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THE MECHANISM OF THE REACTIONS OF 2- AND 4-ALKYLPYRIDINE N-OXIDES WITH ACETIC ANHYDRIDE[1]

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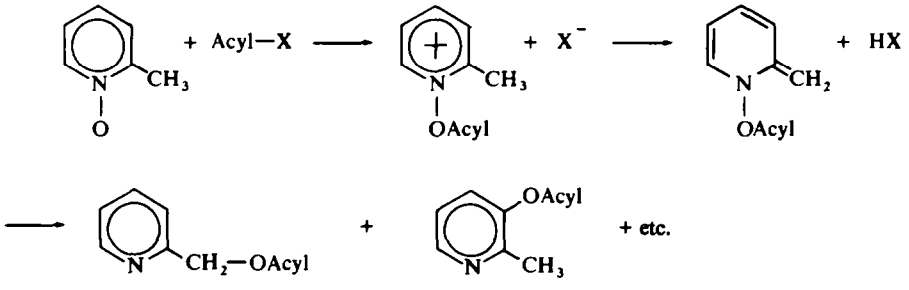
Abstract—The reaction of 2-benzylpyridine, 2- and 4-picoline N-oxides with acetic anhydride has been investigated by means of kinetic and ^{18}O-tracer experiments. The large kinetic isotope effects found for all these reactions suggest the proton-removal step to be rate-determining. The uneven distribution of ^{18}O between the alcohol and carbonyl O- atoms of the esters formed appears to result from the conformational preference of the "anhydrobase" intermediates. The slight effect of salts and substituents on the rate are also discussed.

THE reactions of aromatic amine oxides with acylating agents have been extensively studied.[2-9] In the case of 2- and 4-alkylated pyridine and quinoline N-oxides, the reactions are presumed to proceed via the formation of intermediate anhydrobases, and the following is a general scheme. The intervention of "anhydrobases" in these reactions has been demonstrated by the deuterium tracer experiments.[3] The determination of the



kinetic isotope effects of these reactions with both undeuterated and trideuterated Me compounds has indicated that the rate-determining step is the proton-removal to form "anhydrobases."

Although the essential nature of these reactions has been well-clarified, the kinetic data and data obtained in the ^{18}O-tracer experiments reveal that the mechanisms of the reactions differ from one N-oxide to the other. In addition, the interpretations of the data also can vary, especially, as to the nature of the N—O bond cleavage and the initial equilibrium step.

Consequently, extensive kinetic investigations of these reactions have been carried out in addition to our usual ^{18}O-tracer experiments.

As the N-oxides of benzopyridines, i.e., lepidine, quinaldine, and 1-methylisoquinoline N-oxides, apparently react faster than 2- and 4-picoline and even 2-benzylpyridine

N-oxides, the mechanisms of the reactions of the former N-oxides seem to differ from those of the latter. In this paper we give a full account of our investigations on 2-benzylpyridine, 2- and 4-picoline N-oxides with acetic anhydride.

RESULTS

Kinetic experiments. The rate of the reaction of 2-benzylpyridine N-oxides with acetic anhydride was measured, following the gradual decrease of the UV absorption peak during the reaction in water at *ca* 255 mμ (ε : 10750), characteristic of 2-benzylpyridine N-oxide. When the reaction was carried out in dioxan, the first order rate was found to depend on both the concentration of the N-oxide and acetic anhydride. Thus, a straight line could be drawn from the origin when logarithmic decreases of the N-oxide were plotted against time. In general the rates were measured in a large excess of acetic anhydride and the pseudo-first order rate constants were obtained. Then the second-order rate constants, k_2, were calculated by the equation $v = k_2$[N-oxide] [Ac_2O], namely, by dividing the pseudo-first-order rate constants by the concentration of acetic anhydride charged in the reaction vessel.

A typical set of the relevant data are given in Table 1.

TABLE 1. DEPENDENCE OF RATE CONSTANTS FOR THE REACTION OF 2-BENZYLPYRIDINE N-OXIDE WITH ACETIC ANHYDRIDE ON ACETIC ANHYDRIDE CONCENTRATION IN DIOXAN AT 30°

Ac_2O M	$k_1 \times 10^5$ sec^{-1}	$k_2 \times 10^5 M^{-1}$ sec^{-1}
1·96	2·76	1·40
3·92	5·26	1·34
5·88	7·76	1.32
10·6	15·5	1·46

Both 2- and 4-picoline N-oxides behaved similarly and hence the same procedure was used to determine the rate constants. The wave-lengths used for the UV spectrometric determinations in water were 253 mμ (ε : 10960) for 2-picoline N-oxide and 257 mμ (ε : 13850) for the 4-isomer. In all cases, the experimental error in the rate-determination was kept within the range of 5%.

Effects of solvents and salts. As Table 2 indicates, the rate of 2-benzylpyridine N-oxide was not affected much by the change of solvent. Even in DMF the rate was less than 2-fold of that in dioxan. The reaction of 2-picoline N-oxide was also insensitive to solvent change.

In the case of 4-picoline N-oxide, the rate varied with a change of solvent, namely, the rate in dioxan was slightly faster than that in acetonitrile, whereas in DMF the rate increased markedly.

The addition of lithium perchlorate or lithium chloride did not affect the rate of 2-benzylpyridine N-oxide, but depressed the rate considerably in the reactions of both 2- and 4-picoline N-oxides, when DMF, which readily dissolves lithium salts,[10] was used as the solvent, the addition of these salts no longer depressed the rate. The rate was not affected by the addition of tetraalkylammonium acetate.

The addition of lithium perchlorate apparently leads to the formation of a stable

TABLE 2. EFFECTS OF SOLVENTS AND SALTS FOR THE REACTIONS OF 2-BENZYLPYRIDINE, 2- AND 4-PICOLINE N-OXIDES WITH ACETIC ANHYDRIDE: $(Ac_2O)=5{\cdot}95$ M

N-Oxide	Solvent	Added salt	10^3M	$k \times 10^5$ sec^{-1}
2-Benzylpyridine	Dioxan	none		7·53
(30°C)	Acetonitrile	none		7·64
	DMF	none		14·6
	Dioxan	$LiClO_4$	2·9	5·95
	Dioxan	$LiClO_4$	4·8	5·98
	Dioxan	Bu_4NOAc	2·8	7·76
	DMF	$LiClO_4$	7·8	14·6
2-Picoline	Dioxan	none		14·8
(50°C)	Acetonitrile	none		15·0
	Acetonitrile	$LiClO_4$	7·4	7·32
	Acetonitrile	Bu_4NOAc	3·2	16·0
4-Picoline	Dioxan	none		10·5
(50°C)	Acetonitrile	none		9·04
	DMF	none		40·0
	Dioxan	$LiClO_4$	9·4	3·27
	Dioxan	Bu_4NOAc	2·3	9·87
	Acetonitrile	Bu_4NOAc	2·0	9·84
	DMF	$LiClO_4$	11·5	40·3
	DMF	Bu_4NOAc	3·7	40·3

complex salt, eg., N-acetoxy-2-picolinium perchlorate from 2-picoline N-oxide. Fig. 2 shows the NMR spectrum of the solution containing equimolar amounts of both 2-picoline N-oxide and lithium perchlorate in acetic anhydride, while Fig. 3 depicts the spectrum of N-acetoxy-2-picolinium perchlorate[7] in acetic anhydride. Both spectra are identical. Namely, when lithium perchlorate is dissolved in the acetic anhydride solution of the N-oxide, the acyloxy complex is formed immediately and lithium acetate is precipitated. Fig. 1 shows the NMR spectrum of 2-picoline N-oxide alone in acetic anhydried.

Kinetic isotope effects and activation parameters. 2-α, α-Dideuteriobenzylpyridine, deuterated 2- and 4-picoline N-oxides were prepared by the base-catalyzed H-D exchange and the deuterium content in these N-oxides was determined by their NMR spectra as shown in the experimental. These N-oxides were subjected to the usual kinetic experiments. Kinetic isotope effects obtained are tabulated together with relative rates and activation parameters, in Table 3.

The relatively large isotope effect obtained for 2-benzylpyridine N-oxide indicates that proton-removal is the rate-determining step. The values $6{\cdot}3 \pm 0{\cdot}2$ and $6{\cdot}2 \pm 0{\cdot}2$ obtained for 2-picoline and 4-picoline N-oxides, respectively, also suggest the same step to be the rate-determining.

The relative rates of these N-oxides can be arranged in the following order: 2-benzylpyridine $\gg$ 2,6-lutidine > 4-picoline > 2-picoline N-oxides at acetic anhydride concentration of 5·95 mole/l.

Effects of substituents. The effects of substituents on the pyridine ring cannot be examined readily, since the reaction with a few available 2-substituted picoline N-oxides are known to proceed through different paths. For example, 2,6-lutidine N-oxide reacts with acetic anhydride at both 2- and 3-positions while 4-nitro-2-picoline N-oxide is

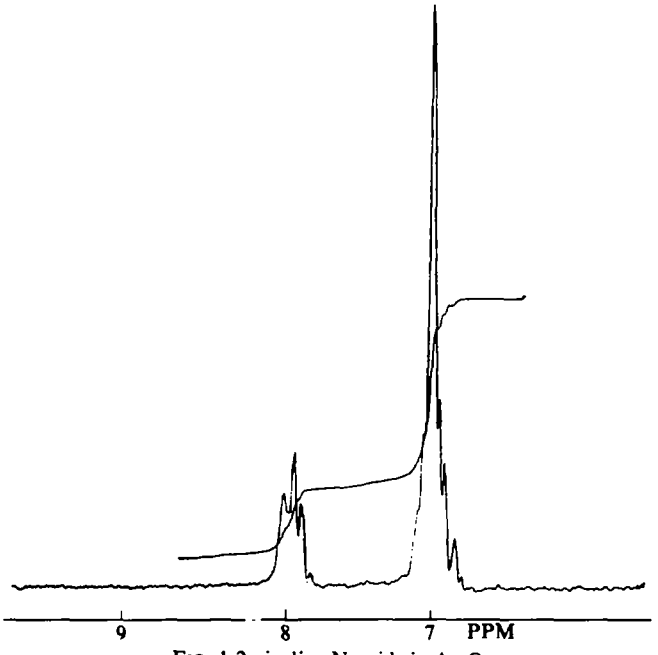


FIG. 1 2-picoline N-oxide in Ac_2O.

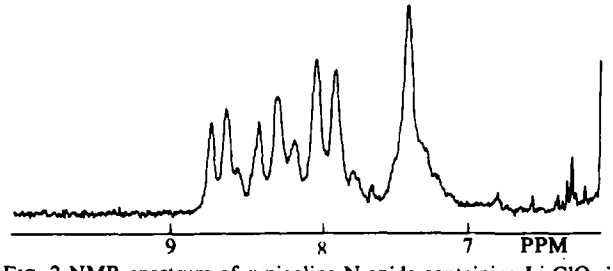


FIG. 2 NMR spectrum of α-picoline N-oxide containing Li ClO_4 in Ac_2O.

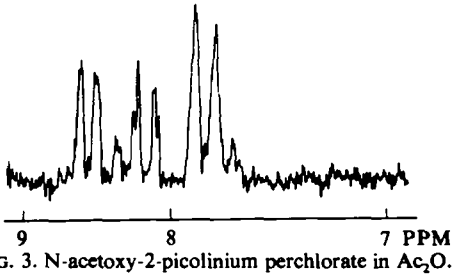


FIG. 3. N-acetoxy-2-picolinium perchlorate in Ac_2O.

TABLE 3. ISOTOPE EFFECTS, RELATIVE RATES AND ACTIVATION PARAMETERS OF THE REACTIONS OF ALKYLPYRIDINE N-OXIDE WITH ACETIC ANHYDRIDE IN DIOXAN: (Ac_2O)=5·95 M at 30°.

N-Oxide	Temp., °C	k_H/k_D	$k_1 \times 10^5 sec^{-1}$	Ea, Kcal/mole
2-Benzylpyridine	30	7·6	7·38	14·8
2-Picoline	60	6·3	0·74*	22·5
4-Picoline	60	6·2	1·05	22·5

* Values extrapolarated from values measured at the higher temperatures.

TABLE 4. SUBSTITUENT EFFECT FOR REACTION OF 2-(SUBSTITUTED BENZYL)PYRIDINE N-OXIDE WITH ACETIC ANHYDRIDE IN DIOXAN AT 30°: (Ac_2O) = 5·95 M

Substituent	$k_1 \times 10^5 sec^{-1}$	k_{rel}
p-NO_2	28·7	3·89
p-Cl	10·8	1·47
H	7·37	1
m-CH_3	7·17	0·97
p-CH_3	6·76	0·92

TABLE 5. PRODUCT DISTRIBUTION RATIO (%) FOR THE REACTION OF 2-PICOLINE N-OXIDE WITH ACETIC ANHYDRIDE IN THE VARIOUS SOLVENTS UNDER REFLUXING

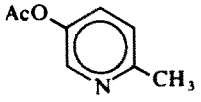
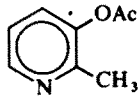
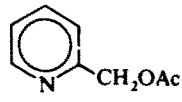
Solvent			
None	15	18	67
Chloroform	15	17	68
Benzene	15	16	69
Acetonitrile	14	18	68
Dioxan	12	13	75

TABLE 6. ^{18}O-ANALYTICAL DATA FOR THE REACTIONS OF 2-(p-METHYL AND p-CHLOROBENZYL)PYRIDINE N-OXIDES IN BENZENE: $(Ac_2{}^{18}O)/(N\text{-OXIDE}) = 1·5$

Substituent	Ester	Alcoholic oxygen	Carbonyl oxygen	Ac_2O used
		excess atom %		
p-Cl	0·46	0·33	0·54	0·94
p-CH_3	0·44	0·29	0·45	0·93

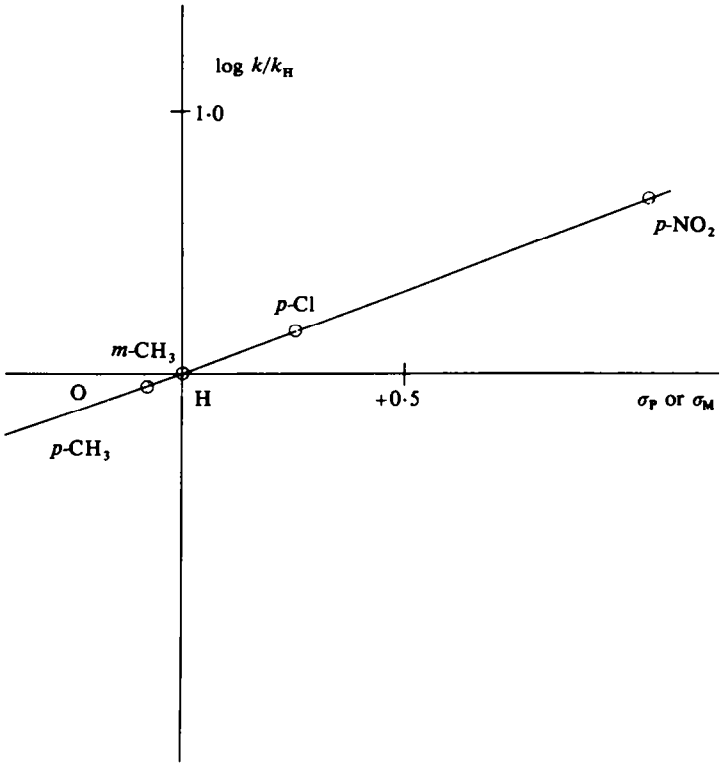


FIG. 4 Plot of logarithmic rates for the substituted 2-benzylpyridine N-oxide with Ac_2O in dioxan at 30°; $(Ac_2O) = 5{\cdot}88$ M, against σ.

unreactive under the same conditions.[11] However, the effects of substituents can be readily examined with 2-benzylpyridine N-oxides with various substituents on the phenyl ring.

The kinetic data obtained for these substituted 2-benzylpyridine N-oxides are listed in Table 4, while the Hammett plot of the logarithmic rates against σ-values is shown in Fig. 4. These data reveal that the rate is increased by the substitution of an electron-withdrawing group such as nitro group and the ρ-value is found to be $+0{\cdot}73$.

Products analysis and ^{18}O*-tracer experiments.* In the reaction of 2-benzylpyridine N-oxide with acetic anhydride, phenyl-2-pyridylmethyl acetate was the only ester isolated, while with 2-picoline N-oxide, 2-acetoxymethylpyridine as well as 3-acetoxy-2-picoline and 5-acetoxy-2-picoline were obtained.[12] 4-Picoline N-oxide yielded both 4-acetoxymethylpyridine and 3-acetoxy-4-picoline.

The change of the product distribution with the change of solvent was scrutinized in the case of 2-picoline N-oxide. The results, shown in Table 5, reveal that the product distribution remains nearly identical regardless of the nature of the solvent.

The ^{18}O tracer experiments with acetic anhydride homogeneously labelled with ^{18}O were performed with all the N-oxides. Since the results and the interpretation of the data have been presented earlier,[3b] only the results obtained for 2-(*p*-chlorobenzyl)pyridine

TABLE 7. ^{18}O-ANALYTICAL DATA FOR THE REACTION OF 2-PICOLINE AND 2,6-LUTIDINE N-OXIDES WITH ^{18}O-LABELLED ACETIC ANHYDRIDE UNDER REFLUXING

N-Oxide	Ester	Carbonyl oxygen	Alcoholic oxygen
		excess atom %	
2-Picoline[a]	A 0·47	0·48	0·35
	B 0·48	0·63	0·34
	C 0·54	0·52	0·47
2,6-Lutidine[b]	D 0·46	0·20	0·31
	E 0·46	0·32	0·28

[a] mole ratio of Ac_2O to N-oxide, 2·5.

[b] mole ratio of Ac_2O to N-oxide, 1·5.

A: 2-acetoxymethylpyridine; B: 3-acetoxy-2-picoline; C: 5-acetoxy-2-picoline; D: 2-acetoxymethyl-6-methylpyridine; E: 3-acetoxy-2,6-lutidine.

N-oxide and *p*-methylisomer are summarized in Table 6. The other data for 2-picoline and 2,6-lutidine N-oxides are collected in Table 7.

Though the ^{18}O concentration of the ester was nearly identical to half of the acetic anhydride employed in this reaction, an uneven distribution of ^{18}O-concentrations between the carbonyl and alcoholic atoms were observed as in other 2-alkylpyridine and quinoline N-oxides.

DISCUSSION

Rate-determining step and substituent effect. In view of the large kinetic isotope effects observed in these reactions, the rate-determining step is undoubtedly the proton-removal. The effects of substituents observed in the reactions of substituted 2-benzylpyridine N-oxides, shown in Table 4, also support the proton-removal as rate-determining, though the ρ-value obtained was smaller than expected from the usual carbanion forming reactions[13] or elimination reactions.[14] The small ρ-value is brought about by the cancellation of a relatively large positive ρ-value for deprotonation by the negative ρ-value of the pre-equilibrium step of acetylation. Since the equilibrium of acetylation is related to the p*Ka* of the N-oxides and if the steric factor is relatively unimportant the ρ-value of the equilibrium is undoubtedly associated with that of p*Ka* values and the two ρ-values would be nearly identical. Actually however, since the acetyl group is bulkier than a proton, the ρ-value for the equilibrium would be substantially larger than that of the p*Ka* values.

If one assigns the lowest ρ-value for the pre-equilibrium, namely, the ρ-value of the p*Ka* value $(-0{\cdot}30)$[15] then the value for the deprotonation step becomes $+1{\cdot}0$, barely large enough to support the proton-removal step as rate-determining. Incidentally the ρ-value for the p*Ka* values of substituted 2-pyridine N-oxides is $-2{\cdot}0$[16] which is large enough to outweigh the succeeding proton-removal step of the reaction. In fact, the inability of 4-nitro-2-picoline N-oxide to undergo rearrangement with acetic anhydride under the same conditions is undoubtedly associated with the very low basicity of the N-oxide.

A question arises if the proton-removal to give "anhydrobase" is also a slow

equilibrium and the "anhydrobase" undergoes either rearrangement with slower N—O bond cleavage or returns back to the acetylated salt by fast protonation.

In the case of 2-benzylpyridine[4] and 2-picoline N-oxides, the deuterated N-oxides, recovered from the reactions with acetic anhydride, apparently have lost very little deuterium unlike the case of quinaldine N-oxide. Also in the reaction with 4-picoline N-oxide, the N-oxide undergoes little hydrogen isotopic exchange before the cleavage of the N—O bond.

Thus, the proton-removal is definitely the rate-determining step and the succeeding steps of the N—O bond cleavage and the recombination to form the final ester must be fast reactions.

Effect of solvent and salt. The very small effects of both solvent and salt found in the reactions of 2-benzylpyridine N-oxide or 2-picoline N-oxide suggest that the pre-equilibrium reaction of acetylation is nearly complete as soon as the N-oxide is brought into contact with acetic anhydride. Even in the case of 4-picoline N-oxide the effects of solvent and salts are small as compared with quinaldine, lepidine, and 1-methylisoquinoline N-oxides, in which the cleavage of the N—O bond is very important and sometimes rate-determining.[3c]

The addition of lithium salt into the system brings about the freezing of acetate anion by forming a tight ion pair or salt of lithium acetate. Therefore, the second step of proton-removal is retarded by the lack of proper base, i.e., acetate in this case, resulting in a depression of the rate of the reaction. This is the case for the reaction without solvent and also in both dioxan and acetonitrile. The formation of N-acetoxypyridinium perchlorates is clearly demonstrated by the observation of NMR spectra of the solution of 2-picoline N-oxide in acetic anhydride with and without lithium perchlorate together with that of authentic N-acetoxy-2-picolinium perchlorate shown in Figs. 1 to 3.

However, in DMF which is capable of dissolving both organic and inorganic lithium salts, the acetate ion is not only unfrozen, but is activated due to the strong solvation of lithium ions, thus usually resulting in an the increased rate due to the facile proton-removal. Such a marked effect is also observed in 4-picoline N-oxide.

Over-all rate of the reaction. Data in Table 3 and the preliminary experiments reveal that the over-all rate of the reaction can be arranged in the following order: 6-phenyl-2-picoline > 2-benzylpyridine $\gg$ 2,6-lutidine > 4-picoline > 2-picoline N-oxides. It is somewhat unexpected to see that the rate of 4-picoline N-oxide is 1·5-fold faster than that of 2-picoline N-oxide in view of the higher acidity of the Me protons of 2-picoline N-oxide than those of 4-picoline N-oxide.[17]

In this case, probably the first pre-equilibrium step is important in controlling the rate of reaction, as it is known that the 4-picoline N-oxide is more basic than the 2-isomer and hence the acylation is expected to be more favorable for the 4-picoline N-oxide than the 2-isomer. Perhaps the higher reactivity of 2,6-lutidine N-oxide than those of 2- and 4-picoline N-oxide may be partly due to the somewhat higher basicity of 2,6-lutidine N-oxide and partly because of the stability of the anhydrobase, derived from 2, 6-lutidine N-oxide due to the hyperconjugative effect of Me group at 6-position. The higher rate of 2-benzylpyridine N-oxide is undoubtedly due to both the higher acidity of the benzylic protons and the resonance stabilization of the anhydrobase formed.

Thus, although the rate-determining step of the reaction is definitely the proton-removal step for any of these N-oxides, the initial equilibrium reaction of acetylation is also quite important to control the over-all rate of the reactions.

The nature of N—O bond cleavage. The foregoing observations and discussions are concerned with the rate-controlling steps of the reactions of these N-oxides with acetic anhydride, and the importance of the proton-removal step and the prior equilibrium reaction of acetylation in the rate-controlling is emphasized together with existence of "Anhydrobase" intermediates in these reactions. Thus, from the kinetic aspects of these reactions, the succeeding step, i.e., N—O bond cleavage and the recombination to form esters are relatively unimportant. However, the mode of N—O bond cleavage is interesting not only because of the controversies hitherto developed in the mechanistic interpretations, but also owing to the fact that the distribution of products is controlled mainly by these fast steps.

Earlier we have shown by ^{18}O tracer experiments that the reaction of 2-picoline N-oxide with acetic anhydride proceeds through an intramolecular process, while that of 4-picoline N-oxide follows an intermolecular path. This means that the cleavage of the N—O bond of the anhydrobase formed from 2-picoline N-oxide and the succeeding recombination takes place intramolecularly while the anhydrobase from 4-picoline N-oxide undergoes N—O bond cleavage prior to addition of acetate ion at the terminal methylene carbon. A new set of ^{18}O-tracer experiments for 2-benzylpyridine and 2,6-lutidine N-oxides with ^{18}O-labeled acetic anhydride reveals that both compounds undergo similar intramolecular rearrangements as in the case of 2-picoline N-oxide, as one can see in the Tables 6 and 7. Now the problem is the nature of the N—O bond cleavage of the anhydrobases derived from the N-oxides that undergo the intramolecular pathway. We have suggested, based on the observations such as the formation of small amounts of methane and carbon dioxide and 2-picoline among the by-products, and nearly equal distribution of ^{18}O in both carbonyl and alcoholic O-atoms of the ester formed in the reaction of 2-picoline N-oxide and acetic anhydride, that the cleavage of N—O bond is homolytic and the ester is formed by the cage recombination process while methane, carbon dioxide, 2-picoline are the products derived from acetoxy and picolyl radicals escaped out of the solvent cage. Meanwhile, the heterolytic cleavage of N—O bond of the anhydrobase has been suggested on the basis of the theoretical consideration[5] and the experimental observations, such as the formation of a rearranged 2-(1-cyclohexenyl)-pyridine together with 2-(1-cyclopentenylmethyl)-pyridine in the reaction of 2-cyclopentylcarbinylpyridine N-oxide with acetic anhydride,[8] and other similar observations.[18]

This ionic process also explains the results of the ^{18}O-distribution, but not the formation of methane, carbon dioxide, and 2-picoline. The only way to reconcile these contradictory observations and considerations is that a major portion of the reaction undergoes the ionic cleavage of the N—O bond of the anhydrobase while the remaining portion of the reaction proceeds via the homolytic cleavage of the N—O bond. Similar binary processes have been known for the decomposition of diacyl peroxide to afford the corresponding esters.[19]

The ^{18}O-uneven distribution and rate of recombination. Earlier, we investigated the effects of solvent on the reactions of 2- or 4-picoline N-oxide with acetic anhydride[6] and found that in the reaction of 4-picoline N-oxide the change of solvent leads to a change in the ratio of both the intramolecular and intermolecular products, though the rates of the reaction of both 4-picoline and 2-picoline N-oxides with acetic anhydride were later found not to be influenced considerably by the solvent change. Therefore, we suggested that the reaction of 4-picoline N-oxide proceeds via the intermolecular path without solvent, or via

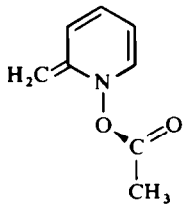
both intra- and inter molecular rearrangement in acetic acid and in non polar solvents. On the other hand, 2-picoline N-oxide always proceeds through the intramolecular path. These differences between 2- and 4-picoline N-oxides were ascribed to the difference in the distances between the N-atom to which the acetoxy group is attached and the terminal C-atom at which the acetoxy group finally rearranges in the two N-oxides. That is to say, in the case of 4-picoline N-oxide the nucleophilic attack of acetate at either the exo-methylene carbon or 3-position of the anhydrobase is fast enough to compete with the intramolecular rearrangement of the acetoxy group from the N-atom to the terminal C-atom. While as for 2-picoline N-oxide the attack of the foreign acetate cannot compete with the intramolecular rearrangement of the acetate group within the anhydrobase.

In order to confirm further the fast recombination of acetoxy group in the intramolecular rearrangement step, the reactions of 2-picoline and 2,6-lutidine N-oxide with acetic anhydride were re-examined by the usual ^{18}O-tracer experiments.

Inspection of the data shown in the Tables 6 and 7 reveals that in the case of both 2-picoline or 2-substituted benzylpyridine N-oxide and 2,6-lutidine N-oxide markedly uneven distributions of the ^{18}O between the carbonyl and alcoholic oxygens in the esters formed via the intramolecular path can be seen in all the cases regardless of the reaction conditions. These results show that the rearranging process, after the N—O bond scission, is so fast that there is not enough time for the O-atoms of the acetoxy groups to be completely scrambled.

If the recombination between the acetoxy group and the pyridine part were slow as compared to the rotation of the acetate group, the distribution of ^{18}O between the carbonyl and alcoholic O-atoms would be equal.

This unequal distribution is not only due to the short distance to rearrange, but also due to the steric effect of the methylene and methyl groups present in the 6-position of the anhydrobase intermediate, that is, due to the conformational preferrence of the anhydrobase intermediate.



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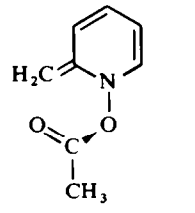

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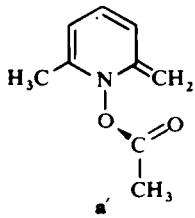

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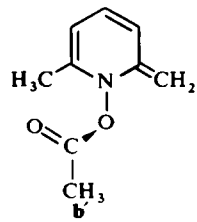

b'

In the 2-picoline N-oxide the carbonyl group was a higher ^{18}O-content than the alcoholic oxygen, whereas, in 2,6-lutidine N-oxide the alcoholic oxygen is richer in the ^{18}O-content than the carbonyl O-atom. The introduction of a bulky Me group at the 6-position of 2-picoline N-oxide results in the reversion of the pattern of the ^{18}O-distribution. Apparently, the following conformational preference for the anhydrobase intermediates, (**a**) over (**b**) or (**a'**) over (**b'**), reflects on the ^{18}O-distribution of the resulting esters from the two N-oxides.

EXPERIMENTAL

Synthesis of 2-(*substituted benzyl*)*pyridine.* 2-Benzylpyridine, containing the isomer, 4-benzylpyridine, was prepared by heating the reaction mixture of pyridine, benzyl chloride and powdered Cu according to the method of Cooks[20] and then purification was done as follows: 28 g of fraction of range of b.p. 277–282° was added to a soln of 60 g picric acid in 1·5 l alcohol and refluxed for 30 min. The soln was then quickly cooled to 32° and impure 2-benzylpyridine picrate which precipitated was quickly filtered off. This picrate was dissolved in 1·5 l hot alcohol, cooled quickly in an ice-bath to about 32° and again filtered. A second recrystallization with the same quantity of alcohol cooled to 20° before filtering, afforded 25 g pure 2-benzylpyridine picrate m.p. 139·5–140·5°.

The picrate was dissolved in about 500 ml hot water and then the soln was made strongly alkaline with NH_4OH extracted with benzene and after evaporation of benzene the residue was distilled under at press: b.p. 277° (lit.[20] 276·6–277·0).

The *m*-CH_3, *p*-CH_3, and *p*-Cl derivatives were obtained similarly: *p*-CH_3: b.p. 101–102°/0·5 mmHg; *m*-CH_3: b.p. 101·5–103·5°/0·5 mmHg; *p*-Cl: b.p. 132·5–135·5°/3·5 mmHg.

Synthesis of 2-(*substituted benzyl*]*pyridine* N-*oxide.* The oxidations of both unsubstituted and substituted benzylpyridines were carried out by the usual method.[21] 2-Benzylpyridine N-oxide was prepared and recrystallized as reported.[22] From 15·3 g 2-benzylpyridine 15·8 g 2-benzylpyridine N-oxide was obtained (95% yield): m.p. 100–100·6° (lit.[22] 100·5°).

The N-oxidations of *p*-CH_3, *p*-Cl and *m*-CH_3 derivatives were carried out similarly. The N-oxides were distilled under reduced press twice. In each distillation, the distilate was divided into 3 parts and the middle portion of the distilate used. For instance 17 g *p*-chlorobenzylpyridine was converted to *p*-chlorobenzylpyridine N-oxide, b.p. 162·5–163·5°/0·8 mmHg, m.p. 69–70°, yield: 18·5 g. The b.ps. for other N-oxides were: *p*-CH_3: 171–172°/0·5 mmHg; *m*-CH_3: 155–157°/0·5 mmHg.

The identification and purity of each N-oxide was established by means of NMR, IR, UV, TLC. The nitration of 2-benzylpyridine N-oxide (22 g) gave 27 g 2-(*p*-nitrobenzyl)pyridine N-oxide (98·7%): m.p. 166·5–167° (lit.[22] 163–165°).

Reactions of 2-(p-CH_3-, m-CH_3-, p-Cl-*benzyl*)*pyridine N-oxide with acetic anhydride.* A mixture of 2·0 g 2-(*m*-methylbenzyl)pyridine N-oxide and 2·0 g Ac_2O in 15 ml benzene was refluxed for 2 hr. After removal of benzene, distillation under reduced press afforded 1·77 g of the slightly yellow oil, b.p. 147–151°/1·0 mmHg.

When the same procedure was applied to 2-(*p*-methylbenzyl) pyridine N-oxide using 3·2 g N-oxide and 3·0 g Ac_2O, 2·62 g ester was obtained, b.p. 127–143°/0·5 mmHg.

Likewise, 2·0 g *p*-chloro isomer and 2·5 g Ac_2O in 15 ml benzene resulted in 1·4 g ester.

Hydrolysis of substituted phenyl-2-pyridylmethyl acetates. p-Chlorophenyl-2-pyridylmethyl acetate was treated with two equiv KOH in MeOH for one day. After removal of MeOH, the residue was extracted with $CHCl_3$. From $CHCl_3$ layer, *p*-chlorophenyl-2-pyridyl methanol was obtained. The other derivatives were hydrolysed similarly: *p*-Chlorophenyl-2-pyridylmethanol: m.p. 84·5°, (Found: C, 65·74; H, 4·59; N, 6·71. $C_{12}H_{10}NOCl$ requires: C, 65·56; H, 4·55; N, 6·38%). *m*-Methylphenyl-2-pyridylmethanol: m.p. 106–107°, (Found: C, 78·36; H, 6·53; N, 7·21. $C_{13}H_{13}NO$ requires: C, 78·36; H, 6·58; N, 7·03%). *p*-Methylphenyl-2-pyridylmethanol: m.p. 99–100°, (Found: C, 78·05; H, 6·50; N, 6·94. $C_{13}H_{13}NO$ requires: C, 78·36; H, 6·58; N, 7·03%).

The reaction of 2-*picoline*[23] *and* 2,6-*lutidine*[24] N-*oxides with labeled acetic anhydride.* 2-Picoline and 2,6-lutidine N-oxide were prepared according to the method reported by Ochiai. To 7·96 g 2-picoline N-oxide (b.p. 103–105°/3 mmHg) was added 10·9 g labeled Ac_2O under N2. The mixture was gently refluxed

for 2 hr. After removal of excess Ac_2O and AcOH, distillation afforded 6·45 g mixed esters: b.p. 79–87°/5 mmHg. 4·10 g Lutidine N-oxide (4·10 g) was treated with 5·43 g labeled Ac_2O at 95–100° for 3 hr. After removal of excess Ac_2O and AcOH, distillation gave 4·60 g colorless oil: b.p. 82–84°/4 mmHg.

The separation of the ester mixture. The esters obtained were separated into components by means of Yanagimoto GCG-3 gaschromatography with PEG 6000 siliconized 80–100 mesh celite 545 3 m.

Determination of ^{18}O-content of carbonyl oxygen in the esters. The separated ester, for example, 3-acetoxy-2-picoline (0·25 g) and phenyl hydrazine (0·42 g) were heated at 130° for 2 hr. The mixture was poured into a mixture of hexane-benzene. The ppt was filtered off and a mixture of 1-acetyl-2-phenylhydrazine and 3-hydroxy-2-picoline 0·33 g m.p. 105–130° obtained.

These solids were recrystallized repeatedly yielding 97 mg 1-acetyl-2-phenylhydrazine, m.p. 128–129° (lit. 129°) and 54 mg 3-hydroxy-2-picoline, m.p. 165–167° (lit.[5] 163–165°) which were subjected to the ^{18}O-analysis. A similar procedure was employed for the other esters. As in the case of 2-acetoxy-methylpyridine and 2-acetoxymethyl-6-methylpyridine the alcohol moities were obtained by direct hydrolysis of these esters. For instance, 0·5 g of labelled 2-acetoxymethylpyridine was dissolved in 10 ml MeOH containing 0·2 g KOH and left over night. After removal of MeOH, the residue was extracted with $CHCl_3$ and dried with Na_2SO_4 and then distillation gave 100 mg of 2-pyridinemethanol.

The ^{18}O-analytical samples for the reaction of 2-benzylpyridine N-oxide with labelled Ac_2O were prepared similarly.

Isotopic analysis. Analysis of ^{18}O-content in the compounds was carried out as described previously.[3a]

Preparation of deuterated N-oxides. 2-(α,α-Dideuteriobenzyl)pyridine N-oxide was prepared according to the literature.[22] Trideuterated 2-picoline and 4-picoline N-oxides were prepared in the following manner. To 5 g D_2O was added a small piece of Na. And 1 g 2-picoline N-oxide was then added to the above alkaline soln in a sealed tube. After heating for 24 hr at 100°, the mixture was extracted with $CHCl_3$ repeatedly and distillation gave 480 mg α,α,α-trideuterio-2-picoline N-oxide; b.p. 127°/10 mmHg (94% atom % D). The same procedure was adopted for the preparation of deuterated 4-picoline N-oxide.

From 1 g N-oxide, 410 mg crystalline solid; m.p. 184–185° (lit 185°) (89% atom % D) was recovered.

Purification of solvents and salts used in rate measurement. Dioxan, acetonitrile, and Ac_2O were all purified according to the directions described in Fieser's "Experiments".[25]

Tetra-n-butylammonium acetate was prepared by the method of Thompson and Kraus.[26]

Rate measurement. As an example, a weighed amount of 2-picoline N-oxide dissolved in dioxan was added to a reaction vessel containing Ac_2O in dioxan. The reaction vessel was thermostated at a constant temp during the reaction. The constant volume of the soln was pipetted out at constant time intervals and worked up into the constant volume of 3% KOHaq in order to measure the optical density by Hitachi R-124 UV Spectrometer.

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