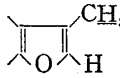
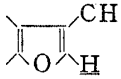
Experimental[5]

Isolation of Dihydropyrocurzerenone (I)——The dried roots (6.7 kg) of *C. serratus* were extracted with hot MeOH. The MeOH extract was condensed to 2 liters, and extracted with AcOEt. The last extract was chromatographed on alumina to prepare many eluates. Among them, the petr. benzine eluate provided colorless needles of dihydropyrocurzerenone (I) 20 mg, after recrystallization from petr. benzine. mp 65—66°. Vanillin–HCl reaction (+). Rf=0.33 on TLC (solvent: petr. benzine). $[\alpha]_D^{17}$ −28° (c=0.84, $CHCl_3$). Mass Spectrum m/e (relative intensity): 214 (100), 199 (28), 172 (93). IR ν_{max}^{KBr} cm^{-1}: 1610 (aromatic ring), 1100 (ether). NMR (CCl_4) ppm: 1.05 (3H, d, J=7 Hz, >CH–C<u>H</u>$_3$), 2.18 (3H, s, Ar–C<u>H</u>$_3$), 2.28 (3H, d, J=1.5 Hz, ), 6.92 (1H, s, aromatic proton), 7.10 (1H, q, J=1.5 Hz, ).

Gas Chromatography–Mass Spectrometric Analysis——The petr. benzine eluates gained from alumina chromatography of the AcOEt extract of this plant, were analysed with combination of gas chromatograph and mass spectrometer. The results are summarized in Table I and II.

Identification of Pyrocurzerenone (II)——The peak at the retention time (t_R) 4.9 min was compared with an authentic sample of pyrocurzerenone by GLC (1% OV-1, 2m, 190°).

Acknowledgement The authors are grateful to the people of the Research Laboratory of the Pharmaceutical Division, Nippon Kayaku Co. for measuring GC–MS.

5) Melting point was not corrected. NMR spectra were measured with JNM-PS 100 spectrometer using tetramethylsilane as an internal standard. GC–MS spectra were taken with LKB-9000s GC–MS spectrometer and gas chromatography was with JEOL JGC-20K gas chromatograph. IR spectrum was recorded on Shimazu IR-27G spectrometer. Optical activity was determined with Hitachi polarimeter. Thin-layer chromatography was done on Kieselgel GF 254 nach Stahl, and column chromatography was done using Sumitomo activated alumina.

[Chem. Pharm. Bull. 24(3) 533—537 (1976)]

UDC 574.821.4'546.21.04 : 547.551.43.04

Reaction of Aromatic N-Oxides with Dipolarophiles. II.[1] Reaction of β-Alkylpyridine N-Oxides with Phenyl Isocyanate[2]

Takuzo Hisano, Toshikazu Matsuoka, and Masataka Ichikawa

Faculty of Pharmaceutical Sciences, Kumamoto University[3]

(Received June 9, 1975)

The reaction of β-alkylpyridine N-oxides (I) with phenyl isocyanate (II) in dimethylformamide at 110° gave the cycloadducts (III and IV), although it was noticed that the reaction of pyridine N-oxide with II directly affords α-anilinopyridine. The duration at elevated temperature resulted in an increased yield of the anilino derivatives, while the cycloadducts tended to decrease. The effect by using various sorts of solvents demonstrated that dimethylformamide and dimethylsulfoxide are suitable for the formation of cycloadducts.

The previous papers from our laboratory[1,4] described that 3-picoline N-oxide (Ia) reacted with phenyl isocyanate (II) at 110° in dimethylformamide (DMF) to afford primary cycloadducts, IIIa and IVa, in 34 and 24% yields, respectively. Under this condition, an excess

1) Part I: T. Hisano, S. Yoshikawa, and K. Muraoka, *Chem. Pharm. Bull.* (Tokyo), **22**, 1611 (1974).
2) A part of this work was presented at the Kyushu Local Meeting of the Pharmaceutical Society of Japan, December 1973.
3) Location: *Oe-honmachi, Kumamoto.*
4) T. Hisano, S. Yoshikawa, and K. Muraoka, *Organic Preparations and Procedures International*, **5**, 95 (1973).

of phenyl isocyanate that requires for equimolar addition to 3-picoline N-oxide results in an increased yield of the cycloadducts, and on the contrary, the use of a large excess of the reactant tends to decrease their yields. The cycloadducts, IIIa and IVa, are stable to heating at 150—160° in DMF (no decomposition to the amine such as an anilinopyridine), although they are easily converted into the corresponding α-amino derivatives on heating in alcoholic potassium hydroxide. The successful isolation of such dihydropyridines, which is the first report to our knowledge, is apparently due to the stabilizing effect of the electron-donating β-methyl group. In addition, it seems of interest to examine further reaction conditions for such cycloadducts as a part of our program directed to the reactivity of heterocyclic N-oxides.

The purpose of the present paper is to study the factors governing the processes of these cycloadducts through reaction times, temperatures, solvents, and developments in the application for the analogous compounds. Consequently, the relationship between the reaction temperature and the duration was investigated in the reaction of 3-substituted pyridine N-oxides (I) with phenyl isocyanate (II). By using double the molar quantity of phenyl isocyanate in DMF, the yields of the cycloadducts (III and IV) reached at maximum after heating at 110° for seven hours, elongation of the reaction time led to the increase of the anilino derivatives (V and VI) while the cycloadducts tended to decrease, and elevation of the reaction temperature to 150° also resulted in an increased yield of the anilino derivatives. However, such stronger conditions have a tendency to disturb the cycloaddition of 3-ethylpyridine N-oxide (Ib) to II along with generating a resinal material, rather than to yield the corresponding anilino-3-ethylpyridines, as can be shown in Table I.

Since then, we have developed this reaction into several compounds having electron-donating and electron-withdrawing group at β-position in pyridine N-oxide as 1,3-dipole. First, 3,5-dimethylpyridine N-oxide (Ic) reacted with II in DMF at 110° for seven hours to afford a cycloadduct (IIIc) in 68% yield. This is of interest with the geometrical similarity on a determining effect of β-methyl group in the course of the cycloaddition because of corresponding to two times yield of IIIa. The new cycloadducts (IIIb, c and IVb) thus obtained

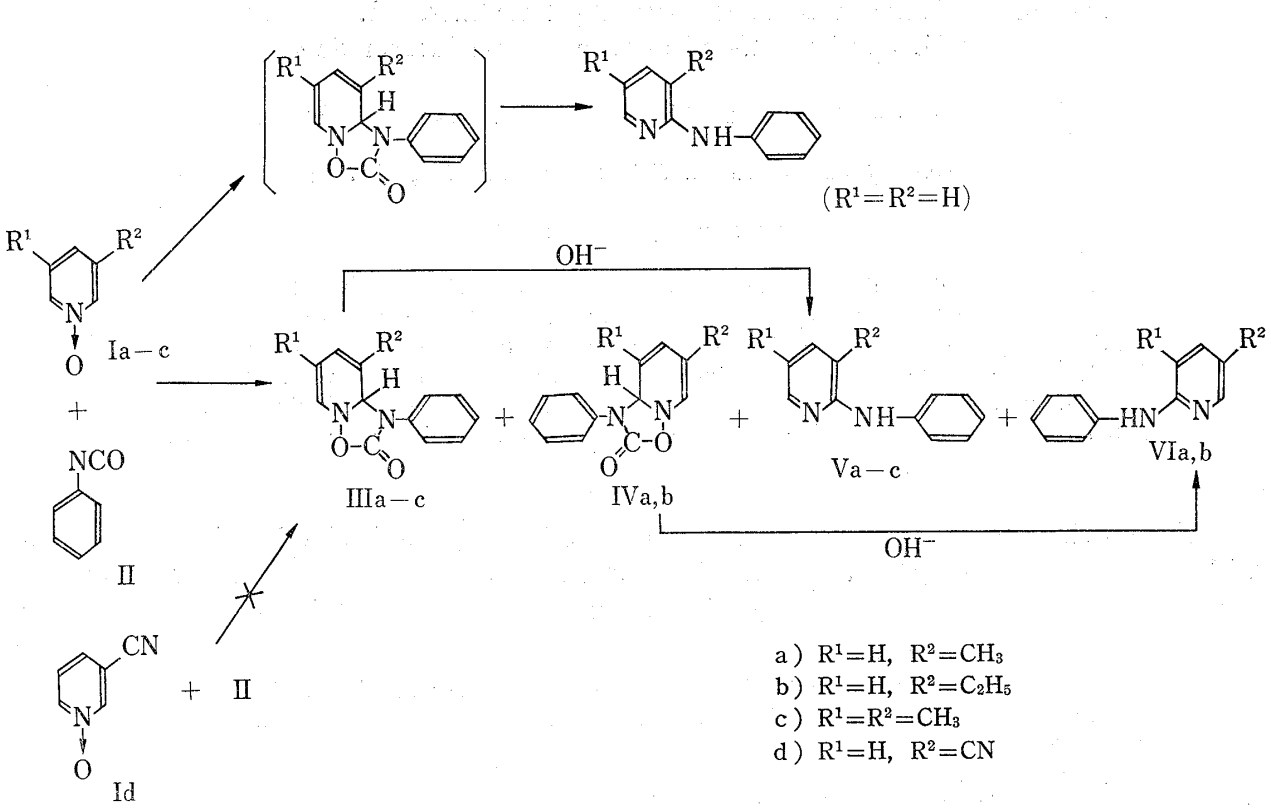
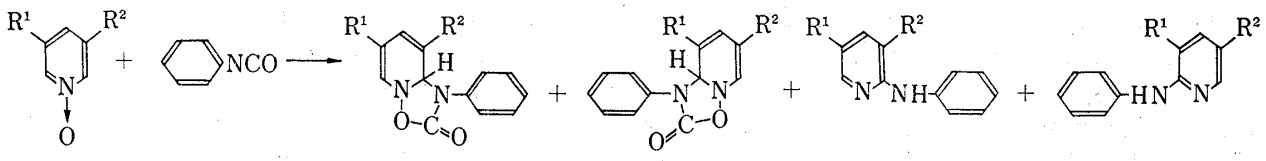


Chart 1

TABLE I. Relationship between Reaction Temperatures and Durations



Ia,b II IIIa,b IVa,b Va,b VIa,b

Condition		Product (%)[a]							
		III		IV		V		VI	
Temp. (°C)	Duration (hr)	a	b	a	b	a	b	a	b
110	3	29.0	14.5	19.0	8.3	—	—	—	—
110	7	34.0	21.5	24.0	16.5	—	—	—	—
110	10	34.0	23.0	24.0	15.0	—	—	—	—
110	15	30.0	20.0	15.0	13.0	trace	—	9.0	—
110	21	13.0		2.0		19.0		19.0	
room temp.	7	—	—	—	—	—	—	—	—
70	7	2.0	—	—	—	—	—	—	—
150	7	4.0	16.4	trace	1.0	30.0	—	24.0	6.1

a) Based on amount of I started and the products from Ia were collected according to the previous report.[1]

gave correct elemental analysis for 1:1 adduct of the two reactants and their structures were spectrochemically identified with the ultraviolet (UV), infrared (IR), and nuclear magnetic resonance (NMR) spectra in the same manner as those of IIIa and IVa.[1] Consequently, these cycloadducts were easily converted in high yields to the corresponding anilino-pyridines along with the elimination of carbon dioxide on reflux in alcoholic potassium hydroxide. Structure assignment of the anilino-pyridines is based on the satisfactory elemental analyses, IR, and NMR spectra similar to those of Va and VIa.

Next, we studied the reaction of II with 3,5-dibromopyridine N-oxide which in contrast to 3-picoline N-oxide, bears electron-withdrawing groups. A novel cyclic product, 6-bromo-2,3-dihydro-2-oxo-3-phenyloxazolo[4,5-*b*]pyridine, was found in 70%, presumably arising from the primary cycloadduct of the N-oxide and II.[5] In this connection, although the reaction of 3-cyanopyridine N-oxide (Id) with II was studied, more than 70% of the N-oxide was unexpectedly recovered unchanged from the reaction solution after seven hours at ambient temperature.

From the limited experience to data, it must be pointed out here that the nature of the substituent is generally an important factor in the reaction of cycloadduct of aromatic N-oxides; thus, it may be that 3-cyanopyridine N-oxide (Id) is much less effective as 1,3-dipole in this reaction. Abramovitch and its group[6] have suggested that a possible explanation of the wide variation in product yields under the comparative condition is that the lower the basicity of the N-oxide, the slower the initial addition to the imidoyl chloride as dipolarophile becomes and the lower the yield of desired product. Some support for this also comes from the fact that no acylamination product could be obtained from 4-nitropyridine N-oxide.[7] Interestingly, Hamana and his group have reported the same type of product from the reaction of 3-nitro- and 3-bromo-quinoline N-oxides with II[8] as that from the reaction of 3,5-dibromo-

5) T. Hisano, T. Matsuoka, and M. Ichikawa, *Heterocycles*, **2**, 163 (1974).
6) R.A. Abramovitch, R.B. Rogers, and G.M. Singer, *J. Org. Chem.*, **40**, 41 (1975).
7) R.A. Abramovitch and G.M. Singer, *J. Org. Chem.*, **39**, 1795 (1974); R.A. Abramovitch and G.M. Singer, *J. Am. Chem. Soc.*, **91**, 5672 (1969).
8) M. Hamana, H. Noda, and M. Aoyama, *Heterocycles*, **2**, 167 (1974).

pyridine N-oxide with II. These results demonstrate that pyridine N-oxides of benzenoid structure may be much less reactive when compared with naphthoidal quinoline N-oxides in this area, as can be seen from reports by Hamana and his group,[9] and Kajiwara.[10]

Although 1,3-dipolar cycloaddition of aromatic amine oxide to II is generally followed more or less readily by the elimination of carbon dioxide from the unstable cycloadduct,[11–15] the fact that both III and IV were rather stable for heating to 150° suggests that the driving force for rearomatization is not very strong. The formation of V and VI from the reaction conducted at 150° is probably due to base-induced decomposition of III and IV by weak bases such as 3-picoline N-oxide or aniline (from partial hydrolysis of phenyl isocyanate). This point was confirmed by the fact that IIIa (or IVa) heated to 150° in DMF in the presence of aniline or 3-picoline N-oxide decomposed to Va (or VIa).[1] The effect by using dimethyl sulfoxide (DMSO) and dioxane as a solvent resulted in relatively approximating to that of DMF, while the solvents having the lower boiling point such as ether, benzene, and chloroform resulted in completely recovering II as diphenylurea similar to the reaction conducted at 70—90° in DMF. Pyridine unexpectedly resulted in affording IIIa and IVa in a poor yield (see Table II). It would seem that the temperature and the duration probably play an important role in the dipolar aprotic solvent effect, such as DMSO and DMF, and the substituents at β-position in pyridine ring for the formation of such dihydro-pyridines.

Table II. Solvent Effect on the Cycloaddition of 3-Picoline N-Oxide (Ia) to Phenyl Isocyanate (II)

Condition			Product (%)[a]	
Solvent	Temp. (°C)	Duration (hr)	IIIa	IVa
Benzene	reflux	7	trace	trace
Ether	reflux	7	—	—
$CHCl_3$	reflux	7	—	—
DMSO	110	7	25	16
DMF	110	7	34	24
Pyridine	110	7	2	1
Dioxane	reflux	7	23	11
$(C_2H_5)_3N$ in dioxane	reflux	7	22	11

a) Calcd. on the basis of Ia

Experimental

All melting points were uncorrected. IR spectra were recorded on Nippon Bunko DS-301 Infrared Spectrophotometer equipped with a grating. NMR spectra were taken with JNM-C-60H spectrometer in *ca.* 5% (w/v) $CHCl_3$ solution with tetramethylsilane as an internal standard and chemical shifts were expressed in τ value.

Reaction of 3-Ethylpyridine N-Oxide (Ib) with II——To a solution of 6.15 g (0.05 mole) of Ib in 40 ml of DMF, was added dropwise 11.9 g (0.1 mole) of II with stirring at room temperature and the mixture heated in an oil bath. After the time indicated in Table I, the reaction mixture was evaporated *in vacuo* at below 70° and the residue dissolved in 30 ml of ether. The solution was allowed to stand at 0—5° for 3 days with

9) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 415 (1963); see also M. Hamana, *Lectures in Heterocyclic Chemistry*, **1**, 51 (1972).
10) S. Kajiwara, *Nippon Kagaku Zasshi*, **86**, 1060 (1965).
11) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, p. 256; see also A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press Inc. London, 1971, p. 330.
12) H. Seidl, R. Huisgen, and R. Grashey, *Chem. Ber.*, **102**, 926 (1969).
13) E. Hayashi and E. Oishi, *Yakugaku Zasshi*, **86**, 576 (1966).
14) J.C. Mason and G. Tennant, *Chem. Commun.*, **1972**, 218.
15) S. Takahashi and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **12**, 1290 (1964).

occasionally shaking. The precipitated crystals were collected by suction, washed with a small amount of cold ether, and recrystallized from acetone to give colorless prisms (IIIb), mp 131—133°. IR ν_{max}^{KBr} cm^{-1}: 1752 (C=O). NMR: 9.0 (3H, t, J=7.5 Hz, $-CH_2-\underline{C}H_3$), 8.1 (2H, q, J=7.5 Hz, $-C\underline{H}_2-CH_3$), 4.52 (1H, d, J=2.5 Hz, C_2–H). *Anal.* Calcd. for $C_{14}H_{14}O_2N_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.43; H, 5.85; N, 11.67.

After removal of IIIb, the viscous filtrate was treated with 200 ml of hot petroleum benzine to remove the resinal material and VIb and then allowed to stand at 0—5° overnight. The resulting solid was collected by suction, washed with a small amount of cold ether, and recrystallized from ether to give colorless needles (IVb), mp 101—103°. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). NMR: 8.86 (3H, t, J=7.5 Hz, $-CH_2-\underline{C}H_3$), 7.72 (2H, q, J=7.5 Hz, $-\underline{C}H_2-CH_3$), 4.85—5.10 (1H, m, C_6–H). *Anal.* Calcd. for $C_{14}H_{14}O_2N_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.65; H, 5.66; N, 11.24.

After removal of IVb, the petroleum benzine soln. was concentrated and cooled in an ice bath to be made solidified. After the solid had been treated with a small amount of cold ether, the separated crystals were collected by suction. Recrystallization from ether gave colorless needles (VIb), mp 97—99°, which was identical with 2-anilino-5-ethylpyridine derived by the following hydrolysis of IVb in all respects.

Hydrolysis of IIIb and IVb——A solution of 4.0 g of IIIb in 10% ethanolic potassium hydroxide was heated at 70—80° for 30 min and the solvent was removed by vacuum distillation. The residue was extracted with ether. Removal of the solvent left a residue which was recrystallized from ether to give 3.0 g (93%) of 2-anilino-3-ethylpyridine (Vb) as colorless needles, mp 65.5—67°. NMR: 8.72 (3H, t, J=7.5 Hz, $-CH_2-\underline{C}H_3$), 7.46 (2H, q, J=7.5 Hz, $-\underline{C}H_2-CH_3$), 1.89 (1H, d. d. J_{6-5}=5.0 Hz, J_{6-4}=2.0 Hz, C_6–H). *Anal.* Calcd. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.11; N, 14.13. Found: C, 78.71; H, 6.89; N, 14.17.

Similarly, 2.0 g of IVb was hydrolyzed to yield 1.4 g (86%) of 2-anilino-5-ethylpyridine (VIb) as colorless needles, mp 97—99°. NMR: 8.81 (3H, t, J=7.5 Hz, $-CH_2-\underline{C}H_3$), 7.48 (2H, q, J=7.5 Hz, $-\underline{C}H_2-CH_3$), 1.95 (1H, d, J=2.5 Hz, C_2–H). *Anal.* Calcd, for $C_{13}H_{14}N_2$: C, 78.75; H, 7.11; N, 14.13. Found: C, 78.42; H, 7.01; N, 14.33.

Reaction of 3,5-Dimethylpyridine N-Oxide (Ic) with Phenyl Isocyanate (II)——To a solution of 2.50 g (0.02 mole) of Ic in 16.4 ml of DMF was added dropwise 4.85 g (0.04 mole) of II with stirring at room temperature and the mixture heated at 110° for 7 hr. After this time, the reaction mixture was concentrated under reduced pressure and allowed to stand at 0—5° overnight. The resulting crystalline mass was recrystallized from benzene, giving product (IIIc), mp 148—150°, as colorless needles in 68% yield. IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). NMR: 8.40 (3H, s, CH_3), 8.09 (3H, d, J=2.5 Hz, CH_3), 4.61 (1H, d, J=3.0 Hz, pyridine C_2–H), 2.18—4.10 (7H, m, aromatic C–H). *Anal.* Calcd. for $C_{14}H_{14}O_2N_2$: C, 69.41; H, 5.83; N, 11.56. Found: C, 69.48; H, 6.03; N, 11.75.

Hydrolysis of IIIc——A mixture of 1.0 g of IIIc was heated under reflux in 5 ml of 10% ethanolic potassium hydroxide for 30 min and the solvent was removed by vacuum distillation. The residue was extracted with 150 ml of ether. The organic layer was dried over anhydrous sodium sulfate and filtered. Removal of the solvent left a crystalline mass which was recrystallized from petroleum benzine (bp 50—70°) to give 0.74 g (91%) of 2-anilino-3,5-dimethylpyridine (Vc) as colorless plates, mp 64.5—65.5°. IR ν_{max}^{KBr} cm^{-1}: 3250 (N–H). NMR: 7.82 (6H, s, pyridine C_3–CH_3, C_5–CH_3), 4.05 (1H, s, broad N–H), 2.48—3.19 (6H, m, pyridine C_4–H and phenyl), 2.17 (1H, d, J=2.0 Hz, pyridine C_6–H). *Anal.* Calcd. for $C_{13}H_{14}N_2$: C, 78.76; H, 7.12; N, 14.12. Found: C, 78.97; H, 6.99; N, 13.85.

Acknowledgement The authors wish to acknowledge the cooperation of Mr. S. Yoshikawa and to thank the members of the Analitical Department of this Faculty for the microanalyses and spectral measurements. The authors also are grateful to Mr. M. Nakatomi, President of Hisamitsu Pharmaceutical Co. Inc., for the supply of several chemicals.