

## 7-(1'-Alkylhydrazino)-1,8-naphthyridines and Related Compounds

Sadao Nishigaki [2], Noriko Mizushima [3], Hashime Kanazawa,

Misuzu Ichiba and Keitaro Senga\*

Pharmaceutical Institute, School of Medicine, Keio University

35, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan

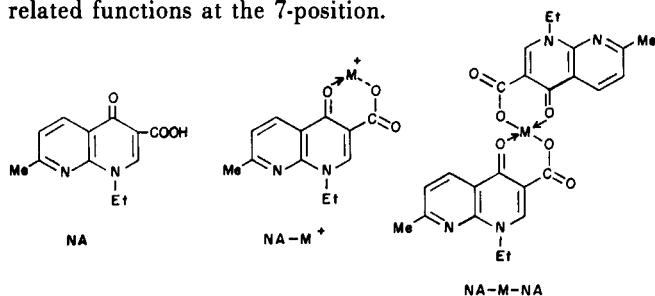
Received December 3, 1984

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.

*J. Heterocyclic Chem.*, **22**, 1029 (1985).

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<sup>+</sup>) 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

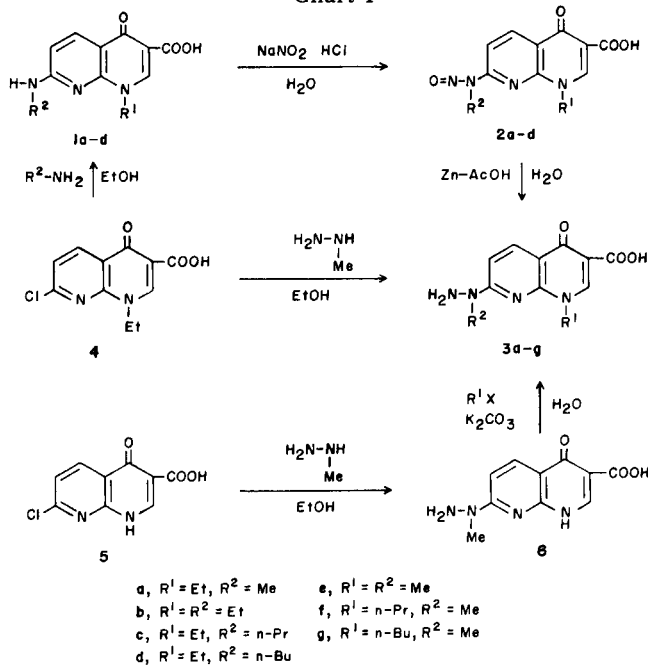


Table I  
1,8-Naphthyridine Derivatives

| Compound No. | Mp (°C) | Yield (%) | Recrystn. Solvent | Formula                                                       | Analysis (%)     |              |                 |
|--------------|---------|-----------|-------------------|---------------------------------------------------------------|------------------|--------------|-----------------|
|              |         |           |                   |                                                               | Calcd. (Found)   | C            | H               |
| 2a           | 251-252 | 45        | DMF               | C <sub>12</sub> H <sub>12</sub> N <sub>4</sub> O <sub>4</sub> | 52.17<br>(52.32) | 4.38<br>4.41 | 20.28<br>20.46) |
| 2b           | 242-243 | 50        | DMF               | C <sub>13</sub> H <sub>14</sub> N <sub>4</sub> O <sub>4</sub> | 53.79<br>(53.91) | 4.86<br>4.87 | 19.30<br>19.20) |
| 2c           | 223-224 | 49        | DMF               | C <sub>14</sub> H <sub>16</sub> N <sub>4</sub> O <sub>4</sub> | 55.25<br>(55.14) | 5.30<br>5.28 | 18.41<br>18.18) |
| 2d           | 219-221 | 47        | DMF               | C <sub>15</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub> | 56.59<br>(56.75) | 5.70<br>5.79 | 17.60<br>17.86) |
| 3a           | 268-271 | 32 [a]    | EtOH              | C <sub>12</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub> | 54.95<br>(55.12) | 5.38<br>5.39 | 21.37<br>21.60) |
|              |         | 76 [b]    |                   |                                                               |                  |              |                 |
|              |         | 35 [c]    |                   |                                                               |                  |              |                 |
| 3b           | 223-225 | 32        | DMF               | C <sub>13</sub> H <sub>16</sub> N <sub>4</sub> O <sub>3</sub> | 56.51<br>(56.78) | 5.84<br>5.94 | 20.28<br>20.30) |
| 3c           | 200-201 | 31        | EtOAc             | C <sub>14</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub> | 57.92<br>(57.87) | 6.25<br>6.16 | 19.30<br>19.25) |
| 3d           | 199-200 | 39        | EtOAc             | C <sub>15</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub> | 59.19<br>(59.23) | 6.62<br>6.71 | 18.41<br>18.56) |
| 3e           | > 290   | 28        | EtOH              | C <sub>11</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> | 53.22<br>(53.07) | 4.87<br>4.73 | 22.57<br>22.60) |
| 3f           | 232-233 | 29        | EtOH              | C <sub>13</sub> H <sub>16</sub> N <sub>4</sub> O <sub>3</sub> | 56.51<br>(56.39) | 5.84<br>5.88 | 20.28<br>20.05) |
| 3g           | 201-203 | 29        | EtOH              | C <sub>14</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub> | 57.92<br>(57.96) | 6.25<br>6.25 | 19.30<br>19.25) |
| 6            | > 290   | 83        | EtOH-DMF          | C <sub>10</sub> H <sub>10</sub> N <sub>4</sub> O <sub>3</sub> | 51.28<br>(51.16) | 4.30<br>4.20 | 23.92<br>23.67) |
| 7a           | 227-230 | 79        | EtOH              | C <sub>15</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub> | 59.59<br>(59.48) | 6.00<br>6.00 | 18.53<br>18.36) |
| 7b           | 169-172 | 22        | EtOH-DMF          | C <sub>16</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub> | 60.74<br>(60.52) | 6.37<br>6.26 | 17.71<br>17.76) |
| 7c           | 178-180 | 47        | EtOH              | C <sub>16</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub> | 60.74<br>(60.86) | 6.37<br>6.42 | 17.71<br>17.52) |
| 8a           | 249-251 | 85        | EtOH-DMF          | C <sub>17</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub> | 62.18<br>(61.88) | 6.14<br>6.27 | 17.06<br>17.36) |
| 8b           | 191-193 | 67        | EtOH              | C <sub>18</sub> H <sub>22</sub> N <sub>4</sub> O <sub>3</sub> | 63.14<br>(62.94) | 6.48<br>6.55 | 16.36<br>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**.

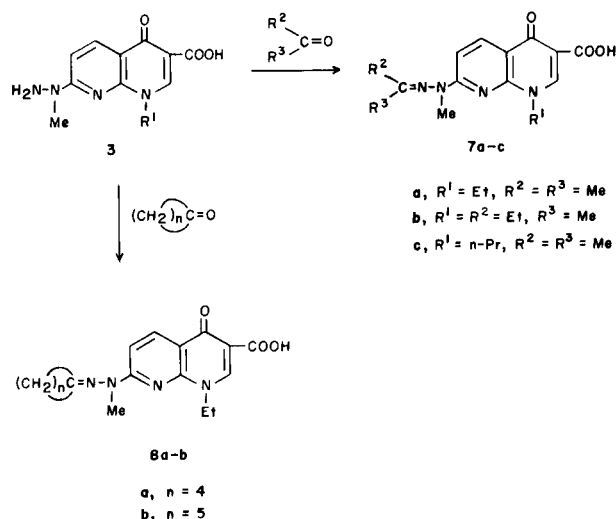
Thus obtained **2a-d** were then subjected to reduction in acetic acid using zinc dust to yield the respective **3a-d** in 31-39% yields after basification with 20% sodium hydroxide, and the primary amino absorption bands were observed at around 3300 cm<sup>-1</sup> in the ir spectra. Among the compounds 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



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.

### 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)

### 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 mullied 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. | <i>Staphylococcus aureus</i> 209P-JC | <i>Escherichia coli</i> NIHJ-JC | MIC, $\mu\text{g/ml}$ [a]<br><i>Proteus vulgaris</i> HX-19 | <i>Pseudomonas aeruginosa</i> 347 | <i>Klebsiella pneumoniae</i> ST-101 |
|--------------|--------------------------------------|---------------------------------|------------------------------------------------------------|-----------------------------------|-------------------------------------|
| <b>2a</b>    | 12.5                                 | 1.56                            | 0.78                                                       | >100                              | 12.5                                |
| <b>2b</b>    | 12.5                                 | 6.25                            | 0.78                                                       | >100                              | 50                                  |
| <b>2c</b>    | 50                                   | 50                              | 12.5                                                       | >100                              | >100                                |
| <b>2d</b>    | 100                                  | >100                            | 50                                                         | >100                              | >100                                |
| <b>3a</b>    | 12.5                                 | 0.78                            | 0.78                                                       | 50                                | 6.25                                |
| <b>3b</b>    | 25                                   | 3.13                            | 0.78                                                       | 100                               | 25                                  |
| <b>3c</b>    | >100                                 | 25                              | 0.56                                                       | >100                              | 100                                 |
| <b>3d</b>    | >100                                 | 100                             | 6.25                                                       | >100                              | >100                                |
| <b>3e</b>    | 50                                   | 50                              | 25                                                         | >100                              | >100                                |
| <b>3f</b>    | 50                                   | 3.13                            | 0.78                                                       | 50                                | 25                                  |
| <b>3g</b>    | 100                                  | 25                              | 1.56                                                       | >100                              | 100                                 |
| <b>6</b>     | >100                                 | >100                            | 100                                                        | >100                              | >100                                |
| <b>7a</b>    | 12.5                                 | 3.13                            | 0.78                                                       | 100                               | 12.5                                |
| <b>7b</b>    | 12.5                                 | 6.25                            | 1.56                                                       | 100                               | 25                                  |
| <b>7c</b>    | 25                                   | 12.5                            | 0.78                                                       | 100                               | 12.5                                |
| <b>8a</b>    | 25                                   | 12.5                            | 1.56                                                       | 50                                | 25                                  |
| <b>8b</b>    | 100                                  | 25                              | 3.13                                                       | 100                               | 25                                  |
| <b>9</b>     | >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 pH 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.

We express our thanks to the Ueno Fine Chemical Industries, Ltd. for elemental analyses and *in vitro* antibacterial activity as well as their kind offer of the screening data on the compound **9**.

## REFERENCES AND NOTES

- [1] Part VII: S. Nishigaki, N. Mizushima and K. Senga, *Chem. Pharm. Bull.*, **25**, 349 (1977).
- [2] Present address: Research Institute, Fujimoto Pharmaceutical Co., Ltd., 1-3-40 Nishiotsuka, Matsubara-shi, Osaka 580, Japan.
- [3] Present address: Department of Pharmacy, Tokai University Hospital, 143, Azakaminodai, Shimokasuya, Isehara-shi, Kanagawa 259-11, Japan.
- [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. Leshner, 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.