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REARRANGEMENT OF TERTIARY AMINE OXIDES—X[1]

THE MECHANISM OF THE REACTION OF 4-PICOLINE N-OXIDE WITH n-BUTYRIC ANHYDRIDE

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Abstract—The reaction of 4-picoline N-oxide with n-butyric anhydride has been investigated using ^{18}O as tracer. The main products, a mixture of 3-butyroxy-4-methylpyridine and 4-butyroxymethylpyridine, obtained by the reaction of 4-picoline N-oxides and n-butyric anhydride uniformly labeled by ^{18}O have been subjected to ^{18}O-analysis. When no solvent is used, the ^{18}O concentration of the ester mixture is nearly identical with that expected when the reaction proceeds *via* an intermolecular process. Whereas, when xylene is used as solvent, the concentration of ^{18}O of the ester mixture becomes quite small and approaches the value expected from the radical cage mechanism. However, n-butyroxy radicals undergo a radical transfer reaction with n-butyric acid, while the ^{18}O concentration of the ester mixture decreases substantially when DPPH is added to the reaction mixture of 4-picoline N-oxide and n-butyric anhydride. These observations and others, support the mechanism of the reaction of 4-picoline N-oxide and n-butyric anhydride as a combination of an intermolecular heterolytic process, an intermolecular homolytic reaction and a radical cage path, and the ratio of these processes changes with a change of solvent.

SOME years ago, Berson and Cohen[2] revealed that the reaction of 4-picoline N-oxide and acetic anhydride gives rise to 4-acetoxy-methylpyridine and a small amount of 3-hydroxy-4-methylpyridine, and suggested the following three possible mechanisms involving the anhydrobase(II). One path involves nucleophilic attack of the acetate ion at the methylene group or at C-3 position of the anhydrobase(II), accompanied by the extrusion of acetate ion from the ring nitrogen, forming either 4-acetoxymethylpyridine or IV, which eventually rearranges to 3-acetoxy-4-methyl pyridine by an allylic shift of the C-3 hydrogen. The second path is an intramolecular rearrangement of the acetoxy group from the ring nitrogen to C-3 by S_{Ni} type migration to give IV, which can either give V by an allylic shift of C-3 hydrogen or undergo further migration of an acetoxy group by a Claisen type rearrangement to give III. The third one is a free radical chain mechanism, suggested previously for the reaction with 2-picoline N-oxide.[3]

Later, Traynelis and Martello in connection with this same reaction made some very important observations.[4] Among the products were not only the acetylated

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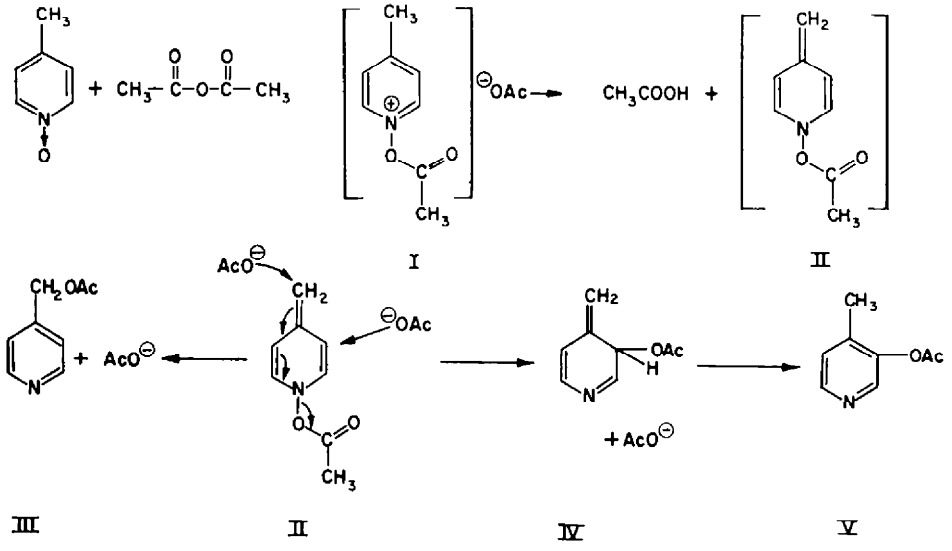
[1] Part IX; S. Oae and S. Kozuka, *Tetrahedron.*

[2] J. A. Berson and T. Cohen, *J. Amer. Chem. Soc.* **77**, 1281 (1955).

[3] V. Boekelheide and D. L. Harrington, *Chem. & Ind.* 1423 (1953).

[4] V. J. Traynelis and R. F. Martello, *J. Amer. Chem. Soc.* **82**, 2744 (1960).

esters, but also small amounts of methane, carbon dioxide and 4-picoline which can only be rationalized on the basis of a free radical cleavage of the N-O bond of the salt(I) or the anhydrobase(II). It was shown that the addition of a radical scavenger such as *m*-dinitrobenzene caused a substantial decrease in the production of carbon dioxide, methane and the esters but did not change the composition of the ester mixture. The other important observation was that only 4-n-butyroxymethylpridine and 3-n-butyroxy-4-methylpyridine and no acetoxy esters are among the ester mixture isolated when 4-picoline N-oxide reacts with n-butyric anhydride in the



presence of an equimolar amount of sodium acetate. Based on these observations, they favoured a radical or ion pair process for the reaction of 4-picoline N-oxide with acetic anhydride.

In the previous papers[5–7] dealing with the reactions of a few t-amine N-oxides with acetic anhydride, it was suggested that the reaction of 4-picoline N-oxide to form 4-acetoxymethylpyridine or 3-acetoxy-4-methylpyridine proceeds through an intramolecular rearrangement involving nucleophilic attack of acetate anion. The evidence supporting this argument is that the ^{18}O concentrations of both carbonyl and ether oxygens of both 4-acetoxymethylpyridine and 3-acetoxy-4-methylpyridine are nearly identical to that which is expected when all the oxygens in the system, i.e., those of 4-picoline N-oxide, acetic anhydride and acetic acid, are completely scrambled, and such a complete scrambling of oxygen atoms in the system can occur only in the case where the rearrangement takes place in the intermolecular fashion by nucleophilic attack of acetate anion on the anhydrobase(II). However, this mechanism apparently contradicts the earlier observation of Traynelis and Martello, i.e., the absence of acetylated esters among the reaction products in the reaction of 4-picoline N-oxide with n-butyric anhydride containing sodium acetate. One explanation suggested for

[5] S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3359 (1962).
[6] S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3362 (1962).
[7] S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3366 (1962).

the lack of acetylated esters is that sodium acetate may not dissociate substantially in the mixture of n-butyric anhydride and n-butyric acid and cannot compete with n-butyrate anions or radicals constantly being regenerated in the reaction system. Another possibility is that the reaction of 4-picoline N-oxide with n-butyric anhydride is different from that with acetic anhydride and possibly proceeds *via* a radical cage or ion pair process, since the n-butyroxy radical may not be as shortlived as the acetoxy radical while the N-O bond of n-butyroxy-anhydrobase may cleave more readily than the acetoxy counterpart.

TABLE 1. ^{18}O ANALYTICAL RESULTS

Experiment no.	Compound	Mole ratio of reacting species (4-Picoline N-oxide:n-butyric anhydride:n-butyric acid)	Atom % ^{18}O Calc. for Intra.	Inter.	Found	Solvent
I	$C_3H_7COOCOC_3H_7$	1:1:0			1·03	
	Esters		0·61	0·82	0·65	Xylene
II	$C_3H_7COOCOC_3H_7$	1:1:1·7			0·54	Xylene and n-butyric acid (0·54 atom % ^{18}O)
	Esters		0·37	0·50	0·42	
III	$C_3H_7COOCOC_3H_7$	1:1:1·7			0·54	n-Butyric acid (0·54 atom % ^{18}O)
	Esters		0·37	0·50	0·49	

With these considerations, we have investigated the nature of the reaction of 4-picoline N-oxide with n-butyric anhydride using ^{18}O technique.

In order to prepare ^{18}O labelled n-butyric anyhydride, n-butyryl chloride was hydrolysed with sodium hydroxide in ^{18}O enriched water.

$$C_3H_7COCl + H_2O^{18} \xrightarrow[\text{in } CH_3OH]{Na} C_3H_7CO^{18}O^{18}Na$$

$$C_3H_7CO^{18}O^{18}Na \xrightarrow{PCl_5} C_3H_7CO^{18}Cl$$

$$C_3H_7CO^{18}Cl + C_3H_7CO^{18}O^{18}Na \longrightarrow C_3H_7CO^{18}O^{18}CO^{18}C_3H_7$$

The resulting ^{18}O labelled n-butyric anhydride, of which three oxygens were all equally enriched, was allowed to react with an equimolar amount of 4-picoline N-oxide under three different conditions; (a) in xylene. (b) in xylene containing 1·7 mole equivalent of n-butyric acid. (c) in 1·7 mole equivalent of n-butyric acid.

The mixture of 4-n-butyroxymethylpyridine and 3-n-butyroxy-4-methylpyridine, collected and redistilled, was subjected to the usual ^{18}O analysis without any fractionation into the two components since the two esters are presumably formed from the common intermediate, the anhydrobase(II), as in the reaction with acetic anhydride. The results of the ^{18}O analyses of the n-butyric anhydride and the mixture of the two esters are shown in Table 1.

If the rearrangement proceeds through an intramolecular process, the value of

^{18}O in the esters will be 0·61 for experiment No. 1 and 0·37 for II and III. Meanwhile, if the rearrangement proceeds through an intermolecular pathway involving all the n-butyroxy groups in the reacting system, the values of ^{18}O in the esters will be 0·82 for I and 0·50 for II and III.

When the reaction was carried out in xylene as the solvent (Expt. No. I), the analytical value, 0·65 atom % ^{18}O, was found to be a little larger than that calculated, i.e. 0·61, for the intramolecular radical pair process. It is apparent that the excess incorporation of ^{18}O (0·04 atom % of ^{18}O) over that of the calculated for the intramolecular process is due to the contribution of the intermolecular path involving the participation of foreign n-butyroxy groups. However, the rearrangement in xylene, undoubtedly proceeds mainly (about 80%) via the intramolecular radical pair process

TABLE 2. ^{18}O ANALYTICAL RESULTS OF EVOLVED CO_2 IN THE DECOMPOSITION OF N-BUTYRYL PEROXIDE

Compound	Atom % ^{18}O
$C_3H_7COOOCOC_3H_7$	0·20
$C_3H_3CO^{18}O^{18}H$	0·54
Evolved CO_2	0·25
Natural CO_2	0·20

as in the case of 2-picoline N-oxide and acetic anhydride and only a small portion (ca. 20%) of the rearrangement proceeds through the intermolecular path. Here, most of the anhyhrobases formed are surrounded by xylene molecules and would have less chance of being attacked by external n-butyrate groups and consequently the main portion of the reaction proceeds *via* a free radical cage process.

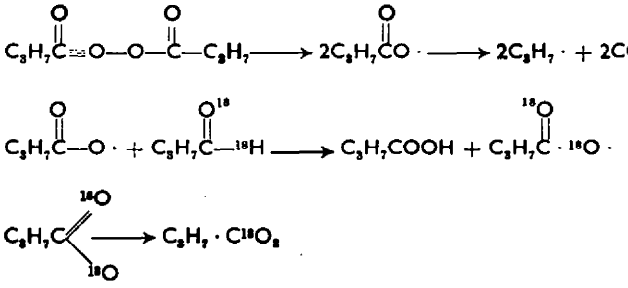
In the second experiment, (II), in which n-butyric acid was added, an increasing amount of ^{18}O incorporation in the product was observed, suggesting that the contribution of nucleophilic attack of the external n-butyroxy group on the anhydrobase is exceedingly important here for the formation of the esters.

When the reaction was carried out in the presence of n-butyric acid without using another non-polar solvent, the incorporation of ^{18}O in the resulting ester was found to be slightly lower than that expected from the intermolecular mechanism involving the n-butyroxy groups in the reacting system. This is to be expected in view of the previous observations on the reaction of 4-picoline N-oxide with acetic anhydride, where the incorporation of ^{18}O in the acetyl esters was found to be what one would expect from the intermolecular mechanism involving all the acetoxy groups in the system.

Contrary to the early assumption, it now appears that the main reaction of 4-picoline N-oxide with n-butyric anhydride in n-butyric acid is an intermolecular rearrangement involving nucleophilic attack of the anhydrobase with the n-butyroxy group and is similar to that with acetic anhydride. If the cleavage of the N—O bond of the anhydrobase takes place homolytically giving longer living n-butyroxy radicals which can cause the scrambling of n-butyroxy groups in the system by free radical transfer, then this may be ascertained by determining the ^{18}O incorporation in CO_2 formed in the decomposition of n-butyryl peroxide in ^{18}O-labelled n-butyric acid, similar to the experiment using the acetylated compounds. When the decomposition of n-butyryl peroxide is performed in ^{18}O-labelled n-butyric acid, the resulting CO_2 contains a small but noticeable excess of ^{18}O as shown in Table 2, suggesting

that there is a definite, though not substantial, radical transfer between n-butyroxy radicals and n-butyric acid while in the case of acetoxy radicals which are known to be short-lived there is no radical transfer between acetoxy radicals and acetic acid.

If this radical transfer is adopted for the rearrangement of n-butyroxy anhydrobase in n-butyric acid, one can postulate a mechanism involving a homolytic cleavage of the N—O bond of the anhydrobase to give 4-picolyl and n-butyroxy radicals which recombine either within the solvent cage or via recombination accompanying radical



transfer or by both processes. However, in view of a small amount of ^{18}O incorporation in the resulting CO_2 formed in the decomposition of n-butyryl peroxide in ^{18}O-labelled n-butyric acid, the contribution of the free radical transfer process is expected to be rather small in the reaction and would not be sufficient to cause the large concentration of ^{18}O in the ester as was found in the reaction with the mixture of n-butyric anhydride and n-butyric acid (Expt. III). Presumably the free radical transfer takes place outside the solvent cage and is therefore suppressed by the addition of a small amount of radical scavenger such as DPPH. When a small amount of DPPH (1 g) is added to the reaction mixture of 4-picoline N-oxide (7 g, 0·064 mole), ^{18}O-labelled n-butyric anhydride (10 g, 0·064 mole, 0·77 atom % ^{18}O) and n-butyric acid (8·0 g, 0·091 mole, 0·77 atom % O^{18}), the yield of the ester (2·4 g, 21%) decreases while tarry products increase substantially (3·5 g) and the ester is incorporated with 0·56 atom % of ^{18}O, which is a decidedly lower ^{18}O concentration from that of n-butyric anhydride as compared with that where no DPPH is used (Expt. III) but is still a lot larger than that expected from the radical pair process (0·49 atom % of ^{18}O). This means that there is a substantial contribution (25–50%) of the nucleophilic attack on the anhydrobase by the n-butyroxy groups while the major portion of the reaction proceeds via a radical cage process in the reaction with a scavenger.

These observations, support the mechanism that the reaction of 4-picoline N-oxide with n-butyric anhydride is a combination of the three different processes (1) a homolytic cleavage of the N—O bond of the anhydrobase(II) followed by free radical recombination of the n-butyroxy and 4-picolyl radicals within the solvent cage, (2) a homolytic cleavage of the N—O bond followed by the recombination of 4-picolyl and n-butyroxy radicals after a certain amount of radical transfer with solvent n-butyric acid, (3) the heterolytic cleavage of the N—O bond by the nucleophilic attack of n-butyroxy groups on the anhydrobase(II). Apparently, the contribution of these three processes varies according to the composition of the solvent used. In xylene solution, the reaction proceeds mainly via a radical cage process, while

in n-butyric acid or in the absence of solvent, the intermolecular processes involving both heterolytic and homolytic cleavage of the N—O bond followed by radical transfer become the main route.

Since it is now found that the reaction of 4-picoline N-oxide with n-butyric anhydride in n-butyric acid is similar to that in acetic acid, the only remaining problem is whether or not the lack of acetylated esters among the products in the reaction with n-butyric anhydride containing sodium acetate is caused by the scant dissociation of sodium acetate in the particular solvent.

A more detailed study of this matter and also the solvent effect in the reaction of the tertiary amine oxide is in progress and will be reported in a future series.

EXPERIMENTAL

^{18}O Labelled n-butyric anhydride. To 130 g (7·24 moles) boiling ^{18}O-labelled water (1·5 ^{18}O atom %) 295 g (2·75 moles) n-butyryl chloride was added in portions. After addition, the mixture was refluxed for 4 hr until the evolution of HCl gas was no longer observed. The mixture was then allowed to stand overnight at room temp in order to complete the exchange of oxygen between water and the resulting n-butyric acid. To this solution, a solution of 63·5 g (2·76 moles) Na in 900 ml methanol was added dropwise under cooling and stirring. To complete the reaction, the mixture was further heated for 2 hr and precipitation of white solids indicated at the end point of the reaction. After removal of methanol and water under red press., the resulting sodium n-butyrate was fused and dried ($CaCl_2$) in a desiccator, yield 327 g (75%).

This sodium n-butyrate was fused once more before use, and powdered carefully without exposing to moisture. With occasional shaking, all the n-butyrate was mixed with 100 g (0·48 mole) PCl_5 under ice-cooling. After an exothermic reaction, the mixture was heated 3 hr under a reflux-condenser. Distillation gave 123 g (54 %) n-butyryl chloride.

To 128 g (1·26 moles) ^{18}O labelled sodium n-butrate, 123 g (1·22 moles) ^{18}O labelled n-butyryl chloride was added under cooling. After refluxing 3 hr, distillation gave 144 g (76%) of O^{18} labelled n-butyric anhydride.

The reaction of 4-picoline N-oxide with ^{18}O labelled n-butyric anhydride

4-Picoline N-oxide was prepared by the procedure reported by E. Ochiai.[8]

Experiment I. To a solution of 20 g (0·19 mole) 4-picoline N-oxide in 100 ml xylene 30 g (0·19 mole of n-butyric anhydride (1·03 atom % ^{18}O) was added. After a violent exothermic reaction, (initiated by a free flame), the mixture was mildly heated and then refluxed for an additional 3 hr. After removal of solvent, distillation gave 7·1 g (24%) of a mixture of 4-n-butyroxymethylpyridine and 3-n-butyroxy-4-methylpyridine, $n_D^{30°}$ 1·4920.

Experiment II. A mixture of 5·5 g (0·05 mole) 4-picoline N-oxide and 9·0 g (0·051 mole) n-butyric acid (0·54 atom % ^{18}O), and 7·5 g (0·086 mole) n-butyric acid (0·54 atom % ^{18}O) was poured into 25 ml xylene. The mixture was treated in the same manner described above, yield 2·9 g (26%) of a mixture of 4-n-butyroxymethylpyridine and 3-n-butyroxy-4-methylpyridine.

Experiment III. To a solution of 10·9 (0·10 mole) 4-picoline N-oxide in 15 g (0·17 mole) n-butyric anhydride (0·54 atom % ^{18}O), 18 g (0·11 mole) n-butyric anhydride (0·54 atom % ^{18}O) was added. After the mixture has been treated by the same procedure described above, distillation gave 5·0 g (28%) of the mixture of 4-n-butyroxymethylpyridine and 3-n-butyroxy-4-methylpyridine (0·49 atom % ^{18}O).

The reaction of 4-picoline N-oxide with n-butyric anhydride in the presence of DPPH

DPPH (1·0 g) and 7·0 g (0·064 mole) 4-picoline N-oxide was dissolved in a mixture of 10 g (0·064 mole) n-butyric anhydride (0·77 atom % ^{18}O) and 8·0 g (0·091 mole) n-butyric acid (0·77 atom % ^{18}O). The mixture of 4-n-butyroxymethylpyridine and 3-n-butyroxy-4-methylpyridine (0·5 atom % ^{18}O) was isolated in a similar manner, yield 2·4 g (21%). $n_D^{24·5°}$ 1·4899, along with 4·3 g of tarry product.

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

Decomposition of n-butyryl peroxide in ^{18}O labelled n-butyric acid

To a mixture of 35 g (0·20 mole) n-butyric anhydride and 100 ml Na dried ether, 10 g (0·13 mole) Na_2O_2 was added under ice-cooling. With occasional shaking, 40 g ice was added below 5° the mixture stirred few min. The ether layer was decanted off and dried ($CaCl_2$). After removal of ether, an oily product was obtained. This showed a positive iodide starch test. This oily product was dissolved in 25 g (0·28 mole ^{18}O labelled n-butyric acid (0·54 atom % ^{18}O). The reaction was carefully initiated by a free flame in a high-vacuum line. The evolved gas was trapped and purified by using liquid N_2 and dry-ice acetone cooled traps. The incorporation of ^{18}O was detected by a mass spectrometer. Evolved CO_2; 0·25 atom % ^{18}O; Natural CO_2; 0·21 atom % ^{18}O.

Isotope analyses. A Hitachi model RMU-5G mass-spectrometer was used to obtain the mass spectra. The analyses of the mass spectra was similar to that previously reported.