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 ν_{max}^{Nujol} 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.

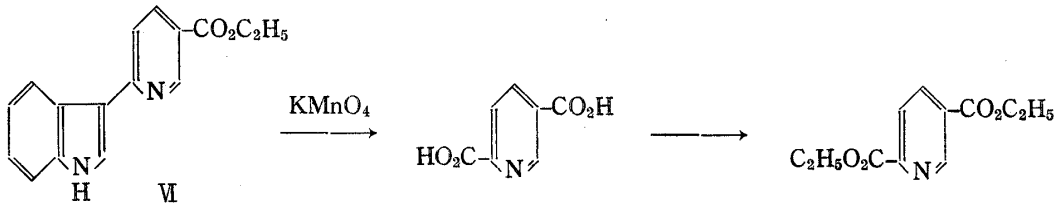

Chart 7.

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

As a part of a continuing study[1] 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*1 (Ⅲ) of aldehydes and ketones, although the reaction of enamines as the dipolarophile had been reported[2] recently using other dipolar species.

5-Nitro-2-furonitrile oxide (Ⅰ) was generated by the addition of triethylamine to 5-nitro-2-furhydroxamoyl chloride[3] (Ⅱ) and isolated as an unstable liquid (IR ν^{liq} 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. Structual 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_3 107~110°, IR ν^{liq} cm^{-1} : 1600, 1545), 1-morpholino-1-(3-pyridyl)-ethylene (b.p_6 131~134°, IR ν^{liq} cm^{-1} : 1605) and 1-piperidino-1-(2-pyridyl)ethylene (b.p_3 117~120°, IR ν^{liq} 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).

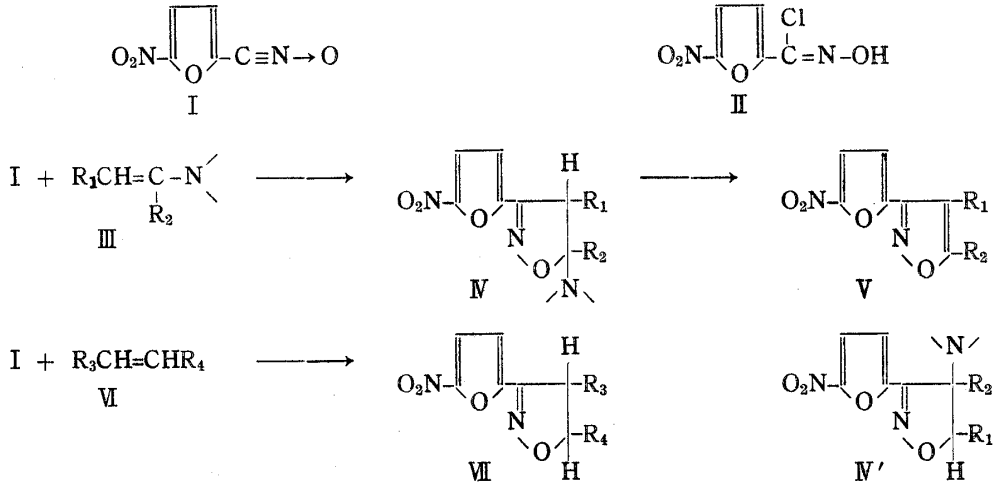
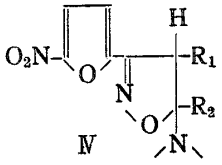
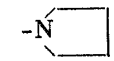
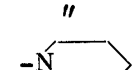
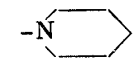
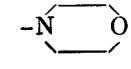
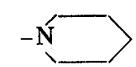
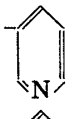
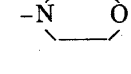
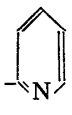
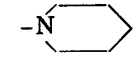


TABLE I.



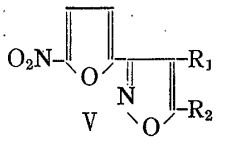
	R_1	R_2	$-\overset{\diagup}{N}\!\!\diagdown$	m.p. (℃)	Yield (%)	Chemical Shift (p.p.m.) H_4	H_5	Coupling constant (c.p.s.)
a	$-(CH_2)_3-$			129～132	72	3.78 (d)		
b	$-(CH_2)_4-$		〃	126～129	69	3.46 (t)		
c	H	C_6H_5		147～149	68	3.31 (d) 3.72 (d)		$J_{4,4'}=18.5$
d	C_6H_5	H	〃	153～155	35	4.41 (d)	5.40 (d)	$J_{4,5}=3.5$
e	CH_3	〃	〃	104～106	82	3.45 (m)	5.12 (d)	$J_{4,5}=3.5$
f	C_2H_5	〃	$-N(C_2H_5)_2$	62～ 63	14	3.25[a]	5.39 (d)	$J_{4,5}=4.0$
g	H	C_2H_5		133～136	34	3.22 (slightly broad s)		
h	CH_3	〃		152～153	58	3.51 (q)		
i	H			270	61	3.27 (d) 3.78 (d)		$J_{4,4'}=18.5$
j	〃			195～197	51	3.39 (d) 3.83 (d)		$J_{4,4'}=19.0$
k	〃			160～163	82	3.76 (s)		

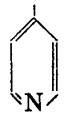
a) The assignment was confirmed by double resonance experiment since that peak was observed within the methylene ($-N(CH_2)_2-$) envelop.

their nuclear magnetic resonance (NMR) spectra.*2 As summarized in Table I, a number of the chemical shifts were common to the spectra at 3.2~4.4 (=C-CH-C-) and 5.1~5.4 p.p.m. (-O-CH-N< for R_2=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 (Ⅳ′) 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 (H_5, J=~0.8 c.p.s.) and 6.49 p.p.m. (H_4, J=~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 structual assignment for the addition products (Ⅳ).

Table Ⅱ.



	R_1	R_2	m.p. (°C)	Yield (%)
b		$-(CH_2)_4-$	126~129	71
c	H	C_6H_5	204~205	93
d	C_6H_5	H	80~ 82	50
e	CH_3	〃	146~149	60
f	C_2H_5	〃	102~103	68
g	H	C_2H_5	137~140	85
h	CH_3	〃	110	85
i	H		280~283	60
j	〃		194~195	62
k	〃		240~243	50

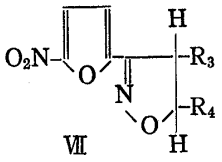
The experimental results clearly indicate that the cycloaddition takes place through the specific course of the addition and thus the oxygen atom (negatively charged end) of the nitrile oxide is directed to the carbon atom of unsaturated linkage bearing the electron-releasing amino group.

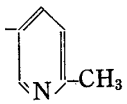
Furthermore, other olefinic dipolarophiles (Ⅵ) similarly underwent the 1,3-cycloaddition to the dipole (I) to give the dihydroisoxazoles (Ⅶ) (Table Ⅲ). The structures of the products were assigned again on the basis of their NMR spectra.

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

*2 NMR spectra were taken in $CDCl_3$ unless otherwise stated.

TABLE Ⅲ.



	R_3	R_4	m.p. (℃)	Yield (%)	Chemical Shift (p.p.m.) H_4	Chemical Shift (p.p.m.) H_5	Coupling Constant (c.p.s.) $J_{4,4'}$	Coupling Constant (c.p.s.) $J_{4,5}$	Coupling Constant (c.p.s.) $J_{4',5}$ (Assignment)
a	H	OC_2H_5	86～87	71	3.27, 3.42 (2H, two q)	5.78 (1H, q)	17.9	7.0	1.6 (ABX)
b	〃	$COCH_3$	110～111	54	3.52, 3.73 (〃)	5.16 (1H, q)	17.5	12.6	5.4 (〃)
c	〃	C_6H_5	132～133	62	3.39, 3.81 (〃)	5.85 (1H, q)	17.2	10.3	9.4 (〃)
d	〃		171～172	13	3.39, 3.75 (〃)	5.85 (1H, q)	17.0	11.3	7.6 (〃)
e	〃		144～145	15	3.40, 3.87 (〃)	5.85 (1H, q)	17.4	10.7	8.8 (〃)
f	〃		138～139	69	3.83 (2H, d)	5.92 (1H, q)			
g	$-(CH_2)_3-O-$		125～126	15	3.61 (1H, d)	6.05 (1H, d)		8.0	(AX)
h	$-CON(C_6H_5)CO-$		245～246	56	5.31 (〃)	5.93 (1H, d)		10.0[a]	(〃)

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 (Ⅶa), 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_4 and H_5 on the isoxazole ring, respectively), and 7.20 and 7.47 (each doublet, J=4.0 c.p.s., for H_3 and H_4 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 ～0°) for the former, and a *trans* (～120°) for the latter, being comparable to the assignment of the stereochemistry for 4,5-dihydro-1,2,3-triazoles[2a] and 2,3-dihydropyrroles.[4]

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

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