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REARRANGEMENT OF TERTIARY AMINE N-OXIDES—XIV[1]

THE MECHANISM OF THE REACTION OF PYRIDINE N-OXIDE WITH ACETIC ANHYDRIDE

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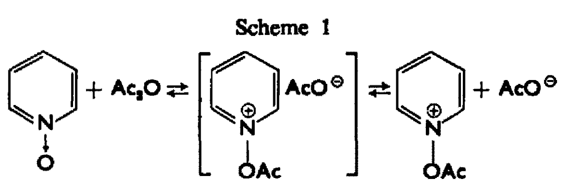
Abstract—In the reaction of pyridine N-oxide with pyridine-2,6-d$_2$ N-oxide the ratio of the rates, k_H/k_D was found to be very small, i.e., 0·92, corresponding to the magnitude of secondary isotope effect. In ^{18}O tracer experiments, the product, 2-pyridone, contained a mean average value of ^{18}O when the N-oxide was treated with an equimolar amount or a small excess of ^{18}O-labelled acetic anhydride. These results strongly suggest an ionic addition-elimination mechanism for this reaction in which the rate determining step is the addition of acetate anion at the 2-position of N-acetoxypyridinium ion.

THE reaction of pyridine N-oxide with acetic anhydride to give 2-acetoxypyridine was first reported by Katada,[2] but the mechanism has only recently been investigated by Markgraf *et al*[3] who made a careful kinetic study of the reaction. The principal observations were as follows: (a) This reaction has psuedo first order kinetic behaviour when the N-oxide is heated with a large excess of acetic anhydride. (b) The rate is slightly decreased when sodium acetate is added in the reaction system. (c) No gaseous products such as methane or carbon dioxide are obtained from the reaction, which excludes any radical process except in the case where radicals formed are securely caged by surrounding solvent. As a result of these observations, the authors favour a reaction path in terms of the equilibria as follows:

Scheme 1



I II III

They suggest that the rate determining step involves both ions II and III. The subsequent path of the above equilibria including both ions II and III to form 2-acetoxypyridine, would require a nucleophilic attack of the anion III at 2-position of the cation II. This kinetic evidence, however, does not give a complete explanation because no reliable distinction is possible between pathways involving free ions

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[1] Paper XIII, S. Oae and K. Ikura, *Bull. Chem. Soc. Japan* **38**, 58 (1965); Paper XII, S. Oae and S. Kozuka, *Tetrahedron* **20**, 2691 (1964).

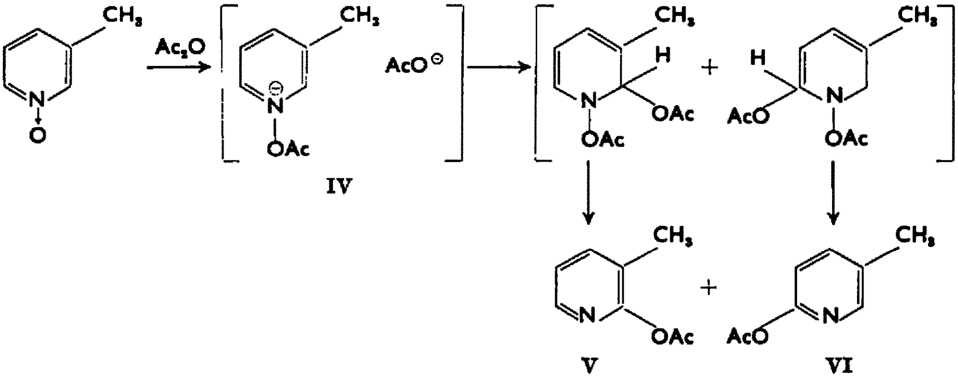
[2] M. Katada, *J. Pharm. Soc. Japan* **67**, 51 (1947); *Chem. Abstr.* **45**, 9536d (1951).

[3] J. H. Markgraf, H. B. Brown, Jr. S. C. Mohr and R. G. Peterson, *J. Amer. Chem. Soc.* **85**, 958 (1963).

and ion pairs, and also the rate deviation caused by the addition of salt is substantially smaller than the change in conductivity of the reaction mixture.

In our previous ^{18}O tracer study for the reaction of 3-picoline N-oxide with acetic anhydride,[4] the product, a mixture of two isomeric pyridyl acetates (V and VI), was found to contain a mean average value of ^{18}O when the N-oxide was treated with an equimolar amount or a small excess of acetic anhydride of which three oxygens were equally labelled by ^{18}O. Hence the mechanism of this reaction was suggested to involve a nucleophilic attack of acetate ion at the 2-carbon of the intermediate, N-acetoxy-3-methylpyridinium ion IV (Scheme 2). It appears that the same mechanism may be applied to the reaction of pyridine N-oxide with acetic anhydride, although the two reactions differ in minor respects. For example, small amounts of 3-picoline and carbon dioxide were detected in the reaction of 3-picoline N-oxide with acetic anhydride,[4] while no gaseous by-products were detected for the similar reaction with pyridine N-oxide.[3]

Scheme 2



The results of a similar ^{18}O tracer study for the reaction with pyridine N-oxide are shown in Table 1.

In these experiments, the ^{18}O content of a possible intermediate, 2-acetoxypyridine could not be analysed, because the ester apparently undergoes rapid hydrolysis and could not be isolated. Therefore, only the ^{18}O value of 2-pyridone was measured and the analytical results agree well with the theoretical value calculated for the intermolecular ionic process. In this case, when the labelled acetic anhydride is used in excess (Expt. 3 and 4) the ^{18}O concentration of the resulting pyridone is increased by the mean average value of all the oxygens in the reaction system. This increased ^{18}O incorporation cannot be explained by any other mechanism because there is no radical transfer reaction between acetoxy radical and acetate ion.[6] Here again, one can safely assume that the ^{18}O content of pyridone agrees with the ester, as in our previous cases, such as those of 2-,[6] 3-[4] and 4-[7] picoline N-oxides with acetic anhydride, that of 4-picoline N-oxide with butyric anhydride,[8] and also that of quinaldine N-oxide with

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[4] S. Oae and S. Kozuka *Tetrahedron* **20**, 2691 (1964).

[5] S. Oae, T. Kitao and Y. Kitaoka, *Tetrahedron* **19**, 827 (1963).

[6] S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3359 (1962).

[7] S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3362 (1962).

[8] S. Oae, Y. Kitaoka and T. Kitao, *Tetrahedron* **20**, 2677 (1964).

TABLE 1. OXYGEN-18 ANALYTICAL RESULTS

Expt. no.	Mole ratio N-oxide: Ac_2O	Oxygen-18 value of (atom %)				
				Theoretical value for		
		Ac_2O (used)	Pyridone (obtained)	Intermol. ionic	Radical pair	Intimate ion pair*
1	1:1	0·89	0·72	0·72	0·55	0·20
2	1:1	0·83	0·65	0·67	0·52	0·20
3	1:1·5	0·89	0·75	0·76	0·55	0·20
4	1:1·5	0·83	0·69	0·72	0·52	0·20
Control 1†	1:1	0·89	0·27	—	—	—
Control 2‡	1:1	0·20	0·20	—	—	—

* Calc. value for the ideal intimate ion pair process similar to the one suggested for the reaction between isoquinoline or pyridine N-oxide with tosyl chloride.[5]

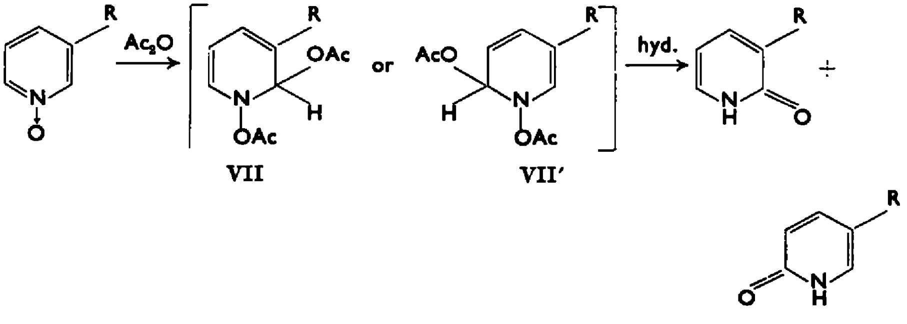
† Ordinary pyridone was refluxed with labelled Ac_2O for 8 hr. The recovered pyridone was subjected to the isotope analysis.

‡ An ordinary reaction mixture was quenched by ^{18}O-enriched water (1·62 atom%) and the obtained pyridone was subjected to the analysis.

benzoyl chloride,[9] in which all these ester products are known to have equally enriched carbonyl and etheral oxygens when they are treated with ^{18}O enriched acylating agents. Also these esters undergo no oxygen exchange either during ester formation or hydrolysis. In this case, the pyridone resulting from the hydrolysis with ^{18}O enriched water (Cont. 2), contains no excess ^{18}O while a small amount of oxygen exchange may take place during ester formation, because the pyridone recovered after heating with the labelled acetic anhydride revealed slight ^{18}O incorporation. (Table 1 and Experimental.) This amount is very small and is calculated to be only 10% of the ^{18}O exchange.

As both the ^{18}O experiment and the kinetic study of Markgraf support the mechanism involving the nucleophilic attack of acetate ion on N-acetoxypyridinium ion, rate determining step of the reaction must be decided. Bain and Saxton[10] have

Scheme 3



shown that equal amounts of isomeric pyridones are obtained when R is methyl,

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[9] S. Oae and S. Kozuka, *Tetrahedron* **20**, 2671 (1964).

[10] B. M. Bain and J. E. Saxton, *J. Chem. Soc.* 5216 (1961).

while the substitution with an electron withdrawing group such as —COOH,[10] —$COOCH_3$,[11] —X[12] or —NO_2[13] at position 3 gives 3-substituted-2-pyridones as the chief products. Consequently, the nucleophilic attack of acetate ion at either the 2- or 6-position is the rate determining step. But since 1,2-elimination of a proton and an acetate ion from the addition intermediate (VII) will also be facilitated by the same electron withdrawing substituents, R, the hydrogen–deuterium kinetic isotope effect of the rearrangement was determined.

Pyridine-2,6-d_2 was therefore prepared by the decarboxylation of dideuterated dipicolinic acid as follows. The deuterium content at the 2- and 6-positions of pyridine analysed by NMR for both pyridine-d_2 and pyridine-d_2-N-oxide, were found to contain 96 and 95% of D at the 2 and 6 positions respectively. The rate constants of pyridine N-oxide and pyridine-2,6-d_2-N-oxide in the reaction with an excess of acetic anhydride at 130° are listed in Table 2.

Scheme 4

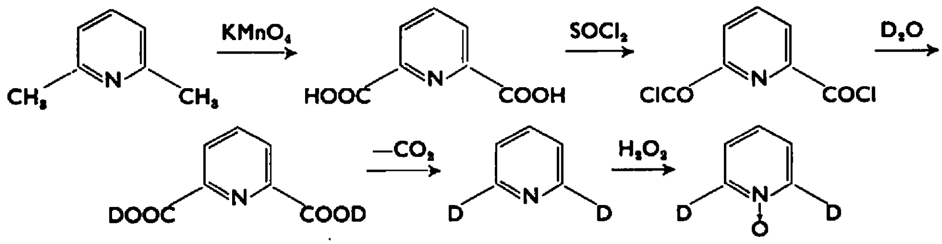
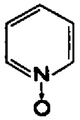
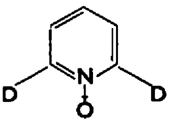


TABLE 2. RATE CONSTANT OF PYRIDINE AND THE ANOMOLOUS N-OXIDE IN EXCESS Ac_2O

Reacting S piece	Initial Concentration of N-oxide × 10^2 M/l	Temp °C	k × $10^5 sec^{-1}$	av. k	k_H/k_D
	3·045	129·97 ± 0·1	7·93	8·04	0·92
	3·025	130·03 ± 0·1	8·14		
	3·129	130·03 ± 0·1	8·90	8·78	
	3·163	129·98 ± 0·05	8·65		

In both cases good pseudo first order plots were obtained. The magnitude of the kinetic isotope effect, $k_H/k_D = 0{\cdot}92$, is very small and of reverse order, therefore the value cannot be accepted as that of the base-catalysed elimination. Usually, the deuterium isotope effect of E_2 reaction ranges roughly between 2·5 to 8[14] dependent upon the nature of base, leaving group and others. When acetate is the leaving group,

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[11] V. Boekelheide and W. J. Linn, *J. Amer. Chem. Soc.* **76**, 1286 (1954).

[12] M. P. Cava and B. Weinstein, *J. Org. Chem.* **23**, 1616 (1958).

[13] E. C. Taylor and J. S. Driscoll, *J. Org. Chem.* **25**, 1716 (1960).

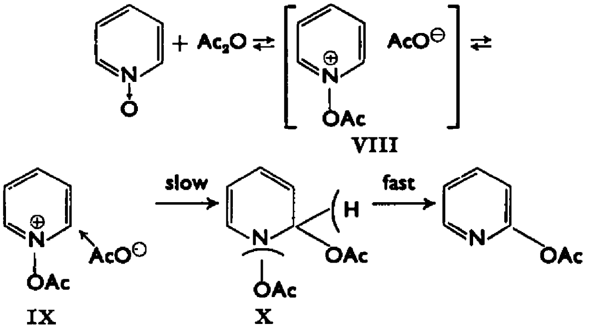
[14] W. H. Saunders, Jr. *Kinetic Isotope Effects* Chap. IX *Investigation of Rates and Mechanism of Reactions.* Interscience, New York (1961).

the deuterium isotope effect in E_2 reaction was found to be 3·5.[15] Therefore the rate determining step cannot be the elimination step. Although the value of $k_H/k_D = 0{\cdot}92$ is smaller than the theoretical value of the secondary isotope effect, ca. 0·8, it is of about the same magnitude as that involving nucleophilic addition.[16] Hence, it is in agreement with the value expected for the rate-determining addition of acetate ion at the position 2 and the reaction proceeds in accordance with scheme 5.

Recently, Markgraf *et al.* determined the kinetic isotope effect of the reaction of acridine N-oxide with acetic anhydride,[17] and found that the rate constant of acridine-9-d N-oxide is similar to that of acridine N-oxide. Therefore, the reaction of acridine N-oxide with acetic anhydride[18] is similar to that between pyridine N-oxide and acetic anhydride, although the rate of the reaction of pyridine N-oxide is 10^6 times slower than that of acridine N-oxide.

A similar ^{18}O tracer experiment for the reaction of acridine N-oxide with acetic anhydride is now under way in this laboratory.

Scheme 5



EXPERIMENTAL

Pyridine-2,6-d$_2$. 2,6-Lutidine (bp. 144°–144·5°) was oxidized to dipicolinic acid[19] and the dicarboxylic acid (25 g; 0·15 mole was recrystallized 4 times from water, m.p. with dec 300°) was chlorinated with $SOCl_2$ (72 g; 0·6 mole) by gentle heating under reflux for 3 days. After evaporation of excess $SOCl_2$, the residual mass was taken up in dry benzene and 2,6-lutidine dicarboxylic acid dichloride obtained from the benzene layer. (26 g; 0·13 mole 85% m.p. 60–60·5°.) This dichloride was again converted to diacid using D_2O (5 g), then decarboxylated by heating in a free flame. Distillation from KOH pellets gave pyridine-2,6-d$_2$ bp. 108–115° (mainly 114–115°) 5·2 g. Pyridine-2,6-d$_2$ was converted to its N-oxide by 30% H_2O_2.[20] b.p. 130–131°/9 mm Hg 4·2 g. NMR study of this pyridine and its N-oxide shows 96% and 95% deuterium at their α-position respectively.

Kinetic runs. The kinetic measurements in accordance with Markgraf *et al.*[3] were conducted in sealed ampoules each containing 1 ml of the reaction mixture. A good pseudo first order kinetic behaviour was observed in each case and the results are shown in Table 2. A typical run for the deuterated compound is shown in Fig. 2.

^{18}O *Tracer study.* The ^{18}O-labelled acetic anhydride was prepared by the previously described method.[6]

A typical run was as follows: Pyridine N-oxide (1·94 g 2·04 × 10^{-2} mole) was refluxed with ^{18}O-labelled acetic anhydride (3·15 g 3·09 × 10^{-2} mole) for 8 hr. After heating, a few ml water was added

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[15] F. G. Bordwell, R. L. Arnold and J. B. Biranowsky, *J. Org. Chem.* **28**, 2496 (1963).

[16] S. Seltzer, *J. Amer. Chem. Soc.* **83**, 1861 (1961).

[17] J. H. Markgraf and C. C. Carson, *J. Org. Chem.* **29**, 2806 (1964).

[18] [a] A. Kliegel and A. Fehrle, *Ber. Dtsch. Chem. Ges.* **47**, 1929 (1914). [b] J. H. Markgraf and M-K. Ahn, *J. Amer. Chem. Soc.* **86**, 2699 (1964).

[19] G. Black E. Depy and B. B. Corson, *J. Org. Chem.* **14**, 14 (1949).

[20] E. Ochiai, *J. Org. Chem.* **18**, 534 (1953).

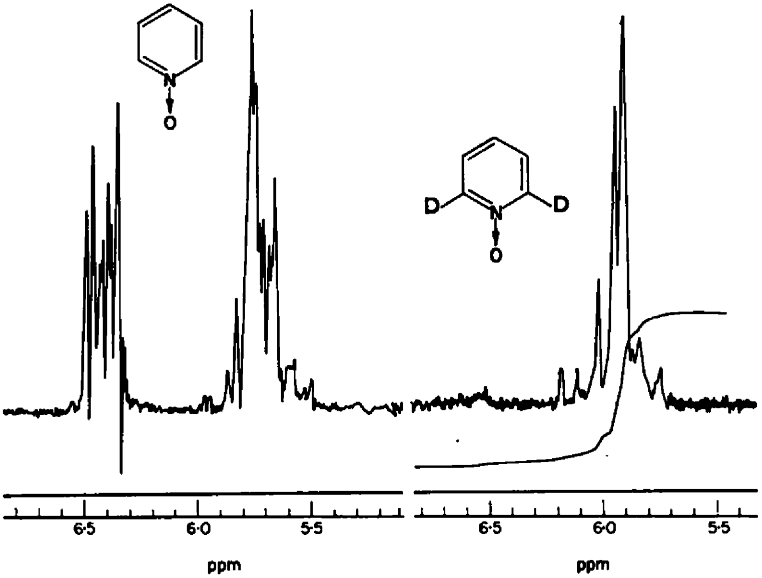

Fig. 1. NMR chart of pyridine N-oxide and the anomalous in D_2O.

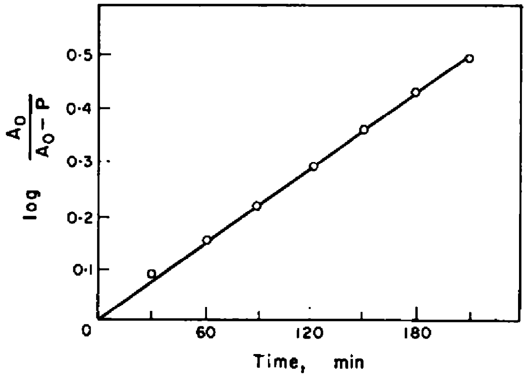

Fig. 2. Pseudo first order plots of the rearrangement of pyridine-2,6-d_2-N-oxide (0·03129 M) in Ac_2O at 130°.

and the mixture distilled yielding crude pyridone. b.p. 110–120°/3 mm Hg 1·5 g. Recrystallization from benzene–hexane gave colourless crystals, m.p. 104–105°. The reaction results using one to one moles reaction mixture are listed in Table 2.

Oxygen exchange reaction of pyridone with ^{18}O *labelled acetic anhydride.* Pyridone (m.p. 105–106° 0·5 g) was heated with ^{18}O-labelled acetic anhydride (0·5 g 0·89 atom % ^{18}O) at 140° for 8 hr. After recrystallization from benzene, the recovered pyridone was subjected to ^{18}O anals. ^{18}O content was 0·27 atom %.

^{18}O *exchange reaction at the hydrolysis of the ester.* Pyridine N-oxide (1·0 g 1·05 × 10^{-2} mole) was heated with acetic anhydride (1·1 g 1·1 × 10^{-2} mole) for 8 hr and the resulting mixture quenched by ^{18}O enriched water (0·5 g 1·62 atom % ^{18}O). The pyridone isolated (m.p. 104–105°) revealed no incorporation of ^{18}O, 0·20 atom %.

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