yield of *N,N*-dimethyl 2,2,4-trimethyl-3-oxovaleramide; and a 60% yield of **22** (yields estimated from vpc and *ir* analysis). The major product was identified as **22** by comparing its ir and pmr spectra and vpc retention time (column A) with the product from **2** and **7**. ^{31}P nmr analysis of the product solution showed a single absorption at -140 ppm.

Upon extending heating at 60 and 90° the same reactants showed no change observable by vpc or ir.

Acknowledgment. We thank Drs. T. V. Liston and D. L. Rabenstein, Chevron Research Co., for the ^{31}P nmr spectra.

Trapping of Picolyl Cations in the Reactions of 2- and 4-Picoline *N*-Oxide with Acetic Anhydride[1a-c]

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Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213. *Received April 30, 1971*

Abstract: Attempts to trap the picolyl cations thought to be intermediates in the reactions of 4-picoline *N*-oxide (**1**) and 2-picoline *N*-oxide (**5**) with acetic anhydride are reported. In anisole, **1** and acetic anhydride yield, in addition to 4-pyridylcarbinol acetate (**3**) and 3-acetoxy-4-methylpyridine (**4**) in a ratio of 55:45, 20% of a mixture of the 4-picolylanisoles, 4-*o*-, 4-*m*-, and 4-*p*-methoxybenzylpyridine (relative yields 65:7:28). The same reaction in benzonitrile produces the esters in the same ratio and 11% of *N*-4-picolyl-*N*-acetylbenzamide (**14**); no product having a picolyl group substituted into the benzonitrile nucleus can be detected. In acetic acid, the ratio of esters **3** to **4** increases to 90:10. The reaction of **5** with acetic anhydride in anisole produces, in addition to 2-pyridylcarbinol acetate (**7**), 5-acetoxy-2-methylpyridine (**8**), and 3-acetoxy-2-methylpyridine (**9**) in relative yields of 76:12:12, 2% of a mixture of 2-*o*-, 2-*m*-, and 2-*p*-methoxybenzylpyridine (**15a**, **b**, and **c**) in relative yields of 57:4:39. The same reaction in acetic acid yields the same ester mixture as in anisole. In benzonitrile less than 2% of a mixture of *N*-2-picolylbenzamide (**17**) and 3-phenyl-2,3a-diazaindene (**18**) is produced. No product having a picolyl group substituted into the benzonitrile nucleus can be detected. The reaction of **1** with pivalic anhydride in anisole and in benzonitrile yields none of the solvent-derived products which are formed in the corresponding reactions using acetic anhydride. The results are consistent with the presence of picolyl cation–acetate anion pairs as principal intermediates in the reactions of both amine oxides with acetic anhydride. Collapse of the ion pairs leads to attack of acetate both on the methylene group and on the ring. On the other hand, neutral, weak nucleophiles attack the picolyl cations only at the methylene position, and probably for reasons of ionic juxtaposition, such solvent capture competes with ion pair collapse more efficiently for the 4- than for the 2-picolyl cation.

The reaction of 4-picoline *N*-oxide (**1**) with acetic anhydride yields a mixture of 4-pyridylcarbinol acetate (**3**) and 3-acetoxy-4-methylpyridine (**4**).[2] Under the same conditions, 2-picoline *N*-oxide (**5**) yields mainly 2-pyridylcarbinol acetate (**7**) and small amounts of 5-acetoxy-2-methylpyridine (**8**) and 3-acetoxy-2-methylpyridine (**9**).[2] It is known that the anhydrobases **2** and **6**, respectively, are reaction intermediates.[2]

Oae has shown by ^{18}O labeling studies that in the presence of aromatic diluents the esters are formed from **6** by a completely intramolecular process and from **2** by a process that is very largely intramolecular.[3] When the reaction is performed in neat acetic anhydride, the conversion of **6** to esters is still intramolecular while the production of esters from **2** is mainly intermolecular.[4]

The substantial ^{18}O shuffling observed in the intramolecular rearrangement in the 2 case indicates that the process is not concerted.[5,6] By analogy, the intramolecular rearrangement of **2** is probably also not concerted.

Until recently, it was believed that the intramolecular rearrangements of the anhydrobases occur by a radical-pair mechanism.[3,7] However, the successful production of esters by the treatment of 2-picoline *N*-oxide with phenylacetic[8,9] and trichloroacetic[9] anhydrides led to the suggestion that ion pairs (**10**) consisting of 2-picolyl cations and acylate anions are involved in the case of **6**. Recent support for such an intermediate has been presented by Bodalski and Katritzky[10] who observed typical carbonium ion rearrangement and elimination products from the reaction of acetic anhydride with various 2-substituted pyridine *N*-oxides. The reaction of 4-picoline *N*-oxide with phenylacetic anhydride produced very low yields of ester and this result was considered inconclusive with regard to the radical or ion pair character of the intermediate in the acetic anhydride case.[8] Very recently, Traynelis and

(1) (a) We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work; (b) taken from the Ph.D. thesis of GLD, University of Pittsburgh, Pittsburgh, Pa., 1969; (c) part of this work has been reported in preliminary form: T. Cohen and G. L. Deets, *J. Amer. Chem. Soc.*, **89**, 3939 (1967); (d) NASA Predoctoral Fellow.

(2) For an excellent review of previous work, see: V. J. Traynelis in "Mechanisms of Molecular Migrations," Vol. II, B. S. Thyagarajan, Ed., Interscience Publishers, New York, N. Y., 1969, p 1.

(3) S. Oae, Y. Kitaoka, and T. Kitao, *Tetrahedron*, **20**, 2685 (1964).

(4) S. Oae, T. Kitao, and Y. Kitaoka, *J. Amer. Chem. Soc.*, **84**, 3359, 3362 (1962).

(5) S. Kozuka, S. Tamagaki, T. Negoro, and S. Oae, *Tetrahedron Lett.*, 923 (1968).

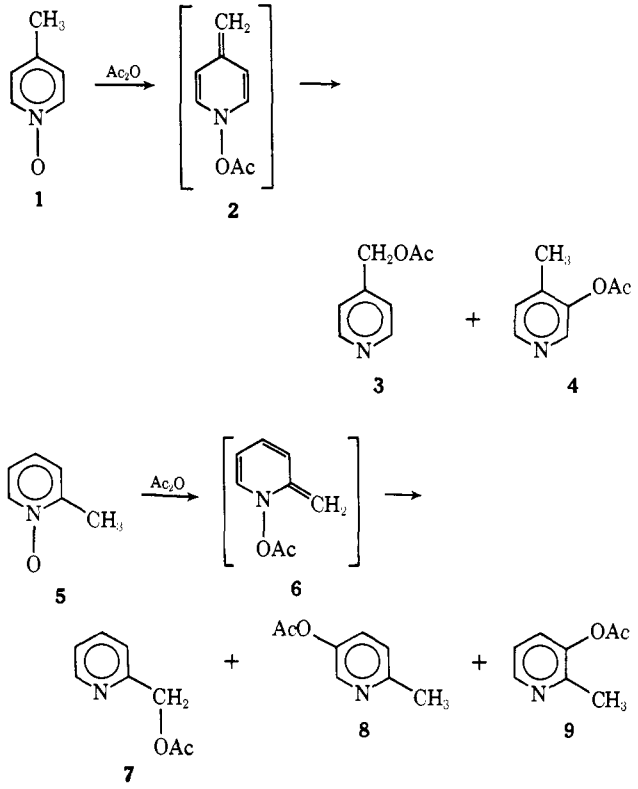
(6) This would only be true if the two oxygen atoms do not equilibrate prior to rearrangement.

(7) (a) R. A. Abramovitch and J. G. Saha, *Advan. Heterocycl. Chem.*, **6**, 229 (1966); (b) V. J. Traynelis and Sr. A. I. Gallagher, *J. Amer. Chem. Soc.*, **87**, 5710 (1965).

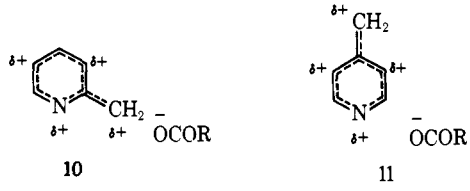
(8) T. Cohen and J. H. Fager, *ibid.*, **87**, 5701 (1965).

(9) T. Koenig, *ibid.*, **88**, 4045 (1966).

(10) R. Bodalski and A. R. Katritzky, *Tetrahedron Lett.*, 257 (1968).



Yamauchi[11] isolated olefins as major products from the reaction of acetic anhydride with 4-isopropyl and 4-α-phenylethylpyridine *N*-oxide. Although this result is consistent with ion-pair intermediates (**11**), radical pairs could possibly lead to the same results. It has been pointed out[8] that the ion-pair rearrangement would not only allow a common intramolecular mechanism in the case of 2- and 4-picoline *N*-oxide but in the 4 case it would no longer be necessary to invoke different modes of N–O bond cleavage for the intramolecular (homolytic) and intermolecular (heterolytic) processes.[3] The intramolecular process could result from recombination of the picolyl cation and acetate anion while the intermolecular reaction could be the result of capture of the picolyl cation by acetic acid in the medium; higher concentrations of carboxylic acid in the solvent have been shown to favor the intermolecular reaction.[12]



We now report the results of trapping experiments designed to distinguish between radical and ion pairs and to determine the reasons for the different behavior in the 2 and 4 cases in the absence of diluent. The reactions of acetic anhydride with both 2- and 4-picoline *N*-oxide were conducted in anisole, benzonitrile, and in acetic acid.

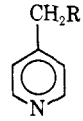
It is well known that anisole is very susceptible to electrophilic attack and that substitution occurs overwhelmingly at the ortho and para positions.[13] Radical substitution, on the other hand, yields more meta than para attack.[14]

Organic cations attack benzonitrile at the nitrogen atom[15] and any electrophilic attack that does occur on the ring leads mainly to meta-substituted products. Radical attack on the ring occurs readily and leads mainly to ortho and para products.[14]

Capture of the picolyl cations by acetic acid would be expected to yield the same esters as the collapse of the ion pairs, **10** and **11**, but the ratio of the isomeric esters might be expected to change in a revealing way.

Results

4-Picoline *N*-Oxide. (a) Anisole. When the reaction with acetic anhydride was conducted in anisole and the products were analyzed by combined gas chromatography–mass spectrometry, there was obtained, in addition to the two esters **3** and **4** (yield ratio 55:45), a 20% yield of a mixture of 4-*o*-, 4-*m*-, and 4-*p*-methoxybenzylpyridine (**12**, R = *o*-methoxyphenyl, *m*-methoxyphenyl, and *p*-methoxyphenyl, respectively). The three substituted anisoles have similar mass spectra, each exhibiting a parent peak at *m/e* 199 and informative fragments corresponding to loss of methyl (*m/e* 184), methoxyl (*m/e* 168), pyridyl (the methoxybenzyl cation, *m/e* 121), and methoxyphenyl (the picolyl cation, *m/e* 92). In view of the intense peak at 121 observed for all 3 isomers, it is likely that none of them arose by attack of anisole at the 3-position of the picoline ring.



An authentic sample of 4-*p*-methoxybenzylpyridine (**12**, R = *p*-methoxyphenyl) was prepared by nitration of 4-benzylpyridine (**12**, R = phenyl) to 4-*p*-nitrobenzylpyridine (**12**, R = *p*-nitrophenyl),[16] followed by reduction to 4-*p*-aminobenzylpyridine, diazotization, and decomposition of the diazonium salt in acidic methanol. The authentic 4-*m*-methoxybenzylpyridine (**12**, R = *m*-methoxyphenyl) was prepared as a mixture with the para isomer by the reaction of the anion of 4-picoline with the benzyne derived from *p*-bromoanisole.[17] One component of this product mixture was identified by glpc retention times as 4-*p*-methoxybenzylpyridine and the other was assumed to be 4-*m*-methoxybenzylpyridine. These two compounds were shown to have the same glpc retention times on three columns and the same mass spectrometric fragmentation patterns as two of the products from the reaction of 4-picoline *N*-oxide with acetic anhydride in anisole. The third isomer formed in the latter reaction was assigned the structure 4-*o*-methoxybenzylpyridine (**12**, R = *o*-methoxyphenyl) on the basis of its mass spectral fragmentation pattern discussed above; this evidence is considered quite convincing, particularly in view of the

(11) V. J. Traynelis and K. Yamauchi, unpublished work cited in reference 2.

(12) S. Oae, Y. Kitaoka, and T. Kitao, *Tetrahedron*, 20, 2677 (1964).

(13) See, for example: P. Kovacic and J. J. Hiller, Jr., *J. Org. Chem.*, 30, 1581 (1965); A. T. Jurewicz, J. H. Bayless, and L. Friedman, *J. Amer. Chem. Soc.*, 87, 5788 (1965).

(14) J. R. Shelton and C. W. Uzelmeier, *ibid.*, 88, 5222 (1966).

(15) R. M. Lusskin and J. J. Ritter, *ibid.*, 72, 5577 (1950); R. F. Borch, *J. Org. Chem.*, 34, 627 (1969).

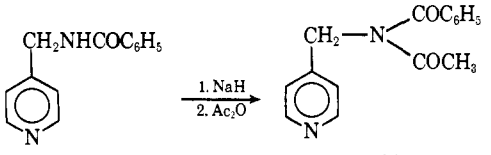
(16) A. J. Nun and K. Schofield, *J. Chem. Soc.*, 586 (1952).

(17) P. H. Dirstine and F. W. Bergstrom, *J. Org. Chem.*, 11, 55 (1946).

strong expectation that the ortho isomer would accompany the already identified meta and para isomers in the product mixture. The relative yields of the ortho, meta, and para isomers were 65, 7, and 28%, respectively.

In order to test the behavior of picolyl radicals in the presence of anisole, the reaction of 4-picoline *N*-oxide with pivalic anhydride was performed in anisole as solvent. Traynelis and Gallagher[7b] have presented fairly convincing evidence that this reaction produces a significant quantity of picolyl radicals.[18] A combined glpc–mass spectrum of the basic fraction revealed the existence of two compounds which are isomeric with the 4-(methoxybenzyl)pyridines but the mass spectral fragmentation pattern clearly showed that these compounds are not 4-(methoxybenzyl)pyridines. It is estimated that a yield of less than 1% of the latter could have been detected.

(b) Benzonitrile. The reaction of 4-picoline *N*-oxide (**1**) with acetic anhydride was performed in benzonitrile as solvent. In addition to the esters **3** and **4** (ratio 55:45), *N*-4-picolyl-*N*-acetylbenzamide (**14**) was produced in 11% yield. No significant amount of product resulting from attack of a picolyl group on the benzonitrile nucleus could be detected. The imide **14** was readily identified by its mass spectral fragmentation pattern: parent peak at *m/e* 254, a base peak at *m/e* 105 (benzoyl cation), and significant fragments at *m/e* 77 (phenyl) and *m/e* 43 (acetyl cation). The compound is identical, according to its glpc behavior and mass spectrum, with an authentic sample prepared by the treatment of *N*-4-picolylbenzamide (**13**) with sodium hydride followed by acetic anhydride.



13 14

The reaction of 4-picoline *N*-oxide with pivalic anhydride was also performed in solvent benzonitrile in order to study the behavior of picolyl radicals in that solvent. No detectable product arising from the reaction of picolyl groups with benzonitrile was found by combined glpc–mass spectrometry.

(c) Anisole and Benzonitrile. When the same reaction was performed in a mixture of anisole and benzonitrile, the product contained only those compounds which were found in the runs performed in the individual solvents. The yield of the picolylanisoles was 9%.

A control experiment demonstrated that none of the products involving solvent were generated by heating 4-pyridylcarbinol acetate (**3**) with acetic anhydride in this mixed solvent.

(d) Acetic Acid. The relative yields of **3** and **4** produced in acetic acid as solvent changes to 90% and 10%, respectively, and they are compared in Table I with those obtained in anisole, benzonitrile, and in the absence of diluent.

(18) For further evidence concerning this type of reaction in related systems, see ref 8 and 19.

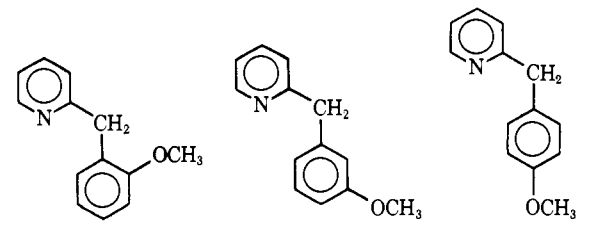
(19) H. Iwamura, M. Iwamura, T. Nishida, and S. Sato, *J. Amer. Chem. Soc.*, **92**, 7474 (1970).

Table I. Ester Composition from Reaction of 4-Picoline *N*-Oxide with Acetic Anhydride at 100°

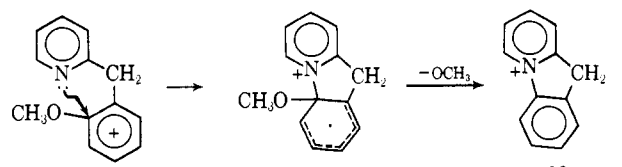
Solvent	% 4-pyridyl-carbinol acetate (**3**)	% 3-acetoxy-4-methyl-pyridine (**4**)
Acetic acid[a]	90	10
None[b]	70	30
Anisole[a]	55	45
Benzonitrile[a]	55	45

[a] Present work—6 hr. [b] Reference 4.

2-Picoline *N*-Oxide. (a) Anisole. The reaction of 2-picoline *N*-oxide (**5**) in anisole produced, in addition to the expected esters, **7**, **8**, and **9** (relative yields 76:12:12), a 2% yield of a mixture of three 2-(methoxybenzyl)pyridines (**15**). The structures of the latter compounds were assigned on the basis of the following evidence. (1) The glpc and mass spectral behavior of two of them is identical with that of an authentic mixture of 2-*m*-methoxybenzylpyridine (**15b**) and 2-*p*-methoxybenzylpyridine (**15c**) prepared by a benzyne reaction of *p*-bromoanisole with the anion of 2-picoline.[17] (2) One of these two compounds was assigned the para structure (**15c**) on the basis of its longer retention time and its intense peak at *m/e* 121 (*p*-methoxybenzyl cation, the other isomer has no significant 121 peak). The para-substitution product in the case of 4-picoline *N*-oxide also possesses these two characteristics. (3) Since the mass spectrum (see Experimental Section) of the third isomer obtained from 2-picoline *N*-oxide indicated that it has a picolyl group attached to an anisole ring, and since the meta and para isomers had been identified, it seems reasonable to assign the ortho structure (**15a**) to this compound. (4) The ortho isomer (**15a**) has the shortest retention time of the three and this is consistent with the behavior of the corresponding isomer from the 4-picoline *N*-oxide reaction. (5) The mass spectrum of the ortho isomer (**15a**) is strikingly different from those of the other two isomers and the difference can be explained very satisfactorily on the basis of the ortho structure. This compound exhibits an extremely intense peak (5 times more intense than any other in the mass spectrum) at *m/e* 168, whereas this is a minor peak in the case of the other two isomers. We attribute this peak to the cation **16** formed by the neighboring group participation shown.



15a 15b 15c



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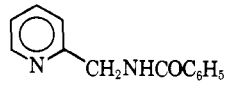
The relative proportions of the three isomers, ortho, meta, and para (**15a**, **b**, and **c**, respectively), were 57:4:39.

(b) Benzonitrile. The reaction of 2-picoline *N*-oxide with acetic anhydride produced, in addition to the three esters, **7**, **8**, and **9**, small yields of *N*-2-picolylbenzamide (**17**) and 3-phenyl-2,3a-diazaindene (**18**). The preliminary structure assignments, which resulted from mass spectrometric data, were confirmed by comparison of their glpc retention times and mass spectra with those of authentic samples. The amide (**17**) was prepared by benzoylation of 2-aminomethylpyridine and the diazaindene (**18**) by dehydration of the amide **17** with phosphorus oxychloride.[20] The combined yield of **17** and **18** was less than 2%.



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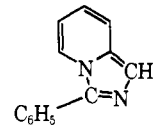

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(c) Acetic Acid. Within experimental error, the relative yields of the three esters **7**, **8**, and **9** were identical (76:12:12) for the reactions performed in acetic acid and in anisole.

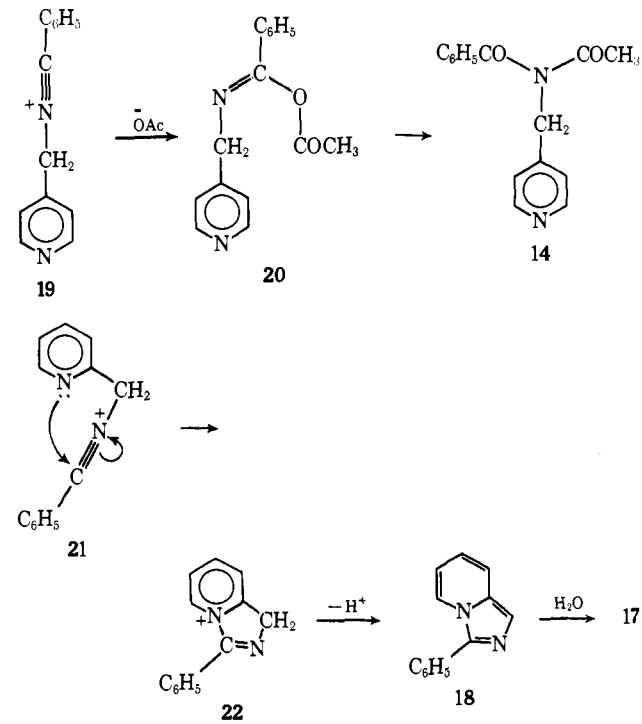
Discussion

Trapping by Anisole and Benzonitrile. The data strongly indicate that picolyl cations have been trapped in both solvents starting from either picoline *N*-oxide. The following arguments may be cited. (1) The intermediate picolyl groups substitute into the anisole nucleus very much more rapidly than into the benzonitrile nucleus. This is just the behavior expected of highly electrophilic particles, but the opposite from that expected of radicals. The benzonitrile ring is 10 times and twice as reactive as the anisole ring toward cyclohexylation and phenylation, respectively.[14] (2) The minor extent of attack of the picolyl group at the meta position of anisole and the substantial attack at the para position is also expected of electrophilic but not of radical substitution. The ortho:para and meta:para ratios are compared in Table II with those for several electrophilic and radical substitutions reported in the literature.[21] (3) Attack of the intermediates occurs exclusively at the nitrogen atom in the case of benzonitrile. As discussed above, this behavior is characteristic only of cations. Bond formation between the methylene groups of the picolyl cations and the nitrogen atom of the nitrile would be expected to produce the nitrilium ions **19** and **21**.[15] Nucleophilic attack of acetate ion on **19** would yield the imino ester **20**, which would readily undergo O to N acyl transfer,[22] to produce the imide (**14**), which was, indeed, the isolated product. In the case of **21**, the nitrogen atom of the pyridine ring is in an excellent position to execute the nucleophilic attack. Loss of a proton from the resulting cation (**22**) would then produce the aromatic system **18**. Hydrolysis of the latter during work-up would lead to the other solvent derived product, the amide **17** (dehydration of which is known to produce **18**[20]). (4) The treatment of 4-picoline *N*-oxide in anisole and in benzonitrile with pivalic anhydride, a reaction believed to produce picolyl radicals,[7b,18] did not yield any of the solvent-derived products that were formed by the reaction of the same amine oxide with acetic anhydride in these solvents.

Table II. Ortho:Para and Meta:Para Ratios in Electrophilic and Radical Substitutions into Anisole

Attacking species	Ortho:para	Meta:para
4-Picolyl[a]	2.3	0.25
2-Picolyl[a]	1.6	0.10
Electrophiles[b]	~0–1.9	~0–0.37
Radicals[c]	5.3–13.5	1.4–5.6

[a] Present work. [b] Reference 13. [c] Reference 14.

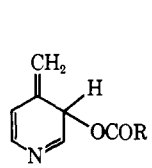


The rather high yield of trapped product in the 4 case makes it appear likely that a very high proportion of the N–O bonds cleave in a heterolytic manner. Indeed, the weakly nucleophilic solvent molecules compete surprisingly effectively with the acetate ions which are produced simultaneously and close to the picolyl cations. In the 2 case the yield of trapped product is much smaller, but in view of previous work discussed above, it seems reasonable to attribute this to inefficient trapping of the picolyl cation part of an ion pair rather than to homolytic cleavage. A rationalization for the inefficient trapping is given below.

Position of Nucleophilic Attack on the Picolyl Cation. In the 4-picoline *N*-oxide case, as can be seen from Table I, there is a dramatic increase in the ratio of 4-pyridylcarbinol acetate to 3-acetoxy-4-methylpyridine (from *ca.* 1.2 to 9) in proceeding from aromatic diluents to an acetic acid medium. Oae[12] had previously found that the reaction with butyric anhydride is intramolecular in aromatic solvents but increasingly intermolecular as the butyric acid concentration is increased. A simple interpretation of this data is that in the absence of external nucleophiles, the picolyl carboxylate ion pair collapses with negligible activation

(20) J. D. Brown and G. R. Ramage, *J. Chem. Soc.*, 2834 (1955).
(21) It seems justified to make the usual assumption here that electrophilic attack rather than the subsequent proton removal is rate determining.
(22) D. Y. Curtin and L. L. Miller, *Tetrahedron Lett.*, 1869 (1965).

energy and therefore rather unselectively to produce nearly equal amounts of the aromatic 4-pyridylcarbinol ester and the much less stable precursor (**23**) of 3-acyloxy-4-methylpyridine.[23] As the concentration of neutral carboxylic acid increases it becomes capable of executing a nucleophilic attack on the picolyl cation in competition with attack by the acylate anion, which in this type of medium may be hydrogen bonded to the carboxylic acid; however, attack by carboxylic acid, being much less exothermic than that by carboxylate ion, occurs mainly or exclusively at the 4-methylene group to yield the aromatic intermediate **24**, which is converted to product by a proton loss.



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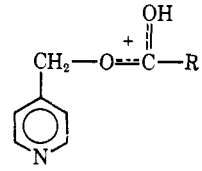

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It is of considerable interest in this regard that anisole and benzonitrile yield only products of attack on the 4-methylene group of the 4-picolyl cation; no product of attack at the 3 position could be detected by gas chromatography. Thus, these neutral molecules behave much like acetic acid molecules in that they combine with the intermediate to yield an aromatic system.

In the case of 2-picoline *N*-oxide, there is no change in the distribution of esters in proceeding from anisole to acetic acid as solvent. This is in excellent accord with Oae's finding that the rearrangement is intramolecular[4] even in the absence of diluent. We conclude that in both anisole and acetic acid the products are formed by the attack of internal acetate ion at the 2-methylene group (76%) and at the 3 and 5 ring positions (12% each). Given the proximity of the acetate ion, as formed, to the 2-methylene group, it is not surprising that collapse of the ion pair strongly favors production of 2-pyridylcarbinol acetate (**7**). Acetic acid, anisole, and benzonitrile are all rather ineffective in competition with the acetate anion at attacking the 2-picolyl cation. The latter two nucleophiles give 2% or less trapped material in marked contrast to the 4 case where much more trapping occurs. Once more the methylene group is the sole cite of attack by these neutral aromatic molecules.

This interpretation is also consistent with the findings by Hershenson and Bauer[24] that 2,6-lutidine *N*-oxide reacts with acetic anhydride in the presence of *tert*-butyl mercaptan to yield some 2-(*tert*-butylmercapto)-methyl-6-picoline but no product of attack of sulfur on the aromatic nucleus and that 2-picoline *N*-oxide reacts under the same conditions to yield 2-picolyl *tert*-butyl sulfide (13.5%) and 5-*tert*-butylmercapto-2-picoline (7.1%), but no 3-*tert*-butylmercapto-2-picoline. As is pointed out in the article, attack of the *tert*-butyl mercaptan at the 5 position probably does not occur by way of an anhydrobase intermediate. Thus, mercaptans attack the picolyl cations only at the methylene groups.

If we accept the postulate that attack of neutral species on 2- and 4-picolyl cations occurs nearly exclusively at the methylene position, then the pattern that Oae[3] has found for the reactions in acetic anhydride is understandable. In the 4 case, the acetic acid, when available in the environment of the 4-picolyl cation, is capable of competing fairly effectively with the acetate anion, which is probably further away, for attack on the 4-methylene group.[25] In the 2 case, at least two factors might be responsible for the inability of acetic acid in the environment to compete with internal acetate in attacking the 2-methylene group. (1) The acetate ion, as formed, is very close to the 2-methylene group. (2) The acetate group, both before and after fragmentation of the anhydrobase, because of its steric effect, probably decreases the concentration of solvent molecules in the vicinity of the methylene group. Of course, what we have said about the attack of acetic acid would be equally true with respect to anisole and benzonitrile; thus, the greater success that these solvents enjoy in intercepting the intermediate in the 4 case than in the 2 case is understandable.

Conclusions

The results of the reactions of 4- and 2-picoline *N*-oxides with acetic anhydride can most coherently be explained by assuming that the intermediate anhydrobases **2** and **6** dissociate mainly to ion pairs **11** and **10**.[26] These can collapse to form a mixture of nuclear and extranuclear acetoxylated picolines. Neutral nucleophilic species such as acetic acid, anisole, and benzonitrile in the environment are capable of attacking the 4-methylene group of the 4-picolyl cation (but not nuclear positions) in competition with intramolecular ion-pair collapse. These same neutral molecules are successful only to a minor extent in attacking the methylene group of the 2-picolyl cation, possibly because of steric hindrance caused by the acetate group and the favorable justaposition of this methylene group and the acetate ion for recombination to ester. The heretofore unexplained differences in the behavior of 2- and 4-picoline *N*-oxide in neat acetic anhydride, as demonstrated by Oae's labeling studies,[4] can readily be rationalized on this basis.

(23) G. W. Hammond, *J. Amer. Chem. Soc.*, 77, 334 (1955). Considering that attack at the 3 position is statistically favored by a factor of 2 and that the acetate, as formed, is probably closer to the 3 position than to the 4-methylene group, it is likely that even in this exothermic ion-pair collapse some selectivity in favor of the formation of aromatic product is manifested.

(24) F. M. Hershenson and L. Bauer, *J. Org. Chem.*, 34, 655 (1969).

(25) It is not certain how much of the small quantity of 3-acetoxy-4-methylpyridine (**4**) formed in acetic acid or of that formed under the higher temperature conditions (heating the neat reactants with a free flame until a vigorous reaction ensued) of the ^{18}O-labeling experiments[4] is produced in an intramolecular reaction. The simplest hypothesis is that it is all formed in an intramolecular process and that neutral solvents are only capable of attacking the methylene group. This hypothesis is not necessarily in conflict with the labeling data[4] which could result if the labeled oxygen atom (originally from the anhydride) of the internal acetate attacks the ring more frequently than the unlabeled oxygen atom (this was found to be true for one of the nuclear substituted esters in the 2 case[5]) and if the phenolic ester undergoes some acetyl exchange with the medium. There is some evidence for such exchange from an experiment[5] in which a mixture of the two esters with an average ^{18}O content of 0.71 atom % was heated in unlabeled acetic acid–acetic anhydride (probably at a considerably lower temperature than in the rearrangement study); the ^{18}O content of the esters decreased to 0.68%. Assuming that the mixture contained 33% 3-acetoxy compound,[5] complete exchange of only the phenolic acetyl group would have given 0.63 atom % ^{18}O.

(26) In order to explain the small yields of methylated picolines and carbon dioxide[2] and the recent CIDNP results[19] it is necessary to assume a minor degree of N–O bond homolysis as well. The degree of homolysis increases significantly when it can become concerted with decarboxylation to produce a stable alkyl radical.[8]

Experimental Section

Melting points were determined on a Kofler block utilizing a stage calibrated thermometer and are thus corrected. Boiling points are uncorrected. Reactions involving picoline *N*-oxides and anhydrides were performed under a continuous stream of nitrogen. Infrared spectra were determined on a Beckman IR-8 spectrophotometer. Proton magnetic resonance spectra were determined on a Varian A-60 instrument; chemical shifts are reported on the τ scale, relative to internal tetramethylsilane. Analytical gas chromatography was performed on F and M 1609 or Varian 1520 A instruments equipped with flame ionization detectors and disc integrators. For determining yields, the flame responses of authentic samples were calibrated against those of various standards. Isomers were assumed to have identical flame responses; this was shown to be true in several cases. Mass spectra were determined at 70 eV on an LKB-9000 combined gas chromatograph–mass spectrometer; the *m/e* values are reported for major peaks followed in parentheses by the intensity as a per cent of the intensity of the base peak.

Reagents. Acetic anhydride was distilled from a 5% quinoline solution through a 6-in. Vigreux column. The fraction bp 135–137° was collected. 4-Picoline *N*-oxide (Beacon) was recrystallized from acetone. 2-Picoline *N*-oxide (Beacon) was distilled through a 6-in. Vigreux column. The fraction bp 91–93° at 0.1 Torr was collected and stored in a vacuum desiccator over Drierite.

Reaction of 4-Picoline *N*-Oxide with Acetic Anhydride in Anisole. A solution of 9.0 g (0.095 mol) of 4-picoline *N*-oxide in 30 ml of chloroform was added dropwise over a period of 1 hr to a solution of 32 g (0.31 mol) of acetic anhydride in 100 ml of anisole at a bath temperature of 100°.

The low boiling components were distilled from a portion of the mixture to a head temperature of 90° (24 Torr) and the residue was analyzed on a 6 ft × 0.25 in. 3% OV 17 column. The temperature of 75°, used for analysis of the esters, was raised to 175° after 28 min. The peaks which emerged were: (1) 3-acetoxy-4-methylpyridine (**4**, 14.2 min), (2) 4-pyridylcarbinol acetate (**3**, 19.2 min), (3) 4-*o*-methoxybenzylpyridine (31.0 min), (4) 4-*m*-methoxybenzylpyridine (31.5 min), and (5) 4-*p*-methoxybenzylpyridine (32.0 min). Peak 1 had the expected mass spectrum with significant peaks at *m/e* 151 (13), 109 (100), 80 (22), 43 (75). Peak 2 had an identical glpc retention time with that of an authentic sample[27] as well as the expected mass spectrum: *m/e* 151 (26), 109 (100), 108 (27), 92 (20), 80 (25), 43 (91). Peak 3 exhibited the following mass spectrum: *m/e* 199 (100), 184 (29), 168 (20), 167 (19), 121 (26), 92 (25); peak 4: *m/e* 199 (100), 184 (20), 121 (32); peak 5: 199 (100), 184 (25), 121 (80). The major fragments for glpc peaks 3–5 are assigned in the "Results" section. The material comprising peaks 4 and 5 had identical retention times on three columns and identical mass spectra with independently prepared samples of 4-*m*- and 4-*p*-methoxybenzylpyridine, respectively. The yield of the three 4-(methoxybenzyl)pyridines was determined to be 19.6% by glpc using the same OV-17 column at 190° and triphenylmethane as a standard. The relative yields of the isomers are reported in the "Results" section.

In a second run in the absence of chloroform and a lower ratio of anisole (15 ml) to anhydride (10.1 g), 1.08 g (9.9 mmol) of amine oxide yielded 46% of the esters and 9% of the picolylanisoles.

4-*p*-Methoxybenzylpyridine. 4-*p*-Aminobenzylpyridine was prepared from 4-*p*-nitrobenzylpyridine (obtained by nitration[16] of 4-benzylpyridine) in the following manner.[28] A solution of 7.2 g (0.034 mol) of the nitro compound in 50 ml of methanol was added dropwise at room temperature to a stirred mixture of 0.34 g of 10% palladium on charcoal suspended in a solution of 6.7 g of sodium borohydride in 50 ml of water through which a stream of nitrogen was passed. After the addition, the solution was filtered to remove catalyst and acidified with 10% HCl in order to destroy excess borohydride. The aqueous solution was made basic with sodium carbonate and extracted with chloroform (3 × 25 ml). Evaporation of the dried (sodium carbonate) extract and recrystallization of the solid residue from ethanol yielded 3.98 g (60%) of 4-*p*-aminobenzylpyridine: mp 138–140°; nmr ($CDCl_3$) τ 1.50–1.60 (q, two α protons of pyridine), 2.90–3.50 (m, 6 aromatic protons), 6.20 (s, CH_2), and 6.68 (s, NH_2).

To a magnetically stirred solution of 5.6 g of this amine in 80 ml of methanol and 20 ml of concentrated sulfuric acid was added slowly at 0° 4.6 g of sodium nitrite. The cold solution was stirred for an additional 45 min and was then heated at reflux for 4 hr. After the heating period the solution was diluted with 100 ml of water, made basic with concentrated aqueous ammonia, and extracted with three 25-ml portions of chloroform. The extract was dried over sodium sulfate, treated with Norite, and evaporated. The resulting light yellow oil, which exhibited one glpc peak, weighed 3.1 g (50%). It was treated with excess aqueous picric acid and the resulting picrate was recrystallized once from ethanol–acetone. Its acetone solution was treated with Norite and it was recrystallized from ether to give a light yellow solid, mp 184.0–184.5°. *Anal.* Calcd for $C_{19}H_{16}N_4O_8$: C, 53.28; H, 3.76. Found: C, 53.15, 53.07; H, 3.64, 3.67.

4-*m*- and 4-*p*-Methoxybenzylpyridine. The procedure was related to that used by Dirstine and Bergstrom[17] for the phenylation of 2-picoline using chlorobenzene.

To 500 ml of liquid ammonia was added with magnetic stirring 9.5 g (0.41 g-atom) of sodium and a small amount of ferric chloride. The solution was stirred until the blue color disappeared indicating formation of sodamide. 4-Picoline (18 g, 0.22 mol) was added dropwise over a 15-min period and the solution was stirred for an additional 15 min. *p*-Bromoanisole (Aldrich) (20 g, 0.10 mol) was then added dropwise over a period of 30 min, the solution was stirred for an additional 20 min, excess ammonium chloride was added, and the ammonia was removed by addition of 150 ml of ether followed by warming on a water bath. The residue was dissolved in water and the aqueous solution was acidified with 10% hydrochloric acid. The aqueous acid layer was removed, made basic with sodium carbonate, and extracted with five 50-ml portions of chloroform. The combined chloroform extract was dried over magnesium sulfate and evaporated. A 5-ml sample of the resulting red oil was chromatographed on 50 g of Brockman Basic Alumina (Fisher) with chloroform as eluent to yield 1.70 g of yellow oil which was shown by glpc to contain only 4-*m*- and 4-*p*-methoxybenzylpyridine. The mass spectra of the two products were identical with those reported above for these compounds obtained in the reaction of 4-picoline *N*-oxide with acetic anhydride in anisole, and the compound assigned the para structure had identical glpc behavior with that of the authentic sample.

Reaction of 4-Picoline *N*-Oxide with Acetic Anhydride in Benzonitrile. A solution of 9.9 g (0.092 mol) of 4-picoline *N*-oxide and 26 g (0.26 mol) of acetic anhydride in 50 ml of benzonitrile was heated for 26 hr at 103°. The low boiling material was removed by distillation to a head temperature of 120° (21 Torr). Analytical glpc on OV-17 indicated the presence of the two esters **4** and **3** (ratio 45:55, retention times 8.6 and 11 min, respectively, at 125°) and *N*-4-picolyl-*N*-acetylbenzamide (**14**, 38 min at 250°). By nmr, using anisole as a standard, the yields of 4-pyridylcarbinol acetate (**3**) and the imide (**14**) were determined to be 21.3% and 10.9%, respectively. The total yield of esters was, thus, 38.8%. The glpc retention time and mass spectrum of the imide were identical with those of an authentic sample. The mass spectrum is reported below.

***N*-4-Picolylbenzamide (13).** To a stirred solution of 14.6 g (0.135 mol) of 4-aminomethylpyridine (Aldrich) and 12 ml of pyridine in 25 ml of benzene was added dropwise 20.6 g (0.146 mol) of benzoyl chloride over a period of 1 hr. After the mixture had been stirred for an additional 4 hr, water was added and the resulting solution was made basic with concentrated ammonia and extracted with chloroform. The solid residue from evaporation of the dried (magnesium sulfate) extract was recrystallized from ether–acetone to yield 21.2 g (74%) of *N*-4-picolylbenzamide: mp 119.0–119.5° (lit.[29] mp 108°); ir ($CHCl_3$) 3440, 3318 (NH), 1650 (CO) cm^{-1}; nmr in $CDCl_3$ τ 1.40–1.59 (q, two α-protons of pyridine), 2.33–2.92 (m, 8 protons, aromatic and NH), 5.30–5.58 (d, CH_2).

***N*-4-Picolyl-*N*-acetylbenzamide (14).** A solution of 0.120 g (0.576 mmol) of *N*-4-picolylbenzamide in 10 ml of toluene was heated at reflux for 12 hr in the presence of 0.370 g (17.0 mmol) of suspended sodium hydride. Acetic anhydride was then added and the reaction mixture was heated at reflux for an additional 12 hr, cooled, and quenched with excess ethanol. After ether had been added to the reaction mixture, it was extracted with four 10-ml portions of 10% hydrochloric acid and the extract was made basic with sodium carbonate and extracted with four 10-ml portions of chloroform. Upon evaporation of the dried chloroform solution there was obtained 10 mg of red oil which had a glpc retention time and mass spectrum identical with those of the imide (**14**) from the

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

(28) T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).

(29) R. Graf, G. Perathoner, and M. Tatzel, *J. Prakt. Chem.*, **146**, 88 (1936).

reaction of 4-picoline *N*-oxide with acetic anhydride in benzonitrile: mass spectrum 254 (13), 107 (15), 106 (10), 105 (100), 77 (43), 51 (14), 43 (20), 39 (6).

Reaction of 4-Picoline *N*-Oxide with Acetic Anhydride in Benzonitrile and Anisole. A solution of 8.41 g (0.0760 mol) of 4-picoline *N*-oxide and 26.7 g (0.262 mol) of acetic anhydride in 25 ml of benzonitrile and 25 ml of anisole was heated for 6 hr at 101°. The reaction mixture was worked up as in the runs in the individual solvents and the products were the same. The yield of 4-(methoxybenzyl)pyridines was 9.0 ± 2%. Because of interference by other signals, the yield of imide could not be determined by the nmr method used in the benzonitrile run. In a control experiment, a solution of 1.18 g (7.8 mmol) of 4-pyridylcarbinol acetate and 1.94 g (19.0 mmol) of acetic anhydride in 20 ml of the same mixed solvent was heated for 6 hr at 97°. No solvent-derived products could be detected.

Reaction of 4-Picoline *N*-Oxide with Acetic Anhydride in Acetic Acid. A solution of 1.40 g (12.8 mmol) of 4-picoline *N*-oxide and 1.59 g (15.5 mmol) of acetic anhydride in 15 ml of acetic acid was heated for 6 hr at 100°. The relative yields of 3-acetoxy-4-methylpyridine and 4-pyridylcarbinol acetate as found by glpc are reported in Table I.

Reaction of Pivalic Anhydride with 4-Picoline *N*-Oxide in Anisole. A solution of 1.34 g (12.2 mmol) of 4-picoline *N*-oxide and 3.04 g (16.3 mmol) of pivalic anhydride in 25 ml of anisole was heated for 16 hr at 101° in a system equipped with a Dry Ice trap and an Ascarite (Fisher) tube for carbon dioxide absorption. This gas was produced in 41% of theory. Basic and neutral fractions were separated by extraction techniques and submitted to glpc on OV-17. The neutral fraction was devoid of products. The basic fraction contained nine peaks, the mass spectra of which indicated that three were due to *tert*-butylpicolines, two to esters (4-pyridylcarbinol-pivalate and 3-trimethylacetoxy-4-methylpyridine), one to a *tert*-butylneopentylpyridine, one to a *tert*-butylbipicolyl, and two contained the elements of both a picolyl and an anisyl group. The mass spectra of the latter two components were different from any of those recorded for the three 4-(methoxybenzyl)pyridines obtained from the reaction of 4-picoline *N*-oxide with acetic anhydride in anisole. Mass spectrum of the component of retention time 31.5 min was: *m/e* 199 (32), 198 (18), 184 (28), 183 (100), 169 (14), 122 (8), 106 (74), 93 (16), 92 (9), 79 (23), 77 (28), 65 (19), 51 (17), 39 (30). That of retention time 33.5 min was: *m/e* 199 (100), 184 (36), 183 (38), 168 (21), 167 (18), 156 (9), 121 (24), 93 (11), 91 (25), 77 (13), 65 (14), 57 (20), 39 (19). The maximum yield of these components is estimated to be 1.5%.

Reaction of Pivalic Anhydride with 4-Picoline *N*-Oxide in Benzonitrile. This reaction yielded the same products as the same reaction in anisole except for the *tert*-butylneopentylpyridine and the two containing the anisyl group. No solvent-derived products could be detected by glpc.

Reaction of 2-Picoline *N*-Oxide with Acetic Anhydride in Anisole. A solution of 2.52 g (23.1 mmol) of 2-picoline *N*-oxide and 2.77 g (27.1 mmol) of acetic anhydride in 20 ml of anisole was heated for 6 hr at 101°. After the volatile materials had been removed from a portion of the reaction mixture, the residue was analyzed on a 10 ft × 0.125 in. 3% OV-17 column at a nitrogen flow rate of 30 ml/min and a temperature program of 4°/min from 100°. The following peaks were identified: (1) 3-acetoxy-2-methylpyridine (**9**, 9.0 min), (2) 5-acetoxy-2-methylpyridine (**8**, 9.8 min), (3) 2-pyridylcarbinol acetate (**7**, 10.7 min), (4) 2-*o*-methoxybenzylpyridine (**15a**, 20.9 min), (5) 2-*m*-methoxybenzylpyridine (**15b**, 21.7 min), (6) 2-*p*-methoxybenzylpyridine (**15c**, 22.1 min). The yield of esters (75.7 ± 2.5%) and the composition of the combined esters (see "Results") were determined on the same column at 100° utilizing 2-methoxynaphthalene as a standard. The yield of the picolylanisoles (2%) and the relative quantities of each (ortho, 56.8 ± 1%; meta, 3.9 ± 1%; para, 39.4 ± 1%) were determined on this column at 165° with triphenylmethane as a standard. The three esters were identified by comparison of their relative retention times and mass spectra with those reported.[30] The identification of the picolylanisoles (see "Results") is based on comparison of the meta and para isomers with independently prepared samples as well as gas chromatographic and the following mass spectral data: 2-*o*-methoxybenzylpyridine, *m/e* 199 (1), 184 (4), 169 (17), 168 (100), 167 (20), 154 (7), 106 (7), 93 (8), 91 (10), 78 (10), 77 (7), 65 (9), 51 (10), 39 (7); 2-*m*-methoxybenzylpyridine, *m/e* 199 (41), 198 (100), 184 (17), 183 (18), 169 (9), 168 (13), 167 (10), 156 (12), 154 (14), 106 (5), 93 (4), 91 (5), 78 (14), 77 (8), 65 (8), 51 (11), 39 (8); 2-*p*-methoxybenzylpyridine, *m/e* 199 (85), 198 (100), 184 (68), 167 (16), 156 (17), 154 (17), 121 (37), 78 (26), 77 (17), 65 (10), 52 (10), 51 (20), 50 (7), 39 (10).

2-*m*- and *p*-Methoxybenzylpyridine (15b and 15c). To a magnetically stirred solution of 40 g (1.00 mol) of sodamide (Fisher) in 500 ml of liquid ammonia was added dropwise over a period of 15 min, 46 g (0.50 mol) of 2-picoline. After the solution had been stirred for an additional 15 min, 47 g (0.25 mol) of *p*-bromoanisole (Aldrich) was added dropwise over a period of 30 min, the solution was stirred for an additional 20 min, and 50 g of ammonium chloride was added. Ammonia was removed by adding 200 ml of ether and warming on a water bath. Water (100 ml) and 10% hydrochloric acid (300 ml) were added and the aqueous acid solution was extracted with two 100-ml portions of ether, made basic with potassium carbonate, and extracted with four 100-ml portions of chloroform. The combined chloroform extract was dried over magnesium sulfate and evaporated.

Distillation of the residue yielded 19.7 g (39.6%) of crude 2-*m*- and 2-*p*-methoxybenzylpyridine, bp 120–126° at 0.3 Torr. The crude product was redistilled yielding a mixture of the two isomers, bp 113–114° at 0.4 Torr. The two products having glpc retention times of 4.9 min for 2-*m*-methoxybenzylpyridine and 5.3 min for 2-*p*-methoxybenzylpyridine (10 ft × 0.125 in. 3% OV-17 column at a carrier flow rate of 30 ml/min and a column temperature of 185°) were identical by glpc and mass spectral analysis with the corresponding products from the reactions of 2-picoline *N*-oxide with acetic anhydride in anisole.

Reaction of 2-Picoline *N*-Oxide with Acetic Anhydride in Benzonitrile. A solution of 2.07 g (19.0 mmol) of 2-picoline *N*-oxide and 7.41 g (72.6 mmol) of acetic anhydride in 20 ml of benzonitrile was heated at 100° for 6 hr. The volatile material was removed from a portion of the reaction mixture and the residue was examined on a 10 ft × 0.125 in. 3% OV-17 column with a nitrogen flow rate of 30 ml/min and a temperature program of 4°/min from 100°. The following peaks were identified: (1) 3-acetoxy-2-methylpyridine (**9**, 7.1 min), (2) 5-acetoxy-2-methylpyridine (**8**, 7.8 min), (3) 2-pyridylcarbinol acetate (**7**, 8.8 min), (4) 3-phenyl-2,3a-diazaindene (**18**, 22.6 min), and (5) *N*-2-picolylbenzamide (**17**, 24.4 min). The diazaindene (**18**) had a retention time and mass spectrum which were identical with those of an authentic sample, prepared[20] by dehydration of *N*-2-picolylbenzamide (**17**).[29] Mass spectrum of **18** showed *m/e* 194 (100), 193 (60), 103 (5), 91 (20), 77 (8), 64 (35), 63 (25), 51 (10). Mass spectrum of **17** showed *m/e* 212 (5), 169 (36), 107 (82), 105 (100), 92 (18), 77 (68), 65 (9), 51 (27).

Reaction of 2-Picoline *N*-Oxide with Acetic Anhydride in Acetic Acid. A solution of 4.43 g (40.5 mmol) of 2-picoline *N*-oxide and 5.06 g (49.5 mmol) of acetic anhydride in 15 ml of acetic acid was heated for 6 hr at 100°. The relative yields of esters were identical with those from the same reaction in anisole.

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