Tetrahedron Vol. 26, pp. 4675 to 4689. Pergamon Press 1970. Printed in Great Britain

REACTION OF LEPIDINE, QUINALDINE AND 1-METHYLISOQUINOLINE N-OXIDES WITH ACETIC ANHYDRIDE[1]

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(*Received in Japan* 4 *August* 1969; *received in the UK for publication* 30 *April* 1970)

Abstract—The mechanism of the reactions of lepidine, quinaldine and 1-methylisoquinoline N-oxides with acetic anhydride has been studied by means of both kinetic and ^{18}O tracer experiments.

In all cases, the over-all rate of the reaction is markedly affected both by the change of solvent and by the addition of salts. In the case of lepidine N-oxide, a large kinetic isotope effect, $k_H/k_D = 7{\cdot}7$ in acetonitrile, suggests that the proton-removal is the rate-determining step. This is also the case for 6-methylquinaldine N-oxide which gives the kinetic isotope effect, $k_H/k_D = 7{\cdot}4$ (at 30°). In the case of quinaldine N-oxide, however, the kinetic isotope effect is small, $k_H/k_D = 2{\cdot}0$ (at 30°), while quinaldine N-oxide originally trideuterated loses deuterium during the reaction, depicting that the proton-removal is a reversible step and the succeeding N—O bond cleavage is the rate-determining step. In the case of 1-methylisoquinoline N-oxide, in which k_H/k_D is 3·5 in dioxan at 30° both proton-removal and N—O bond cleavage are equally important in the energy profile of the reaction.

THE preceding paper describes the mechanisms of the reactions of 2-picoline, 4-picoline and 2-benzylpyridine N-oxides with acetic anhydride in which the rates are shown to increase in the following order: 2-ethyl ~ 2-methyl < 4-methyl < 2,6-dimethyl < 2-phenyl-6-methyl < 2-benzylpyridine N-oxides. While this rate order can be accounted for by consideration of both the pre-equilibrium and the rate-controlling proton removal steps, the large kinetic isotope effects ($k_H/k_D = 6$–7) suggest that for all the N-oxides, the rate-determining step is the proton-removal. The lack of solvent and salt effects on these rates support the above conclusions. The present paper is an extension of the same reaction to lepidine, quinaldine, and 1-methyl-isoquinoline N-oxides. The kinetic investigations were carried out in the presence or absence of salts and in various solvents. Unlike the previous cases of substituted pyridine N-oxides, the addition of a small amount of lithium perchlorate was found to accelerate the reaction rates considerably. The effects of solvent and temperature changes and deuterium substitution on the rates also differ from those with the N-oxides described. This different behaviour can be interpreted in terms of the different nature of the transition states of the reaction and the modes of N—O bond cleavage.

Kinetic experiments. The kinetic studies of the reactions of lepidine, quinaldine, and 1-methylisoquinoline N-oxides with acetic anhydride were carried out spectrophotometrically, taking advantage of the strong UV absorption maxima at 318, 327 and 295 mμ in water for quinaldine, lepidine, and 1-methyl-isoquinoline N-oxides, respectively. The detailed procedures are described in the Experimental. Usually, the reactions of quinaldine, lepidine, and 1-methylisoquinoline N-oxides were investigated by employing a 6×10^{-3} M concentration of the N-oxide and excess of acetic anhydride under

conditions in which the pseudo-first-order rate constants can be obtained. For every kinetic run, the pseudo-first-order rate plot was drawn. Variation of concentration of the N-oxides did not influence the rate constants (Table 1–3). Then second-order rate constants (k_2) were calculated from the pseudo-first-order rate constants. The resultant second-order rate constants were independent of the concentrations of both the N-oxide and acetic anhydride. This was confirmed by running the reaction under conditions in which the second order rate equations $-dx/dt = k_2(a_0 - x)(b_0 - x)$ could be applied and the rate constants calculated (Table 4).

As shown in Tables 1, 2 and 3 the reactions are expressed by the second-order rate $v = k_2$(N-oxide)(Ac_2O), i.e., the first-order with respect to both N-oxides and acetic anhydride, respectively.

TABLE 1. THE REACTION OF QUINALDINE N-OXIDE WITH ACETIC ANHYDRIDE: Ac_2O CONCENTRATION DEPENDENCY OF THE RATE IN CH_3CN AT 60°

Concentration of Ac_2O, 10^2M	Concentration of N-Oxide, 10^2M	2nd-Order rate const., 10^5k_2, $M^{-1}sec^{-1}$
6·39	3·51	77·4
10·34	3·65	76·8
26·5	3·54	77·6

TABLE 2. THE REACTION OF LEPIDINE N-OXIDE WITH ACETIC ANHYDRIDE: Ac_2O CONCENTRATION DEPENDENCY OF THE RATE IN CH_3CN AT 30°

Concentration of Ac_2O, M	Pseudo-1st-order rate const., 10^5k_1, sec^{-1}	2nd-Order rate const., 10^5k_2, M^{-1} sec^{-1}
0·174	5·03	6·35
1·24	8·14	6·56
2·48	14·8	5·86
3·98	22·8	5·86
5·95	33·1	5·76

TABLE 3. DEPENDENCE OF RATE ON Ac_2O CONCENTRATION FOR THE REACTION OF 1-METHYLISOQUINOLINE N-OXIDE WITH ACETIC ANHYDRIDE IN DIOXAN AT 10°

Concentration of Ac_2O, M	Pseudo-1st-order rate const., 10^5k_1, sec^{-1}	2nd-Order rate const., 10^5k_2, M^{-1} sec^{-1}
0·75	0·545	0·7
1·50	1·58	1·1
3·0	3·95	1·3

Kinetic isotope effects and substituent effects. Approximate energy profiles including the rate-determining step of these reactions become clear by examination of both the kinetic isotope effects and substituent effects. Thus, several substituted quinaldine, lepidine and 1-methylisoquinoline N-oxides and a few corresponding trideuterated

TABLE 4. TYPICAL KINETIC RUN OF THE REACTION OF QUINALDINE N-OXIDE WITH ACETIC ANHYDRIDE IN CH_3CN

Time, sec	optical density (318 mμ)	$\ln \frac{a_0(b_0 - x)}{b_0(a_0 - x)}$
0	0·924	—
1000	0·800	0·022
2400	0·764	0·056
3480	0·709	0·077
4680	0·652	0·102
6000	0·598	0·125
7200	0·538	0·163
8400	0·500	0·187
10800	0·420	0·246

a_0: Initial concn. of N-oxide 0·377M, b_0: Initial concn. of Ac_2O 0·104M, Temp. 60·13 ± 0·02°.

TABLE 5. DEPENDENCE OF THE RATE OF THE REACTION OF LEPIDINE N-OXIDE WITH ACETIC ANHYDRIDE ON THE N-OXIDE CONCENTRATION AT 30° IN CH_3CN

Lepidine N-oxide, M	10^5k_1, sec^{-1}	10^5k_2, M^{-1} sec^{-1}
$5·7 \times 10^{-3}$	14·8	5·98
$2·9 \times 10^{-3}$	14·4	5·80

* Concn. of Ac_2O 2·48M.

compounds were synthesized and subjected to the usual kinetic experiments. The observed kinetic isotope effects, measured in acetonitrile or dioxan are summarized in Tables 6 and 7. The rates of deuterated compounds were always markedly lower than those of the corresponding undeuterated ones. For example in the reaction of unsubstituted lepidine N-oxide with acetic anhydride, the rate ratio of the deuterated to the undeuterated compounds was 7·9 while that for unsubstituted quinaldine N-oxide was only 2·0 which was a considerably smaller value than normal for the isotope effect. Several substituted quinaldine and lepidine N-oxides were synthesized, and the

TABLE 6. DEUTERIUM ISOTROPIC EFFECTS AND SUBSTITUENT EFFECTS OF THE REACTION OF 6-X-4-Y-LEPIDINE N-OXIDE AT 30° IN CH_3CN

Substituent Y	Substituent X	2nd-order rate const., 10^5k_2, M^- sec^{-1}	k_{rel}	k_H/k_D
CH_3	H	6·09	1	—
CD_3	H	0·77	—	7·9
CH_3	CH_3	4·13	0·68	—
CH_3	CH_3O	2·29	0·36	—
CH_3	Cl	2·76	0·50	—
CD_3	Cl	0·356	—	7·7

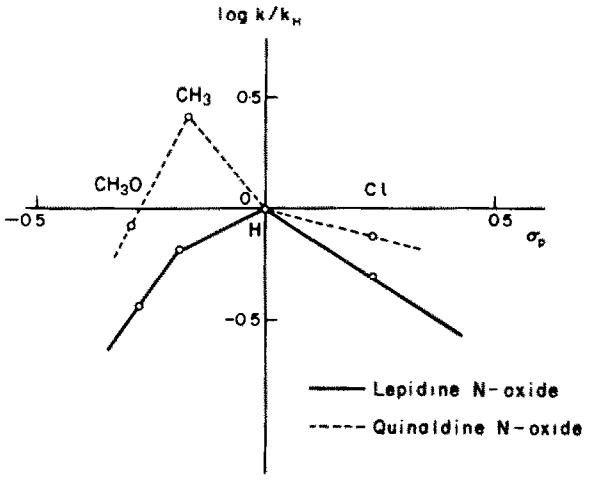


FIG. 1. Hammett plot for the reaction of 6-substituted lepidine or quinaldine N-oxide with Ac_2O: Data from Table 6 and 7.

TABLE 7. RATE OF THE REACTION OF 6-SUBSTITUTED QUINALDINE N-OXIDE WITH ACETIC ANHYDRIDE IN ACETONITRILE AT 30°

Substituent	Pseudo-1st-order rate const., 10^4k_1, sec^{-1}	k_H/k_D	Pseudo-1st-order rate const., $10^4k_1{}^1$, sec^{-1}
CH_3O	1·51	—	0·73
CH_3	2·41	7·4	2·22
H	1·29	2·0	1·07
Cl	0·38	2·2	0·66

$k_1{}^1$ is the rate constant in the presence of $LiClO_4$ at 10°.

TABLE 8. ISOTOPE EFFECT OF THE REACTION OF 1-METHYLISOQUINOLINE N-OXIDE WITH Ac_2O IN DIOXAN AT 10°

N-Oxide	10^5k_1, sec^{-1}	k_H/k_D
Undeuterated	15·8	
Deuterated	4·57	3·5

Concn. of Ac_2O 1·5M.

effects of substituents on the kinetic isotope effect were examined while the results are shown in Tables 6 and 7.

Solvent effects and activation energies. The solvent effect was quite significant in the reaction of lepidine, quinaldine and 1-methylisoquinoline N-oxides, as shown in Table 9. In more polar media the rates of the reactions of lepidine, quinaldine, and 1-methylisoquinoline N-oxides with acetic anhydride increased by a factor of about 2 more than those in non-polar media, and the increasing rates reflect in the lower activation energy by as much as 2 Kcal/mol.

TABLE 9. THE EFFECTS OF TEMPERATURE ON 2ND-ORDER REACTION RATE AND ACTIVATION ENERGY

N-Oxide	Solvent	$10^5 k_2$, M^{-1} sec^{-1}			Ea, Kcal/mol
Lepidine	dioxan	k_{25}· 1·21	k_{30}· 2·00	k_{34}·	18·3
	CH_3CN	k_{20} 2·73	k_{25} 3·87	k_{30} 5·80	13·4
Quinaldine	dioxan	k_{20} 2·64	k_{25} 4·16	k_{30} 6·00	14·6
	CH_3CN	k_{40} 27·7	k_{50} 42·4	k_{60} 77·2	
1-Methylisoquinoline	dioxane	k_{10} 10·5	k_{15} 14·7		
	CH_3CN	k_{10} 20·9			

Effect of salts. The addition of lithium perchlorate which is known to shift the pre-equilibrium completely toward right hand side, did not alter the substituent effect, as shown by Table 7 and Fig 1 although the rates were increased by a factor of 2 as compared to that in the reaction without the salt.

The effects of lithium perchlorate on the rates of reactions of lepidine and quinaldine N-oxides have never been examined by varying the concentration of the salts. The addition of lithium perchlorate retarded the rate of the reactions of 2-, 4-picoline and 2-benzylpyridine N-oxides, which fact is assumed to be due to the formation of the stable complex, i.e., N-acetoxypyridinium perchlorate:

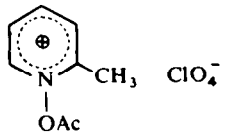


TABLE 10. SOLVENT EFFECT ON THE RATE OF THE REACTION OF VARIOUS N-OXIDES WITH ACETIC ANHYDRIDE

Lepidine N-oxide	solvent	$k_2 \times 10^5$ M^{-1} sec^{-1}
	Dioxan	2·34
	CH_3CN	5·79
	DMF	8·46 at 30°
Quinaldine N-oxide	solvent	$k_2 \times 10^5$ M^{-1} sec^{-1}
	Dioxan	2·64
	CH_3CN	5·70
	DMF	7·78 at 20°
1-Methylisoquinoline N-oxide	solvent	$k_2 \times 10^5$ M^{-1} sec^{-1}
	Dioxan	10·5
	CH_3CN	20·9 at 15°

In the cases of lepidine and quinaldine N-oxides, a 2-fold rate increase in acetonitrile was observed till the addition of about equimolar amount of lithium perchlorate, and further addition of the salt brought about the retardation of rates. The results are represented in Table 11 and Fig 2.

TABLE 11. SALT EFFECT ON THE RATE OF THE REACTION OF LEPIDINE N-OXIDE WITH ACETIC ANHYDRIDE IN CH_3CN AT 30°

$LiClO_4 \times 10^3$, M	Half-life time, min
0	77·5
1·5	37·5
3·5	31·0
8·2	30·0
11·9	35·0
15·0	40·0
22·0	50·0
49·0	63·0
98·5	118·0

Initial concn. of N-oxide $5{\cdot}70 \times 10^{-3}$ M, concn. of Ac_2O 2·45 M.

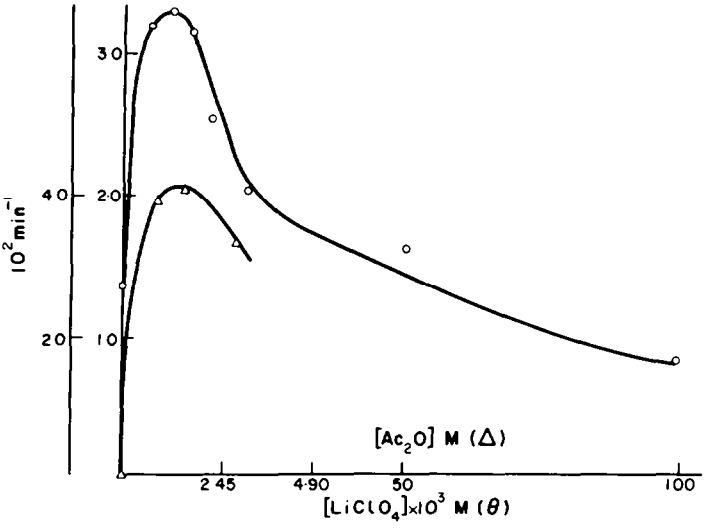


FIG 2. Dependence of the rate for the reaction of lepidine N-oxide with Ac_2O on the concentration of $LiClO_4$ (O). Dependence of the rate on the concentration of Ac_2O under the condition of const. $LiClO_4$. $LiClO_4$. Concn. at $7{\cdot}8 \times 10^{-3}$ M (Δ). (Data from Table 11).

Thus, the addition of an equimolar amount of lithium perchlorate to the N-oxide in 2·45 M of acetic anhydride in acetonitrile increased the rate markedly at first and then further addition of the salt converted the remaining free N-oxide to the stable N-acetoxy perchlorate. The formation of such a stable salt was also observed in the cases of 2-, and 4-picoline N-oxides.

TABLE 12. EFFECT OF ACETIC ANHYDRIDE CONCENTRATION ON THE REACTION RATE OF QUINALDINE N-OXIDE IN THE PRESENCE OF $LiClO_4$* IN DIMETHYLFORMAMIDE AT 20°

Ac_2O, M	10^5k_2, M^{-1} sec^{-1}
1·96	7·90
3·95	8·00
5·96	7·98

* Concn. of $LiClO_4$ $8·15 \times 10^{-3}$ M, Initial concn. of quinaldine N-oxide $5·5 \times 10^{-3}$ M

TABLE 13. EFFECT OF SOLVENT CHANGE ON THE RATE OF THE REACTION OF QUINALDINE N-OXIDE WITH ACETIC ANHYDRIDE* IN THE PRESENCE OF CONSTANT AMOUNT OF LITHIUM PERCHLORATE† AT 20°

DMF-dioxan v/v %	10^5k_2, M^{-1} sec^{-1}
0	58·9
8·5	17·3
41·5	7·84
100	7·87

* Concn. 3·92 M, † Concn. $8·15 \times 10^{-3}$ M

TABLE 14. SOLVENT EFFECTS ON THE REACTION OF QUINALDINE N-OXIDE WITH ACETIC ANHYDRIDE IN VARIOUS SOLVENT IN THE PRESENCE OF $LiClO_4$*

Solvent (X)	$k_X(LiClO_4)/k_X$(none)
Dioxane	8
CH_3CN	2
DMF	1

* Initial concn. of N-oxide $5·5 \times 10^{-3}$ M; concn. of Ac_2O 3·94 M; concn. of $LiClO_4$ $8·2 \times 10^{-3}$ M.

TABLE 15. HYDROGEN DEUTERIUM EXCHANGE REACTION FOR THE REACTION OF THE N-OXIDES WITH ACETIC ANHYDRIDE IN Ac_2O

N-Oxide.	Reaction temp °C	Deuterium content %	Reaction %
Quinaldine	75		35
Starting N-oxide		0	
Recovered N-oxide		62	
6-Methylquinaldine	75		60
Starting N-oxide		0	
Recovered N-oxide		25	

As shown in Table 11 this could also be observed by varying the concentration of acetic anhydride containing a constant concentration of lithium perchlorate. Apparently, the increase of acetic anhydride or the addition of lithium perchlorate shifts the pre-equilibrium to the right to produce the stable, kinetically unreactive N-acetoxy perchlorate. The formation of the salt by the addition of lithium perchlorate into the mixture of the N-oxide and acetic anhydride could also be seen in the down field NMR chemical shift of the ring protons of quinaldine N-oxide as well as 2-picoline N-oxide.[2]

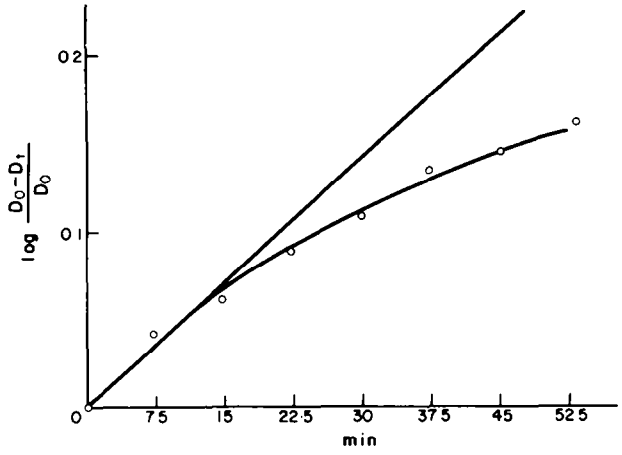


FIG 3. The reaction of quinaldine N-oxide with Ac_2O in the presence of $LiClO_4$ in acetonitrile at 30°: $(LiClO_4) = 10{\cdot}4 \times 10^{-3}$ M, (N-oxide) = $5{\cdot}23 \times 10^{-3}$ M, $[Ac_2O] = 3{\cdot}9$ M.

In the presence of lithium perchlorate the kinetic plots deviate from the integrated pseudo-first-order relationship as illustrated in Fig 3. Same is true for the reaction of lepidine N-oxide.

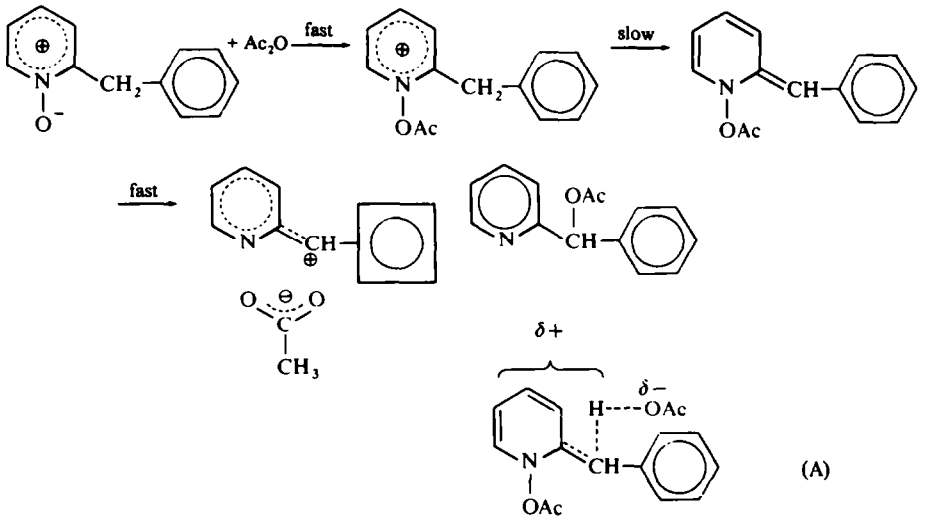
When DMF was used as solvent, the variation of rate by the addition of lithium perchlorate disappeared completely as shown in Table 12. DMF is known to solvate small cations such as Li^{+3} and hence the acetate ion is free to become a good nucleophile as shown in Table 13. The extent of solvation of the Li^+ cation, roughly estimated by the extent of deactivation by solvent change on the effect of lithium perchlorate, may be placed in the following order, DMF>CH_3CN> dioxan as shown in Table 14.

DISCUSSION

Rate-determining step and solvent effect. In the previous paper,[2] the reaction of 2-benzylpyridine N-oxide with acetic anhydride was suggested to proceed via the anhydrobase intermediate which resulted from the rate-determining proton-removal reaction of the N-acetoxy-2-benzylpyridinium acetate. The succeeding steps, i.e., the N—O bond fission and the recombination to form the corresponding acetate esters, were considered to be very fast.

In view of the scant solvent and salt effects, the activated complex at the transition state is considered to assume a less polar structure (A) in which the original full positive charge on the N-atom is dispersed.

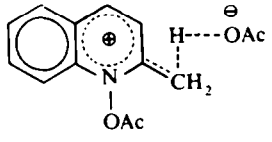
SCHEME 1



(A)

Therefore, the transition state may be resembled to the anhydrobase intermediate. In the case of lepidine and quinaldine N-oxides, however, as the data in Table 10 indicate, the rates of the reaction are accelerated by a factor of 2–3 by changing the solvent from the nonpolar dioxan to polar acetonitrile. These solvent effects may be due to the forward reaction of the pre-equilibrium acetylation step being rather slow and partially controlling the over-all rate. In addition, the N-acetoxy salt is considered as being in a steady state condition. However, this interpretation cannot be accepted because the addition of lithium perchlorate, which is known to shift effectively the first-equilibrium step to the right hand side, only slightly changes the size of the isotope effects, k_H/k_D = 1·8 to 2·3 at 60°.

It could be rationalized by assuming that the activated complex of the transition state attains a more charge-separated structure and resembles the N-acetoxyquinaldinium salt as in Fig (B).



(B)

Although the size of the kinetic isotope effect suggests that the proton-removal step is involved in the transition state of the rate-determining reaction step, only one of the above depicted structures for the transition state cannot explain the widely ranged values of both the kinetic isotope effects and the solvent effect.

The third possibility for the relatively low kinetic isotope effect for quinaldine (2·0 at 30°) and 1-methylisoquinoline (3·5 at 30°) N-oxides may be due to an equilibrium between the anhydrobase and N-acetoxyquinaldinium or 1-methylisoquinolinium acetate and that the cleavage of the N—O bond is the rate-determining step. This

interpretation, though somewhat strange, can explain not only the observed over-all rate of the reaction, but also the diminishing of the isotope effect and the increase of the solvent dependency of the rate.

In the case of 6-methylquinaldine N–oxide the kinetic isotope effect becomes substantial. Here, the electron-donating power of the Me group undoubtedly facilitates the heterolysis of the N—O bond, but retards the proton-removal which in turn becomes the rate-determining step resulting in the increase of the kinetic isotope effect ($k_H/k_D = 7{\cdot}4$). As the reaction of quinaldine N-oxide with acetic anhydride in acetic acid-1-d accompanies the deuterium exchange at the 2-Me group of the N-oxide shown in Table 15, this indicates that the proton-removal is an equilibrium and the forward equilibrium reaction is faster than the N—O bond cleavage. This is not the case for 6-methylquinaldine N-oxide. This observation is compatible with the fact that the kinetic isotope effect of the 6-methylquinaldine N-oxide is 7·4 which is much larger than that of quinaldine N-oxide.

The Modes of N–O bond cleavage. As in the preceding paper,[2] in the reactions of lepidine, quinaldine and other benzopyridine N-oxides with acetic anhydride, a small amount of carbon dioxide (about 1 %) are formed together with the normal corresponding rearranged esters. This indicates that the homolytic cleavage of the N—O bond takes place together with the major heterolytic process to form the esters. In these reactions, the heterolytic cleavage is more evident, since the rates of lepidine, quinaldine and 1-methylisoquinoline N-oxides are much more sensitive to the solvent change than 2-, 4-picoline and 2-benzylpyridine N-oxide with acetic anhydride in a polar solvent, acetonitrile, is twice that in non-polar dioxan. This is in keeping with the argument that the N—O bond heterolytic cleavage is the rate-determining step of the reaction of quinaldine N–oxide.

TABLE 16. THE REACTION OF QUINALDINE N-OXIDE WITH ^{18}O-LABELLED ACETIC ANHYDRIDE IN DIOXAN AND ACETONITRILE

Solvent	Mole ratio (N-oxide : Ac_2O)	Ac_2O (used)	Ester	Carbonyl oxygen	Alcoholic oxygen
		excess atom %			
Dioxan	1:2·2	0·685	0·335	0·185	0·445
Acetonitrile	1:1·5	0·985	0·475	0·455	0·505

The ^{18}O distribution in the resulting esters as shown in Table 16 is also affected by the solvent change. Because of the conformational preference for the anhydrobase derived from quinaldine N-oxide, the ester contains more ^{18}O in the etheral oxygen than in carbonyl oxygen. In a non-polar solvent apparently the ^{18}O content of the carbonyl oxygen tends to decrease. This is reasonable because acetate can dissociate and hence is scrambled more in a polar solvent than in non-polar media.

The ratio of the two products, 4-acetoxymethylquinoline (C) and 3-acetoxylepidine (D), also changes with the change of solvent as shown in Table 17.

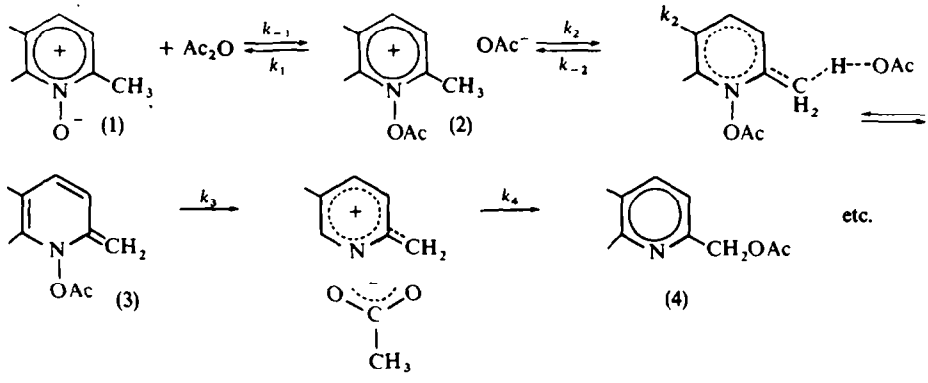
In view of the lack of the solvent effect on the product ratio in the case of 2-picoline N-oxide,[2] the recombination is believed to be slower in the case of lepidine N-oxide and hence more prone to the polar solvent effect.

TABLE 17. THE PRODUCT RATIO FOR THE REACTION OF LEPIDINE N-OXIDE WITH ACETIC ANHYDRIDE IN VARIOUS SOLVENTS

Solvent	none	Benzene	Dioxan	Chloroform	Acetonitrile
Dielectric constant	—	2·3	2·3	5·0	38·8
Product (C)/(D) ratio	0·73	0·32	0·32	0·26	0·16

The energy diagrams. In general the reaction scheme for the reactions of 2-, and 4-picoline, lepidine, quinaldine, and 1-methylisoquinoline N-oxides with acetic anhydride is depicted as shown below.

SCHEME 2



The reaction consists of the four steps, i.e., the initial acetylation (k_1), the proton-removal (k_2), the N—O bond cleavage (k_3), and the recombination (k_4). The relative importance of these steps in determining the reaction mode differs from one N-oxide to the other. In 2-, 4-picoline and 2-benzylpyridine N-oxides, the proton-removal step is definitely rate-determining and very slow as compared with the other steps, i.e., both succeeding and preceding.

The activation energy is calculated to be as high as 22 Kcal/mole in the case of 2-, and 4-picoline N-oxides, whereas that for 2-benzylpyridine N-oxide which has active benzylic protons is substantially lower, i.e. 14·8 Kcal/mol. Meanwhile, as for the benzopyridine N-oxides the activation energy usually decreases down to as low as 15 Kcal/mole or less.

These decreasing activation energies are associated with the high stabilization of the resultant anhydrobases. Therefore, both the N—O bond fission and the proton-removal steps require comparable energies, thus resulting in the competition for the rate-control. In the extreme case the proton-removal step may not require the highest energy, while, the succeeding N—O bond cleavage becomes important in determining the rates. This is

obviously the case for quinaldine N-oxide. In the case of 1-methylisoquinoline N-oxides, both the proton-removal and the N—O bond cleavage steps are presumed to be equally important. These energy relationships are shown in Fig 4.

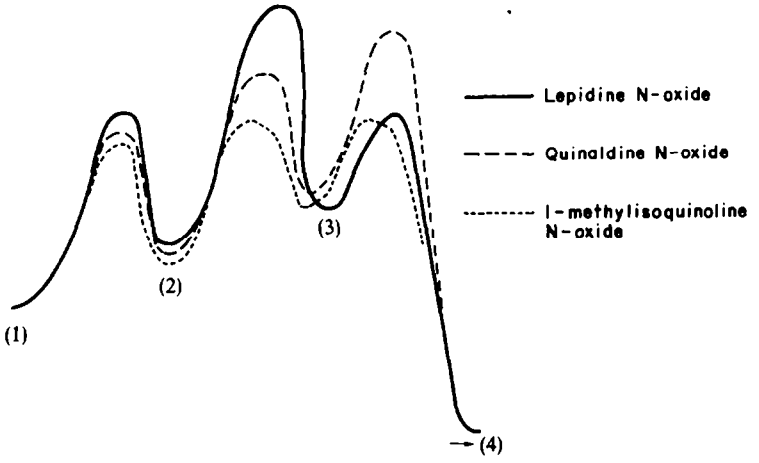


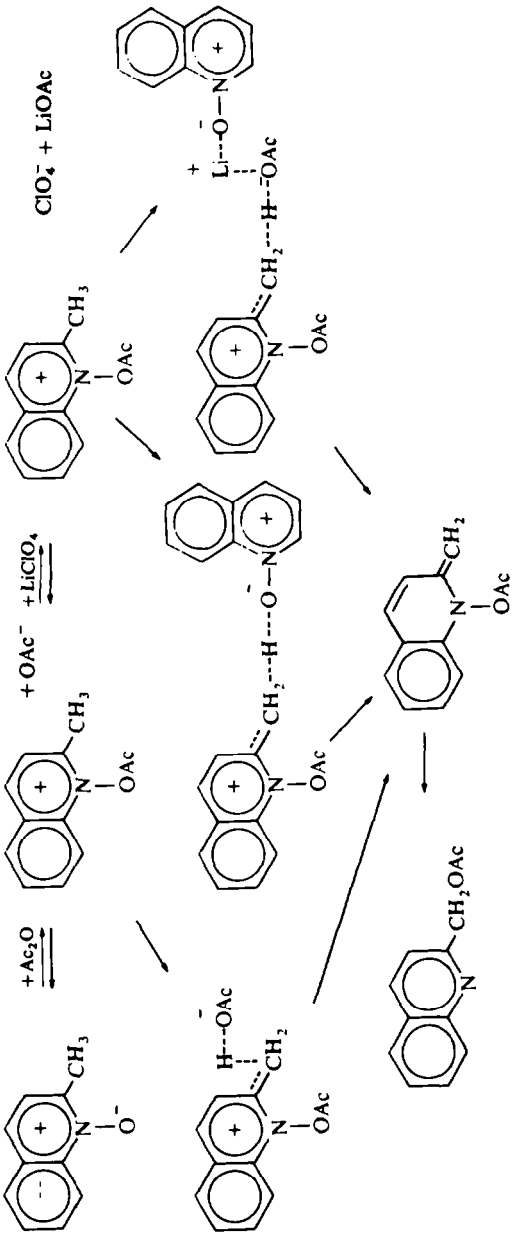
FIG. 4. Energy profile of the reaction of lepidine, quinaldine, and 1-methyl-isoquinoline N-oxides with Ac_2O.

Salt effects. Rate increases of 10-fold or less are observed for the reactions of quinaldine and lepidine N-oxides with acetic anhydride in dioxan when lithium perchlorate is added. This is partly due to the shift of the equilibrium toward the right-hand side of the reaction and also due to the increase of ionic strength to facilitate the heterolysis of the N—O bond. In this case, however, the reaction gradually deviates from the second-order equation $v=k_2$ [N-oxide] [Ac_2O] and tends to fit the equation of the second order with respect to the N-oxide concentration. Further addition of lithium perchlorate depressed the rate gently. These facts can be accounted for by the schematic assumption that the addition of lithium perchlorate leads to the formation of the stable N-acetoxyquinaldinium or lepidinium perchlorate and lithium acetate in such solvents as dioxan and acetonitrile, which is so tightly bound that the acetate anion cannot function as a proton removing base. Then the remaining free N-oxide begins to play the role of base for the proton abstraction from the N-acetoxylated compound or for the removal of lithium cations. Accordingly more than one equimolar amount of lithium perchlorate depresses the free N-oxide concentration and thus the rate retardation may result. This argument is supported by the experimental observation that the use of DMF as solvent completely eliminates the effect of lithium perchlorate due to the reactivation of the acetate anions which have been made free from tight ion pair formation with lithium cations.

Therefore, the rate fits the normal second-order rate equation with respect to N-oxide and acetic anhydride irrespective of the concentrations of both acetic anhydride and lithium perchlorate.

In conclusion, the reaction of a representative N-oxide, i.e., quinaldine N-oxide with acetic anhydride, may be illustrated by the following scheme.

SCHEME 3



EXPERIMENTAL

Materials. Dioxan, acetonitrile, DMF, and Ac_2O were purified by distillation according to the method of Fieser & Fieser.[4]

1-Methylisoquinoline N-oxide: To 9·0 g 1-methylisoquinoline, distilled under reduced press at b.p. 93–95°/3·5 mmHg, in 30 ml glacial AcOH, 8 ml 30% H_2O_2aq was added and the mixture was heated for 2 h at 70–80°. An additional 8 ml H_2O_2aq was added and then the mixture was concentrated *in vacuo* and neutralized with Na_2CO_3aq. The N-oxide was extracted with $CHCl_3$ 3 times. The removal of $CHCl_3$ gave a crystalline solid which weighed 8·1 g (81%), and recrystallized from hexane-benzene as slightly hygroscopic colorless prisms, m.p. 58–59°. (Found; C, 74·91; H, 6·04; N, 8·54 $C_{10}H_9NO$ requires: C, 75·50; H, 5·66; N, 8·81%); NMR spectrum had the peaks at 2·69 (Me: s) 7·79 and 8·07 (3-H: d), and 7·85–7·30 ppm (4,5,6,8-H; v) in CCl_4 peak strength was 3 : 1 : 5, respectively.

Lepidine N-oxide, m.p. 119–121°, was obtained by the oxidation[5] of lepidine[6] which was prepared from methylvinyl-ketone, aniline hydrochloride and hydrated ferric chloride and recrystallized from hexane-benzene (lit [7] 121–122°). Synthesis of quinaldine[8] and the oxidation of quinaldine to quinaldine N-oxide: (lit[9] m.p. 77–78°) were carried out in the usual manner.

Preparation of 6-substituted lepidine (6-CH_3, 6-Cl, 6-CH_3O). The substituted lepidines were synthesized according to the method of Campbell.[5]

The lepidines were oxidized to the N-oxides as usual. These Noxides had the following m.p.:

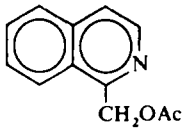
6-methyllepidine N-oxide: 118·5–119·5°, 6-Chloro-lepidine N-oxide: 141–142°. (Found: C, 62·00; H, 4·33; N, 7·31. $C_{10}H_8NO_4$ requires: C, 62·04; H, 4·15; N, 7·24) 6-Methoxylepidine N-oxide: (Found: C, 69·85; H, 5·88; N, 7·31 $C_{11}H_{11}NO_2$ requires: C, 69·99; H, 5·82; N, 7·42).

Reactions of lepidine, and 1-methylisoquinoline N-oxides with acetic anhydride. To 2·11 g 1-methylisoquinoline N-oxide in 15 ml benzene was added 2·7 g Ac_2O. The mixture turned red exothermically and then was refluxed gently for 1·5 hr. The excess Ac_2O was removed and the residue was distilled under reduced press. The volatile portion of the product was collected at 127°/0·7 mmHg, weighed 2·26 g (85%).

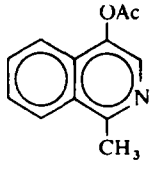
The IR spectrum indicated two peaks corresponding to carbonyl stretching bond at 1745 and 1722 cm^{-1} and the presence of ester function at 1190–1240 cm^{-1}.

The NMR spectrum consisted of the peaks at 8·51 (s), 8·41 (s), 8·32 (s), 2·78 (s), 2·36 (s) and 2·08 (s) ppm.

The product ratio for these two esters (E and F) was determined as 3 : 2 from NMR spectrometric determination.



E



F

Upon a similar treatment, lepidine N-oxide and Ac_2O gave the mixture of esters, 2-acetoxymethylquinoline and 3-acetoxylepidine in 55–65% yields, (b.p. 127–129 mmHg; lit. b.p. 200/2 mmHg).[8] The product ratio of these two esters was determined spectrophotometrically by converting them to 2-lepidylalcohol (C) and 4-hydroxylepidine (D).

The ^{18}O-tracer experiments. Oxygen-18 labelled Ac_2O was prepared by the method previously described.[10]

A typical run was as follows: a mixture of ^{18}O-labelled Ac_2O 3 g, (0·0294 mole), and quinaldine N-oxide 2 g, (0·0125 mole), was refluxed in acetonitrile for 8 hr. The distillation of the mixture gave 1·9 g (0·0094 mole) of 2-acetoxymethylquinoline (74·4%) at 112°/1 mmHg.[9]

The obtained ester (0·2 g) was heated at 130° for 2 hr with an equimolar amount of phenylhydrazine.

To the reaction mixture benzene was added. The resulting crystalline solid was recrystallized from benzene affording acetylphenylhydrazide of m.p. 128–129°: yield 0·1 g, which was subjected to ^{18}O-analysis in order to determine the ^{18}O-distribution in the carbonyl oxygen of 2-acetoxymethylquinoline. The alcoholic part was directly obtained by the hydrolysis of the ester with 0·5 g KOH in 5 cc of MeOH. From 0·5 g of the ester was obtained the 2-hydroxylmethylquinoline (0·2 g) m.p. 69–69·5°. The reaction of the N-oxide with ^{18}O-labelled Ac_2O in dioxan was carried out similarly.

Preparation of deuterated N-*oxide*. General methods were as follows:[11] the N-oxides were heated in sealed tubes with a mixture of Et_3N (5 equivs amount to one equimolar N-oxide) and D_2O (10–15 equivs amount to one equimolar N-oxide) at 100–120° for 24–48 hr and then the D_2O and Et_3N were removed and the N-oxides were handled by distillation or recrystallization according to their properties. The yields were nearly quantitative.

The D contents were determined by means of the NMR spectrometry from the disappearance of Me signals.

Lepidine N-oxide; 98% D, quinaldine N-oxide; 94% D, 1-methylisoquinaline; 97% D.

Typical rate measurements. A weighed amount of quinaldine N-oxide dissolved in acetonitrile was added to a reaction vessel containing Ac_2O in acetonitrile.

The reaction vessel was thermostated at 30·00° ± 0·03°. The constant volume of soln was pipetted out at constant time intervals and then quenched into the 3% KOH aq and diluted to the concentration appropriate for measurement. A Hitachi R-124 UV spectrometer with quarts cells was used for the measurement of optical density. Photoabsorption maxima for measurement were 317 (ε:7179), 327 (ε:6120) and 295 mμ (ε:8270) for lepidine, quinaldine, and 1-methylisoquinoline N-oxide, respectively.

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