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

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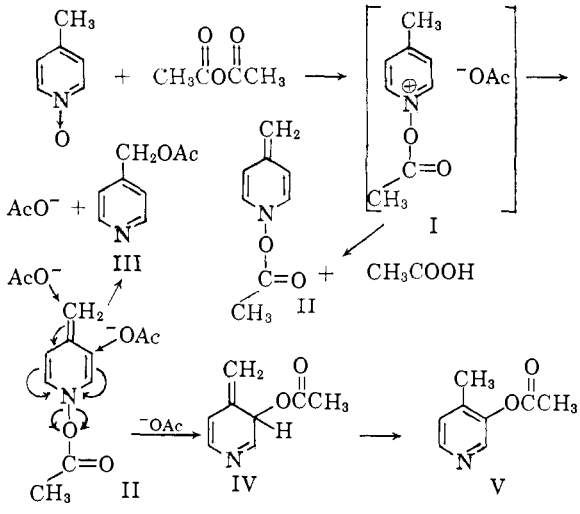
4-Picoline N-oxide was allowed to react with acetic anhydride, of which all three oxygens were equally enriched by oxygen-18. The main products, 4-acetoxymethylpyridine and 3-acetoxy-4-methylpyridine, were separated by vapor phase chromatography. These acetoxy compounds and their hydrolyzed products, *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).

Earlier, Berson and Cohen[2] obtained 4-acetoxymethylpyridine together with a small amount of 3 - hydroxy - 4 - methylpyridine by this reaction. They also showed that interconversion of 4-acetoxymethylpyridine to 3-hydroxy-4-methylpyridine did not occur under the conditions which gave rise to both products from 4-picoline N-oxide and then suggested three possible mechanisms involving the anhydrobase II. One path involves nucleophilic attack by acetate anion at the methylene group or at the C-3 position of the anhydrobase II accompanied by extrusion of acetate bound to nitrogen to give either 4-acetoxymethylpyridine or



IV, which eventually rearranges to 3-acetoxy-4-methylpyridine by an allylic shift of the C-3 hydrogen. The second possibility is an intramolecular rearrangement of the acetoxy group from nitrogen to C-3 by an SNi′-type migration giving IV, which can undergo an allylic shift to give V or can undergo second migration of an acetoxy group by a Claisen type rearrangement to give III. The other alternative is a free radical mechanism of the type suggested previously for the reaction with 2-picoline N-oxide.[3]

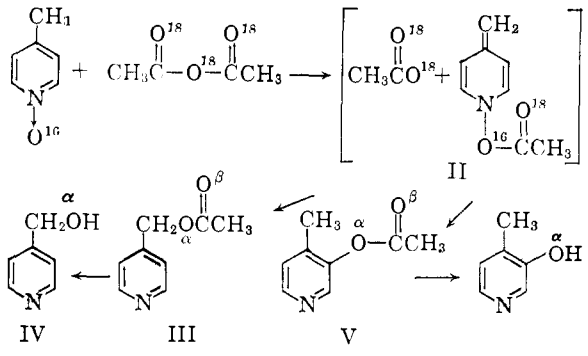
Recently, Traynelis and Martello[4] have studied the same reaction in detail and made several interesting observations. They have found not only 4-acetoxymethylpyridine and 3-acetoxy-4-methylpyridine among the reaction products, but also small amounts of carbon dioxide, methane, 4-picoline and a few others that can be rationalized only by the formation of acetoxy radicals during the reaction. They have also shown that the addition of a radical acceptor such as *m*-dinitrobenzene caused a substantial decrease in the production of carbon dioxide, methane and the ester mixture without changing the composition of the ester mixture. Their other important observation was that the only ester isolated was a mixture of 4-butyroxymethylpyridine and 3-butoxy-4-methylpyridine when the reaction of 4-picoline N-oxide with butyric anhydride was carried out in the presence of an equimolar amount of sodium acetate. With these observations, they rejected a free radical chain mechanism and one involving nucleophilic attack of acid anion on the anhydrobase II for this rearrangement, and favored a rearrangement proceeding by way of a radical pair which results from a homolytic cleavage of the nitrogen–oxygen bond of the anhydrobase II. These authors admit that the intramolecular cyclic rearrangement and rearrangement *via* an ion pair formed by a heterolytic cleavage of the nitrogen–oxygen bond of II cannot be ruled out.

Our approach to this problem was comparable to that of our previous work[1] involving 2-picoline N-oxide. One difficulty was the quantitative separation of 4-acetoxymethylpyridine and 3-acetoxy-4-methylpyridine. This was achieved as described in detail in the Experimental section by vapor phase chromatography, using a column packed with fire-brick which was impregnated with coal-tar pitch. There was no isomerization or degradation of these esters under the conditions used for the separation. By this separation, the ester mixture, collected by a fractional distillation, was found to contain about 30% of 3-acetoxy-4-methylpyridine and about 70% of 4-acetoxymethylpyridine, and this ratio fluctuated little even under different reaction conditions. The ester mixture had previously been presumed to contain nearly 90% 4-acetoxymethylpyridine on the basis of infrared spectroscopic analysis.[4]

Oxygen-18 labeled acetic anhydride,[1] of which all three oxygens were equally enriched by O^{18}, was allowed to react with an equimolar amount of 4-picoline N-oxide to yield the ester mixture in about 65% yield. 4-Acetoxymethylpyridine and 3-acetoxy-4-methylpyridine, separated from a portion of the ester mixture by gas phase chromatography, were collected, while the rest of the ester mixture was first hydrolyzed by refluxing with methanolic potassium hydroxide, and then the 4-pyridinemethanol and 3-hydroxy-4-methylpyridine formed were fractionally separated by distillation of the hydrolyzed mixture. In separate control experiments, we found that there is no exchange or scrambling of O^{18} in each step of the reaction process.

The outcome of the distributions of oxygen-18 from three distinctly different mechanisms is illustrated below. The intermolecular rearrangement by nucleophilic attack of acetate anion requires all the oxygen atoms of both external acetoxy anion and that formed by the cleavage of the nitrogen–oxygen bond to become equilibrated, eventually giving rise to an equal concentration of oxygen-18 for both the ether and the carbonyl oxygens of both esters. In the intramolecular cyclic mechanism, the excess oxygen-18 should be incorporated into the ether group and the carbonyl oxygen should have the natural abundance of O^{18} for 3-acetoxy-4-methylpyridine while the distribution of O^{18} should be reversed for 4-acetoxymethylpyridine. The formation of 4-acetoxymethylpyridine and 3-acetoxy-4-methylpyridine *via* a "free radical pair" will provide products in which both oxygens of the acetoxy radical are scrambled and the two oxygen atoms contain an average concentration of a natural and an excess oxygen-18.

(2) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **77**, 1281 (1955).
(3) V. Boekelheide and W. J. Linn, *ibid.*, **76**, 1286 (1954).
(4) V. J. Traynelis and R. F. Martello, *ibid.*, **82**, 2744 (1960).



For 4-Acetoxymethylpyridine

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

For 3-acetoxy-4-methylpyridine

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

The analytical values of oxygen-18 for 4-acetoxymethylpyridine, 4-pyridinemethanol, 3-acetoxy-4-methylpyridine and 3-hydroxy-4-methylpyridine obtained by the usual method[1,5] are given in Table I.

TABLE I

OXYGEN-18 ANALYTICAL RESULTS

Compound	Atom % oxygen-18
$CH_3COOCOCH_3$	0.91
$4\text{-}C_5H_4NCH_2OCOCH_3$	.72
$4\text{-}C_5H_4NCH_2OH$	.71
$4\text{-}CH_3C_5H_3N\text{-}3\text{-}OCOCH_3$	.71
$4\text{-}CH_3C_5H_3N\text{-}3\text{-}OH$	.70
$4\text{-}CH_3C_5H_4NO$	.21

Inspection of the data excludes clearly both the intramolecular cyclic rearrangement and the radical pair process for this reaction, because the cyclic mechanism requires oxygen-18 values to be 0.56 atom % for both 4-acetoxymethylpyridine and 3-acetoxy-4-methylpyridine and 0.21 atom % for 4-pyridinemethanol and 0.91 atom % for 3-hydroxy-4-methylpyridine, while the radical pair mechanism demands that both esters and the hydrolyzed hydroxy compounds acquire 0.56 atom % of oxygen-18. Therefore, the only surviving mechanism is the intermolecular rearrangement by nucleophilic attack of acetate anion on the anhydrobase II, because this mechanism requires the oxygen-18 concentration to be 0.73 atom % for all these four compounds. If this is the case, one can expect an increase of oxygen-18 concentration in the resulting ester when 4-picoline N-oxide is allowed to react with an increasing amount of oxygen-18 labeled acetic anhydride. In one experiment, we have carried out the reaction using a 5-fold amount of the acetic anhydride. The observed data, Table II, satisfactorily agree with the value (0.87 atom % O^{18}) that can be expected from the intermolecular rearrangement.

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

TABLE II

OXYGEN-18 ANALYTICAL RESULTS

Compound	Atom % oxygen-18
Acetic anhydride (5-fold mole used)	0.91
Mixt. of 3-acetoxy-4- and 4-acetoxymethylpyridine	0.83

All these observations support the supposition that the main reaction is the intermolecular rearrangement, whereby nucleophilic attack of acetate anion takes place at the methylene group or at the C-3 position of the anhydrobase II with elimination of the acetate group bound to nitrogen to give either 4-acetoxymethylpyridine or IV, which rearranges to 3-acetoxy-4-methylpyridine by an allylic shift of the C-3 hydrogen. The formation of small amounts of carbon dioxide, methane, alkylpyridines and a few other substances together with the polymerization of styrene in the reaction mixture suggests that a small portion of the reaction undergoes free radical decomposition.

On the other hand, these results could also be explained in accordance with a radical mechanism, if one assumes that there is a complete exchange between the acetoxy radical and the acetic acid or acetic anhydride present in the reaction mixture.[6] In fact, the life of acetoxy radical in acetic acid has been suggested to be abnormally long. This could mean that acetoxy radicals are constantly regenerated by the reaction.[7] However, such an exchange reaction appears to be negligible in view

$$CH_3COO\cdot + HOCOCH_3 \rightleftharpoons CH_3COOH + \cdot OCOCH_3$$

of the C^{14}-tracer work of Fry, Tolbert and Calvin,[8] who demonstrated that the radioactivity of C^{14}-labeled acetic acid, used as a solvent for the decomposition of acetic peroxide, remained the same after the decomposition. Our preliminary study on the decomposition of acetyl peroxide in oxygen-18 labeled acetic acid also indicates little or no exchange between acetoxy radical and acetic acid.[9]

Earlier, Traynelis and Martello[4] have indicated that the only esters isolated were mixtures of butyrated esters when the reaction of 4-picoline N-oxide with butyric anhydride was performed in the presence of sodium acetate and butyric acid, this observation was cited as evidence against the intermolecular rearrangement involving nucleophilic attack of acid anions. A possible explanation might be that sodium acetate dissociates so little or is solvated so tightly in the solvent medium that it cannot compete with newly formed butyrate anion formed during the reaction in the product formation. An alternative explanation is that the reaction of 4-picoline N-oxide with butyric anhydride proceeds through a different path, presumably by a "radical cage process," from that of acetic anhydride.[10]

(6) The authors are indebted to the referee for this point of view.

(7) W. A. Waters, "The Chemistry of Free Radicals," Oxford University Press, London, 1949, pp. 19, 139 and 143.

(8) A. Fry, B. N. Tolbert and M. Calvin, *Trans. Faraday Soc.*, **49**, 1444 (1953).

(9) S. Oae, T. Kitao and S. Kawamura, unpublished work.

(10) The reactions of picoline N-oxides with other oxygen-18 labeled acyl anhydrides are now under study in our laboratory.

An interesting outcome of this and previous work[1] is that the reaction of 2-picoline N-oxide with acetic anhydride proceeds *via* solvent caged "free radical pair" intermediate while that of 4-picoline N-oxide proceeds through the intermolecular rearrangement involving nucleophilic attack of acetate anion. The difference may find its origin in the difference of bond strengths of the nitrogen–oxygen linkages of the anhydrobases derived from 2- and 4-picoline N-oxides, respectively. The infrared spectra of 2- and 4-picoline N-oxides were taken, and the stretching frequencies of N → O bond[11] for these two compounds were found to be 1200 and 1233 $cm.^{-1}$, respectively. From these values, the force constants were calculated[12] to be 6.35×10^5 and 6.67×10^5 dyn./cm., respectively, for 2- and 4-picoline N-oxides. Although the difference appears to be quite small, it might be more pronounced in the respective anhydrobases, because the anhydrobase from 2-picoline N-oxide is more sterically strained than that from 4-isomer, becoming more prone to radical dissociation. It is interesting to note that N,N-dimethylaniline oxide, which has its N → O stretching frequency of 960 $cm.^{-1}$ corresponding to a force constant of 4.05×10^5 dyn./cm., was found to react violently with acetic anhydride even at −30°[13] and the reaction was found to proceed through a "radical pair" path.[14]

Acknowledgment.—The authors are grateful to Professor S. Okazaki of Nara Women's College for the generous gift of O^{18}-enriched water. Appreciation is also expressed to Dr. S. Mima of Govt. Ind. Research Inst., Osaka, for his collaborations in mass-spectroscopic analyses.

Experimental

Oxygen-18 Labeled Acetic Anhydride.—The method of preparation was similar to that reported in the previous paper.[1] From 50.0 g. of O^{18}-enriched water (1.5 atom % O^{18}) there was obtained after redistillation 95.2 g. of oxygen-18 labeled acetic anhydride (0.91 atom % O^{18}), b.p. 137–139°.

Determination of Oxygen-18 Content of Carbonyl Oxygen in the Acetic Anhydride.—The method of determination was described in the previous paper.[1] The results obtained by analyzing oxygen-18 were identical for both acetanilide and acetamide, 0.91 atom % O^{18}, and indicated the equal concentration of oxygen-18 labeled at both carbonyl and ether oxygens of the acetic anhydride.

The Reaction of 4-Picoline N-Oxide with the Oxygen-18 Labeled Acetic Anhydride.—The preparation of 4-picoline N-oxide was carried out by the oxidation of 4-picoline with 30% hydrogen peroxide in glacial acetic acid. 4-Picoline N-oxide was obtained in 60% yield as white crystals, m.p. 182°. A mixture of 4-picoline N-oxide (21.8 g., 0.200 mole) and the oxygen-18 labeled acetic anhydride (21.0 g., 0.206 mole, 0.91 atom % O^{18}) was carefully heated with a free flame. In a few minutes, the reaction started suddenly with evolution of heat and turned dark brown. After the initial vigorous reaction ceased, heating was continued for an additional 5 minutes. The volatile substances were removed; distillation of the residue gave 19.0 g. (63%) of a mixture of oxygen-18 labeled 4-acetoxymethylpyridine and 3-acetoxy-4-methylpyridine (0.71 atom % O^{18}) b.p. 85–86° (3 mm.).

Using the same procedure and reaction conditions but changing the oxygen-18 labeled acetic anhydride (0.91 atom % O^{18})–4-picoline N-oxide to a mole ratio of 5:1, produced an ester mixture, b.p. 97–100° (5 mm.), in 65% yield. The ester mixture was redistilled and subjected to oxygen-18 analysis. The mixture contained 0.83 atom % O^{18}.

Separation of the Ester Mixture by Vapor Phase Chromatography.—The ester mixture was separated effectively by vapor phase chromatography using a Yanagimoto model GCG-2 gas chromatograph. Prior to the separation, coal tar pitch (obtained from Osaka Gas Works) was extracted with benzene in a Soxhlet extraction apparatus, and the benzene extract was distilled at 250° under reduced pressure (2 mm.) until no volatile distillate came over; the residue, a dark brown cake, was used for the stationary phase material. This residue, 5 g., was used to impregnate 50 g. of 42–60 mesh fire-brick using benzene as solvent. Conditioning of the column (5 mm. diameter, 200 mm. length) was done at 200° with a nitrogen flow of 50 ml./min. for 24 hours and the actual run was done at 160° with a hydrogen flow of 40 ml./min. Both esters were separated without overlapping, when 0.04 ml. of the ester mixture was injected into the column. The retention time of 3-acetoxy-4-methylpyridine was 38 min. while that of 4-acetoxymethylpyridine was 60 min. Both compounds were collected by several repeated runs, and were identified by the comparison of their refractive indexes with those in the literature.[4] The composition of the ester mixture was determined from the individual peak areas. The mixture was found to contain 33% 3-acetoxy-4-methylpyridine (0.71 atom % O^{18}) and 67% 4-acetoxymethylpyridine (0.71 atom % O^{18}).

Hydrolysis of the Mixture of Oxygen-18 Labeled 4-Acetoxymethylpyridine and 3-Acetoxy-4-methylpyridine.—The ester mixture (17.0 g., 0.113 mole) was dissolved in 40 ml. of 20% potassium hydroxide solution and heated at 120° for 15 hours. After the reaction mixture was cooled to room temperature, the alkaline solution was extracted with ether continuously using a liquid–liquid Soxhlet apparatus for 48 hours. After the removal of ether from the extract, distillation gave 7.5 g. (61%) of oxygen-18 labeled 4-pyridinemethanol, b.p. 142° (12 mm.), 0.71 atom % O^{18}, which solidified on standing, m.p. 50–51° (lit. m.p. 47–50°,[15] 44–47° [4]). The residue remaining in the distillation flask also solidified into light yellow crystals, and was recrystallized twice from a mixture of benzene and ether to give 0.5 g. (4.1 %) of oxygen-18 labeled 3-hydroxy-4-methylpyridine, 0.70 atom % O^{18}, m.p. 119–121° (lit.[15] m.p. 120°).

The Exchange Reaction between Oxygen-18 Labeled Ester Mixture and Acetic Acid–Acetic Anhydride.—The mixture of oxygen-18 labeled 3-acetoxy-4-methylpyridine and 4-acetoxymethylpyridine, 0.71 atom % O^{18}, 5 g., was dissolved in 100 ml. of acetic acid and acetic anhydride (1:1) solution, and then refluxed for 10 hours. The recovered ester mixture revealed no incorporation of natural oxygen: oxygen-18 analysis of the ester mixture, 0.68 atom %.

Infrared Spectra.—A Perkin–Elmer model 221 spectrophotometer equipped with sodium chloride optics was used to obtain the spectra in the Nujol mull method.

Isotopic Analysis.— The experimental procedure and calculation were similar to those in the previous paper.[1]

(11) L. J. Bellamy, "The Infrared Spectra Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 298, 308.

(12) L. N. Ferguson, "Electron Structures of Organic Molecules," Prentice-Hall, Inc., New York, N. Y., 1952, pp. 269.

(13) R. Huisgen, E. Bayerlein and W. Heydkamp, *Chem. Ber.*, **92**, 3223 (1959).

(14) S. Oae, T. Kitao and Y. Kitaoka, *J. Am. Chem. Soc.*, **84**, 3366 (1962).

(15) P. Rabe, O. Sprecheli and L. Wilhelm, *J. prakt. Chem.*, **151**, 65 (1938).