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THE REACTION OF AROMATIC AMINE OXIDES WITH STYRENE OXIDE

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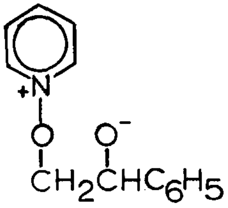
Earlier and continuing work in this laboratory have shown that dimethyl sulfoxide (DMSO) reacts with epoxides to give acyloins and glycols via alkoxydimethylsulfonium ion intermediates (1). Compounds other than DMSO having large dipole moments and well-localized negative charges would also be expected to behave as nucleophiles with epoxides. Well-known and readily available compounds in this category are the amine oxides. Previous work has indeed shown that pyridine N-oxide and styrene oxide react at high temperatures to give small yields of phenacyl alcohol and benzaldehyde (2); compound 1 was the proposed intermediate, though no evidence was provided.



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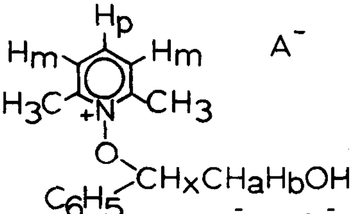
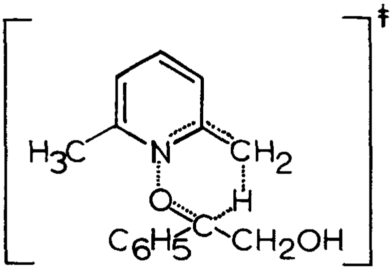


2

2a : $A^- = CF_3CO_2^-$

2b : $A^- = ClO_4^-$



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We have now shown by nmr and also by isolation of products that aromatic amine oxides react readily at ambient temperatures with styrene oxide in the presence of strong acids to give alkoxyammonium salts, such as compound 2. In this report we describe (a) the use of nmr to demonstrate the formation in solution of 2 from 2,6-lutidine N-oxide, styrene oxide, and trifluoroacetic or perchloric acid, and (b) the isolation of analytically pure 2b in good yield.

The nmr spectral changes occurring with time in a mixture of 2,6-lutidine N-oxide, styrene oxide, and trifluoroacetic acid in nitromethane (molar ratio 1:1:1:5, respectively) were investigated first. Trifluoroacetic acid, and later perchloric acid (3), was selected as the acid because of low nucleophilicity of the anion. Nitromethane was used because of its high polarity, inertness, and simple nmr spectrum. 2,6-Lutidine N-oxide was selected because the signal from its methyl groups could be monitored to show whether the lutidine ring were being incorporated into any new species. Styrene oxide was chosen for comparison of the results with those previously obtained with DMSO.

At 37° in the absence of a strong acid no reaction could be observed. Addition of the acid caused the lutidine oxide methyl singlet (δ 2.5) to diminish at exactly the rate of development of a new singlet slightly downfield (δ 2.8). In 40 minutes the δ 2.8 signal had reached 43% of the total area of the δ 2.5 and δ 2.8 signals. Accompanying the development of the δ 2.8 signal and always exactly 1/6 its area, a doublet of doublets appeared at δ 5.8. (When 2-picoline N-oxide was used in place of 2,6-lutidine N-oxide, a similar nmr pattern developed; as expected, the doublet of doublets this time was 1/3 the area of the new methyl signal.) Since these new signals were comparable to those observed for the $(CH_3)_2S^+OCH(C_6H_5)CH_2OH$ species (1), they were assumed to be those of an analogous alkoxyammonium ion intermediate 2. Protonated styrene oxide would be expected to undergo nucleophilic attack at the benzylic carbon due to the partial S_N1 character of this process.

Furthermore, just as in the DMSO case, quenching of the reaction mixture with pyridine caused the disappearance of the signals assigned to structure 2. When the methyl groups of lutidine oxide were labelled with deuterium (4), the nmr spectrum of the pyridine-quenched reaction indicated that the protium on the benzylic carbon atom of 2 had been transferred to a methyl group during this decomposition. This suggests that the decomposition may proceed via initial abstraction of a methyl hydrogen (ylid formation), followed by intramolecular abstraction of the benzylic hydrogen through a sterically favorable transition state 3. This proposal is similar to that of Fenselau and Moffatt for the decomposition of alkoxydimethylsulfonium salts (5). Further research on the mechanism of decomposition of 2 is in progress using pyridine N-oxide and deuterated 2-and 4-picoline N-oxides. Decomposition via structure 3 should then yield lutidine and phenacyl alcohol as the products, but this phase of the study has not yet been completed.

The presence of compound 2 was unequivocally confirmed by actual isolation of the alkoxyammonium perchlorate 2b. A reaction mixture of 2,6-lutidine N-oxide, perchloric acid (3),

styrene oxide, and nitromethane (1.0:0.5:1.0:7.5 molar ratio, respectively) was allowed to stand for one hour at 37° and then poured into a large excess of ether. The precipitated oil solidified overnight in a vacuum desiccator. Nmr analysis showed it to be about 80% intermediate and about 20% lutidine oxide. Recrystallization by dissolving it in acetone, adding ether until the cloud point was reached, followed by adding one drop of acetone to redissolve the incipient precipitate and cooling in a freezer to -10° yielded the analytically pure intermediate 2b, 1-(α-phenyl-β-hydroxyethoxy)-2,6-dimethylpyridinium perchlorate (colorless sheets, 62% yield), m.p. 104.0-104.5°. Anal.,Calcd. for $C_{15}H_{18}NO_6Cl$: C 52.41; H 5.28; N 4.08; Cl 10.31. Found: C 52.68; H 5.32; N 4.33(D); Cl 10.49. The nmr spectrum is consistent with the assigned structure, and its interpretation is outlined below (6):
Signals in DMSO-d_6 (and in acetone-d_6) were found at δ 8.4 (8.3) (1H, multiplet, H_p); δ 7.9 (7.9) (2H, doublet, H_m); δ 7.5 (7.5) (5H, singlet, C_6H_5); δ 5.7 (5.8) (1H, doublet of doublets, J_{xa} = 3.2 cps, J_{xb} = 7.9 cps, H_x); δ 5.3 (5.1) (variable δ) (1H, singlet, OH); δ 4.4 (4.5) (1H, doublet of doublets, J_{bx} = 7.9 cps, J_{ba} = 13.6 cps, H_b); δ 3.9 (4.1) (1H, doublet of doublets, J_{ax} = 3.2 cps, J_{ab} = 13.6 cps, H_a); and δ 2.7 (2.8) (6H, singlet, CH_3).

Major infrared absorptions (7) (in KBr) were found at 3500, 3100, 1620, 1600, 1500, 1460, 1385, 1240, 1080-1100, 1040, 1000, 886, 842, 816, 770, and 705 cm^{-1}.

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2. R. Oda, Y. Hayashi, T. Yoshida, Nippon Kagaku Zasshi, 87, 975 (1966).
3. Anhydrous perchloric acid was not separately prepared and then added. Addition of 70% perchloric acid to chilled amine oxide yields a crystalline anhydrous salt of the composition (lutidine oxide)$_2$.$HClO_4$, as described by M. Szafran, Bull. Acad. Polon. Sci, Ser. Sci. Chim., 11 (3), 111-116 (1963) and C. W. Muth and R. S. Darlak, J. Org. Chem., 30, 1909 (1965). This allowed addition of anhydrous perchloric acid, but at a molar ratio to the amine oxide of 1:2.
4. Refluxing 2,6-lutidine N-oxide with D_2O and NaOH at 130° for 2 hours with two equivalents of deuterium per equivalent of exchangeable hydrogen, followed by removal of water by

distillation, and repetition three more times, exchanges 98% of the methyl protons. After distillation of the remaining water at 30°/12 torr, anhydrous labelled lutidine oxide is distilled from the remaining NaOD at 120-122°/9.5 torr. Bases weaker than NaOH are not effective in exchanging the methyl hydrogens. C. W. Muth, R. S. Darlak, M. L. DeMatte, and G. F. Chovanec, J. Org. Chem., **33**, 2762 (1968), have described a similar procedure for labelling 2-methylquinoline N-oxide.

5. A. H. Fenselau and J. G. Moffatt, J. Amer. Chem. Soc., **88**, 1762 (1966).
6. Nmr spectra were obtained with a Varian A-60A spectrometer; δ values are relative to tetramethylsilane.
7. The infrared spectrum was obtained with a Perkin-Elmer Infracord Spectrophotometer.