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

THE MECHANISM OF THE REACTION OF 3-PICOLINE N-OXIDE WITH ACETIC ANHYDRIDE

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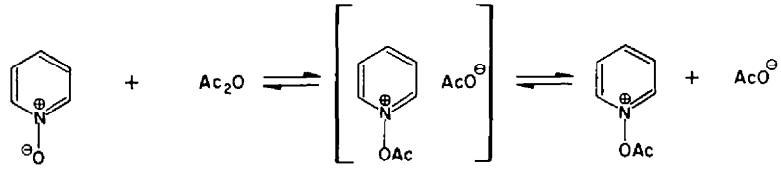
Abstract—The reaction of 3-picoline N-oxide with acetic anhydride to give 2-acetoxy-3-methylpyridine and 2-acetoxy-5-methylpyridine has been investigated using ^{18}O as tracer. The ^{18}O concentration of the ester mixture was found to be of an average value of one natural and three oxygens with excess ^{18}O when the N-oxide reacted with an equimolar amount of uniformly ^{18}O-labelled acetic anhydride. When ^{18}O-labelled acetic anhydride was used in excess, the ^{18}O value of both the etheral and carbonyl oxygens of the ester mixture attained an average value of all the oxygens of the reaction mixture. These results and others strongly suggest an intermolecular ionic process for this reaction.

ONE of the earliest works related to the rearrangements of hetero aromatic N-oxides with acylating agents involves the reaction of pyridine N-oxide with acetic anhydride to give 2-acetoxypyridine.[2] This rearrangement, however, unlike the reactions of 2- and 4-picoline and quinaldine N-oxides with acylating agents,[1,3,4] has received very little attention until the recent kinetic work by Markgraf *et al.*,[5] who have suggested an



I II III IV

ionic pathway involving a nucleophilic attack at C-2 position of N-acetoxypridinium ion (III) either by free acetate anion (IV) or by that in the ion pair (II). In this reaction there is no possibility of forming anhydrobases such as V, VI or VII, which were postulated by Traynelis and Martello[3] and later accepted by us,[4] as the key intermediates in the rearrangement of 2- and 4-picoline N-oxide with either acetic

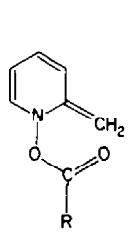
[1] Part XI; S. Oae, Y. Kitaoka and T. Kitao, *Tetrahedron*.

[2] M. Katada, *J. Pharm. Soc., Japan* **67**, 51 (1947).

[3] [a] V. J. Traynelis and R. F. Martello, *J. Amer. Chem. Soc.* **80**, 6590 (1958), review most of the important previous works related to the mechanisms; [b] V. J. Traynelis and R. F. Martello, *ibid.* **82**, 2744 (1960); [c] V. J. Traynelis, S. A. I. Gallagher, I. H. M. and R. F. Martello, *J. Org. Chem.* **26**, 4365 (1961).

[4] [a] S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3359 (1962); [b] S. Oae, T. Kitao and Y. Kitaoka, *ibid.*, **84**, 3362 (1962); [c] S. Oae, S. Kozuka, *Tetrahedron*; [d] S. Oae, Y. Kitaoka and T. Kito, *ibid.*

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



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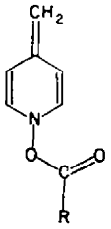

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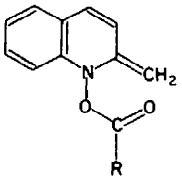


VII

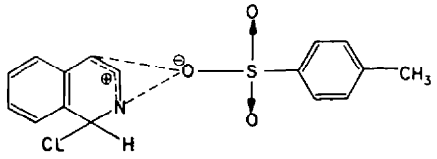
anhydride[1,4a,b] or n-butyric anhydride[4d] and also of quinaldine N-oxide with benzoyl chloride.[4c] Therefore, as was suggested by Markgraf *et al.*, the mechanism of this reaction should be simpler than in the case of picoline and quinaldine N-oxides with acylating agents and also isoquinoline or pyridine N-oxides with tosyl chloride where the tosyloxy group was suggested to migrate via an intimate ion pair (VIII) with the initial addition and the final elimination of a chloride ion at position 1. Although the reaction of pyridine N-oxide with acetic anhydride was suggested by Markgraf *et al.* to proceed through the ionic pathway involving a nucleophilic attack of acetate ion at position 2, their work does not completely exclude the free radical mechanism, because it is known that these reactions give a small amount of carbon dioxide,

TABLE 1. THE ANALYTICAL RESULTS OF ^{18}O IN THE MIXTURE OF 2-ACETOXY-3-METHYL- AND 2-ACETOXY-5-METHYLPYRIDINES AND IN THE MIXTURE OF 3-METHYL- AND 5-METHYL-2-PYRIDONES

Experiment no.	Mole ratio of reacting species 3-picoline N-oxide: acetic anhydride	Compound	Atom% ^{18}O			
			Calc. for			Found.
			Intermol. nucleophilic process	Free radical cage process	Intimate ion pair process*	
1	1:1	$(CH_3CO)_2O$				0·89
		The ester mixture	0·72	0·55	0·55	0·73
		The pyridone mixture	0·72	0·55	0·20	0·70
2	1:1·5	$(CH_3CO)_2O$				1·30
		The ester mixture	1·11	0·75	0·75	1·10
		The pyridone mixture	1·11	0·75	0·20	1·14

* Calculated values for the ideal intimate ion pair process similar to the one suggested for the reaction between isoquinaline or pyridine N-oxide with tosyl chloride.[6]

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



VIII

methane and pyridine bases. Even although the reaction is ionic, the kinetic evidence fails to distinguish between an intermolecular path and the one involving an intimate ion pair. These different pathways can, however, be distinguished by the ^{18}O-tracer technique using uniformly ^{18}O-labelled acetic anhydride. The extremely facile hydrolysis of the product, 2-acetoxypyridine has created an enormous difficulty in the isolation of the ester in pure form, therefore the usual ^{18}O tracer technique has not yet been successfully applied.

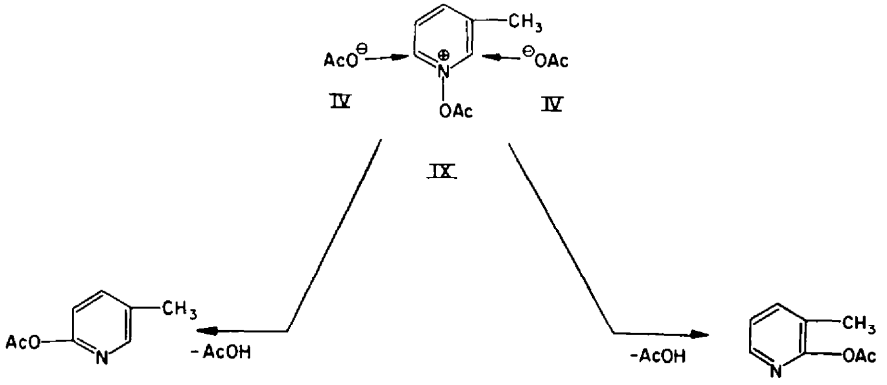
Meanwhile, a similar reaction between 3-picoline N-oxide and acetic anhydride has been observed independently by two different groups.[7,8] This reaction gives a mixture of 2-acetoxy-3-methylpyridine and 2-acetoxy -5-methylpyridine as the main products and both esters are quite stable during distillation and are readily obtained in a pure state. Therefore, an investigation of the mechanism of this reaction, was undertaken using ^{18}O tracer technique. The 3-picoline N-oxide was reacted with an equimolar amount or a slight excess of uniformly labelled ^{18}O acetic anhydride. After refluxing for an hour under nitrogen atmosphere, the ester mixture was collected by fractional distillation. As several attempts made to separate the ester mixture into two components by GLC, were unsatisfactory, the mixture was hydrolysed to yield the mixture of 3-methyl-2-pyridone and 5-methyl-2-pyridone. Both the ester mixture and the pyridone mixture were subjected to ^{18}O-analyses. The results are summarized in Table 1.

When the ordinary ester mixture was gently refluxed with ^{18}O-labelled acetic anhydride-acetic acid mixture and the ester mixture subsequently recovered and hydrolysed, the resulting pyridone mixture contained no excess ^{18}O. Similarly, the ordinary ester mixture was hydrolysed with ^{18}O-enriched water, the resulting pyridone mixture also contained no excess ^{18}O. Thus, under similar reaction conditions, there is no ^{18}O exchange during the ester formation, nor is there any ^{18}O exchange during the hydrolysis of the ester mixture. Although the ^{18}O incorporation of each ester could not be determined separately, it is safe to assume that the two esters are formed in a similar process, and differ only by the attachment of the acetoxy group either at position 2 or 6.

The ^{18}O-analyses of the resulting esters and pyridones clearly exclude the intimate ion pair process similar to the one suggested for the reaction between isoquinoline or pyridine N-oxide with tosyl chloride,[6] because the particular mechanism demands that the pyridone mixture contains no excess ^{18}O. The same ^{18}O-analyses data also completely reject the free radical cage process since it requires both ether and carbonyl oxygens to be incorporated with a mean average concentration of one natural and one excess ^{18}O of the acetic anhydride used. The only mechanism which is in

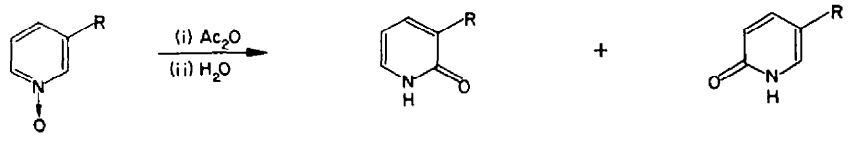
[7] V. Boekelheide and W. J. Linn, *J. Amer. Chem. Soc.* **76**, 1286 (1954).
[8] B. M. Bain and J. E. Saxton, *J. Chem. Soc.* 5216 (1961).

accord with the ^{18}O analytical data is the intermolecular nucleophilic attack of acetate ion (IV) on N-acetoxy-3-methylpyridinium ion (IX) at either position 2, to give 2-acetoxy-3-methylpyridine or position 6 to yield 3-methyl-6-acetoxypyridine (2-acetoxy-5-methylpyridine). If this is the case, one would expect an increase of ^{18}O concentration in the resulting ester mixture with an increasing amount of ^{18}O-labelled acetic anhydride. In fact, when acetic anhydride is used in excess (Expt. 2), the ^{18}O



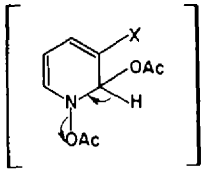
concentration of the resulting esters and pyridones is increased to the mean average concentration of all the oxygens in the reaction system. These ^{18}O analytical data together with the kinetic work by Markgraf *et al.* on a similar reaction with pyridine N-oxide support that the main reaction leading to the ester mixture is the intermolecular rearrangement, whereby nucleophilic attack of acetate anion takes place at either the C-2 or C-6 position of the N-acetoxy-3-methylpyridinium ion (IX) with subsequent or simultaneous elimination of proton from either the C-2 or C-6 position and acetate anion from the ring nitrogen atom. Although the formation of small amounts of CO_2 (2·5%) and 3-picoline was observed, indicating that a small portion of the reaction undergoes free radical decomposition, such a free radical decomposition is of a minor significance to the reaction as a whole.

The rate-determining step of this rearrangement is related to the work of Bain and Saxton[8] who recently have shown that equal amounts of the isomeric pyridones are obtained when R is methyl, but the 3-substituted 2-pyridone always becomes predominant when R is a electron-withdrawing group, such as —COOH,[8]



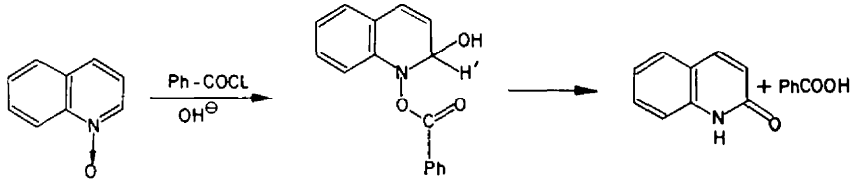
—$COOCH_3$[7], —X[9], or —NO_2[10]. These observations together with the kinetic data on a similar reaction with pyridine N-oxide support the idea that the nucleophilic attack of acetate anion at either the C-2 or C-6 position is the rate-determining step. However, the concerted 1, 2-elimination of proton and acetate from the addition

[9] M. P. Cava and B. Weinstein, *J. Org. Chem.* **23**, 1616 (1958).
[10] E. C. Taylor and J. S. Driscoll, *J. Org. Chem.* **25**, 1716 (1960).



X

intermediate (X) will also be facilitated by the electron-withdrawing nature of the substituent (X). It is interesting to note in this connection that Hamana *et al.*[11] have recently isolated a possible intermediate (XI) in the process of the base-catalysed reaction between quinoline N-oxide and benzoyl chloride to give carbostyril (XII). Although the reaction system is different, this work suggests that the rate-determining step is the 1, 2-elimination of carboxylic acid. The final answer to this problem may be determined by the hydrogen-deuterium kinetic isotope effect of the rearrangement and this work is now being undertaken.



XI XII

EXPERIMENTAL

Materials. The preparation of 3-picoline N-oxide was similar to that reported by Boekelheide.[7] ^{18}O-Labelled acetic anhydride was prepared by the procedure which was described in the earlier part of this series.[4a]

The reaction of 3-picoline N-oxide with ^{18}O-labelled acetic anhydride

A typical run was as follows: A mixture of 3-picoline N-oxide (10·9 g 0·10 mole) and ^{18}O-labelled acetic anhydride (1·53 g 0·15 mole) was refluxed for 1 hr under N_2 using a flask that was connected with a trap filled with $Ba(OH)_2$aq at the end and generated CO_2 was measured as $BaCO_3$ (0·49 g; 0·0025 mole; 2·5%). After refluxing, the mixture was distilled *in vacuo* and crude 2-acetoxy-3- and -5-methylpyridine mixture was collected. (b.p. 81–110°/2 mm 2·55 g; 0·17 mole.) This crude ester mixture was purified by fractional distillation and a fraction boiled at 81–82°/2 mm (1·35 g; n_D^{20} 1·5008; lit.[7] 1·4997) was used for ^{18}O-analysis.

Hydrolysis of the ester mixture

2-Acetoxy-3- and -5-methylpyridine (0·2 g), thus obtained, was warmed to 80° with a few drops water for 30 min. Evaporation to dryness of the mixture left a light tan solid, which after recrystallization from hexane containing a small amount of benzene, gave 3-methyl-2-pyridone and 5-methyl-2-pyridone mixture, as colourless needles m.p. 106–110°. ^{18}O analytical results of these esters and pyridones are listed in Table 1.

Further repeated recrystallization of this pyridone mixture from benzene gave 5-methyl-2-pyridone m.p. 180–181° lit.[8] 184–185°. (Found: C, 66·90; H, 6·51; calc. for C_6H_7ON: C, 67·25; H, 6·59%).

[11] M. Hamana and K. Funagoshi, *J. Pharm. Bull., Japan* **80**, 1031 (1960).

^{18}O Exchange reaction of the esters with ^{18}O-enriched water

2-Acetoxy-3- and -5-methylpyridine mixture was hydrolysed with ^{18}O-enriched water. (ca. 1·5 atom% of ^{18}O) Pyridones thus obtained, revealed no excess concentration of ^{18}O.

^{18}O Analysis of the pyridones: 0·21 atom%.

^{18}O Exchange reaction of the esters with ^{18}O-labelled acetic acid–acetic anhydride

The esters (0·4 g) were heated (150° bath temp) with the same amount of 1:1 mixture of ^{18}O-labelled acetic anhydride–acetic acid (1·24 atom % ^{18}O) for 1 hr. The resulting mixture was treated with a few drops water and the pyridone mixture separated by recrystallization from hexane–benzene after evaporation to dryness, m.p. 107–112°. ^{18}O Analysis of the pyridones revealed no concentration of ^{18}O; 0·20 atom %.

The pyridone mixture was again heated with ^{18}O-labelled acetic anhydride–acetic acid mixture (1·24 atom %) and then recovered by recrystallization from hexane–benzene. The recovered pyridones also contained no excess ^{18}O; 0·20 atom %.

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