

Attempted reactions between acyl-adduct of pyridine 1-oxide or 1-methoxypyridinium iodide and indoles under various conditions failed and the starting materials were recovered. However, application of ethyl nicotinate 1-oxide to quinoline 1-oxide resulted in formation of ethyl 2-(3-indolyl)pyridine-5-carboxylate (VI), m.p. 169~170°, IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3250 (NH), 1690 (ester C=O), 1600 (indole C=C). The structure of VI was deduced from its conversion with potassium permanganate to pyridine-2,5-dicarboxylic acid, followed by transformation into the diethylester.

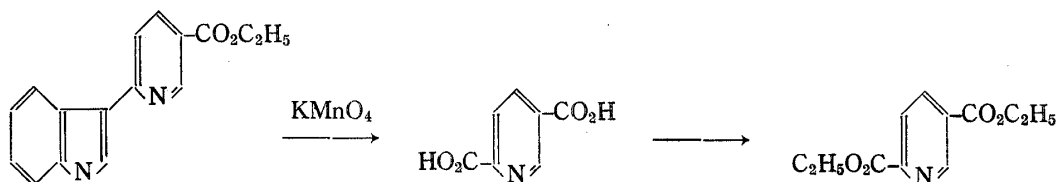


Chart 7.

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### 1,3-Dipolar Cycloaddition of 5-Nitro-2-furonitrile Oxide

As a part of a continuing study<sup>1)</sup> of 5-nitrofuran antimicrobials, an interest in the 1,3-dipolar cycloaddition of 5-nitro-2-furonitrile oxide (I) has led to the synthesis of (5-nitro-2-furyl)isoxazole derivatives, which possess excellent antimicrobial activities. We now report examples of this reaction with various olefinic dipolarophiles involving a series of enamines<sup>\*1</sup> (III) of aldehydes and ketones, although the reaction of enamines as the dipolarophile had been reported<sup>2)</sup> recently using other dipolar species.

5-Nitro-2-furonitrile oxide (I) was generated by the addition of triethylamine to 5-nitro-2-furhydroxamoyl chloride<sup>3)</sup> (II) and isolated as an unstable liquid (IR  $\nu_{\text{max}}^{\text{liq}}$   $\text{cm}^{-1}$ : 2240). The cycloaddition, however, was conveniently effected by mixing equimolar amounts of I, the enamine (III) and triethylamine at room temperature to form easily amino-3-(5-nitro-2-furyl)-4,5-dihydroisoxazole (IV) as the exclusive product in a good yield. Structural assignment of the products was made on the basis of a study of

\*1 The enamines employed in this experiment were prepared according to the procedure of Mannich (for the aldehyde enamines; C. Mannich, H. Davidsen: Ber., **69**, 2106 (1963)) and Stork (for the ketone enamines; G. Stork, *et al.*: J. Am. Chem. Soc., **85**, 207 (1963)). The following are new enamines; 1-piperidino-1-(4-pyridyl)ethylene (b.p. 107~110°, IR  $\nu_{\text{max}}^{\text{liq}}$   $\text{cm}^{-1}$ : 1600, 1545), 1-morpholino-1-(3-pyridyl)ethylene (b.p. 131~134°, IR  $\nu_{\text{max}}^{\text{liq}}$   $\text{cm}^{-1}$ : 1605) and 1-piperidino-1-(2-pyridyl)ethylene (b.p. 117~120°, IR  $\nu_{\text{max}}^{\text{liq}}$   $\text{cm}^{-1}$ : 1585, 1563).

1) Part VI: Yakugaku Zasshi, **86**, 1014 (1966); The present paper constitutes Part VII of the series entitled "Studies on Nitrofuran Derivatives."

2) a) M. E. Munk, Y. KiKim: J. Am. Chem. Soc., **86**, 2213 (1964). b) M. E. Kuehne, S. J. Weaver, P. Franz: J. Org. Chem., **29**, 1582 (1964).

3) R. Lenaers, F. Eloy: Helv. Chim. Acta, **46**, 1067 (1963).

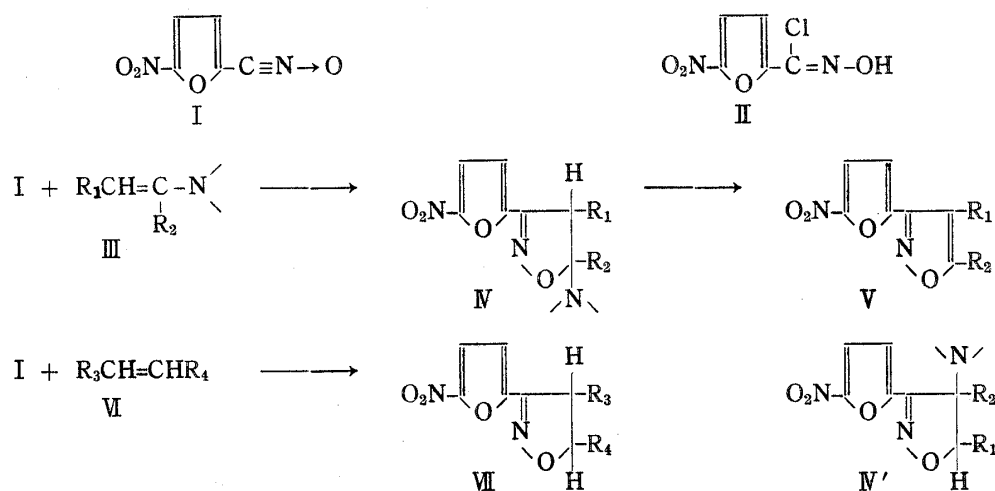
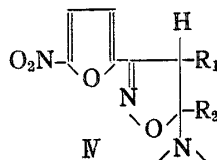


TABLE I.

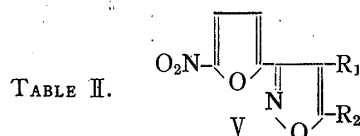


|   | $\text{R}_1$           | $\text{R}_2$           | $-\text{N} \begin{array}{c} \diagup \\ \diagdown \end{array}$ | m.p.<br>(°C) | Yield<br>(%) | Chemical Shift<br>(p.p.m.) |              | Coupling<br>constant<br>(c.p.s.) |
|---|------------------------|------------------------|---------------------------------------------------------------|--------------|--------------|----------------------------|--------------|----------------------------------|
|   |                        |                        |                                                               |              |              | $\text{H}_4$               | $\text{H}_5$ |                                  |
| a | $-(\text{CH}_2)_3-$    |                        |                                                               | 129~132      | 72           | 3.78<br>(d)                |              |                                  |
| b | $-(\text{CH}_2)_4-$    |                        | "                                                             | 126~129      | 69           | 3.46<br>(t)                |              |                                  |
| c | H                      | $\text{C}_6\text{H}_5$ |                                                               | 147~149      | 68           | 3.31<br>(d)                |              | $J_{4,4'}=18.5$                  |
|   |                        |                        |                                                               |              |              | 3.72<br>(d)                |              |                                  |
| d | $\text{C}_6\text{H}_5$ | H                      | "                                                             | 153~155      | 35           | 4.41<br>(d)                | 5.40<br>(d)  | $J_{4,5}=3.5$                    |
| e | $\text{CH}_3$          | "                      | "                                                             | 104~106      | 82           | 3.45<br>(m)                | 5.12<br>(d)  | $J_{4,5}=3.5$                    |
| f | $\text{C}_2\text{H}_5$ | "                      | $-\text{N}(\text{C}_2\text{H}_5)_2$                           | 62~63        | 14           | 3.25 <sup>a)</sup>         | 5.39<br>(d)  | $J_{4,5}=4.0$                    |
| g | H                      | $\text{C}_2\text{H}_5$ |                                                               | 133~136      | 34           | 3.22<br>(slightly broad s) |              |                                  |
| h | $\text{CH}_3$          | "                      |                                                               | 152~153      | 58           | 3.51<br>(q)                |              |                                  |
| i | H                      |                        |                                                               | 270          | 61           | 3.27<br>(d)                |              | $J_{4,4'}=18.5$                  |
|   |                        |                        |                                                               |              |              | 3.78<br>(d)                |              |                                  |
| j | "                      |                        |                                                               | 195~197      | 51           | 3.39<br>(d)                |              | $J_{4,4'}=19.0$                  |
|   |                        |                        |                                                               |              |              | 3.83<br>(d)                |              |                                  |
| k | "                      |                        |                                                               | 160~163      | 82           | 3.76<br>(s)                |              |                                  |

a) The assignment was confirmed by double resonance experiment since that peak was observed within the methylene ( $-\text{N}(\text{CH}_2)_2-$ ) envelop.

their nuclear magnetic resonance (NMR) spectra.\*<sup>2</sup> As summarized in Table I, a number of the chemical shifts were common to the spectra at 3.2~4.4 ( $=\text{C}-\underset{\text{H}}{\underset{|}{\text{CH}}}-\underset{\text{H}}{\underset{|}{\text{C}}}-$ ) and 5.1~5.4 p.p.m. ( $-\text{O}-\underset{\text{H}}{\underset{|}{\text{CH}}}-\text{N}<$  for  $\text{R}_2=\text{H}$ ) with correct relative areas in the respective cases, being consistent with each assigned structure. A difference in the chemical shifts and areas would be expected for the products if the alternative structure (V') resulting from another mode of the addition were correct.

Acid treatment of IV gave rise to corresponding isoxazole (V) under the elimination of the amine in an excellent yield (Table II); however, IVa, containing the more rigid three carbon bridge which would lead to some angle strain through the transformation into isoxazole system, were stable to be recovered unchanged on prolonged acid treatment. The NMR spectra of the isomeric Vf and Vg showed crude triplets at 8.33 ( $\text{H}_5$ ,  $J=\sim 0.8$  c.p.s.) and 6.49 p.p.m. ( $\text{H}_4$ ,  $J=\sim 0.5$  c.p.s.) coupling with the allylic methylene protons, respectively, in agreement with the structure. This transformation of IV to V provided a further confirmation of the structural assignment for the addition products (IV).



|   | R <sub>1</sub>                | R <sub>2</sub>                     | m.p. (°C) | Yield (%) |
|---|-------------------------------|------------------------------------|-----------|-----------|
| b |                               | -(CH <sub>2</sub> ) <sub>4</sub> - | 126~129   | 71        |
| c | H                             | C <sub>6</sub> H <sub>5</sub>      | 204~205   | 93        |
| d | C <sub>6</sub> H <sub>5</sub> | H                                  | 80~82     | 50        |
| e | CH <sub>3</sub>               | "                                  | 146~149   | 60        |
| f | C <sub>2</sub> H <sub>5</sub> | "                                  | 102~103   | 68        |
| g | H                             | C <sub>2</sub> H <sub>5</sub>      | 137~140   | 85        |
| h | CH <sub>3</sub>               | "                                  | 110       | 85        |
| i | H                             |                                    | 280~283   | 60        |
| j | "                             |                                    | 194~195   | 62        |
| k | "                             |                                    | 240~243   | 50        |

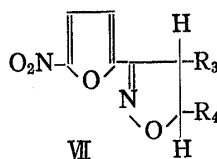
The experimental results clearly indicate that the cycloaddition takes place through the specific course of the addition and thus the oxygen atom (negatively charged end) of the nitrile oxide is directed to the carbon atom of unsaturated linkage bearing the electron-releasing amino group.

Furthermore, other olefinic dipolarophiles (VI) similarly underwent the 1,3-cycloaddition to the dipole (I) to give the dihydroisoxazoles (VII) (Table III). The structures of the products were assigned again on the basis of their NMR spectra.

The dehydrogenation of 3-(5-nitro-2-furyl)-5-(2-pyridyl)-4,5-dihydroisoxazole (VII f) with N-bromosuccinimide afforded 3-(5-nitro-2-furyl)-5-(2-pyridyl)isoxazole which was identical with V<sub>k</sub> derived from the addition product (IV<sub>k</sub>) of I with the piperidine

\*<sup>2</sup> NMR spectra were taken in CDCl<sub>3</sub> unless otherwise stated.

TABLE III.



|   | R <sub>3</sub>                          | R <sub>4</sub>                 | m.p.<br>(°C) | Yield<br>(%) | Chemical Shift<br>(p.p.m.) |                 | Coupling Constant<br>(c.p.s.) |                    |                                     |
|---|-----------------------------------------|--------------------------------|--------------|--------------|----------------------------|-----------------|-------------------------------|--------------------|-------------------------------------|
|   |                                         |                                |              |              | H <sub>4</sub>             | H <sub>5</sub>  | J <sub>4,4'</sub>             | J <sub>4,5</sub>   | J <sub>4',5</sub> (Assign-<br>ment) |
| a | H                                       | OC <sub>2</sub> H <sub>5</sub> | 86~87        | 71           | 3.27<br>3.42 (2H, two q)   | 5.78<br>(1H, q) | 17.9                          | 7.0                | 1.6<br>(ABX)                        |
| b | "                                       | COCH <sub>3</sub>              | 110~111      | 54           | 3.52<br>3.73 ( " )         | 5.16<br>(1H, q) | 17.5                          | 12.6               | 5.4<br>( " )                        |
| c | "                                       | C <sub>6</sub> H <sub>5</sub>  | 132~133      | 62           | 3.39<br>3.81 ( " )         | 5.85<br>(1H, q) | 17.2                          | 10.3               | 9.4<br>( " )                        |
| d | "                                       |                                | 171~172      | 13           | 3.39<br>3.75 ( " )         | 5.85<br>(1H, q) | 17.0                          | 11.3               | 7.6<br>( " )                        |
| e | "                                       |                                | 144~145      | 15           | 3.40<br>3.87 ( " )         | 5.85<br>(1H, q) | 17.4                          | 10.7               | 8.8<br>( " )                        |
| f | "                                       |                                | 138~139      | 69           | 3.83 (2H, d)               | 5.92<br>(1H, q) |                               |                    |                                     |
| g | -(CH <sub>2</sub> ) <sub>3</sub> -O-    |                                | 125~126      | 15           | 3.61 (1H, d)               | 6.05<br>(1H, d) |                               | 8.0                | (AX)                                |
| h | -CON(C <sub>6</sub> H <sub>5</sub> )CO- |                                | 245~246      | 56           | 5.31 ( " )                 | 5.93<br>(1H, d) |                               | 10.0 <sup>a)</sup> | ( " )                               |

a) The spectrum was measured in acetone.

enamine of 2-acetylpyridine followed by the elimination of the piperidine molecule. By analogy with the case of aminodihydroisoxazoles (IV), 3-(5-nitro-2-furyl)-5-ethoxy-4,5-dihydroisoxazole (VIa), arising from the addition of ethyl vinyl ether, underwent the elimination of ethanol on acid treatment to afford 3-(5-nitro-2-furyl)isoxazole (NMR p.p.m. : 6.87 and 8.63 (each doublet,  $J=1.5$  c.p.s., for H<sub>4</sub> and H<sub>5</sub> on the isoxazole ring, respectively), and 7.20 and 7.47 (each doublet,  $J=4.0$  c.p.s., for H<sub>3</sub> and H<sub>4</sub> on the 5-nitrofuran ring, respectively)) in a nearly quantitative yield.

In NMR data of IV and VII, protons at positions 4 and 5 on the dihydroisoxazole ring for VIIg and VIIh showed a coupling of 8.0 and 10.0 c.p.s., respectively, while those for IVd, IVe and IVf coupled in the range of 3.5~4.0 c.p.s. This is suggestive of a *cis* relationship (dihedral angle of  $\sim 0^\circ$ ) for the former, and a *trans* ( $\sim 120^\circ$ ) for the latter, being comparable to the assignment of the stereochemistry for 4,5-dihydro-1,2,3-triazoles<sup>2a)</sup> and 2,3-dihydropyrroles.<sup>4)</sup>

A correlation between the structure and antimicrobial activities will be discussed in a full paper.

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