuyu 114	*Escherichia coli* O-55	*Klebsiella pneumoniae* ST-101	*Proteus vulgaris* HX-19	*Pseudomonas aeruginosa* 347
3	3.13	1.56	1.56	NT[b]	6.25	25	12.5	6.25	12.5	>25
4	0.39	0.19	1.56	NT	3.13	3.13	3.13	3.13	3.13	3.13
5	0.78	0.39	0.78	0.19	3.13	3.13	1.56	1.56	0.39	6.25
6	1.56	0.78	0.78	0.39	3.13	3.13	3.13	1.56	1.56	6.25
7	>25	25	>25	>25	>25	>25	>25	>25	>25	>25
8	25	12.5	>25	>25	>25	>25	>25	>25	>25	>25
9	12.5	12.5	25	>25	>25	>25	>25	>25	>25	>25
10	6.25	3.13	6.25	1.56	12.5	25	25	12.5	6.25	>25
11	6.25	6.25	25	3.13	25	>25	25	12.5	12.5	>25
12	3.13	0.78	3.13	0.78	12.5	25	12.5	12.5	12.5	12.5
13	12.5	3.13	6.25	0.39	25	>25	25	12.5	12.5	12.5
14	6.25	3.13	6.25	0.78	12.5	25	12.5	12.5	12.5	12.5
15[c]	<0.14	0.31	1.56	<0.19	0.78	0.78	0.78	3.13	0.78	0.39

a) Minimum inhibitory concentration (MIC) is the lowest concentration of the compound that prevents visible growth after 48 hr of incubation at 37°.
b) NT; not determined
c) 1-Ethyl-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid[3a]

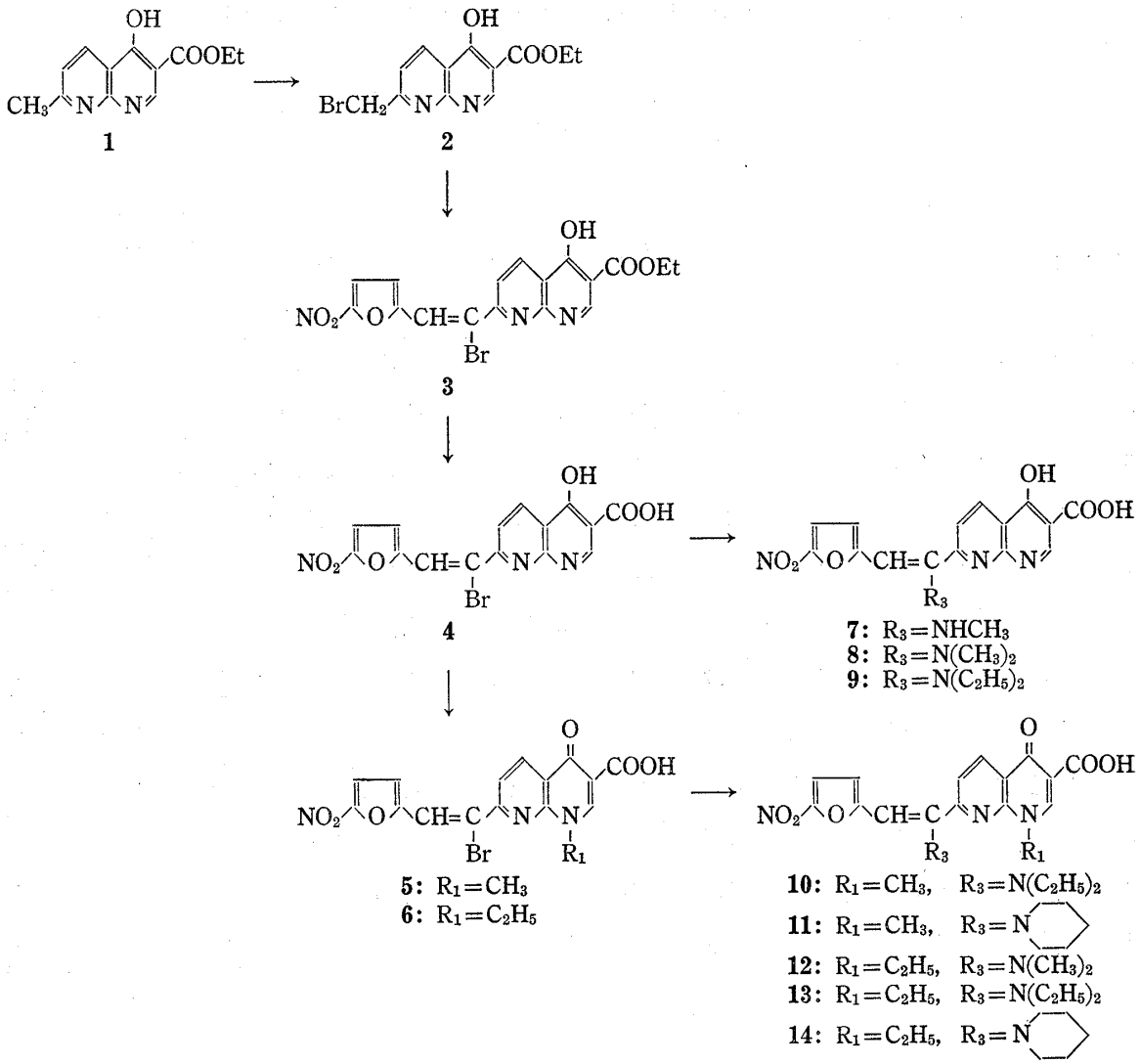


Chart 1

amines gave the corresponding 7-[1-alkylamino-2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridine derivatives (**7**—**14**) (Table I).

Screening Results

The compounds were screened for *in vitro* against a wide variety of bacteria. As can be seen from Table II, **4**, **5**, and **6** possess sufficient activity against both Gram-positive and Gram-negative bacteria, and **3**, **10**, **11**, **12**, **13**, and **14** possess marginal activity against only Gram-positive bacteria. Although none of the compounds was active as the model compound, 1-ethyl-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (**15**),[3a] these results indicate that an electron-withdrawing substituent is preferable to an electron-releasing substituent for *in vitro* activity. These facts are compatible with our previous findings.[1]

Experimental[6]

Ethyl 7-Bromomethyl-4-hydroxy-1,8-naphthyridine-3-carboxylate (**2**)——A mixture of ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (**1**)[5] (13.92 g, 0.06 mole) and AcONa (9.84 g, 0.12 mole) in AcOH (255 ml) was heated at 60°, and a solution of Br_2 (10.56 g, 0.066 mole) in AcOH (12 ml) was added dropwise to the mixture with good stirring over a period of 1.5 hr at the same temperature. When the addition was com-

6) All melting points were uncorrected. The NMR spectrum was recorded on a Hitachi Perkin-Elmer Model R-20 (60 MHz) spectrometer.

pleted the mixture was allowed to stir for 3 hr at 60°. The AcOH was removed *in vacuo* and the residue was diluted with H_2O (300 ml). The precipitated solid was filtered, washed with hot $(CH_3)_2CO$ and recrystallized from EtOH to give 6.2 g (33%) of pure product (**2**), mp 213—215°. *Anal.* Calcd. for $C_{12}H_{11}O_3N_2Br$: C, 46.32; H, 3.56; N, 9.00. Found: C, 46.21; H, 3.40; N, 9.23. NMR (CF_3COOH) δ: 1.65 (t, 3H, J=6.7 Hz, CH_2CH_3), 4.66 (s, 2H, $-CH_2Br$), 4.68 (q, 2H, J=6.7 Hz, CH_2CH_3), 8.08 (d, 1H, J=9 Hz, H-6), 9.02 (d, 1H, J=9 Hz, H-5), 9.50 (s, 1H, H-2).

Ethyl 7-[1-Bromo-2-(5-nitro-2-furyl)vinyl]-4-hydroxy-1,8-naphthyridine-3-carboxylate (**3**)——To a solution of **2** (0.16 g, 0.0005 mole) in AcOH (5 ml) and conc. H_2SO_4 (0.5 ml), 5-nitrofurfural (0.07 g, 0.0005 mole) was added and a mixture was heated at 100° for 3 hr. After cooling, the reaction mixture was diluted with H_2O and the precipitated solid was filtered to give the product (**3**).

7-[1-Bromo-2-(5-nitro-2-furyl)vinyl]-4-hydroxy-1,8-naphthyridine-3-carboxylic Acid (**4**)——A mixture of **3** (0.1 g, 0.00025 mole), 90% AcOH (2.7 ml) and conc. HCl (0.3 ml) was heated at 130° for 1 hr. After cooling, the precipitated solid was filtered to give the product (**4**).

1-Alkyl-7-[1-bromo-2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic Acids (5 and 6) General Procedure——A mixture of **4** (0.01 mole), anhydrous K_2CO_3 (0.02 mole) and appropriate alkyl iodide (0.05 mole) in dimethyl formamide (DMF) (30 ml) was heated at 100° for 3 hr. The reaction mixture was evaporated *in vacuo*, and the residue was washed with H_2O, then with EtOH to give the corresponding alkylated product (**5** and **6**).

7-[1-Alkylamino-2-(5-nitro-2-furyl)vinyl]-4-hydroxy-1,8-naphthyridine-3-carboxylic Acids (**7—9**)——A mixture of **4** (0.0005 mole) and appropriate amine (0.0015 mole) in DMF (10 ml) was heated at 100° for 5 hr. DMF was removed *in vacuo* and the residue was washed with H_2O to give the corresponding product (**7—9**).

1-Alkyl-7-[1-alkylamino-2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic Acids (**10—14**) **General Procedure**——A mixture of **5** (or **6**) (0.0005 mole) and appropriate amine (0.0015 mole) in DMF (10 ml) was heated at 100° for 5 hr. DMF was removed *in vacuo* and the residue was washed with H_2O to give the corresponding product (**10—14**).

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Substrate Specificity of Carboxylesterase (E.C.3.1.1.1)[1] from Several Animals

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Experiments were made to see the substrate specificity of purified esterase from various origins using *p*-nitrophenyl acetate, α-naphthyl acetate and *trans*-4-aminomethylcyclohexanecarboxylic acid esters as a substrate. And attension was focused on the influence of structural properties of *trans*-4-aminomethylcyclohexanecarboxylic acid esters. The hydrolysis rate of α-naphthyl acetate of *p*-nitrophenyl acetate differed markedly according to animal species. In all the enzymes from rats, guinea pigs, rabbits, and pigs, phenyl ester was hydrolyzed more readily than benzyl ester or alkyl ester. The hydrolysis rate of phenyl esters was affected by the steric as well as electronic effect of the substituents.

Carboxylesterases[1] are widely distributed in animals, plants, and bacteria. They hydrolyze a variety of esters, and are sensitive to organophosphate inhibitors.[3] Esterases have been purified from the liver of pigs,[4] oxen,[5] rats,[6] and rabbits.[7]

1) Enzyme: Carboxyl ester hydrolase (E.C. 3.1.1.1).
2) Location: *1432-1 Horinouchi, Hachioji-shi, Tokyo, 192-03, Japan.*
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