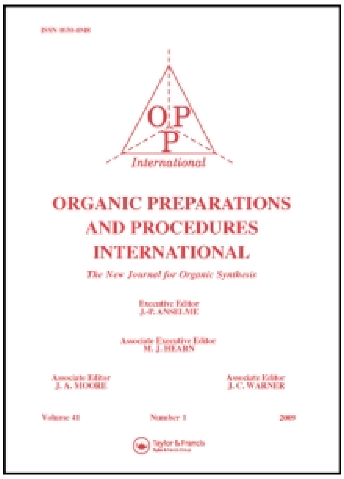


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

REACTION OF 3-SUBSTITUTED AND 3,5-DISUBSTITUTED PYRIDINE N-OXIDES WITH PHENYL ISOCYANATE

Takuzo Hisano[a]; Toshikazu Matsuoka[a]; Masataka Ichikawa[a]
[a] Faculty of Pharmaceutical Sciences, Kumamoto University, Kumamoto, JAPAN

To cite this Article Hisano, Takuzo , Matsuoka, Toshikazu and Ichikawa, Masataka(1974) 'REACTION OF 3-SUBSTITUTED AND 3,5-DISUBSTITUTED PYRIDINE N-OXIDES WITH PHENYL ISOCYANATE', Organic Preparations and Procedures International, 6: 5, 243 — 250

To link to this Article: DOI: 10.1080/00304947409355113

URL: http://dx.doi.org/10.1080/00304947409355113

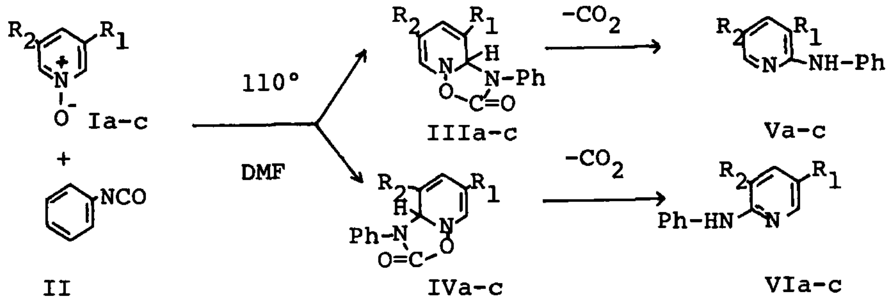
ORGANIC PREPARATIONS AND PROCEDURES INT. 6(5), 243-250 (1974)

REACTION OF 3-SUBSTITUTED AND 3,5-DISUBSTITUTED PYRIDINE N-OXIDES WITH PHENYL ISOCYANATE

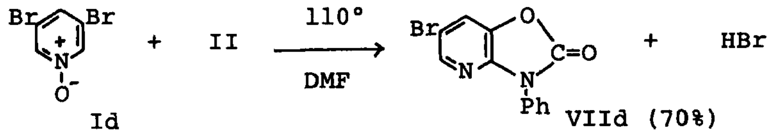
Takuzo Hisano*, Toshikazu Matsuoka, and Masataka Ichikawa

Faculty of Pharmaceutical Sciences, Kumamoto University
5-1 Oe-honmachi, Kumamoto 862, JAPAN

The 1,3-dipolar reactivity of 3-substituted pyridine N-oxides(I) toward phenyl isocyanate(II) has been a subject of recent interest.[1-3] We studied the reaction of II with 3,5-dibromopyridine N-oxide(Id) which in contrast to Ia and Ib, bears electron-withdrawing groups. A novel cyclic product, 2,3-dihydro-2-oxo-3-phenyl-6-bromooxazolo[4,5-b]pyridine(VIId), was found in 70%, presumably arising from the primary cycloadducts of Id and II.[4] Interestingly, Hamana and his group[5] have



a: $R_1 = CH_3$, $R_2 = H$ b: $R_1 = C_2H_5$, $R_2 = H$ c: $R_1 = R_2 = CH_3$



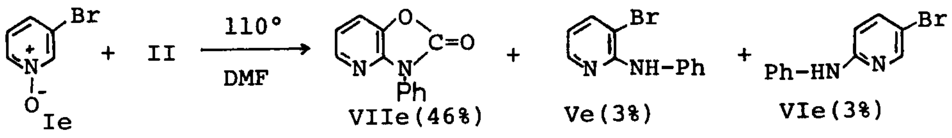
reported the same type of product from the reaction of 3-nitro- and 3-bromoquinoline N-oxides with II. We now report on reactions of 3-bromo- and 3,5-dimethylpyridine N-oxides with II.

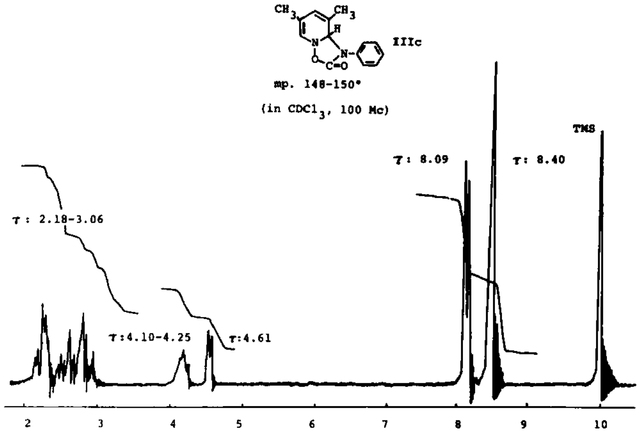
3,5-Dimethylpyridine N-oxide(Ic) reacted with II in dimethylformamide(DMF) at 110° to afford a cycloadduct(IIIc), mp. 148-150°, as colorless needles in 68% yield, similar to that of the reaction of Ia and II; the cycloadduct(IIIc) gave correct elemental analysis for 1:1 adduct of the two reactants, namely $C_{14}H_{14}N_2O_2$. The infrared(ir) spectrum of IIIc exhibited carbonyl absorption at 1725 cm^{-1}, but did not display any bands ascribable to a carboxylic acid group. In addition to the two methyl hydrogen peaks at τ 8.09 and 8.40, the nmr spectrum (see Figures) showed a single hydrogen peak at τ 4.61(doublet); the remaining seven hydrogens appeared at τ 4.10-2.18 as complex multiplets. Although IIIc is stable to heating (no decomposition at 150-160° in DMF), it was easily and quantitatively converted in a high yield to 2-anilino-3,5-dimethylpyridine(Vc), mp. 64.5-65.5°, on reflux in alcoholic potassium hydroxide.

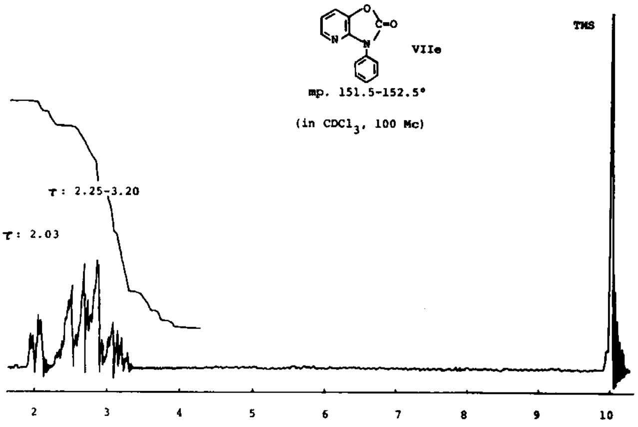
In connection with the 1,3-dipolar reactivity of 3,5-dibromopyridine N-oxide(Id),[4] 3-bromopyridine N-oxide(Ie) also reacted with II under the same condition. The crystalline residue obtained on evaporation of the reaction mixture was washed with cold ether and recrystallized from methanol to afford a 46% yield of 2,3-dihydro-2-oxo-3-phenyloxazolo-[4,5-b]pyridine(VIIe), mp. 151.5-152.5°, as colorless needles.

The structural assignment of VIIe (similar to that of VIId[4]) is based on the satisfactory elemental analysis

[$C_{12}H_8N_2O_2$], the ir spectrum [1760 cm^{-1}(C=O)], the mass [M^+: m/e 212, calcd. 212; $M^+ - CO_2$: m/e 168, calcd. 168], and the nmr spectrum [τ 2.03 as a doublet of doublets for α-proton of pyridine nucleus; τ 2.25-3.20 as complex multiplets for the remaining seven protons] (see Figures).



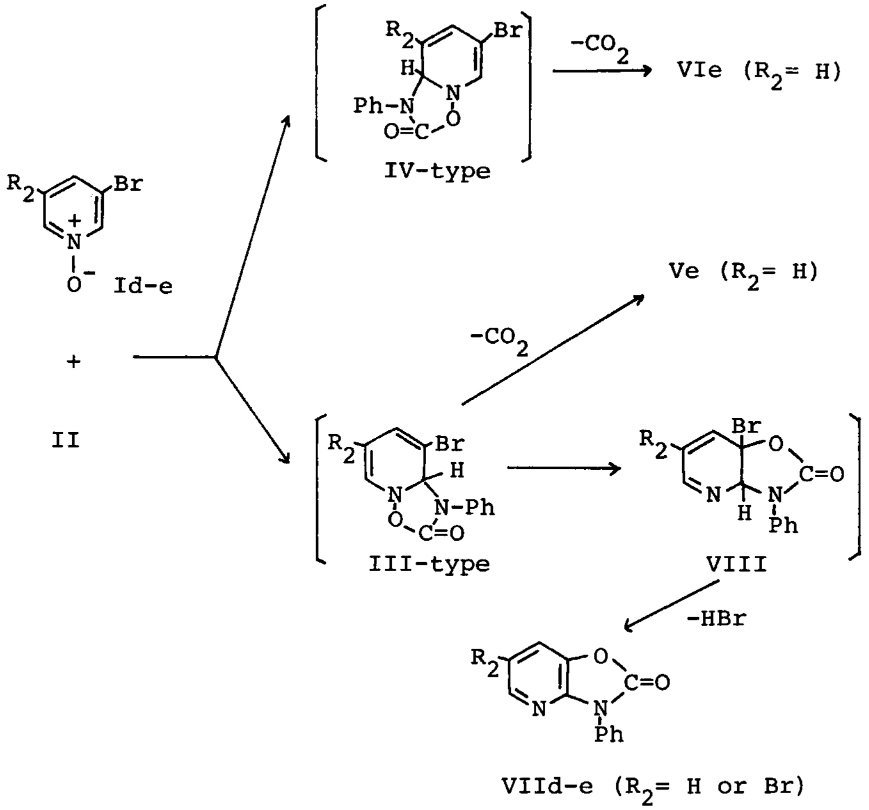




After the removal of VIIe, the filtrate was concentrated to give a gummy residue. The residue was extracted with hot petroleum benzine(bp. 50-80°) and removal of the solvent left a light yellow liquid which was chromatographed on silica gel, benzene being used as eluent, to afford 2-anilino-3-bromopyridine(Ve) as a light yellow liquid in 30% yield; picrate, mp. 147-148°, as yellow needles. The structure of Ve was assigned on the basis of a satisfactory elemental analysis [$C_{11}H_9N_2Br \cdot C_6H_3N_3O_7$], its ir spectrum [3450 cm^{-1}(N-H); no CO_2H, C=O in the 3200-2500 and 1700 cm^{-1} regions], and its nmr spectrum [τ 2.04 as a doublet of doublets for the C_6-proton of the pyridine nucleus; τ 2.35-3.54 as complex multiplets for the seven remaining aromatic protons].

After the isolation of Ve, the residue was dissolved in benzene and chromatographed on silica gel, benzene being used as eluent. From the first fraction, 6-anilino-3-bromopyridine (VIe), mp. 111-112°, was obtained as a colorless crystalline mass in 3% yield. Its structure was assigned on the basis of a satisfactory elemental analysis [$C_{11}H_9N_2Br$], its ir spectrum which was similar to that of Ve, and its nmr spectrum [τ 1.90 as a narrow doublet for the C_2-position of the pyridine nucleus].

These observations suggest that the successful isolation of such dihydropyridines(III and IV) is apparently due to the stabilizing effect of the electron-donating β-alkyl group. In contrast, the cycloaddition reactions of the pyridine N-oxides such as Id-e bearing electron-attracting group on β-position afforded a second cyclic intermediate(VIII) which can formulate as shown below.



EXPERIMENTAL

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 hrs. 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 (in $CDCl_3$) at 100 Mc: τ 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 $C_{14}H_{14}N_2O_2$: 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. The solvent was removed by vacuum distillation and the residue was extracted with 150 ml. of ether. The organic extract 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 (in $CDCl_3$) at 100 Mc: τ 7.82 (6H, s, pyridine C_3-$C\underline{H}_3$, C_5-$C\underline{H}_3$), 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.

Reaction of 3-Bromopyridine N-Oxide(Ie) with II.- To a solution of 8.60 g.(0.05 mole) of Ie in 40 ml. of DMF was added dropwise 11.9 g.(0.10 mole) of II with stirring at room temperature and the mixture was heated at 110° for 7 hrs. After this time, the mixture was allowed to stand at 0-5° overnight and the precipitated solid was filtered. The filtrate was concentrated under reduced pressure to give a crystalline residue which was washed with cold ether to afford colorless crystals. Recrystallization from methanol afforded product (VIIe), mp. 151.5-152.5°, as colorless needles in 46% yield. IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O). nmr (in $CDCl_3$) at 100 Mc: τ 2.25-3.20 (7H, m, aromatic C-H), 2.03 (1H, d-d, J_{6-5}=5.0 Hz, J_{6-4}=2.0 Hz, pyridine C_6-H). Mass spectrum: M^+ m/e: 212, 168 (M^+-CO_2).

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20; MW, 212. Found: C, 67.82; H, 3.67; N, 13.16; MW (mass spectrum), 212.

After the removal of VIIe, the filtrate was evaporated to give a gummy residue. The residue was extracted under reflux in 200 ml. of petroleum benzine(bp. 50-80°) for 30 min. The solvent was removed by vacuum distillation to give a residue of light yellow liquid which was chromatographed on 50 g. of silica gel (200 mesh), benzene being used as eluent. From the first fraction(100 ml.), 0.38 g. of 2-anilino-3-bromopyridine(Ve) was obtained as light yellow liquid which was purified by the repeated chromatography on silica gel using benzene as the eluent. IR ν_{max}^{KBr} cm^{-1}: 3450 (N-H). nmr (in $CDCl_3$) at 100 Mc: τ 3.54 (1H, d-d, J_{5-6}=5.0 Hz, J_{5-4}=7.0 Hz, pyridine C_5-H), 2.35-3.28 (7H, m, aromatic C-H and N-H), 2.04 (1H, d-d, J_{6-5}=5.0 Hz, J_{6-4}=2.0 Hz, pyridine C_6-H).

Anal. Calcd. for $C_{11}H_9N_2Br \cdot C_6H_3N_3O_7$(picrate): C, 42.70; H, 2.53; N, 14.64. Found: C, 42.75; H, 2.61; N, 14.35.

After the extraction of Ve, the residue was dissolved in a small amount of benzene and chromatographed on 60 g. of silica gel(200 mesh), benzene being used as eluent. From the first fraction, 0.37 g. of a colorless crystalline mass was obtained. Recrystallization from n-hexane gave 6-anilino-3-bromopyridine (VIe), mp. 111-112°, as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 3230 broad (N-H). nmr (in $CDCl_3$) at 100 Mc: τ 2.44-3.46 (8H, m, aromatic C-H and N-H), 1.90 (1H, d, J=2.5 Hz, pyridine C_2-H). Anal. Calcd. for $C_{11}H_9N_2Br$: C, 53.04; H, 3.64; N, 11.24. Found: C, 53.29; H, 3.74; N, 11.09.

ACKNOWLEDGEMENT.- The authors wish to thank the members of the Analytical Department of this Faculty for the microanalyses and the spectral measurements. We are also grateful to Mr. M. Nakatomi, President of Hisamitsu Pharmaceutical Co. Inc. for the supply of several chemicals.

REFERENCES

* To whom inquires should be directed.

1.- T. Hisano, S. Yoshikawa, and K. Muraoka, Org. Prep. Proced. Int., 5, 95(1973).

2.- T. Hisano, S. Yoshikawa, and K. Muraoka, Chem. Pharm. Bull. (Tokyo), 22, 1611(1974).

3.- T. Hisano, T. Matsuoka, and M. Ichikawa, ibid., in press.

4.- T. Hisano, T. Matsuoka, and M. Ichikawa, Heterocycles, 2, 163(1974).

5.- M. Hamana, H. Noda, and M. Aoyama, ibid., 2, 167(1974).

(Received August 5, 1974; in revised form August 5, 1974)