Reaction of Pyridine 1-Oxides with Isocyanates: Structure of the Intermediates. Rationalization of Rearrangements of Six-membered Heteroaromatic N-Oxide Derivatives.

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Sir:

The addition of isocyanates to heteroaromatic N-oxides is well known (1-5), and has been pictured as a 1,3-dipolar addition to the nitrone function followed by aromatization with loss of carbon dioxide. A breakthrough was achieved when the isolation of the 1,2-dihydro intermediates from the reaction of 3-picoline 1-oxide with phenylisocyanate was reported (6) and that these were relatively thermally stable but did aromatize with loss of carbon dioxide on heating with base. More recently, the isolation of 1,2-dihydro intermediate (2) from the reaction of 3,5-lutidine 1-oxide (1) with phenylisocyanate was claimed (7). We were particularly struck by the similarity between the published nmr spectrum of 1,2-dihydro intermediate and that of the 2,3-dihydropyridine isolated from the reaction of 1 with benzyne (8). Most obvious are the methyl resonances, one of which is a doublet, the other a singlet. A 1,2-dihydro derivative might have been expected to show two doublets with allylic coupling of ca. 1.5 Hz. We have reinvestigated the structure of the adduct and present evidence that it is the 2,3-dihydro derivative (3).

Reaction of 1 with phenylisocyanate in refluxing toluene gave the 1:1 adduct, m.p. 149-150° (lit. (7) m.p. 148-150°) in 80.5% yield; nmr: δ 7.88 (m, 1, H$_6$), 7.2-7.9 (m, 5, phenyl). 5.92 (dq, 1, H$_4$), 5.50 (d, 1, $J_{2,6}$ = 2.3 Hz, H$_2$), 1.93 (d, 3, $J_{4,5}$-Me = 1.8 Hz, 5-Me) and 1.60 (s, 3, 3-Me). Spin decoupling confirmed the above assignments. Similarly, the reaction of 1 with p-bromophenylisocyanate gave the 2,3-dihydro 1:1-adduct (3b), m.p. 129-130° in 53.8% yield (9). Reduction of the adducts (3) with sodium borohydride in ethanol at room temperature gave the tetrahydropyridines (4a), m.p. 89-90° and (4b), m.p. 130-131° dec., in 86.3 and 95% yields, respectively. Compounds 4a and 4b both exhibited an NH band in the ir; 4a; nmr: δ 7.33 (m, 5, phenyl), 5.42 (m, 1, H$_4$), 5.11 (s, 1, H$_2$), 2.93 (m, 2, H$_6$), 2.48 (s, 1, NH, deuterium oxide exchange), 1.72 (d, 3, $J_{4,5}$-Me < 1.0 Hz, 5-Me) and 1.60 (s, 3, 3-Me). Spin decoupling studies confirmed the assignments. Had the adducts had structures 2 reduction to give an NH would have been accompanied by formation of a

carbamic acid which would have decarboxylated, none of which was observed. On heating alone (160°, 76.9% yield) or with base (ethanol-potassium ethoxide, 92.4%) 3a rearranged to give 2-anilino-3,5-lutidine (5) as reported (7).
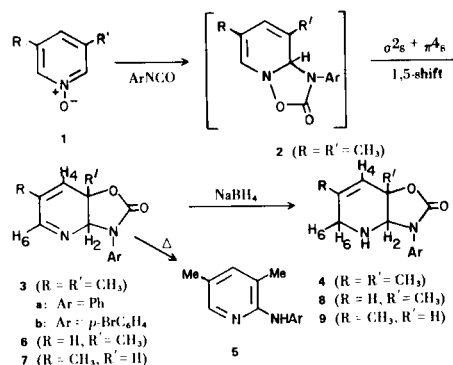

The reaction of 3-picoline 1-oxide with phenylisocyanate was also reinvestigated. The nmr spectra (11) of the two dihydro intermediates isolated again suggested that they were 2,3-dihydro derivatives, 6 and 7, rather than the 1,2-dihydro analogs. Reduction of 6 and 7 with sodium borohydride in ethanol gave the tetrahydropyridines 8 (m.p. 121-122°, 88.2%) and 9, (m.p. 41-42°, 89.9%), respectively. The ir and nmr spectra of these tetrahydropyridines confirmed their structures.

We propose that these intermediates arise by a 1,5-sigmatropic shift from the 1,2-dihydro compound formed initially (12), and that it is these which lose the C_2-H proton and aromatize. Indeed, it is tempting to rationalize many of the rearrangements now reported in the literature (12,13) in terms of a general principle, namely that fused bicyclo-1,2-dihydropyridine 1-oxides (A) are less stable than their 2,3-dihydro counterparts (B) and rearrange readily to these, and that aromatization occurs mainly (if not invariably) from B if a choice is available (e.g., if R = H
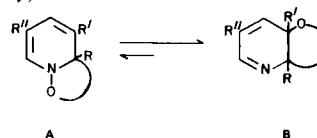
in **B**). This argument will be elaborated in full elsewhere (14).

That the rearrangement **A** → **B** should be an easy process is supported by MINDO/2' calculations carried out on the relative heats of formation of **10** and **11** (15). The geometries were optimized using the SIMPLEX method (16). ΔH_f (**10**)$_{calc}$ = -48.75 kcal/mole and ΔH_f (**11**)$_{calc}$ = -84.70 kcal/mole, so that $\Delta\Delta H_f$ = 35.0 kcal/mole. Though MINDO/2' is known (16) not to be able to take into
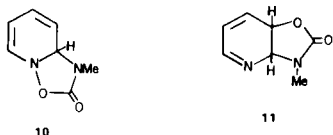
account satisfactorily bonds such as N-O it does appear to predict the order of stabilities observed in the above reactions.

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(9) All new compounds had the expected analyses and mass spectra.

(10) **3b**: nmr, δ 7.48-7.90 (m, 5, H_6 and phenyl), 5.92 (dq, 1, $J_{4,5\text{-Me}}$ = 1.8 Hz, $J_{4,6}$ = 2.2 Hz, H_4), 5.43 (d, 1, $J_{2,6}$ = 2.4 Hz, H_2), 1.97 (d, 3, $J_{4,5\text{-Me}}$ = 1.8 Hz, 5-Me), and 1.63 (s, 3, 3-Me).

(11) **6**: nmr, δ 1.66 (s, 3, 3-Me), 5.52 (s, 1, H, $J_{2,6}$ = 2.2 Hz, H_2), 6.10 (m, 2, H_4 and H_5) 7.1-7.9 (m, 6, H_6 and phenyl); **7**: nmr, δ 1.99 (d, 3, $J_{4,5\text{-Me}}$ = 1.4 Hz, 5-Me), 4.98 (dd, 1, $J_{2,3}$ = 9.0 Hz, $J_{3,4}$ = 4.0 Hz, H_3), 5.80 (dd, 1, $J_{2,6}$ = 1.9 Hz, $J_{2,3}$ = 9.0 Hz, H_2), 6.08 (m, 1, $J_{3,4}$ = 4.0 Hz, $J_{4,6}$ = 2.1 Hz, H_4), 7.15-7.90 (m, 6, H_6 and phenyl); **8**: nmr, δ 1.64 (s, 3, 3-Me), 2.37 (s, 1, NH, deuterium oxide exchange), 3.07 (m, 2, H_6), 5.13 (s, 1, H_2), 5.63 (dd, 1, $J_{4,5}$ = 10.6 Hz, $J_{4,6}$ = 1.0 Hz, H_4), 5.97 (dt, 1, $J_{4,5}$ = 10.6 Hz, $J_{5,6}$ = 2.8 Hz, H_5), 7.20-7.48 (m, 5, phenyl); **9**: nmr, δ 1.69 (d, 3, $J_{4,5\text{-Me}}$ = 1.3 Hz, 5-Me), 2.34 (s, 1, NH, deuterium oxide exchange), 2.93 (m, 2, H_6), 4.83 (m, 1, H_3), 5.26 (d, 1, $J_{2,3}$ = 9.10 Hz, H_2), 5.47 (m, 1, H_4), 7.0-7.53 (m, 5, phenyl).

(12) A similar 1,5-sigmatropic shift was observed in the reaction of 3,5-dihalogenopyridine 1-oxides with acetylenes [R. A. Abramovitch and I. Shinkai, *J. Am. Chem. Soc.*, 97, 3227 (1975)].

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(15) We would like to thank Dr. W. W. Paudler for allowing Mr. R. Van Dahm to participate in this project by carrying out the MINDO/2' calculations.

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