(Table II). The table suggests that all dimethylcycloheptanes will have essentially the same energy, equal minimum-energy conformations being available for all, whereas four of the thirteen possible trimethyl isomers should be of higher energy than the rest by about 1.4 kcal./mole. The only relevant cycloheptanes studied to date are the *cis*- and *trans*-3,5-dimethylcycloheptanones, which differ in energy by 0.8 kcal./mole[11] and suggest the presence of several conformations, but since the effects studied here are fairly delicate and strongly influenced by geometrical changes, the presence of a carbonyl group is very likely to vitiate conclusions drawn on the hydrocarbons, so that this case cannot be taken as a relevant test.

The presence on cycloheptanes of other substituents which, unlike carbonyls, retain the tetrahedral configuration of the ring carbon may reasonably be treated like the methyl groups above in conformational analysis. Application of Winstein's A-values[12] for different substituents to the axial-methyl energies at different conformational positions should provide a first approximation to the conformations of such derivatives of cycloheptanes. Thus, for example, all-*trans*-1-hydroxy-3,5-dimethylcycloheptane should take up the conformation with the hydroxyl group at the 4-axial position, since its steric interference is about half that of the methyl group, leaving the methyls to occupy equatorial positions at (1, 3'e) or (2e, 2'e).

(11) N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 232 (1959).
(12) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

TABLE II
PREFERRED CONFORMATIONS OF DI- AND TRI-METHYLCYCLOHEPTANES

Isomer[a]		Preferred conformations	ΔE,[b] kcal./mole
1,2	c	(1,2e)	0
1,2	t	(1,2e), (2e,3e), (3e,4e), (4e,4'e)	0
1,3	c	(1,3e), (2e,4e), (3e,4'e)	0
1,3	t	(1,3e), (2e,2'e)	0
1,4	c	(1,4e), (2e,3'e)	0
1,4	t	(1,4e), (2e,4'e), (3e,3'e)	0
1,2,3	c,c	(3,4a,4'e)	1.4
1,2,3	c,t	(1,2e,3e), (2'e,1,2e)	0
1,2,3	t,t	(1,2e,3e), (2e,3e,4e), (3e,4e,4'e)	0
1,2,4	c,c	(1,2e,4e), (2e,1,3'e)	0
1,2,4	c,t	(1,2e,4a), (3e,4a,3'e), (4'e,4a,2e), (4a,3e,1)	1.4
1,2,4	t,c	(1,2e,4e), (2e,3e,4'e), (3e,4e,3'e), (4'e,4e,2e), (4e,3e,1)	0
1,2,4	t,t	(2e,1,3'e), (3e,2e,2'e), (4e,3e,1)	0
1,2,5	c,c	(1,2e,4'a), (4e,4'a,1)	1.4
1,2,5	c,t	(1,2e,4'e)	0
1,2,5	t,c	(1,2e,4'e), (2e,3e,3'e), (3e,4e,2'e), (4e,4'e,1)	0
1,3,5	c,c	(1,3e,4'e), (2e,4e,3'e)	0
1,3,5	c,t	(3e,1,3'e), (4e,2e,2'e), (4e,3'e,1)	0
1,3,5	t,t	(1,3e,4'a), (2'e,2e,4a)	1.4

[a] As an example of the isomer notation used, "1,2,5-c,t" refers to 1,2-*cis*,2,5-*trans*-trimethylcycloheptane. [b] The energy difference from the relevant all-equatorial isomer.

In a similar vein the conclusions derived herein should provide a valid basis for conformational analysis of a wide variety of cycloheptane derivatives.

The author gratefully acknowledges the generosity of the U.C.L.A. Computing Facility in providing computing facilities and time on the IBM 7090 computer.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, RADIATION CENTER OF OSAKA PREFECTURE, SAKAI, OSAKA, JAPAN]

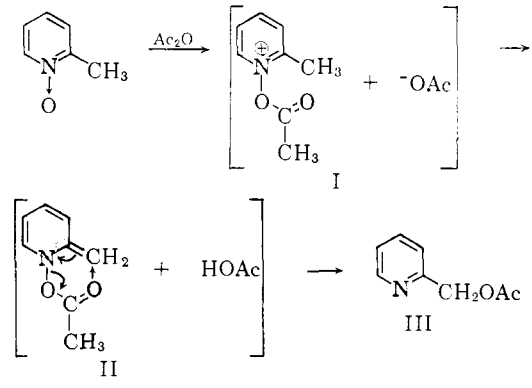
The Mechanism of the Reaction of 2-Picoline N-Oxide with Acetic Anhydride[1]

BY SHIGERU OAE, TEIJIRO KITAO AND YOSHINORI KITAOKA

RECEIVED JANUARY 31, 1962

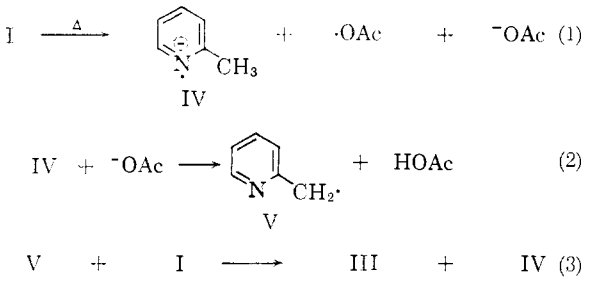
2-Picoline N-oxide was allowed to react with acetic anhydride of which all three oxygens were equally enriched by oxygen-18, and the 2-acetoxymethylpyridine obtained was hydrolyzed to 2-pyridinemethanol. Oxygen-18 analyses of these two compounds revealed that both carbonyl and ether oxygens of 2-acetoxymethylpyridine have a mean value of one enriched oxygen-18 and one natural oxygen. The additions of large amounts of solvent and of DPPH did not affect the yield of the main product. These observations, together with earlier findings, were considered as suggesting that the reaction proceeds *via* a "free radical pair" in solvent cage.

The reaction of 2-picoline N-oxide with acetic anhydride has been shown independently by several different laboratories[2-4] to give 2-acetoxymethylpyridine. The benzoylation of quinaldine N-oxide has also been shown to give 2-benzoxymethylquinoline.[5] The mechanism suggested then for the rearrangement is shown below, and this has been generally accepted for this and related reactions.[2,4-7]

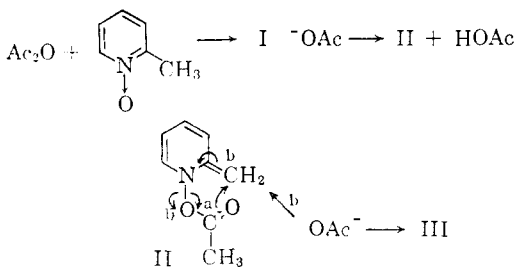


(1) Paper III on "Rearrangements of Tertiary Amine Oxides." A preliminary report appeared in paper I of this series: S. Oae, T. Kitao and Y. Kitaoka, *Chemistry & Industry*, 515 (1961); paper II: S. Oae, T. Fukumoto and M. Yamagami, *Bull. Chem. Soc., Japan*, **34**, 1873 (1961).
(2) G. Kobayashi and S. Furukawa, *Pharm. Bull. Japan*, **1**, 347 (1953).
(3) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).
(4) O. H. Bullitt and J. T. Maynard, *ibid.*, **76**, 1370 (1954).
(5) I. J. Pachter, *ibid.*, **75**, 3026 (1953).
(6) J. A. Berson and T. Cohen, *ibid.*, **77**, 1281 (1955).
(7) E. Matsumura, *Memoirs of the Institute for Arts and Sciences, Univ. of Osaka*, **1**, 1 (1952).

Boekelheide and Harrington,[8] however, have postulated the following free radical chain mechanism which involves a homolytic cleavage of the nitrogen–oxygen bond in I giving the radical ion IV and an acetoxy radical, based on their observations that (a) this reaction was strongly exothermic after passing through an initial induction period; (b) the rate of the rearrangement was very little affected by the nature of the solvent, and (c) polymerization of styrene occurred when the rearrangement was carried out in the presence of styrene.



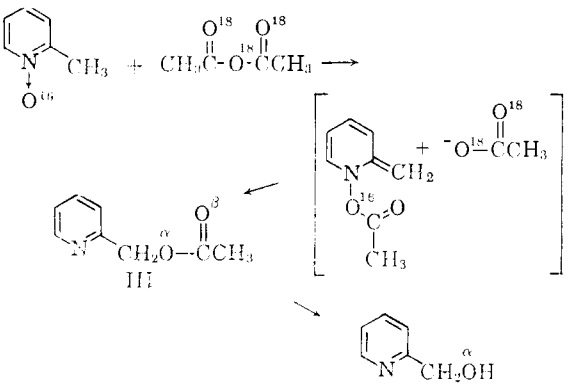
Meanwhile, Traynelis and Martello[9] have demonstrated that the yield of 2-acetoxymethylpyridine was unaltered while the yield of the products such as polystyrene and methane known to be derived from free radicals decreased drastically when they used increasing quantities of free radical scavenger such as *p*-benzoquinone and *m*-dinitrobenzene in this reaction. They also showed that 2-butyroxymethylpyridine was the only product from the reaction of 2-picoline N-oxide and butyric anhydride in the presence of sodium acetate. On the basis of these findings, they have suggested that the main reaction is an intramolecular cyclic rearrangement which involves shifts of electron pairs in the anhydrobase II as illustrated by path a, while a small portion of the anhydrobase II goes through free radical decomposition eventually giving rise to methane, carbon dioxide and 2-picoline.



These results do not permit clearly a choice between an ionic intramolecular mechanism and one involving intermediate free radicals. Even the lack of acetoxymethylpyridine formation from the reaction of 2-picoline N-oxide and butyric anhydride in the presence of sodium acetate cannot rule out an intermolecular mechanism by a nucleophilic attack of acetate anion on the methylene carbon with elimination of acetate anion, in view of our observations on the similar reaction of 4-picoline N-oxide.[10]

We have investigated the mechanism of this reaction using oxygen-18 as a tracer. The oxygen-18 labeled acetic anhydride, of which all three oxygens were equally enriched by O^{18}, was prepared by first hydrolyzing acetonitrile with O^{18}-enriched sodium hydroxide in O^{18}-enriched water and then by treating the resulting oxygen-18 labeled sodium acetate with acetyl chloride. The equal concentration of oxygen-18 at both carbonyl and ether oxygens of acetic anhydride was confirmed by the equal concentration of oxygen-18 in both acetanilide and acetamide,[11] which were derived from the acetic anhydride. Oxygen-18 labeled acetic anhydride, thus prepared, was allowed to react with an equimolar amount of 2-picoline N-oxide to give 2-acetoxymethylpyridine in about 70% yield. The hydrolysis of 2-acetoxymethylpyridine was performed by treatment with methanolic potassium hydroxide under reflux, yielding 2-pyridinemethanol in about 60% yield. Under the same conditions, there was no exchange between 2-acetoxymethylpyridine and the oxygen-18 labeled acetic anhydride–acetic acid mixture, nor was there any exchange of oxygen-18 in the reaction of 2-acetoxymethylpyridine with O^{18}-enriched potassium hydroxide in the hydrolysis.

Let us now consider the outcome of the distributions of oxygen-18 from the three different mechanisms conceivable, as illustrated.



Intramol. cyclic rearrangement	$\alpha = O^{18}$, $\beta = O^{16}$, total $= (\alpha + \beta)/2$
Intermol. nucleophilic attack by AcO^-	$\alpha = \beta = (3 \cdot O^{18} + O^{16})/4 =$ total
Free radical process	$\alpha = \beta = (O^{18} + O^{16})/2 =$ total

The intramolecular cyclic rearrangement requires all the excess oxygen-18 in 2-acetoxymethylpyridine to be incorporated in the ether group and the carbonyl oxygen to be natural. In the intermolecular mechanism which involves a nucleophilic attack by acetate ion, all the oxygen atoms of both the external acetoxy anion and that formed by the cleavage of the nitrogen–oxygen bond become equivalent by scrambling three O^{18}-enriched oxygens and one natural, eventually giving rise to an equal value of oxygen-18 for both the ether and the carbonyl oxygens of 2-acetoxymethylpyridine. The formation of 2-acetoxymethylpyridine by a

(8) V. Boekelheide and D. L. Harrington, *Chemistry & Industry*, 1423 (1955).

(9) V. J. Traynelis and R. F. Martello, *J. Am. Chem. Soc.*, **80**, 6590 (1958).

(10) S. Oae, T. Kitao and Y. Kitaoka, *ibid.*, **84**, 3362 (1962).

(11) D. B. Denney and M. A. Greenbaum, *ibid.*, **79**, 979 (1957).

TABLE I
OXYGEN-18 ANALYTICAL RESULTS

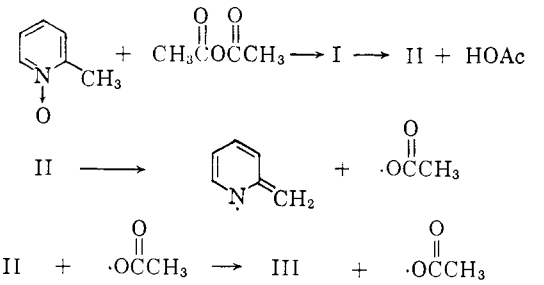
Compound	Atom % oxygen-18
$CH_3COOCOCH_3$	0.782
$2\text{-}C_5H_4NCH_2OCOCH_3$	.498
$2\text{-}C_5H_4NCH_2OH$	.477
$2\text{-}C_5H_4(NO)CH_3$	.210

free radical mechanism will give a product in which the two oxygens of the acetoxy radical are scrambled and both oxygen atoms contain an identical average value of one natural and one enriched oxygen-18.

The analytical values of oxygen-18 for both 2-acetoxymethylpyridine and 2-pyridinemethanol obtained by the usual analytical procedure[12] are shown in Table I.

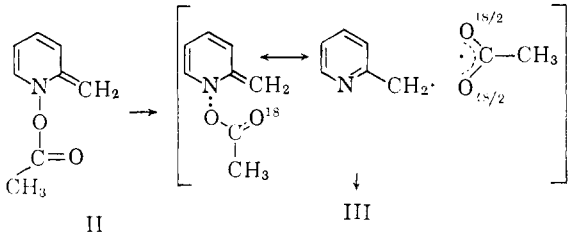
These results favor a free radical mechanism involving the complete scrambling of oxygen-18 in an acetoxy radical, and clearly exclude both ionic paths, *i.e.*, (a) the cyclic mechanism and (b) that involving a nucleophilic attack of acetate anion on the methylene carbon, because the cyclic mechanism requires oxygen-18 values to be 0.50 atom % for 2-acetoxymethylpyridine and 0.78% for 2-pyridinemethanol, while mechanism b demands them to be 0.64% for both compounds.

The free radical chain mechanism postulated by Boekelheide and Harrington,[3] however, is not entirely adequate. Their mechanism, which involves the attack of 2-pyridinemethyl radical on O-acetoxy-2-picoline, does not necessarily require both the ether and the carbonyl oxygens to acquire an equal concentration of oxygen-18. Other alternatives are (i) a free radical chain mechanism in which the attack of acetoxy radical on anhydrobase II is the radical chain propagating step as shown below and



(ii) a radical pair, one which involves a homolytic cleavage of nitrogen–oxygen bond, followed by immediate recombination of acetoxy and 2-picolyl radicals in the "solvent cage." We have considered earlier[1] that the reaction proceeded through the former path, since the reaction was unusually rapid after an initial induction period when no solvent was used. However, this mechanism calls for the acetoxy radical to exist in solution for a period of time sufficiently long for reaction with the anhydrobase II to occur, and this could not be the case, because the acetoxy radical is known[13–15] to be extremely unstable and short-lived. These data, with others[16] of similar importance, led us to believe that the anhydrobase II cannot be an efficient enough scavenger to trap acetoxy radicals as demanded by the radical chain mechanism.

On the other hand, if the reaction takes place in the "solvent cage," it will not be affected by such changes as the amount or kind of solvents and the addition of radical scavengers. Boekelheide and Harrington have already shown that there were very little changes in the yield of 2-acetoxymethylpyridine when they carried out the reaction in various solvents. We have carried out the reaction changing the amount of solvent, three-, ten-, thirty- and 100-fold, and find that the yield remains practically the same, 67–75% in all cases. The addition of a strong scavenger, DPPH, in the reaction mixture also gave no change, giving 2-acetoxymethylpyridine in 73% yield. All these observations strongly suggest that the main reaction proceeds through the "radical pair" process as shown below, which involves a homolytic cleavage of the nitrogen-oxygen bond of the anhydrobase II, scrambling oxygen-18 of acetoxy radical in the solvent cage, and rapid recombination of the acetoxy



II III

and 2-picolyl radicals. The formation of small amounts of carbon dioxide and methane are considered as derived from the acetoxy radical that escapes out of solvent cage while the polymerization of styrene could be initiated by escaped radicals such as methyl and picolyl. As further supporting evidence for this mechanism, we have learned that 2-acetoxymethylpyridine was obtained by the reaction of 2-picoline N-oxide with substituted phenyl acetate.[17] This work is quite significant because the presence of the anhydrobase II is unequivocally demonstrated and also the even more nucleophilic aryloxy anion was shown not to participate in the product formation.

Acknowledgment.—The authors are highly grateful to Professors E. I. Eliel and V. J. Traynelis for their helpful comments and suggestions, and to Professor S. Okazaki for the generous gift of O^{18}-enriched water. Appreciation is also expressed to Dr. S. Mima for his generous collaboration in mass-spectroscopic analyses.

Experimental

Sodium Acetate ($CH_3CO^{18}O^{18}Na$).—To a solution of 25 g. (1.4 moles) of O^{18}-enriched water (*ca.* 1.5 atom % O^{18}) and 160 ml. of absolute ethanol, 16 g. (0.70 mole) of metallic sodium was added piece by piece with stirring and cooling. To this solution 28.4 g. (0.70 mole) of acetonitrile was added and the reaction mixture was refluxed for 3 hours to complete

(12) D. Rittenburg and L. Ponticorvo, *J. Appl. Rad. Isotopes*, **1**, 208 (1956).

(13) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 491.

(14) C. Walling and R. Hodgson, *J. Am. Chem. Soc.*, **80**, 228 (1958).

(15) L. Herk, M. Feld and M. Szwarc, *ibid.*, **83**, 2998 (1961).

(16) See J. C. Martin and E. H. Drew, *ibid.*, **83**, 1232 (1961), and refs. cited therein.

(17) V. J. Traynelis, S. A. I. Gallagher, I. H. Mand and R. F. Martello, *J. Org. Chem.*, **26**, 4305 (1961); private communication.

the reaction and then was evaporated to dryness. The resulting white solid was heated further until it fused. The yield of this anhydrous labeled sodium acetate (*ca.* 1.3 atom % O^{18}) was 37.5 g. (66%).

Acetic Anhydride ($(CH_3CO^{18})_2O^{18}$).—Acetyl chloride (35.4 g. 0.45 mole) was added dropwise to 37.0 g. of labeled sodium acetate (*ca.* 1.3 atom % O^{18}) and the mixture was refluxed for 2 hours. Distillation gave 38.5 g. (84 %) of labeled acetic anhydride (0.78 atom % O^{18}), b.p. 128–139°, $n^{20}D$ 1.3851. Redistillation gave an analytical sample, b.p. 136–139°, $n^{20}D$ 1.3889.

Determination of Oxygen-18 Content of Carbonyl Oxygen in the Labeled Acetic Anhydride.—One gram (0.011 mole) of freshly distilled aniline was dissolved in 5 ml. of dry ether and to the solution was added 1.1 g. (0.011 mole) of the labeled acetic anhydride with cooling. Crude labeled acetanilide thus precipitated was collected and was recrystallized either from water or dry ether, giving colorless crystals, m.p. 114.5°. By the determination of oxygen-18 content of this acetanilide, the amount of oxygen-18 of carbonyl oxygens of the labeled acetic anhydride was determined. The value obtained was 0.78 atom % O^{18}. Boiling with water for recrystallization of acetanilide did not change the content of oxygen-18 in the acetanilide. Labeled acetamide was prepared by adding the acetic anhydride to liquid ammonia following the procedure used by Denney and Greenbaum.[11] After recrystallization from benzene, it had m.p. 80–81° and 0.78 atom % O^{18}. These results indicated equal concentration of oxygen-18 labeled for both the carbonyl and the ether oxygens of the acetic anhydride.

The Reaction of 2-Picoline N-Oxide and Labeled Acetic Anhydride.—The procedure employed for preparing 2-picoline N-oxide was similar to that reported by Ochiai for preparing pyridine N-oxides.[18] To 10.2 g. (0.10 mole) of labeled acetic anhydride (0.78 atom % O^{18}) was added 8.1 g. (0.075 mole) of 2-picoline N-oxide. The mixture was gently heated to around 140°, when the reaction occurred and the mixture became dark brown. Heating was continued for an additional 5 minutes. After removal of acetic acid, distillation gave 7.5 g. (67%) of labeled 2-acetoxymethylpyridine (0.50 atom % O^{18}), b.p. 95° (5 mm.), $n^{20}D$ 1.4991 (lit.[9] $n^{20}D$ 1.4990).

Using the same quantities of reactants as above, four experiments were carried out in the presence of various amounts of xylene as a solvent (24 g., 3-fold by weight of 2-picoline N-oxide; 80 g., 10-fold by weight; 240 g., 30-fold by weight; 800 g., 100-fold by weight). Following the same procedure described above, distillation gave 2-acetoxymethylpyridine: 7.5 g. (67%), 8.0 g. (72%), 7.7 g. (69%), 7.4 g. (67%), respectively. In the presence of a radical scavenger, DPPH, another experiment was carried out using the same quantities of reactants and condition as described above. The yield of 2-acetoxymethylpyridine was 8.1 g. (73%) when 0.54 g. (1.37×10^{-3} mole) of DPPH was added.

Hydrolysis of Labeled 2-Acetoxymethylpyridine.—A mixture of 5.5 g. (0.036 mole) of labeled 2-acetoxymethylpyridine (0.50 atom % O^{18}) and 2.0 g. (0.036 mole) of potassium hydroxide in 18 ml. of methanol was refluxed for 2 hours. The solvent was removed and the residue was extracted with chloroform. The chloroform solution was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The oily residue was carefully distilled. The yield of oxygen-18 labeled 2-pyridinemethanol (0.48 atom % O^{18}) was 2.2 g. (57%), b.p. 110–112° (15 mm.) (lit.[19] b.p. 112° (16 mm.)). Its picrate melted at 158° after four crystallizations from ethanol (lit.[19] m.p. 159°).

The Exchange Reaction between 2-Acetoxymethylpyridine and Oxygen-18 Labeled Acetic Anhydride–Acetic Acid Mixture.—To 3.0 g. (0.029 mole) of oxygen-18 labeled acetic anhydride (0.40 atom % O^{18}) was added a few drops of O^{18}-enriched water (0.50 atom % O^{18}) and the solution was refluxed for 20 minutes. To the resulting solution was added 3.0 g. (0,019 mole) of 2-acetoxymethylpyridine and the mixture was refluxed for 20 minutes and then distilled. The recovered 2-acetoxymethylpyridine revealed no incorporation of excess O^{18}: oxygen-18 analysis of 2-acetoxymethylpyridine, 0.210 atom %.

Exchange Reaction of Oxygen-18 of 2-Pyridinemethanol with Potassium Hydroxide in the Hydrolysis of 2-Acetoxymethylpyridine.—A mixture of 6.0 g. (0.038 mole) of 2-acetoxymethylpyridine and 2.2 g. (0.038 mole) of potassium hydroxide (1.5 atom % O^{18}) in 20 ml. of methanolic solution containing 1 ml. of O^{18}-enriched water (*ca.* 1.5 atom % O^{18}) was refluxed for 2 hours. The solution was distilled. The isolated 2-pyridinemethanol revealed no incorporation of excess O^{18}: oxygen-18 analysis of 2-pyridinemethanol, 0.210 atom %.

Isotopic Analysis.—Analysis of oxygen-18 content in the compounds was carried out by an adaptation of the method of Rittenburg and Ponticorvo.[12] The compound (*ca.* 50 mg.) is introduced together with a 1:1 mixture (100 mg.) of mercuric chloride and mercuric cyanide into an 8 mm. tube (27 cm. long) having a break off-seal at one end and a seal-off constriction at the other. The tube is sealed under vacuum and then heated at 500° for 3–5 hours. After cooling, the tube is opened in a vacuum line and the hydrogen chloride formed is removed by adding a few drops of quinoline. The gases formed are condensed by cooling with liquid nitrogen and the non-condensable gases formed are pumped off. After repeated fractionation, the carbon dioxide is subjected to mass-spectrometric analysis. The atom % O^{18} was calculated from the peaks of masses 44 and 46.

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

(19) C. D. Harries and G. H. Lenart, *Ann.*, **410**, 107 (1915).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, RADIATION CENTER OF OSAKA PREFECTURE, SAKAI, OSAKA, JAPAN]

The Mechanism of the Reaction of 4-Picoline N-Oxide with Acetic Anhydride[1]

BY SHIGERU OAE, TEIJIRO KITAO AND YOSHINORI KITAOKA

RECEIVED JANUARY 31, 1962

4-Picoline N-oxide was allowed to react with acetic anhydride, of which all three oxygens were equally enriched by oxygen-18. The main products, 4-acetoxymethylpyridine and 3-acetoxy-4-methylpyridine, were separated by vapor phase chromatography. These acetoxy compounds and their hydrolyzed products, *i.e.*, 4-pyridinemethanol and 3-hydroxy-4-methylpyridine, were subjected to oxygen-18 analysis. Both carbonyl and ether oxygens of these two acetoxy compounds had an equal concentration of oxygen-18 which resulted from complete scrambling of all the oxygen atoms of both the external acetoxy anion and that formed by the cleavage of the nitrogen–oxygen bond. When the reaction was carried out using an increased amount of oxygen-18 labeled acetic anhydride, the resulting ester mixture was found to have an increased concentration of oxygen-18. From these observations intermolecular rearrangement by nucleophilic attack of acetate anion on the anhydrobase II was suggested for the mechanism of this reaction. This different mode of reaction of 4-picoline N-oxide from that of the 2-isomer is briefly discussed.

In the previous paper,[1] we have considered the reaction of 2-picoline N-oxide and acetic anhydride. Tracer studies with oxygen-18, together with other evidence favored a radical cage reaction, and ruled out both intramolecular and intermolecular ionic mechanisms and also a free radical chain process.

In this communication, we should like to report our observations and views on the reaction of 4-picoline N-oxide and acetic anhydride.

(1) Paper IV on "Rearrangements of Tertiary Amine Oxides"; paper III, S. Oae, T. Kitao and Y. Kitaoka, *J. Am. Chem. Soc.*, **84**, 3359 (1962).