Aromatic N-Oxides. VIII. Dual Bond Cleavage of the Anhydro Base Intermediate in 4-Alkylpyridine N-Oxide–Acid Anhydride Reactions[1-3]

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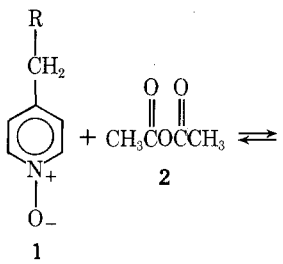
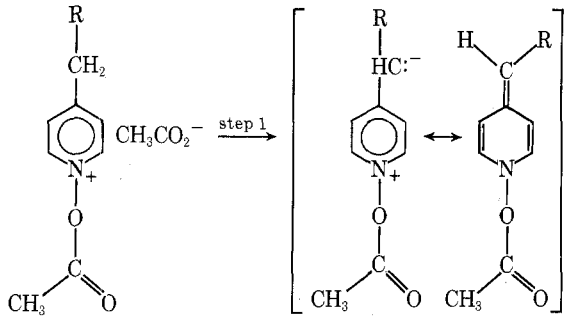
The CIDNP effect in the reaction of 4-methylpyridine N-oxide and acetic anhydride was confirmed for the partial formation of ester **5** (R = H); however, attempts to observe the CIDNP effect using 4-neopentylpyridine N-oxide or 4-benzylpyridine N-oxide proved negative. The NMR study with 4-benzylpyridine N-oxide–acetic anhydride revealed a transient intermediate assigned to anhydro base **4** (R = C_6H_5). 1-Acetoxy-4-methylpyridinium perchlorate in neutral refluxing acetonitrile was stable while addition of tri-*n*-butylamine gave ester and alkylpyridine products similar in yield to those from the reaction of 4-methylpyridine N-oxide and acetic anhydride under comparable corditions.These results are interpreted via a dual bond cleavage of anhydro base **4**.

The generally accepted mechanistic pathway for the reaction of 4-alkylpyridine N-oxides and acid anhydrides has been reviewed previously[1,5,6] and is outlined below. Step 1 has been established as rate determining[7,8] and evi-

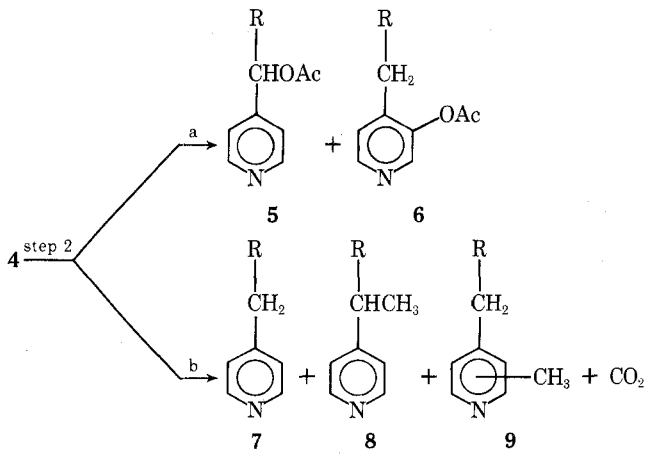


1 + CH_3COCCH_3 ⇌ **2**



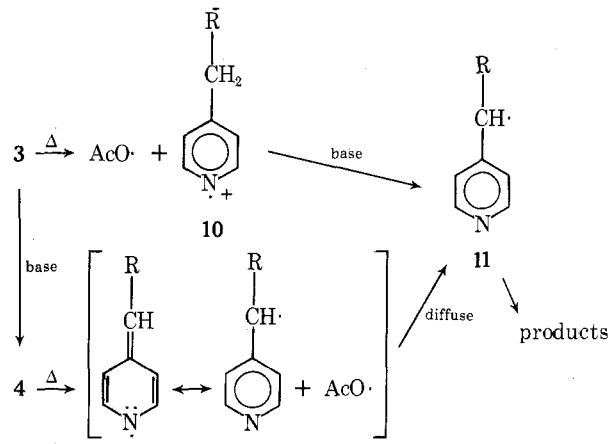
3 → **a** **4** **b**

dence has been obtained for the intermediacy of the anhydro base **4**;[7] however, the formation of esters **5** and **6** via step 2a has been somewhat controversial. Recent evidence[1,6] fa-



vors the heterolytic fragmentation of the N–O bond of **4** producing ion pairs which on recombination form **5** and **6**. The alternate explanation entailed homolytic fission of the N–O bond forming radical pairs which can recombine to give **5** and **6** or diffuse and lead to **7**, **8**, **9**, and carbon dioxide.[9-12] Iwamura and coworkers[13] have reported the CIDNP effect in the generation of **5** (R = H) and proposed that at least a portion of ester formation occurred via recombination of radical pairs. They also observed the CIDNP effect in the formation of methane and ethylpyridine (**8**, R = H) supporting their radical origin. Although evidence for the presence of radicals in these reactions is substantial, the source of radicals has not been established. In this report we wish to describe the source of free radicals, to provide additional evidence for the intermediate anhydro base **4**, and to present some results of CIDNP studies.

A review of the mechanistic pathway reveals two intermediates that seem to be reasonable candidates for radical production: the 4-alkyl-1-acetoxypyridinium ion (**3**), as initially suggested by Boekelheide and Harrington,[14] or the anhydro base **4**. In either case homolytic N–O bond fission is required as the initial step. Fragmentation of **3** leads to radical cation **10**, which upon deprotonation forms radical **11** that proceeds to products, while N–O bond cleavage of **4** produces radical pairs which can liberate **11** via diffusion.



The reaction of 4-methylpyridine N-oxide with acetic anhydride in refluxing acetonitrile produced CO_2 (13.5%), 4-methylpyridine (**7**, R = H) (9.3%), 2,4-lutidine (**9**, R = H) (0.9%), 4-ethylpyridine (**8**, R = H) (3.1%), 4-pyridylmethyl acetate (**5**, R = H) (17%), and 4-acetoxy-4-methylpyridine (**6**, R = H) (16%). When 1-acetoxy-4-methylpyridinium perchlorate in refluxing acetonitrile was treated with tri-*n*-butylamine under the same conditions as the preceding experiment, the products formed were CO_2 (4.8%), 4-methylpyridine (4.7%), and a mixture of 4-pyridylmethyl acetate and 3-acetoxy-4-methylpyridine (15%). In this latter experiment the yields are somewhat reduced but both radical products and esters were formed in about the same ratio. However, if 1-acetoxy-4-methylpyridinium perchlo-

rate were refluxed alone in acetonitrile for the same time as in the above two experiments, no evolution of carbon dioxide was observed and upon work-up the 1-acetoxy-4-methylpyridinium ion was hydrolyzed to regenerate 86% of 4-methylpyridine *N*-oxide.

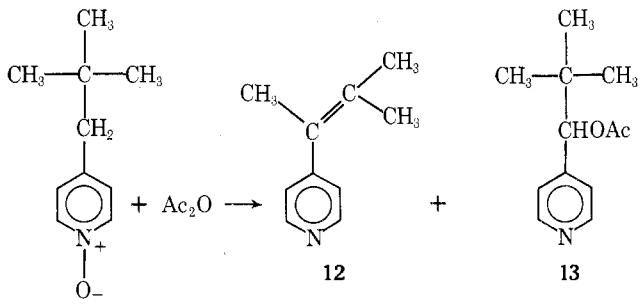
The homolytic N–O bond fragmentation of **3** under neutral conditions should be detectable by the loss of carbon dioxide from the acetoxy radical produced. No carbon dioxide was evident in the last experiment. These experiments clearly demonstrated that 1-acetoxy-4-methylpyridinium ion (**3**, R = H) is thermally stable under conditions that permit the anhydro base **4** (R = H) to fragment, producing esters and radical-originated products. Therefore, we assign the origin of radicals to the homolytic N–O cleavage of **4** followed by diffusion. Since **4** also serves as the source of esters via heterolytic fission followed by ion-pair recombination, we encounter here an example of a dual bond cleavage process (competing heterolytic and homolytic fission) for **4**. The effect of structure variation in the reactants on enhancing heterolytic N–O bond fission or homolytic fission has been summarized in a previous paper.[1]

The reaction of 4-benzylpyridine *N*-oxide and acetic anhydride was studied previously and provided spectroscopic evidence (uv) for the intermediacy of the anhydro base (**4** R = C_6H_5) in rearrangement to ester **5**, R = C_6H_5.[7] We have reexamined this reaction looking especially for radical-generated products and obtained the following results: CO_2 (2%), 4-benzylpyridine (20%), and 1-phenyl-1-(4-pyridyl)-methyl acetate (**5**, R = C_6H_5) (54%). A careful search for 1-phenyl-1-(4-pyridyl)ethane (**8**, R = C_6H_5) revealed the absence of this material. Carbon dioxide formation has been taken as a minimum measure of radical production and usually exceeds the amount of alkylpyridines formed in the reaction.[12] The low yield of carbon dioxide and absence of **8** (R = C_6H_5) is consistent with a low production of radicals; however, the unusually high yield of 4-benzylpyridine is puzzling.

During an NMR study of the 4-benzylpyridine *N*-oxide–acetic anhydride reaction a transient absorption signal (singlet) was observed at δ 5.65. This band reached a maximum intensity at about 35 sec reaction time and decayed to zero in about 100 sec reaction time. The formation of ester **5** (R = C_6H_5) was complete in 160 sec. The assignment made to the δ 5.65 band is the exocyclic proton of the anhydro base **4b** (R = C_6H_5) and we offer this observation in support of the intermediacy of the anhydro base **4** in the formation of ester **5** (R = C_6H_5). The polyolefinic structure of **4b** (R = C_6H_5) has been established as the preferred structure in classical anhydro bases which show absorption of exocyclic olefinic protons at δ 5.2–5.4.[15]

Although the evidence appears convincing[1,6] that ester **5** formation proceeds by heterolytic N–O bond fission of the anhydro base **4** followed by recombination of ion pairs, we note above that the anhydro base **4** also undergoes homolytic N–O bond cleavage. Iwamura and coworkers[13] attributed the CIDNP effect observed in the reaction of 4-methylpyridine *N*-oxide and acetic anhydride to ester **5** formation by recombination of radical pairs. We have repeated Iwamura's work to develop our technique in observing the CIDNP effect in these *N*-oxide reactions. Our results with the reaction of 4-methylpyridine *N*-oxide and acetic anhydride (studied at six different temperatures, 70–140 ± 0.5°) were essentially identical with those of Iwamura.

CIDNP studies were extended to reactions of 4-neopentylpyridine *N*-oxide and 4-benzylpyridine *N*-oxide with acetic anhydride. In the case of 4-neopentylpyridine *N*-oxide, the products of reaction with acetic anhydride were 2-(4-pyridyl)-3-methyl-2-butene (**12**, 54%) and 1-(4-pyridyl)-2,2-dimethyl-1-propyl acetate (**13**, 31%).[1] An appreciable degree of reaction was diverted by carbon skeletal rearrangement via carbonium ions followed by elimination and thus favored a substantial, if not exclusive, contribution of ion-pair formation from anhydro base **4** (R = t-Bu). A search for the CIDNP effect in this reaction was negative. Likewise an NMR study of the 4-benzylpyridine *N*-oxide–acetic anhydride reaction showed no CIDNP effect (neither emission nor enhanced absorption) for any bands associated with 1-phenyl-1-(4-pyridyl)methyl acetate (**5**, R = C_6H_5) or 4-benzylpyridine. Thus the absence of the CIDNP effect in the 4-neopentylpyridine and 4-benzylpyridine *N*-oxides reduces the prospects of ester **5** formation via radical pairs and further strengthens the ion pair mechanism.



1 (R = *t*-Bu)

Experimental Section

4-Benzylpyridine *N*-oxide, mp 104–106° (recrystallized from dry benzene, lit.[7] mp 104–105°), was prepared in 86% yield from 4-benzylpyridine[16] (50 g, 0.29 mol), glacial acetic acid (150 ml), and 30% H_2O_2 (70 ml) by the method of Hands and Katritzky.[17]

Reaction of 4-Benzylpyridine *N*-Oxide with Acetic Anhydride. The apparatus used for this reaction was described previously.[12] A solution of 4-benzylpyridine *N*-oxide (9.0 g, 48.6 mmol) and acetic anhydride (50 ml, 530 mmol) was refluxed under N_2 for 3.0 hr. Rapid titration[18] of aliquots taken from the $Ba(OH)_2$ traps showed that 0.99 mmol (2%) of CO_2 had been evolved. GLC analysis[19] of the crude reaction mixture showed the presence of acetic anhydride, 4-benzylpyridine (R_f 4.5 min), 1-phenyl-1-(4-pyridyl)methanol[20] (R_f 6.6 min), 1-phenyl-1-(4-pyridyl)methyl acetate (R_f 8.8 min), and a small amount of unidentified material (R_f 10.5 min). Addition of authentic samples to the crude mixture gave peak enhancement without distortion; however, addition of 1-phenyl-1-(4-pyridyl)ethane[21] to the reaction mixture gave a new peak (R_f 5.4 min).

The reaction mixture was treated with water (100 ml), basified (solid $NaHCO_3$), and extracted ($CHCl_3$). The extract was decolorized (Nuchar) and dried ($MgSO_4$) and the solvent was removed in vacuo to give 8.9 g of a brown liquid residue. NMR analysis of the residue[22] showed the presence of 20% 4-benzylpyridine and 80% 1-phenyl-1-(4-pyridyl)methyl acetate. The brown residue (8.8 g) was chromatographed on Fluorisil (200 g, 60–100 mesh) and elution with benzene gave 6.4 g (58%) of 1-phenyl-1-(4-pyridyl)methyl acetate. Further elution with $CHCl_3$–benzene (4:1) gave 4-benzylpyridine (1.67 g, 20%). The ir and NMR were identical with those of known samples.

Chemically Induced Dynamic Nuclear Polarization (CIDNP) Studies. A. 4-Methylpyridine *N*-Oxide with Acetic Anhydride.[13] A solution of 4-methylpyridine *N*-oxide[16] (130 mg, 1.2 mmol) in acetic anhydride (0.60 ml, 6.2 mmol) was placed in a precision NMR tube and frozen rapidly (Dry Ice–acetone). The sample was degassed by bubbling N_2 through the solution as thawing occurred, and the tube was sealed under N_2 with a pressure cap and refrozen (−70°) until used. The sample (thawed in a water bath to room temperature) was inserted into a preheated (90° ± 0.5°) NMR cavity[23] and spectrum scanning was begun immediately at a sweep rate of 500 Hz/100 sec. In 9 sec emission (E) and enhanced absorption signals (A) appeared at δ 5.13 (E) (s, 4-$CH_3CO_2CH_2C_5H_4N$); 2.86 (E), 2.73 (E), 2.60 (A), 2.46 (A) (q, 4-$CH_3CH_2C_5H_4N$); 1.33 (E), 1.21 (A), 1.08 (A) (t, 4-$CH_3CH_2C_5H_4N$);

and 0.05 (E) (s, CH_4). In addition a singlet at δ 1.91 (4-$CH_3CO_2CH_2C_5H_4N$) showed no E or A and increased steadily to a constant absorption (in ca. 180 sec), while a singlet at δ 2.36 (4-$CH_3C_5H_4N^+O_2CCH_3$) with no E or A decreased in intensity to zero (ca. 180 sec). These signal assignments were made by comparison with spectra of authentic samples.

Repetitive scans were run over selected regions of the spectrum to monitor peak intensities vs. time. The intensity of the emission singlet at δ 5.13 passed through a maximum at ca. 40 sec, decayed to an apparent zero in ca. 110 sec, and grew to a constant absorption intensity in ca. 180 sec.[24] The skewed quartet (E and A) at δ 2.86–2.46 and the triplet (E and A) at δ 1.33–1.08 passed through maximum intensity at ca. 55 sec (irrespective of sign) and reached a constant absorption value in ca. 400 sec.[24] The emission singlet at δ 0.05 was not rigorously obsrrved as a function of time.

Additional studies of the reaction of 4-methylpyridine N-oxide with acetic anhydride was made at the following temperatures: 70, 106, 123, 134, and 140° (±0.5°). In every instance the same E and A signals were observed with slight variation of signal intensity with temperature.

B. 4-Neopentylpyridine N-Oxide with Acetic Anhydride. NMR tubes containing 4-neopentylpyridine N-oxide[1] (100 mg, 0.66 mmol) and acetic anhydride (0.50 ml, 5.14 mmol) were prepared as described above and the reaction was studied at the following temperatures: 70, 90, 106, 123, 134, and 140° (±0.5°). No indication of any CIDNP effect (E or A) was observed under any of these conditions in any region of the spectrum. The NMR spectrum of samples run at 70, 90, or 106° exhibited no change over a period of 1 hr; however runs at 123, 134, and 140° exhibited the steady growth of an absorption signal at δ 5.5 due to the methine proton of 1-(4-pyridyl)-2,2-dimethyl-1-propyl acetate. Assignment was confirmed by comparison with the spectrum of an authentic sample. Five NMR samples were combined after the CIDNP studies and analysis by GLC gave results comparable to those previously reported.[1]

C. 4-Benzylpyridine N-Oxide with Acetic Anhydride. Using the above procedure the reaction of 4-benzylpyridine N-oxide (111 mg, 0.60 mmol) and acetic anhydride (0.50 ml, 5.14 mmol) was studied over temperature ranges from ambient to 141 ± 0.5°. Below 70° an absorption band at δ 6.82 (4-$C_6H_5CH(OAc)C_5H_4N$) appeared and gradually increased in intensity while the band at δ 3.99 (4-$C_6H_5CH_2C_5H_4NO$ or 4-$C_6H_5CH_2C_5H_4N^+O_2CCH_3$) gradually decreased. Above 90° an emission band at δ 4.20 (E) and enhanced absorption band at δ 3.99 (A) appeared in 3 sec. The band intensity of the δ 4.20 (E) passed through a maximum at ca. 50 sec, decayed to zero in ca. 100 sec, and increased to a very small constant absorption band in ca. 160 sec.[24] The band intensity of δ 3.99 (A) increased to a maximum at ca. 50 sec and slowly decreased to a low-intensity band at ca. 500 sec while a band at δ 3.85 (4-$C_6H_5CH_2C_5H_4N$) slowly grew to constant intensity in ca. 500 sec.[24] A transient absorption signal was observed at δ 5.65 (4-$C_6H_5CH{=}C_5H_4NO_2CCH_3$)[14] which passed through a maximum at ca. 35 sec and decayed to zero after ca. 100 sec.[24] The band at δ 6.82 increased steadily to a constant value with no evidence of E or A at any time under all conditions studied.[24] The aromatic band at δ 7.25 (4-$C_6H_5CH_2C_5H_4NO$) decreased while δ 7.33 (4-$C_6H_5CH(OAc)C_5H_4N$) increased, reaching a constant intensity in ca. 160 sec.[24] Signal assignments were based on addition of authentic samples or by comparison with the spectra of authentic samples. Five NMR samples were combined and analysis by GLC[19] gave results comparable to those described in the earlier experiment.

Reaction of 4-Methylpyridine N-Oxide with Acetic Anhydride in Acetonitrile. The apparatus used for this experiment was described previously.[12] Acetic anhydride (5.10 g, 0.05 mol) was added dropwise over 10 min to a solution of 4-methylpyridine N-oxide[16] (3.3 g, 0.03 mol) in acetonitrile (30 ml) and the mixture was refluxed for 2.8 hr and allowed to cool. Rapid titration[18] of aliquots taken from the $Ba(OH)_2$ traps showed that 13.5% CO_2 had been evolved. After the acetonitrile was evaporated, analysis of the residue by GLC[25] showed the following composition: 4-methylpyridine (9.3%, R_f 3.0 min), 2,4-lutidine (0.9%, R_f 4.0 min), 4-ethylpyridine (3.1%, R_f 4.7 min), 4-pyridylmethyl acetate (17%, R_f 12 min), and 3-acetoxy-4-methylpyridine (16%, R_f 14.5 min). Peak identification was made by addition of authentic samples to the residue and observing peak enhancement without distortion.

Reaction of 1-Acetoxy-4-methylpyridinium Perchlorate with Base. The apparatus used for this reaction was described previously.[12] Tri-n-butylamine (7.7 g, 0.04 mol) was added dropwise over 5 min to a refluxing solution of 1-acetoxy-4-methylpyridinium perchlorate[26] (10.0 g, 0.037 mol) in dry acetonitrile (35 ml) and the mixture was refluxed for 3 hr total and cooled. Titration[18] of the excess $Ba(OH)_2$ in the traps showed that 4.8% CO_2 was evolved. Acetonitrile was distilled and analysis of the residue was achieved by GLC,[27] which showed the presence of 4-methylpyridine (4.7%, R_f 3 min) and a mixture[28] of 4-pyridylmethyl acetate (major component) and 3-acetoxy-4-methylpyridine (15%, R_f 11.5 min). Peak enhancement without distortion was observed when authentic samples were added to the residue.

Thermal Stability of 1-Acetoxy-4-methylpyridinium Perchlorate. The apparatus used was the same as in the preceding two experiments. A solution of 1-acetoxy-4-methylpyridinium perchlorate[26] (16.50 g, 0.066 mol) in acetonitrile (50 ml) was refluxed for 3 hr. No barium carbonate was formed in the $Ba(OH)_2$ traps. After the acetonitrile was distilled, the residue was treated with ca. 30% NaOH solution and extracted with $CHCl_3$. The extract was dried and the solvent was removed to give 6.14 g (86%) of 4-methylpyridine N-oxide, mp 187–188° (lit.[29] mp 185–186°). The ir spectrum was identical with that of an authentic sample.

Registry No.—1 (R = Ph), 7259-53-2; 1 (R = H), 1003-67-4; 1 (R = t-Bu), 54410-45-6; **2**, 108-24-7; **3** perchlorate, 1658-37-3; **4**, **55410-46-7**; **tri-n-butylamine**, 102-82-9.

References and Notes

(1) For Part VII in this series see V. J. Traynelis, K. Yamauchi, and J. P. Kimball, *J. Am. Chem. Soc.*, **96**, 7289 (1974).
(2) Presented in part before the Organic Division at the 164th National Meeting of the American Chemical Society, New York, N.Y., Aug 1972.
(3) Grateful acknowledgment is made to the National Science Foundation for a research grant (NSF GP-3858) in partial support of this work.
(4) Abstracted from a portion of the Ph.D. Dissertation submitted by J.P.K. in May 1972 and by K.Y. in Aug 1969 at West Virginia University.
(5) V. J. Traynelis in "Mechanisms of Molecular Migrations", Vol. II, B. S. Thyagarajan, Ed., Interscience, New York, N.Y., 1969, p 1.
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(7) V. J. Traynelis and A. I. Gallagher, *J. Org. Chem.*, **35**, 2792 (1970).
(8) S. Oae, S. Tamagaki, T. Negoro, K. Ogino, and S. Kozuka, *Tetrahedron Lett.*, 917 (1968).
(9) V. J. Traynelis and R. F. Martello, *J. Am. Chem. Soc.*, **82**, 2744 (1960).
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(12) V. J. Traynelis and A. I. Gallagher, *J. Am. Chem. Soc.*, **87**, 5710 (1965).
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(14) V. Boekelheide and D. L. Harrington, *Chem. Ind. (London)*, 1423 (1955).
(15) J. A. Benvenuto, Ph.D. Dissertation, West Virginia University, Dec 1972. The classical anhydro bases 1-methyl-4-phenylmethylene-1,4-dihydropyridine and 1-benzyl-4-phenylmethylene-1,4-dihydropyridine showed a singlet absorption at δ 5.2–5.4 for the exocyclic olefinic proton (4-$C_6H_5CH{=}C_5H_4NCH_2R$).
(16) The authors wish to thank Reilly Tar and Chemical Co., Indianapolis, Ind., for a generous supply of this compound.
(17) A. R. Hands and A. R. Katritzky, *J. Chem. Soc.*, 1754 (1950).
(18) G. J. van Nieuwenberg and L. A. Hegge, *Anal. Chim. Acta*, **5**, 68 (1951).
(19) Analysis was performed with a Victoreen Model 4000 gas chromatograph using a 0.125 in. × 6 ft copper column packed with 20% Carbowax 20M on Chromosorb W. AW. HMDS (80/100 mesh) at an oven temperature of 210° and He pressure of 70 psi.
(20) In a separate experiment pure 1-phenyl-1-(4-pyridyl)methyl acetate was placed on the above GLC column and showed partial conversion to 1-phenyl-1-(4-pyridyl)methanol. TLC analysis of the crude reaction mixture showed the absence of 1-phenyl-1-(4-pyridyl)methanol.
(21) This material was prepared by the method described in ref 1.
(22) The analysis was based on the ratio of integration areas of the benzylic protons at δ 3.85 and the ester methine proton at δ 6.92.
(23) The CIDNP studies were performed using a Varian Associates HA-60-EL proton-stabilized high-resolution NMR spectrometer (60 MHz) with H_2O proton resonance used for the lock signal. Probe temperatures in these studies ranged from 35 to 141 ± 0.5° and were calibrated with ethylene glycol before and after each experiment. All N-oxides used were analytically pure and the acetic anhydride was distilled prior to use. Repetitive spectral scans were obtained over 10–120-min time periods at intervals of 3 sec or longer dependent on the scan region or reaction rate. At least five and usually ten identical samples were prepared for each. Emission (E) and/or enhanced absorption (A) were noted in some cases and recorded as a function of time. All reported chemical shift values (δ) are relative to Me_4Si.
(24) Spectral reproductions of the repetitive scan data are recorded in the Ph.D. Dissertation[4] of J.P.K.
(25) Analysis was performed with the column and instrument described in ref 19 at an oven temperature of 162° and He flow rate of 50 ml/min.
(26) This substance was prepared by the method of C. W. Muth and R. S. Darlak, *J. Org. Chem.*, **30**, 1909 (1965).
(27) Analysis performed as described in ref 25 at an oven temperature of 165°. 4-Isopropylpyridine was used as an internal standard to calculate yields.
(28) The interval between the two peaks of the esters was too close to obtain area ratios.
(29) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).