REEXAMINATION OF THE REACTION OF PYRIDINE 1-OXIDE WITH PHENYL ISOCYANATE. THE ISOLATION OF 2,3-DIHYDROPYRIDINE INTERMEDIATE AND THE STUDY ON THE REACTION COURSE.

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Abstract - A 2,3-dihydropyridine (4a) was isolated from the reaction of pyridine 1-oxide (1a) with phenyl isocyanate (2) at 90° in DMF. Heating 4a at 110° in DMF gave 2-anilinopyridine (5a). The time course studies on the reactions of 1a and 2 demonstrated that the initially formed 1,2-dihydropyridine (3a) immediately rearranged to 4a, and 5a was formed not from 3a but from 4a.

Aromatic N-oxides are well known to undergo 1,3-dipolar cycloaddition with phenyl isocyanate to afford α-anilino derivatives[1,2]. The reaction has been generally assumed, for example in the reaction of pyridine 1-oxide (1a), to follow course a) involving the initial formation of the primary cycloadduct (3a) followed by its decarboxylative re-aromatization to the product (5a) (Scheme 1).
In 1973 Hisano and his co-workers[3] have isolated two dihydropyridines from the reaction of 3-picoline 1-oxide and phenyl isocyanate (2) at 110° in DMF, to which 1,2- and 1,6-dihydropyridine structures (3b and 3b') were assigned, and shown that these could be converted into 2- and 6-anilino-3-picolines (5b and 5b'), respectively, upon heating with ethanolic potassium hydroxide. They have further reported that a similar reaction of 3,5-lutidine 1-oxide with 2 gives also a dihydropyridine (3c) which is convertible to 2-anilino derivative (5c)[4]. However recently, Abramovitch et al. have revealed that these dihydropyridines are not 1,2-

dihydro derivatives, 3b, 3b', and 3c, but the corresponding 2,3-dihydropyridines (4b, 4b', and 4c)[5]. More recently, Hisano et al. have isolated two dihydropyridines from the reaction of 3-picoline 1-oxide with p-chlorophenyl isocyanate under the same conditions, and unambiguously established their structures by X-ray diffraction study as 2,3-dihydropyridines (4d and 4d')[6].

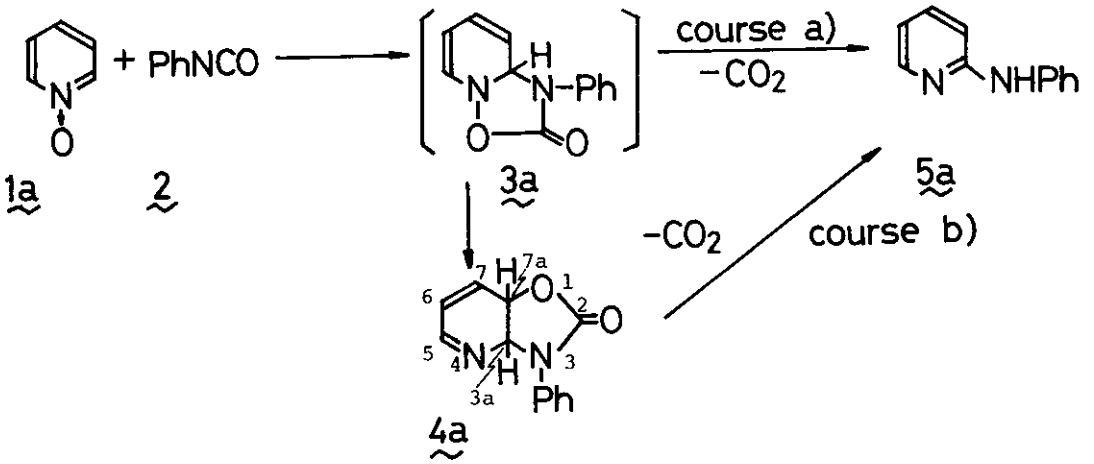
In continuation of studies on the reaction of pyridine 1-oxides with 2, we succeeded in isolation of a 2,3-dihydropyridine (4a) from the reaction of pyridine 1-oxide (1a) with 2. While no reaction occurred when a solution of 1a and 2 (2 equiv.) in DMF was warmed at 70°, heating the same solution at 90° for 7 hr afforded 4a, colorless prisms, mp 160-161° (MeCN), in 50 % yield. Its structural assignment is based on the satisfactory elemental analysis [$C_{12}H_{10}N_2O_2$], the mass spectrum [m/e: 214 (M^+), 170 (M^+-CO_2)], the IR spectrum [ν_{max}^{KBr} cm^{-1}: 1735 (C=O)], and the NMR spectrum [τ (d_6-DMSO): 4.80 (1H, d-d, $J_{7a,3a}$=9.0 Hz, $J_{7a,7}$=5.0 Hz, C_{7a}-H), 3.26-4.00 (3H, m, C_{3a}-H, C_6-H, and C_7-H), 2.00-3.00 (6H, m, C_5-H and five phenyl protons]. Compound 4a is fairly stable but can be readily transformed into 2-anilinopyridine 5a by heating in DMF at 110°.

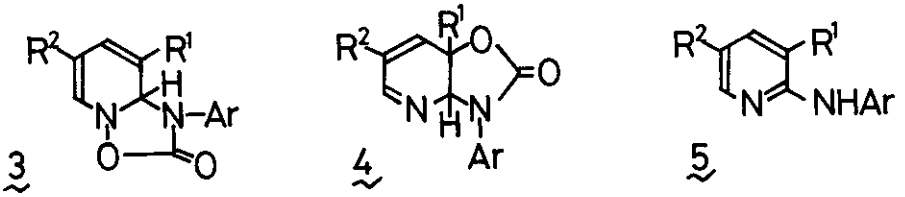
Abramovitch et al.[5] have described that the primary cycloadducts 3, initially formed from pyridine 1-oxides with 2, are markedly unstable, and readily rearrange by 1,5-sigmatropic shift to the corresponding 2,3-dihydropyridines, 4, which lose the C_2-proton of pyridine ring and carbon dioxide to give 5. Thus, they have proposed that the reaction proceeds not through course a) but through course b) as exemplified by the reaction of 1a in Scheme 1.

In order to gain some insight into the reaction course, the time course studies were carried out for reactions of 1a with 2 equivalents of 2 in DMF at 90° and that at 110°[7] by determining the product composition (1a, 4a, and 5a) by means of quantitative thin-layer chromatography[8]; the change of the amount of 2 was not recorded because that the reaction of 2 involves other reactions such as that with DMF. The results thus obtained are shown in Figures 1 and 2.

In the reaction at 90°, the formation of 4a monotonously increased comparably to the decrease in the amount of 1a with the reaction time, and reached a maximum (ca. 50 %) after ca. 7 hr. The formation of a minute amount of 5a was observed after 7 hr, but no other pyridine derivatives were detected (Fig. 1).

Figure 2 shows that the reaction proceeds more readily at 110°. Although the consumption of 1a occurred monotonously, the formation of 4a was fairly fast, and its yield reached a maximum (ca. 52 %) already after 4-5 hr and then decreased also





3 4 5

b : R^1= Me, R^2=H, Ar=Ph
b′ : R^1=H, R^2=Me, Ar= Ph
c : R^1 = R^2= Me, Ar= Ph
d : R^1= Me, R^2= H, Ar=p-Cl-C_6H_4
d′ : R^1= H, R^2=Me, Ar=p-Cl-C_6H_4

Sheme 1

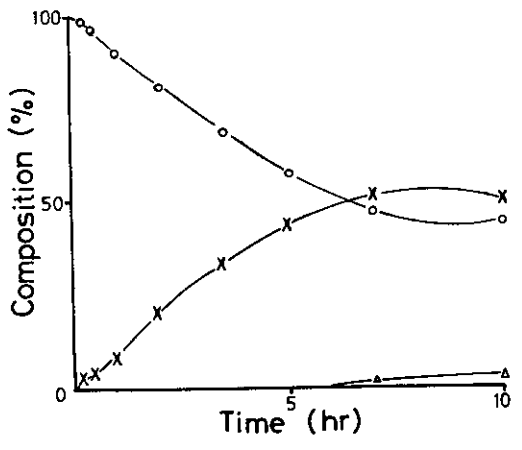


Figure 1. The reaction of 1a with 2 in DMF at 90°
o : 1a x : 4a Δ : 5a

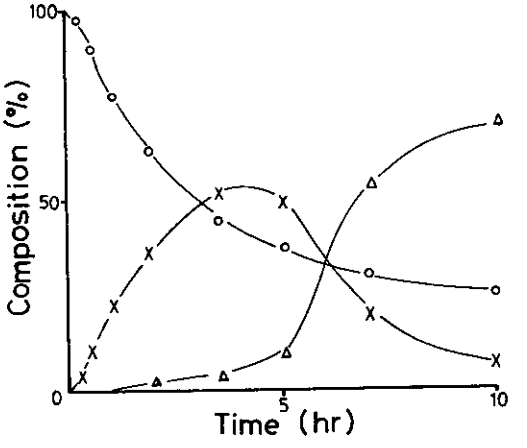


Figure 2. The reaction of 1a with 2 in DMF at 110°
o : 1a x : 4a Δ : 5a

rapidly. The formation of 5a occurred slowly till 5 hr, but since then increased rapidly in proportion to the decrease of 4a and reached 70 % yield after 10 hr. These results cannot be rationalized by course a), and it seems reasonable to conclude that the reaction proceeds by course b) at least in this reaction as proposed by Abramovitch et al.[5] Nevertheless, it seems very unlikely that reactions of 2 with other aromatic N-oxides, such as phenanthridine 5-oxide[9], isoquinoline 2-oxide[7] and 3-methylbenzimidazole 1-oxide[10], follow this course ; the possibility of course a) may not be ruled out in these reactions.

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