Synthetic Antibacterials. VIII [1]. 7-(1′-Alkylhydrazino)-1,8-naphthyridines and Related Compounds

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Synthesis and *in vitro* antibacterial activity of 7-(1′-alkylhydrazino)-1,8-naphthyridines related to nalidixic acid were investigated. Namely, treatment of 7-alkylamino-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids **1a-d** with sodium nitrite in the presence of hydrochloric acid gave the 1-ethyl-1,4-dihydro-7-(*N*-nitrosoalkylamino)-4-oxo-1,8-naphthyridine-3-carboxylic acids **2a-d**, which upon reacting with zinc dust in acetic acid gave the 7-(1′-alkylhydrazino)-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids **3a-d**. The compound **3a** was alternately obtained by the reaction of 7-chloro-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**4**) with methylhydrazine. The reaction of 7-chloro-4-hydroxy-1,8-naphthyridine-3-carboxylic acid (**5**) with methylhydrazine gave the 4-hydroxy-7-(1′-methylhydrazino)-4-oxo-1,8-naphthyridine-3-carboxylic acid (**6**), which upon treatment with alkyl halides afforded the 1-alkyl-1,4-dihydro-7-(1′-methylhydrazino)-4-oxo-1,8-naphthyridines **3a** and **3e-g**. The reaction of the appropriate **3** with ketones gave the corresponding 7-(1′-methylalkylidenehydrazino)-1,8-naphthyridines **7a-c** and **8a-b**. Among the compounds prepared, certain **3** and **7** exhibited good activity against Gram-negative bacteria.

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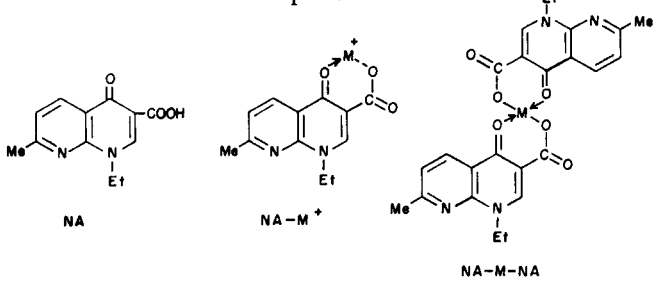
Nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid: NA) has been well known as a clinically useful antibacterial agent against Gram-negative bacteria and has been widely employed for the treatment of urinary-tract infections [4]. It has been presumed that the antibacterial activity of NA is due to the inhibition of bacterial DNA synthesis by forming either cationically charged metal complex (NA-M^+) or neutral metal complex (NA-M-NA) in the presence of divalent cations [4]. Although the 4-oxopyridine-3-carboxylic acid moiety of NA retains a pertinent structure for the formation of metal complexes, the methyl group at the 7-position would also play an additional important role for the chelation since the electron releasing methyl group would increase an electron density of an oxygen at the 4-position by attribution of resonance.

Consequently, it was expected that the introduction of a stronger electron releasing group than methyl group at the 7-position might lead to enhancement of the antibacterial activity by increasing an electron density of the oxygen atom. On the basis of this speculation, we now report the synthesis and *in vitro* antibacterial activity of NA derivatives which carry an 1′-alkylhydrazino group and its related functions at the 7-position.



As shown in Chart 1, 7-(1′-alkylhydrazino)-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids **3a-d** were synthesized in two steps starting with the readily available 7-alkylamino-1-ethyl-1,8-naphthyridines **1a-d** [5]. Namely, the reaction of **1a-d** [5] with sodium nitrite in the presence of hydrochloric acid resulted in *N*-nitrosation of the primary amino group to give the corresponding 1-ethyl-7-(*N*-nitrosoalkylamino)-1,8-naphthyridines **2a-d** in approximately 50% yields. The *N*-nitrosation was supported by disappearance of the secondary amino absorption band in the ir spectra.

Chart 1

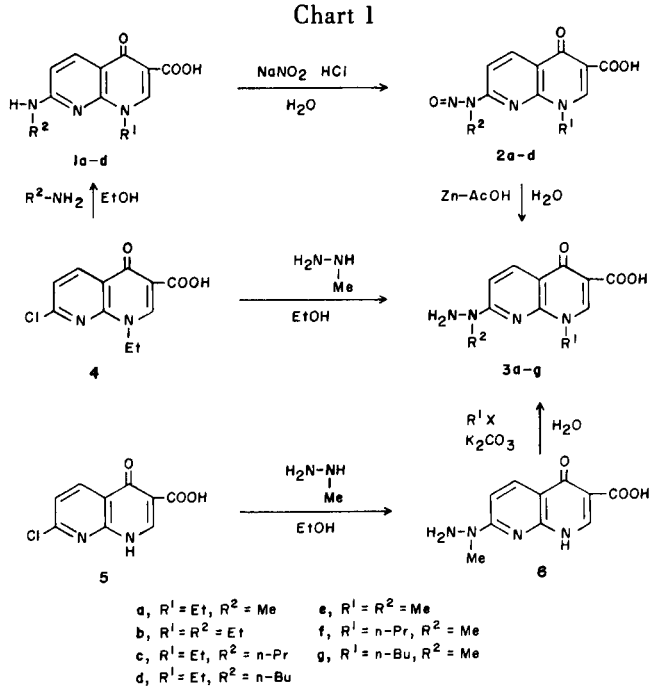


Table I

1,8-Naphthyridine Derivatives

Compound No.	Mp (°C)	Yield (%)	Recrystn. Solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
2a	251-252	45	DMF	$C_{12}H_{12}N_4O_4$	52.17 (52.32	4.38 4.41	20.28 20.46)
2b	242-243	50	DMF	$C_{13}H_{14}N_4O_4$	53.79 (53.91	4.86 4.87	19.30 19.20)
2c	223-224	49	DMF	$C_{14}H_{16}N_4O_4$	55.25 (55.14	5.30 5.28	18.41 18.18)
2d	219-221	47	DMF	$C_{15}H_{18}N_4O_4$	56.59 (56.75	5.70 5.79	17.60 17.86)
3a	268-271	32 [a] 76 [b] 35 [c]	EtOH	$C_{12}H_{14}N_4O_3$	54.95 (55.12	5.38 5.39	21.37 21.60)
3b	223-225	32	DMF	$C_{13}H_{16}N_4O_3$	56.51 (56.78	5.84 5.94	20.28 20.30)
3c	200-201	31	EtOAc	$C_{14}H_{18}N_4O_3$	57.92 (57.87	6.25 6.16	19.30 19.25)
3d	199-200	39	EtOAc	$C_{15}H_{20}N_4O_3$	59.19 (59.23	6.62 6.71	18.41 18.56)
3e	>290	28	EtOH	$C_{11}H_{12}N_4O_3$	53.22 (53.07	4.87 4.73	22.57 22.60)
3f	232-233	29	EtOH	$C_{13}H_{16}N_4O_3$	56.51 (56.39	5.84 5.88	20.28 20.05)
3g	201-203	29	EtOH	$C_{14}H_{18}N_4O_3$	57.92 (57.96	6.25 6.25	19.30 19.25)
6	>290	83	EtOH-DMF	$C_{10}H_{10}N_4O_3$	51.28 (51.16	4.30 4.20	23.92 23.67)
7a	227-230	79	EtOH	$C_{15}H_{18}N_4O_3$	59.59 (59.48	6.00 6.00	18.53 18.36)
7b	169-172	22	EtOH-DMF	$C_{16}H_{20}N_4O_3$	60.74 (60.52	6.37 6.26	17.71 17.76)
7c	178-180	47	EtOH	$C_{16}H_{20}N_4O_3$	60.74 (60.86	6.37 6.42	17.71 17.52)
8a	249-251	85	EtOH-DMF	$C_{17}H_{20}N_4O_3$	62.18 (61.88	6.14 6.27	17.06 17.36)
8b	191-193	67	EtOH	$C_{18}H_{22}N_4O_3$	63.14 (62.94	6.48 6.55	16.36 16.41)

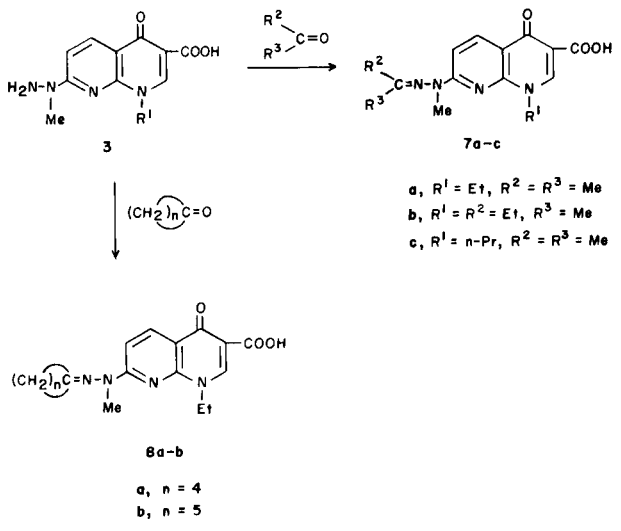
[a] The yield in the reduction of **2a**. [b] The yield in the reaction of **4** with methylhydrazine. [c] The yield in the ethylation of **6**.

Thus obtained **2a-d** were then subjected to reduction in acetic acid using zinc dust to yield the respective **3a-d** in 31-39% yields after basification with 20% sodium hydroxide, and the primary amino absorption bands were observed at around 3300 cm^{-1} in the ir spectra. Among the compounds prepared, **3a** could directly be obtained in 76% yield by nucleophilic displacement of the 7-chloro-1-ethyl-1,8-naphthyridine (**4**) [5] with methylhydrazine in ethanol, however, the indirect method described above definitely allows the introduction of almost any desired 1'-alkylhydrazino group into the 7-position.

On the other hand, 1-alkyl-1,4-dihydro-7-(1'-methylhydrazino)-4-oxo-1,8-naphthyridine-3-carboxylic acids **3a** and **3e-g** were synthesized by the following sequence. Namely, nucleophilic displacement of the 7-chloro-4-hydroxy-1,8-naphthyridine (**5**) [5] with methylhydrazine in ethanol gave the 4-hydroxy-7-(1'-methylhydrazino)-1,8-naphthyridine (**6**) in 83% yield, and subsequent alkylation with the appropriate alkyl halides in the presence of base gave the desired **3a** and **3e-g** in 35% and 28-29% yields, respectively.

In order to clarify the effect of *N*-amino group at the 7-position on the antibacterial activity, we also synthesized some masked hydrazino-1,8-naphthyridine derivatives as shown in Chart 2. Namely, heating of the appropriate **3** with ketones or cyclic ketones yielded the corresponding 7-(1'-methylalkylidenehydrazino)-1,8-naphthyridines **7a-c** and **8a-b**. The 1,8-naphthyridine derivatives prepared were summarized in Table I.

Chart 2



Screening Results.

A series of 1,8-naphthyridine derivatives prepared was tested for *in vitro* antibacterial activity against a variety of microorganisms and the results were summarized in Table II.

Inspection of the Table revealed that some compounds showed superior activity to NA or piromidic acid (PA) against Gram-negative bacteria, and the most potent activity was found in the compound **3a**. A survey of the length of an alkyl group at the 1- and 1′-positions on a series of **3** reveals that the activity is highly dependent on the length of an alkyl group. Namely, the optimal alkyl group was found to be an ethyl for the 1-position and a methyl for the 1′-position. The importance of an alkyl group at the 1- or 1′-position on the activity was suggested that the 4-hydroxy-7-(1′-methylhydrazino)-1,8-naphthyridine (**6**) and 1-ethyl-7-hydrazino-1,8-naphthyridine (**9**) [6] did not exhibit any comparable activity to those of **3a-d**. In general, 1′-alkyl group showed a greater effect on the activity over that of 1-alkyl group. It is interesting to note that the compounds **2a-d** also exhibit some degree of activity even in the presence of an electron attracting nitroso group.

Among the masked hydrazino-1,8-naphthyridines, **7a, 7b, 8a** and **8b** exhibited marginal or equivalent activity against Gram-negative bacteria to that of NA or PA.

EXPERIMENTAL

Melting points were determined on a Yanaco micro-hot-stage melting point apparatus and are uncorrected. The ir spectra were recorded on a Jasco IR-A spectrophotometer from samples mulled in Nujol.

1-Ethyl-1,4-dihydro-7-(*N*-nitrosoalkylamino)-4-oxo-1,8-naphthyridine-3-carboxylic Acids **2a-d**. General Procedure.

Table II

In Vitro Antibacterial Activity of 1,8-Naphthyridine Derivatives

Compound No.	*Staphylococcus aureus* 209P-JC	*Escherichia coli* NIHJ-JC	*Proteus vulgaris* HX-19	*Pseudomonas aeruginosa* 347	*Klebsiella pneumoniae* ST-101
	MIC, μg/ml [a]				
2a	12.5	1.56	0.78	>100	12.5
2b	12.5	6.25	0.78	>100	50
2c	50	50	12.5	>100	>100
2d	100	>100	50	>100	>100
3a	12.5	0.78	0.78	50	6.25
3b	25	3.13	0.78	100	25
3c	>100	25	0.56	>100	100
3d	>100	100	6.25	>100	>100
3e	50	50	25	>100	>100
3f	50	3.13	0.78	50	25
3g	100	25	1.56	>100	100
6	>100	>100	100	>100	>100
7a	12.5	3.13	0.78	100	12.5
7b	12.5	6.25	1.56	100	25
7c	25	12.5	0.78	100	12.5
8a	25	12.5	1.56	50	25
8b	100	25	3.13	100	25
9	>100	>100	25	>100	>100
NA [b]	>100	6.25	3.13	>100	6.25
PA [c]	25	6.25	3.13	>100	25
PPA [d]	>100	1.56	3.13	6.25	6.25
OA [e]	3.13	6.25	3.13	6.25	6.25

[a] Minimum inhibitory concentration (MIC) is the lowest concentration of the compound that prevents visible growth after 48 hours of incubation at 37°. [b] NA: naldixic acid. [c] PA: piromidic acid. [d] PPA: pipemidic acid. [e] OA: oxolinic acid.

To a suspension of 7-alkylamino-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, **1a-d** [5] (0.002 mole) in water (2 ml) containing concentrated hydrochloric acid (0.3 g), sodium nitrite (1.4 g, 0.02 mole) was added dropwise at 0-5° with stirring. After stirring for 1 hour at the same temperature, the precipitates were filtered off and recrystallized to give the corresponding **2a-d**.

7-(1'-Alkylhydrazino)-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids **3a-d**. General Procedure.

To a suspension of the appropriate **2a-d** (0.0002 mole) in acetic acid (3 ml), a suspension of zinc dust (0.195 g, 0.003 g-atom) in water (5 ml) was added dropwise at 0-5° with stirring. After stirring until the mixture reached the ambient temperature, the mixture was heated at 80° for few minutes. The insoluble material was filtered off, and the filtrate was adjusted to *p*H 6-7 by adding 20% sodium hydroxide. The precipitated material was filtered off, washed with water, dried, and recrystallized to give the corresponding **3a-d**.

1-Ethyl-1,4-dihydro-7-(1'-methylhydrazino)-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**3a**).

A mixture of 7-chloro-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, (**4**) [5] (0.253 g, 0.001 mole) and methylhydrazine (0.092 g, 0.002 mole) in ethanol (5 ml) was refluxed for 2 hours. After cooling to the ambient temperature, the precipitates were filtered off and recrystallized to give **3a** (0.2 g, 76%), which was identical to the sample obtained by the reduction of **2a**.

4-Hydroxy-7-(1'-methylhydrazino)-1,8-naphthyridine-3-carboxylic Acid (**6**).

A mixture of 7-chloro-4-hydroxy-1,8-naphthyridine-3-carboxylic acid (**5**) [5] (0.9 g, 0.004 mole) and methylhydrazine (0.46 g, 0.01 mole) in ethanol (30 ml) was refluxed for 2 hours. After cooling to the ambient temperature, the precipitates were filtered off and recrystallized to give **6** (0.4 g, 83%).

1-Alkyl-1,4-dihydro-7-(1'-methylhydrazino)-4-oxo-1,8-naphthyridine-3-carboxylic Acids **3a** and **3e-g**. General Procedure.

A mixture of **6** (1.4 g, 0.006 mole), 10% potassium hydroxide (5 ml), water (20 ml), and ethanol (30 ml) containing the appropriate alkyl halide (0.024 mole) was refluxed for 2 hours. After cooling to the ambient temperature, the precipitates were filtered off and recrystallized to give the corresponding **3a** and **3e-g**.

1-Ethyl-1,4-dihydro-7-(1'-methylalkylidenehydrazino)-4-oxo-1,8-naphthyridine-3-carboxylic Acids **7a-c**. General Procedure.

A suspension of the appropriate **3** (0.0005 mole) in ketones (5 ml) was refluxed for 3 to 5 hours. After cooling to the ambient temperature, the precipitates were filtered off and recrystallized to give the corresponding **7a-c**.

1-Ethyl-1,4-dihydro-7-(1'-methylcycloalkylidenehydrazino)-4-oxo-1,8-naphthyridine-3-carboxylic Acids **8a-b**. General Procedure.

A suspension of **3a** (0.131 g, 0.0005 mole) in the appropriate cyclic ketones (5 ml) was refluxed for 1 hour. The reaction mixture was evaporated *in vacuo* and the residue was recrystallized to give the corresponding **8a-b**.

Acknowledgement.

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REFERENCES AND NOTES

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[4] G. C. Crumplin, J. M. Midgley and J. T. Smith, "Topics in Antibiotic Chemistry", Vol 4, P. G. Sammes, ed, John Wiley and Sons, New York, 1980, pp 1-38 and references cited therein.

[5] G. Y. Lesher, U. S. Patent 3,590,036 (1971); *Chem. Abstr.*, **58**, 7953 (1963).

[6] This compound has been claimed in the patent [5] and the minimum inhibitory concentration data were kindly provided from the Ueno Fine Chemical Industries, Ltd.