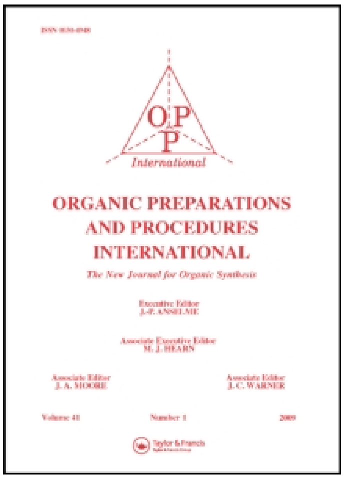

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ISOLATION AND CHARACTERIZATION OF TWO PRIMARY CYCLOADDUCTS FROM THE REACTION OF PHENYLISOCYANATE WITH 3-PICOLINE-N-OXIDE

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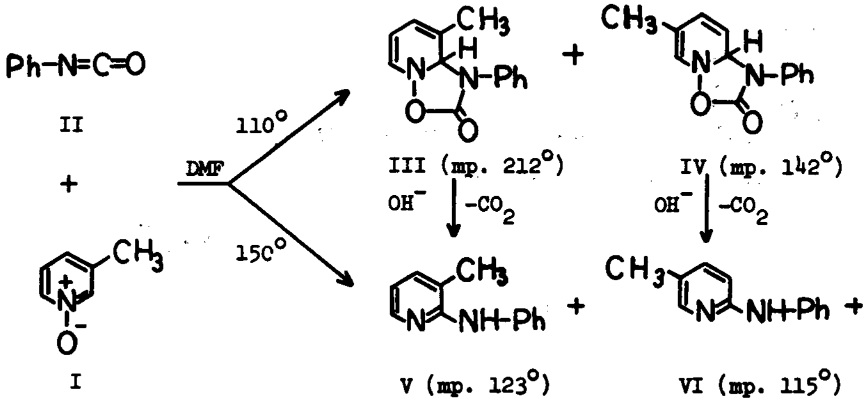
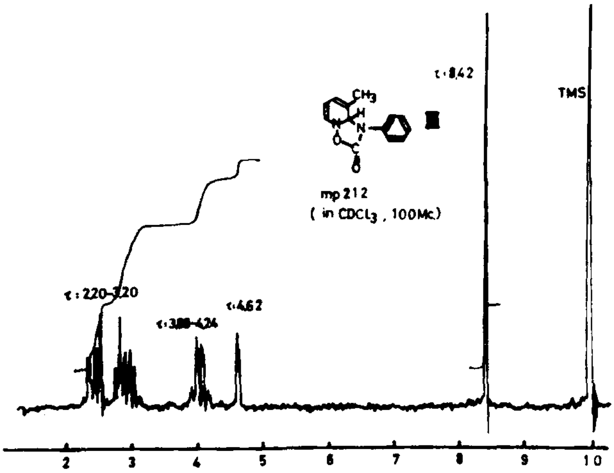
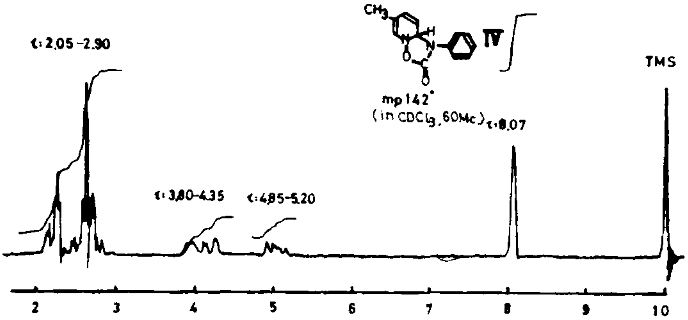
Although cycloaddition reactions of aromatic amine N-oxides[1-6] have been extensively investigated, there is no study of the reaction with 3-picoline-N-oxide(I). In a previous paper,[7] we showed that the reaction of 2-(N-oxido-2-pyridyl)benzothiazoles with phenylisocyanate(II) in dimethylformamide(DMF) did not give the corresponding anilino derivatives. We now report the results of our investigation of the reaction of I with II.



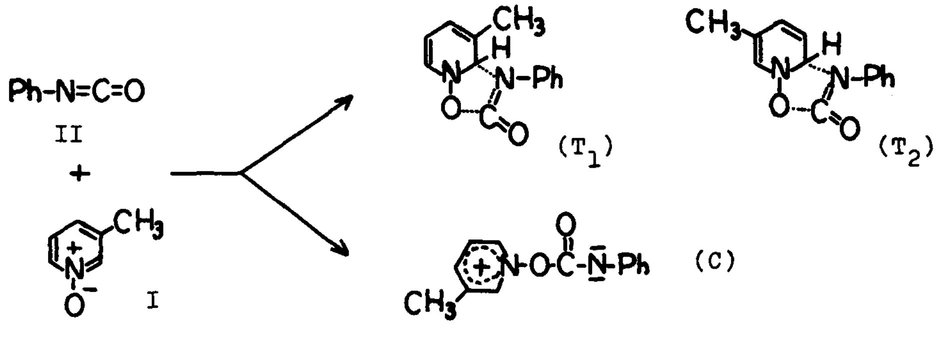
3-Picoline-N-oxide(I) reacted with phenylisocyanate(II) in DMF at 110° to afford two products, A, mp. 212° and B, mp. 142° as colorless needles in 34% and 24% yields respectively. The mass spectra of A and B both showed a characteristic molecular ion peak at m/e 228 and both compounds gave correct elemental analyses for 1:1 adducts of the two reactants, namely $C_{13}H_{12}N_2O_2$. The infrared spectra of these adducts exhibited carbonyl absorptions at 1727 and 1740 cm^{-1} respectively; neither compounds displayed bands ascribable to a carboxylic acid group in the 3300 and 2700-2500 cm^{-1} regions. In addition to the methyl hydrogen peaks at τ 8.42 and 8.07, the nmr spectra(see Figures) showed a single hydrogen peak at τ 4.62(doublet) for A and 4.85-5.20(multiplet) for B; the remaining eight hydrogens





appeared at τ 2.20-4.24 and 2.05-4.35 as complex multiplets. The ultraviolet spectra of A and B showed only one absorption at 234 mμ. Although both A and B are stable to heat(no decomposition at 150-160° in DMF), they were easily converted in high yields to 2-anilino-3-methylpyridine(V) and 2-anilino-5-methylpyridine(VI) respectively on reflux in alcoholic potassium hydroxide. On the basis of these data, we deduced A and B to be the isomeric cycloadducts of 3-picoline-N-oxide with phenylisocyanate, III and IV respectively.

When the reaction of I with II was conducted at 150° in DMF, the only compounds isolated were V and VI in 30% and 24% yields respectively; III was also formed in 3.2% yield under these conditions. Authentic samples of V and VI prepared from the zinc chloride catalyzed condensation of aniline with 2- and 6-bromo-3-picolines respectively, were identical in all respects with our products.



Our findings are significant in two respects. To our knowledge, not only is this the first report of the isolation of primary adducts in the cycloaddition of an N-oxide with an isocyanate, but even more interesting is the isolation of two isomeric such adducts. Although our data could be interpreted in terms of two different transition states(T_1 and T_2) leading to III and IV, an alternate possibility would involve a stabilized ionic intermediate(C) which could cyclize to either the 2- or the 6-position of the ring. Although III is stable to heating to 150-160° in DMF, IV is somewhat sensitive to similar temperatures, elimination of carbon dioxide occurring to some extent to yield VI. The fact that both III and IV were rather stable to heat suggests that the driving force for rearomatization is not very strong. The formation of V and VI from the reaction conducted at 150°(even then a small amount of III was isolated), 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 phenylisocyanate). This point was confirmed by the fact that III(or IV) heated to 150° in DMF in the presence of aniline or 3-picoline-N-oxide decomposed to V(or VI).

Although no definite conclusions can be reached at this time, it is clear that the presence of the methyl group at the 3-position has a determining effect on the course of the reaction and that its steric effect is at best, extremely small if not insignificant. We are continuing our investigations of this reaction in order to elucidate the factors controlling the unusual formation of and the stability of these cycloadducts.

EXPERIMENTAL[9]

Reaction of 3-Picoline-N-oxide(I) with Phenylisocyanate(II).-

Reaction at 110°.- To a solution of 5.45 g.(0.05 mole) of I in 40 ml. of DMF, was added dropwise 11.91 g.(0.10 mole) of II with stirring at room temperature and the mixture heated in an oil bath at 110° for 7 hrs. After this time, the reaction mixture was allowed to stand at 0-5° overnight. The precipitated colorless crystals were collected and washed with small amounts of cold DMF to give colorless crystals(3.85 g., 34%), mp.201-207°. Recrystallization from benzene yielded colorless needles of III, mp. 212°. IR ν_{max}^{KBr} cm^{-1}: 1727(C=O); UV λ_{max}^{EtOH} mμ(log ε): 234(4.11) (4 x 10^{-5} mole). Mass spectrum: (M^+ m/e: 228), 184 (M^+-CO_2), 183(M^+-CO_2H). nmr(in $CDCl_3$) at 100 Mc: τ 8.42(3H, s, -CH_3), 4.62(1H, d, J= 3.5 Hz, C_2-H).

<u>Anal.</u> Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27; MW, 228. Found: C, 68.45; H, 5.39; N, 12.19; MW(mass spectrum), 228.

After removal of III, the filtrate was concentrated to one-half its initial volume under reduced pressure and allowed to stand at 0-5°overnight. The precipitated crystals were collected and washed with small amounts of cold ether to afford 2.75 g.(24%) of colorless crystals, mp. 139-142°. Recrystallization from benzene gave fine colorless needles of IV, mp. 142°. IR ν_{max}^{KBr} cm^{-1}: 1740(C=O). UV λ_{max}^{EtOH} mμ(log ε): 234.5(4.09) (4 x 10^{-5} mole). Mass spectrum: (M^+ m/e: 228, 184(M^+-CO_2), 183(M^+-CO_2H). nmr(in$CDCl_3$) at 60 Mc: τ 8.07(3H, s broad, -CH_3), 4.85-5.20 (1H, m, C_2-H).

<u>Anal.</u> Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27; MW, 228. Found: C,68.45; H, 5.38; N, 12.21; MW(mass spectrum), 228.

<u>Reaction at 150°</u>.- To a solution of 5.45 g.(0.05 mole) of I in 40 ml. of DMF was added dropwise 11.91 g.(0.10 mole) of II with stirring at room temperature and the mixture was heated

in an oil bath at 150° for 7 hrs. After this time, the mixture was allowed to stand at 0-5° overnight. The colorless crystals which had precipitated were collected washed with cold DMF to give 0.37 g.(3.2%) of colorless crystals, mp. 204-208°. Recrystallization from benzene afforded colorless needles of III, mp. 212°.

After the removal of III, the filtrate was to dryness under reduced pressure. The residue was dissolved in benzene and chromatographed on silical gel(50 g.), benzene being used as eluent. From the first fraction(200 ml.), 2.72 g.(30%) of a colorless crystalline mass was obtained. Recrystalliza ion from ether gave colorless prisms of V, mp. 122-123°, identical to an authentic sample(see below). IR ν_{max}^{KBr} cm^{-1}: 3280, 3180 (N-H); UV λ_{max}^{EtOH} mμ(log ε): 270(4.27), 310(3.92) (4×10^{-5} mole). nmr(in $CDCl_3$) at 100 Mc: τ 7.69(3H, s, $-CH_3$), 3.48(1H, s broad, -NH), 1.88-3.00(7H, aromatic C-H), 1.38(1H, d-d, J = 5.5 Hz, pyridine C_6-H).

<u>Anal.</u> Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.22; MW,184. Found: C, 78.11; H, 6.59; N,15.22; MW(mass spectrum): 184

After the elution of V, 2.18 g.(24%) of VI was obtained as a crystalline mass from the second fraction(100 ml.). Recrystallization from ether gave colorless prisms, mp. 114.5-115°, identical with an authentic sample(see below). IR ν_{max}^{KBr} cm^{-1}: 3210, 3150(N-H). UV λ_{max}^{EtOH} mμ(log ε): 275.5(4.37), 320 (3.85) (4×10^{-5} mole). nmr in $CDCl_3$) at 100 Mc: τ 7.72(3H, s, $-CH_3$), 2.20-2.92(8H, m, aromatic C-H and N-H), 1.57(1H, s broad, pyridine C_6-H).

Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.22; MW, 184. Found: C, 78.26; H, 6.48; N, 15.16; MW(mass spectrum), 184.

Hydrolysis of III and IV.- A mixture of 0.50 g. of III was heated under reflux in 10 ml. of 5% ethanolic potassium hydroxide for 2 hrs. and the solvent was removed by vacuum distillation. The residue was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered. Removal of the solvent left a residue which was recrystallized from ether to give 0.36 g.(94%) of 2-anilino-3-methylpyridine(V) as colorless prisms, mp. 122-123°.

Similarly, 1.0 g. of IV was hydrolyzed to yield 0.46 g. (57%) of 2-anilino-5-methylpyridine(VI) as colorless prisms, mp. 114-115°.

Authentic Synthesis of V and VI.- Authentic samples of V and VI were prepared by the reported procedure[2] from 2-bromo-(VII) and 6-bromo-3-picoline(VIII). A mixture of 1.0 g. of VII (or VIII) and 0.54 g. of aniline in the presence of 0.95 g. of anhydrous zinc chloride was heated to 170° for 3 hrs. after the reaction was over, 6 ml. of 10% sodium carbonate solution was added and the reaction mixture was heated at 105° for an additional 2 hrs. After cooling and extraction with chloroform, the organic phase was dried over anhydrous sodium sulfate and filtered. Removal of the solvent left a residue of colorless prisms of V(or VI).

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9.- All melting points are uncorrected. The UV spectra were determined in ethanol on a Hitachi EPS-3T spectrophotometer. IR spectra were taken on a Nippon Bunko DS-301 Infrared Spectrophotometer equipped with a grating. nmr spectra were obtained on JNM-MH-100 and JNM-C-60H spectrometers (Japan Electron Optics Lab. Co., Ltd.) in about 5% (w/w) solutions

5% (w/w) solutions using tetramethylsilane as an internal standard. The mass spectra were determined on a JMS-OISG Spectrometer(Japan Electron Optics Lab. Co., Ltd.).

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