Acknowledgment. We are grateful to the National Institutes of Health for financial support (Grant No. AM-04288). During this investigation, B. A. C. was supported by a Training Grant (2G-53) of the U. S. Public Health Service (1963–1964) and was a Predoctoral Fellow of the National Institute of General Medical Sciences, U. S. Public Health Service (1964–1965).

The Reactions of 2- and 4-Picoline N-Oxide with Phenylacetic Anhydride[1]

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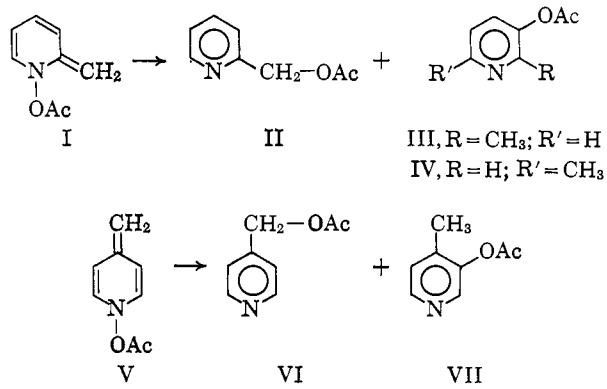
The reactions of 2- and 4-picoline N-oxide with phenylacetic anhydride yield the oxidation–reduction products, benzaldehyde, carbon dioxide, picolines, and small quantities of diphenylmaleic anhydride (XII), in addition to rearrangement products. The latter consist predominantly of 2-pyridinemethanol phenylacetate (X) and 2-phenylethylpyridine (XI), in a ratio of about 1.5:1 in the case of 2-picoline N-oxide, and of 4-pyridinemethanol phenylacetate (XIV) and 4-phenylethylpyridine (XV), in a ratio of about 0.06:1 in the case of 4-picoline N-oxide. The product composition is unchanged when the reactions are performed in the presence of the radical trap m-dinitrobenzene. The rearrangement but not the oxidation products are thought to arise via the anhydrobase intermediates XIX and XX. The ester products in this case (and in the corresponding acetic anhydride reaction with 2-picoline N-oxide) are thought to be formed by nonradical paths while the phenylethylpyridines are probably formed by geminate recombination of benzyl and picolyl radicals or ions which are produced by fragmentation of the anhydrobases XIX and XX.

Introduction

The reaction of 2-picoline N-oxide (VIII) with acetic anhydride yields mainly 2-pyridinemethanol acetate[2] (II) and smaller quantities of 3-acetoxy-2-picoline (III) and 5-acetoxy-2-picoline (IV).[3–5] Under similar conditions 4-picoline N-oxide (XIII) yields a binary ester mixture which is richer in 4-pyridinemethanol acetate (VI)[2] than in 3-acetoxy-4-picoline (VII).[8] The mechanism in both cases is generally believed to involve acetylation of the N-oxide function followed by the removal of a proton from the ring methyl group of the resulting N-acetoxypicolinium ion to yield an anhydrobase intermediate (I or V).[9] (The postulation of the intermediate formation of these anhydrobases (I and V) is also reasonable in view of the great ease of these reactions compared to that of acetic anhydride with pyridine N-oxide, a reaction in which an anhydrobase is precluded. In unpublished work, we have shown that 4-picoline N-oxide (XIII) reacts with acetic anhydride in refluxing benzene and that the 2-isomer (VIII) reacts at room temperature in pyridine solution. On the other hand, pyridine N-oxide reacts with this anhydride very slowly at temperatures below 100°.[10])



Recent tracer studies utilizing O^{18}-labeled acetic anhydride[11] indicate that both in the presence and

(1) (a) This work was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research Grant No. AF-AFOSR 344-63; (b) presented in part at the XIXth International Congress of Pure and Applied Chemistry, London, July 1963; (c) taken from the Ph.D. thesis of J. H. Fager, University of Pittsburgh, April 1965.

(2) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, 76, 1286 (1954); O. H. Bullitt, Jr., and J. T. Maynard, *ibid.*, 76, 1370 (1954).

(3) S. Okuda, *Pharm. Bull. Japan*, 3, 316 (1955). Okuda's report that these three esters are formed in the ratio of 3:1:1 has frequently been ignored in the literature, the product being treated as consisting only of 2-pyridinemethanol acetate (II). We have confirmed by gas chromatography that the ester mixture obtained in this reaction contains three components in the ratio 3:1:1 and that the major component is 2-pyridinemethanol acetate (II). In very recent work, Ford and Swan,[4] utilizing v.p.c., n.m.r., and mass spectrometry, have further confirmed the nature of this reaction mixture.

(4) P. W. Ford and J. M. Swan, *Australian J. Chem.*, 18, 867 (1965).

(5) An earlier report,[6] that the reaction of 2-picoline N-oxide with acetic anhydride produces, after hydrolysis, a 5:2 mixture of 2-pyridinemethanol and 6-methyl-2-pyridone, is probably in error. The latter compound was identified by its melting point (163–165°), its conversion to an acetate ester, and the hydrolysis of this ester back to the compound, m.p. 163–165°. In view of the fact that this pyridone was not isolated by several other groups,[2–4] there appears to be no reason to believe that this substance is not either 2-methyl-3-pyridinol, m.p. 163–165°,[8] 169–170°,[7] or 2-methyl-5-pyridinol, m.p. 167°,[8] both of which were later identified by Okuda[3] as products of this reaction.

(6) G. Kobayashi and S. Furukawa, *Pharm. Bull. Japan*, 1, 347 (1953).

(7) N. Clauson-Kaas, N. Elming, and Z. Tyle, *Acta Chem. Scand.*, 9, 1 (1955).

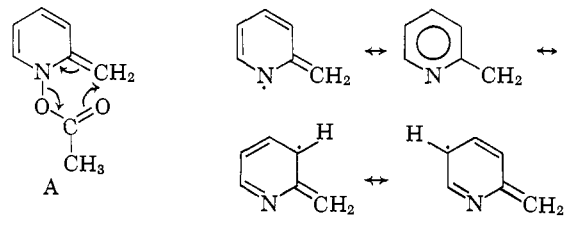
(8) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, 77, 1281 (1955).

(9) For a recent discussion of the substantial evidence for these steps in the reaction of 2-picoline N-oxide, see V. J. Traynelis and P. L. Pacini, *ibid.*, 86, 4917 (1964).

(10) T. Cohen, Ph.D. Thesis, University of Southern California, 1955, p. 65; J. H. Markgraf, H. B. Brown, Jr., S. C. Mohr, and R. G. Peterson, *J. Am. Chem. Soc.*, 85, 958 (1963).

(11) (a) S. Oae, T. Kitao, and Y. Kitaoka, *ibid.*, 84, 3359 (1962); (b) S. Oae, Y. Kitaoka, and T. Kitao, *Tetrahedron*, 20, 2685 (1964).

absence of a diluent the product in the 2-case is formed by an *intramolecular* rearrangement of the anhydrobase I. Because the O^{18} label was found to be equally distributed between the two oxygen atoms of the ester product,[12] a cyclic mechanism (A) of the type originally proposed in an analogous system by Pachter[13] was considered to be excluded. Instead a mechanism (B) involving an intermediate radical pair was favored. This latter mechanism had been suggested earlier as one possible reaction path by Traynelis and Martello, who showed that free radicals are present during the reaction, although no evidence was adduced by these authors that radicals actually are involved in the mechanism of formation of the ester products.[14]

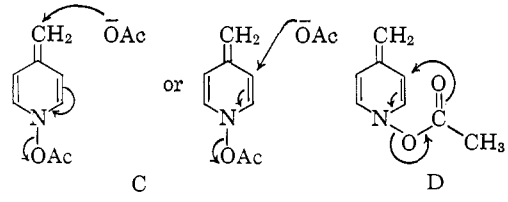


A

AcO·

B

In an analogous tracer study of the reaction of 4-picoline N-oxide (XIII) with acetic anhydride, with no diluent present, Oae and collaborators[15] found that the isotropic enrichment of the ester products was approximately that expected from a complete equilibration of all of the oxygen atoms in the reaction mixture and that both oxygen atoms of each ester product were equally enriched. They interpreted this result as supporting the mechanism, originally suggested by Berson and Cohen,[8] which involves the attack of external acetate ion on the anhydrobase V with the simultaneous expulsion of the acetate group (mechanism C). However, as recognized by Oae,[11a] the incorporation of *external* acetate ion into the product is somewhat at odds with the results of the reaction of 4-picoline N-oxide with *n*-butyric anhydride in the presence of added sodium acetate, in which it was found[16] that only butyrate esters are produced. In later work,[11b]



C D

it was found that the use of aromatic diluents leads to an intramolecular rearrangement of the anhydrobase V. This was explained by assuming that the decrease in acetate ion concentration caused a decrease in the rate of the external acetate attack referred to above, thus allowing the occurrence of an intramolecular rearrangement which was postulated to be of the radical-pair variety suggested earlier by Traynelis and Martello[16] on the basis of their experiments with radical traps.

It should be pointed out that several alternative mechanisms are allowed by the tracer results. For example, in the clearly intramolecular rearrangements, the intermediate formation of ion pairs rather than radical pairs cannot be excluded. The former could consist of a resonance-stabilized (benzylic type) picolyl cation and an acetate anion. The opposite charge type seems very unlikely owing to the great instability of acyloxy cations.[17] Furthermore, the concerted mechanisms A and D[21] are not ruled out for the intramolecular rearrangements since the two oxygen atoms of the anhydrobase could become equivalent in a prior equilibration. Finally, the apparently intermolecular rearrangement in the 4-case (no diluent) is not necessarily initiated by acetate ion (mechanism C) but may involve capture of a picolyl cation by acetic acid.

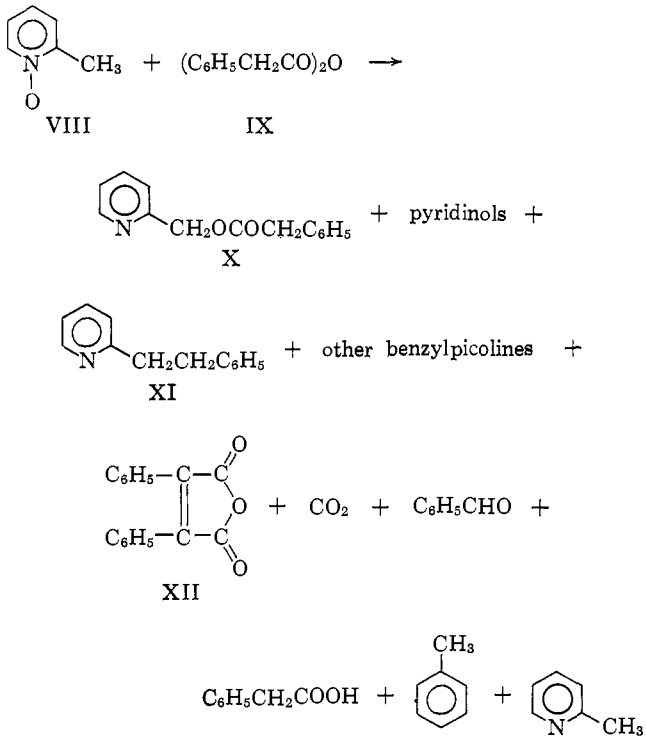
In this paper we report the results of an investigation of one of the implications of the radical-pair mechanisms discussed above. Recent studies[22] indicate that the acetoxy radical is exceedingly unstable, decomposing very soon after or possibly, in some cases, during its formation to the methyl radical and carbon dioxide. The phenylacetoxy radical is even less stable and it is indeed extremely unlikely that it is capable of existence. Decompositions of peroxy anhydrides and peresters of phenylacetic acid result in simultaneous O–O and C–C homolysis to yield carbon dioxide and benzyl radicals directly, rather than phenylacetoxy radicals.[20a,22a,23–25] The latter, according to the discussion of Szwarc,[22a] would be expected to decompose with no activation energy and any reaction which might appear capable of producing this species should instead proceed by such a concerted fragmentation. Therefore, if the radical-pair mechanism is valid, the use of phenylacetic anhydride instead of acetic anhydride should result in the formation of no ester products. Instead, products resulting from the combination of benzyl and picolyl radicals might be expected.[26]

Results

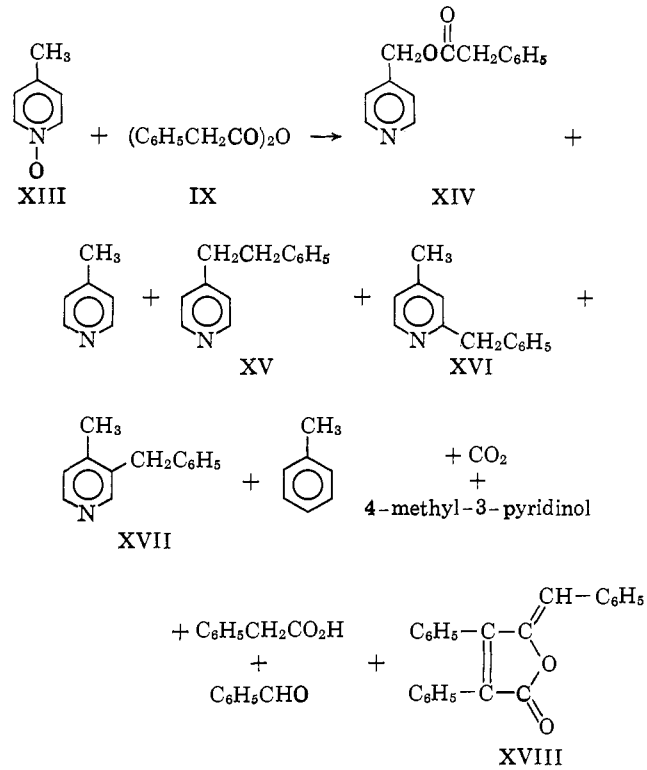
2-Picoline N-Oxide. In a large-scale isolation experiment, an equimolar mixture of 2-picoline N-oxide

(12) The ester product was treated as if it consisted only of 2-pyridinemethanol acetate (II).
(13) I. J. Pachter, *J. Am. Chem. Soc.*, **75**, 3026 (1953).
(14) V. J. Traynelis and R. F. Martello, *ibid.*, **80**, 6590 (1958).
(15) S. Oae, T. Kitao, and Y. Kitaoka, *ibid.*, **84**, 3362 (1962).
(16) V. J. Traynelis and R. F. Martello, *ibid.*, **82**, 2744 (1960).
(17) Reactions which might be expected to lead to acyloxy cations usually proceed *via* the carboxy inversion mechanism[18,19] or by a fragmentation which produces carbonium ions and carbon dioxide.[20]
(18) J. E. Leffler, *J. Am. Chem. Soc.*, **72**, 67 (1950).
(19) D. Z. Denny, T. M. Valega, and D. B. Denny, *ibid.*, **86**, 46 (1964), and references cited therein.
(20) (a) P. D. Bartlett and J. E. Leffler, *ibid.*, **72**, 3030 (1950); (b) H. Hart and R. A. Cipriani, *ibid.*, **84**, 3697 (1962); (c) C. Rüchardt and H. Schwarzer, *Angew. Chem. Intern. Ed. Engl.*, **1**, 217 (1962).
(21) This was suggested as one possibility by Berson and Cohen.[8] The proximate product of this rearrangement could tautomerize to VII or undergo a Claisen-type rearrangement to give VI.
(22) (a) M. Szwarc, "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., Interscience, Division of John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 156–174; (b) L. Herk, M. Feld, and M. Szwarc, *J. Am. Chem. Soc.*, **83**, 2998 (1961); T. C. Vogt and W. H. Hamill, *J. Phys. Chem.*, **67**, 292 (1963); M. J. Goldstein, *Tetrahedron Letters*, 1601 (1964); M. J. Goldstein, Abstracts, 149th Meeting of the American Chemical Society, Detroit, Mich., April 1965, p. 54P; however, see H. J. Shine, J. A. Waters, and D. M. Hoffman, *J. Am. Chem. Soc.*, **85**, 3613 (1963).
(23) P. D. Bartlett, *Experientia Suppl.*, 7, 275 (1957).
(24) P. D. Bartlett and D. M. Simons, *J. Am. Chem. Soc.*, 82, 1753 (1960); P. D. Bartlett and C. Rüchardt, *ibid.*, **82**, 1756 (1960).
(25) F. D. Greene, H. P. Stein, C.-C. Chu, and F. M. Vane, *ibid.*, **86**, 2080 (1964).
(26) Traynelis and Martello[16] detected a trace (0.6% yield) of 4-ethylpyridine among the products from the reaction of 4-picoline N-oxide (XIII) with acetic anhydride. They assumed that this was formed from picolyl and methyl radicals. A larger yield (9.9%) of 4-*n*-butylpyridine was detected from the reaction of the same amine oxide with butyric anhydride. Neither of the corresponding products was detected in the reaction mixture from the treatment of 2-picoline N-oxide (VIII) with these anhydrides.[14]

(VIII) and phenylacetic anhydride (IX) in benzene solution was observed to evolve carbon dioxide at room temperature. After the mixture had been allowed to remain at room temperature overnight with nitrogen ebullition, it was heated at reflux for 8 hr. The following products were identified; the yields in parentheses are given as moles of product *per* mole of either reactant: (A) carbon dioxide (0.159); (B) toluene (0.0055); (C) 2-picoline (0.269); (D) phenylacetic acid (1.08); (E) 2-pyridinemethanol phenylacetate (X, 0.328), which was identified by its saponification to 2-pyridinemethanol and phenylacetic acid, and by comparison with an authentic sample prepared from the latter two reagents; (F) a small quantity of an unidentified pyridinol, m.p. 163–165°, which presumably arose by hydrolysis of 3- or 5-phenylacetoxy-2-picoline (both hydrolysis products have melting points in this range[5]); (G) a fraction containing benzylpicolines (0.068), which was shown by gas chromatography to consist of four components (The major component (*ca.* 85%) was collected by preparative gas chromatography and identified as the known 2-(β-phenylethyl)-pyridine (XI). The three lesser components are almost certainly isomeric benzylpicolines, having the benzyl group attached to the pyridine ring.); (H) benzaldehyde (0.025); (I) diphenylmaleic anhydride (DPMA, XII, 0.02), identified by its nuclear magnetic resonance and infrared spectra and by a comparison of its physical and chemical properties with those reported in the literature.



4-Picoline N-Oxide. In an isolation run, an equimolar mixture of 4-picoline N-oxide (XIII) and phenylacetic anhydride (IX) in benzene was allowed to remain at room temperature overnight with nitrogen ebullition and was then heated at reflux (82°) for 13 hr. The following products were identified: (A) carbon dioxide (0.28); (B) toluene (0.0035); (C) picoline (0.645); (D) phenylacetic acid (1.07); (E) 4-pyridinemethanol phenylacetate (XIV, 0.025), which was isolated by preparative gas chromatography and identified by comparison with an authentic sample prepared from phenylacetic acid and 4-pyridinemethanol; (F) a trace of 4-methyl-3-pyridinol; (G) a distillation fraction containing benzylpicolines (0.095), which was shown by gas chromatography to consist of three components. (Filtration of this semisolid fraction yielded the major component 4-(β-phenylethyl)pyridine (XV), which was identified by its equivalent weight and by a comparison of its properties with those reported. A second component was isolated by gas chromatography and shown to be 2-benzyl-4-picoline (XVI). The decisive factor in its structural assignment was the fact that the area of the β-hydrogen signal in its n.m.r. spectrum was twice that of the α-hydrogen signal. Although the third component could not be isolated, it is undoubtedly 3-benzyl-4-picoline (XVII), the only other possible benzylpicoline. This assignment follows from the fact that a mixture of this component with XVI had an equivalent weight of 187 (calculated for benzylpicoline, 183) and an infrared spectrum which was not markedly different from that of XVI alone.[27] The rather large variation in the relative proportions of these three substances with changes in reaction conditions is discussed in the Experimental Section); (H) benzaldehyde (0.081); (I) a compound which is thought to be 5-oxo-3,4-diphenyl-2-benzaldihydrofuran (XVIII, 0.037), the condensation product of diphenylmaleic anhydride (XII) with phenylacetic acid.[28] Its melting point and spectral properties are consistent with this structure.



Comparison of Product Distribution from 2- and 4-Picoline N-Oxide. At this stage in the investigation,

(27) The possibility that component B might be 4-stilbazole, equiv. wt. 181, produced by the reaction of 4-picoline with benzaldehyde, was ruled out when it was shown that an authentic sample of the stilbazole (Fisher Scientific Co.) had a much longer gas chromatographic retention time.

(28) S. Gabriel and G. Cohn, *Ber.*, 24, 3229 (1891).

reaction conditions and analytical techniques had been sufficiently developed and standardized so that a meaningful comparison of the reactions of 2- and 4-picoline N-oxide with phenylacetic anhydride could be made. In conducting the reactions, a mixture of equimolar quantities of phenylacetic anhydride and the appropriate picoline N-oxide in benzene was heated at reflux (82°), with nitrogen ebullition, for 8 hr. The effect of a free-radical inhibitor was determined by making similar runs incorporating *m*-dinitrobenzene (10% by weight of the N-oxide charged) into the reaction mixture. The product distributions (excluding the traces of toluene and pyridinols) were determined by a quantitative analytical scheme which is described in the Experimental Section. The results for the four runs are summarized in Table I.

Table I. Product Distribution in a Series of Reactions of Picoline N-Oxides with Phenylacetic Anhydride

Product	Yield, moles/mole of reactant — 2-Picoline N-oxide A[a]	2-Picoline N-oxide B[b]	4-Picoline N-oxide A[a]	4-Picoline N-oxide B[b]
2- or 4-Pyridinemethanol phenylacetate (X or XIV)	0.275	0.281	0.006	0.006
Benzylpicolines	0.183[c]	0.176[d]	0.094[e]	0.084[e]
Carbon dioxide	0.313	0.302	0.422	0.398
2- or 4-Picoline	0.463	0.455	0.771	0.762
Benzaldehyde	0.081	0.089	0.183	0.185
Diphenylmaleic anhydride (XII)	0.002	0.004	0.068	0.055
Phenylacetic acid	1.02	1.01	1.07	1.08

[a] No inhibitor. [b] 10% *m*-dinitrobenzene. [c] By v.p.c., it is estimated that this consists of *ca.* 80% XI and 20% of the other three components. [d] 85% XI. [e] 80% XV, 10% XVI, and 10% XVII.

A control experiment was then performed in the 4-case in order to determine whether the products of the reaction are stable under the reaction conditions. The reaction of equimolar quantities of 4-picoline N-oxide with phenylacetic anhydride in refluxing benzene was carried out exactly as previously described with the exception that the following known products of the reaction were added before heating was commenced: benzaldehyde, 10 mole %; 4-pyridinemethanol phenylacetate XIV, 2 mole %; benzylpicolines fraction (a mixture of the three isomers), 9 mole %. Analysis of the reaction mixture by the standardized procedure gave the yields indicated in Table II.

Table II. 4-Picoline N-Oxide–Phenylacetic Anhydride Control Experiment

Product	Yield, moles/mole of reactant — Obsd.		Corrected for amount added Obsd.	Calcd.
Carbon dioxide	0.395		0.395	0.422
4-Picoline	0.740		0.740	0.771
Benzylpicolines	0.173	(−0.090)	0.083	0.093
4-Pyridinemethanol phenylacetate (XIV)	0.025	(−0.020)	0.005	0.006
Benzaldehyde	0.221	(−0.100)	0.121	0.183
Diphenylmaleic anhydride (XII)	0.081		0.081	0.068
Phenylacetic acid	1.08		1.08	1.07

The control tests show that the corrected yields of the 4-ester and the benzylpicolines are in line with the expected values. This is satisfactory evidence that neither of these products was consumed during the reaction. On the other hand, the corrected yield of benzaldehyde is substantially less than would have been anticipated on the basis of nonconsumption of the added benzaldehyde. This undoubtedly means that benzaldehyde is being consumed during the reaction, presumably by condensation with phenylacetic acid or its anhydride.[29,30]

Discussion

At the time that this work was performed, the production of benzaldehyde, diphenylmaleic anhydride (XII), and large quantities of picolines was quite unexpected. Since then, it has been shown[31] that pyridine N-oxide itself is capable of oxidizing phenylacetic anhydride (or phenylacetic acid in the presence of acetic anhydride) to benzaldehyde and XII. Pyridine and carbon dioxide are major by-products of these reactions. A number of anhydrides (but not acetic anhydride) can be oxidized to aldehydes and ketones by this method.[31,32]

In the present case, it is clear that this type of oxidation is competing with the expected reactions which produce ester, benzylpicolines, and carbon dioxide. This is indicated not only by the production of benzaldehyde, diphenylmaleic anhydride, and picolines but also by the fact that the molar ratio of carbon dioxide to benzylpicolines greatly exceeds unity. The stoichiometric relationships in the oxidation–reduction reactions are

$$2C_6H_7NO + (C_6H_5CH_2CO)_2O \longrightarrow C_6H_5CH_2CO_2H + C_6H_5CHO + CO_2 + 2C_6H_7N \quad (1)$$

$$2C_6H_7NO + 3(C_6H_5CH_2CO)_2O \longrightarrow \text{(diphenylmaleic anhydride)} + 4C_6H_5CH_2CO_2H + 2C_6H_7N \quad (2)$$

The importance of reaction 1 cannot be judged by the yield of benzaldehyde since this substance is destroyed under the reaction conditions. It can, however, be estimated approximately by subtracting the yield of benzylpicolines (each mole of which must be accompanied by 1 mole of carbon dioxide) from the total yield of carbon dioxide. Considering the reactions without added inhibitor in Table I, about 13 and 33% of starting anhydride (IX) is destroyed by reaction 1 in the cases of 2- and 4-picoline N-oxide, respectively.[33]

(29) I. H. Song, in this laboratory, has isolated the condensation product, α-benzylidenephenylacetic acid, from the reaction of pyridine N-oxide with phenylacetic acid in the presence of acetic anhydride, a reaction which yields benzaldehyde as one product (see below).

(30) Only an insignificant quantity of benzaldehyde is expected to be destroyed by loss of hydrogen atoms to free radicals which have escaped from the solvent cage. Evidence is presented in the Discussion that very little escape from the cage occurs.

(31) T. Cohen, I. H. Song, and J. H. Fager, *Tetrahedron Letters*, 237 (1965).

(32) C. Rüchardt, S. Eichler, and O. Krätz, *ibid.*, 233 (1965).

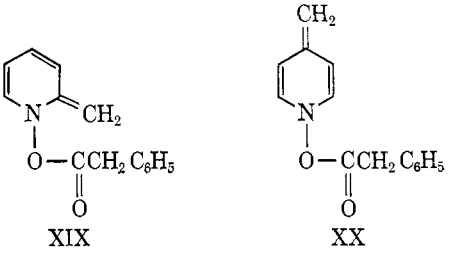
(33) When the yields of benzaldehyde actually isolated are subtracted from these percentages, it can be determined that about $^5/_{13}$ of the benzaldehyde formed in the 2-case and $^{15}/_{33}$ of that formed in the 4-case are destroyed during the reaction. These fractions are very comparable to that noted in the control run reported in Table II.

When these percentages are added to the percentages of the anhydride (X) destroyed by reaction 2 (as judged by the production of DMPA, XII), it is estimated that a total of about 14 and 53% of the phenylacetic anhydride is utilized in the 2- and 4-cases, respectively, for these oxidation–reduction reactions. The corresponding percentages for the destruction of picoline N-oxides by reactions 1 and 2, as judged by the yields of carbon dioxide and DPMA, are about 27 and 79%. However, in the case of 2-picoline N-oxide, oxidation–reduction reactions which do not produce carbon dioxide or DPMA (for example, the formation of acetylmandelic and phenylglyoxylic acids)[31] must also occur, since the yield of 2-picoline (46%) exceeds the 27% expected from reactions 1 and 2. In the 4-case, on the other hand, the 77% yield of 4-picoline corresponds closely with the 79% estimated from (1) and (2).

Considering the fact that the quantities of unreacted picoline N-oxide and phenylacetic anhydride were not determined, and taking into account the loss of benzaldehyde, the material balances indicated in Table I are quite acceptable. In the 2-case, about 92% of the picoline and 81% of the benzyl groups are accounted for *as products*. The corresponding figures in the 4-case are 87 and 82%. The constancy of the yields in the presence and absence of *m*-dinitrobenzene serves to demonstrate the reproducibility of the results, as well as to establish the probable lack of radical-chain character.[34] Indeed, it is unlikely that *free* radicals play a very significant role in the production of any of the products listed in the table. This is further borne out by the very small quantity of toluene (the hydrogen abstraction product of benzyl radicals) produced, and by the absence in the reaction products of diphenylmethane (the reaction product of benzyl radicals with the solvent, benzene)[25] and the coupling products bipicolyl and bibenzyl.[35] It is estimated that each of these products would have been detected if it had been present in greater than about 0.5% yield.

Since pyridine N-oxide, which cannot form an anhydrobase, has been shown to be a very efficient oxidizing agent of phenylacetic anhydride,[31,32] it is reasonable to assume that the oxidation–reduction reactions occur at some stage prior to the formation of the anhydrobases XIX and XX. By the reasoning expressed in the Introduction, it can thus be considered that the rearrangement products (esters and benzylpicolines) are formed *via* an independent reaction path in which these anhydrobases (XIX and XX) are key intermediates. Because the nature of the oxidation–reduction reactions is being studied separately[31,32] and will be discussed in future papers, we shall comment here only on the reactions proceeding through the anhydrobases.

An examination of the results in Table I indicates that of the 54% of 2-picoline N-oxide which is not reduced to 2-picoline, at least 27% is converted to ester,[36] about 18% is converted to benzylpicolines, and an undetermined quantity, not exceeding 9% (54–27–18), remains unreacted. Of the 23% of 4-picoline N-oxide which is not reduced, about 0.6% is converted to ester, 9.4% is converted to benzylpicolines, and a quantity not exceeding 13% remains unreacted. The yield ratio of ester to benzylpicolines is thus about 1.5 in the reaction of 2-picoline N-oxide and only 0.063 in the case of 4-picoline N-oxide. For reasons outlined in the Introduction, these ester products are presumably generated in nonradical reactions. Assuming an intramolecular reaction in the 2-case as was shown[11] for the acetic anhydride reaction, the very high yield of ester (well over 50% of the product resulting from anhydrobase) probably results from the efficient collapse of an ion pair, involving a picolyl cation and a phenylacetate anion or conceivably by a concerted rearrangement similar to A. The ionic cleavage of XIX is presumably in competition with a concerted fragmentation[20a,23a,24] which yields carbon dioxide and resonance-stabilized benzyl and picolyl radicals, the combination of which, presumably within a solvent cage, results mostly in the formation of 2-phenylethylpyridine (XI).[37] In the 4-case the recombination of the picolyl cation and the phenylacetate anion to form ester is much less likely due to the unfavorable juxtaposition of the reactive sites of the two ions as formed. Recombination to reform the anhydrobase XX is probably preferred. This anhydrobase can then fragment to yield carbon dioxide and two radicals, or ions,[37] which can combine in a geminate fashion to yield mostly 4-phenylethylpyridine (XV).



XIX XX

The rather efficient conversion of XIX to ester by an apparently nonradical path strongly suggests that the corresponding acetic anhydride reaction also proceeds by a nonradical path (perhaps one of the possibilities outlined in the Introduction) in the case of 2-picoline N-oxide.[38] In the reaction of 4-picoline N-oxide, the inefficient conversion of XX to ester, relative to that of the anhydrobase V, from acetic anhydride is compatible in the latter case with either a nonradical or a radical-pair rearrangement. However, by analogy with the 2-case, the nonradical path seems more likely. The

(34) It has been shown that benzyl radicals can be trapped by *m*-dinitrobenzene: R. A. Jackson and W. A. Waters, *J. Chem. Soc.*, 1653 (1960).

(35) This statement may be more true for the 2- than for the 4-case. Dr. C. Rüchardt of the University of Munich has kindly informed us that experiments in his laboratory have shown that styrene and acrylonitrile are only slightly polymerized during the reaction of 2-picoline N-oxide with both phenylacetic and diphenylacetic anhydrides, while polymerization was appreciable during the corresponding reactions with 4-picoline N-oxide.

(36) The small quantities of 3- and 5- esters, which are hydrolyzed during work-up to water-soluble pyridinols, were not determined in the experiments summarized in Table I, although such pyridinols were isolated in the large-scale runs described above.

(37) An ionic fragmentation of the anhydrobase leading to benzyl cations or anions cannot be ruled out. However, the cleavage leading to benzyl cations would be very much more favorable in the pyridinium ion precursor of XIX, and yet it does not seem to occur to an appreciable extent. See also footnote 3 of ref. 31.

(38) There would be no reason to believe that the anhydrobase XIX would undergo a nonradical rearrangement while the related acetoxy analog (I) would preferentially undergo N–O homolysis to form a radical pair.

concerted fragmentation, with loss of carbon dioxide, is simply more favorable than the ester-producing mechanisms in the case of the anhydrobase XX but not in the case of V, which would yield the unstable methyl radical (or ion) in such a fragmentation.

Since the odd electron of the picolyl radical (see mechanism B) exists to some extent at the 3-position of the ring as well as on the methylene group, the combination of the picolyl and benzyl radicals (or ions) to form products such as 3-benzyl-4-picoline (XVII) is reasonable. However, it seems very unlikely that 2-benzyl-4-picoline (XVI) could be formed by the collapse of such a radical pair. This product (XVI) is formed in very low yield and it may be that it results from the attack of a small quantity of *free* benzyl radicals on 4-picoline, although other routes are also available.[39] One of the intriguing questions raised by this work is the mechanism of the formation of this product and the reason for the dramatic changes in the composition of the benzylpicoline fraction with reaction conditions (see Table III).

Table III. Effect of Reaction Conditions on the Composition of the Benzylpicoline Fraction

Component	Total fraction, %: Room temp., CO_2, O_2 present	Room temp., N_2 ebullition	Reflux (82°), N_2 ebullition
2-Benzyl-4-picoline (XVI)	40	5	10
3-Benzyl-4-picoline (XVII)	50	50	10
4-(β-Phenylethylpyridine (XV)	10	45	80
Total yield of benzylpicoline, mole/mole of reactant	0.081	0.083	0.093

Experimental Section[40]

Phenylacetic Anhydride (IX). Literature methods[41] were considered inappropriate for the efficient, large-scale preparation of this anhydride. The following method proved very satisfactory.

To a stirred slurry of phenylacetic acid (374 g., 2.75 moles) and 200 ml. of water was added rapidly at room temperature a solution of 161 g. (*ca.* 2.50 moles of base) of potassium hydroxide pellets in 500 ml. of water. Phenylacetyl chloride (Fisher) (309 g., 2.00 moles) was added dropwise at 30–35° with vigorous stirring and ice cooling After the 1-hr. addition and 10 min. of additional stirring, the white solid was filtered and washed thoroughly with water. The crude anhydride was divided into two equal portions because of its bulk, and each portion was worked up separately. Each was stirred with *ca.* 800 ml. of acetone and filtered free of potassium chloride. The filtrate was placed in a 4-l. beaker and, with stirring, water was carefully added (*ca.* 250 ml.) until crystallization of the anhydride commenced. The mixture was allowed to stand for 15 min. while crystal growth proceeded, after which more water was added, slowly and with stirring, until the 4-l. beaker had been filled. The white, needle-like crystals were removed by filtration, washed thoroughly with water, and dried on the benchtop overnight, then in an oven at 50° (caution: higher drying temperature gives partially hydrolyzed product) for 4 hr. and, finally, overnight in a vacuum desiccator. The yield of pure white phenylacetic anhydride, m.p. 72.5–73.0° (lit.[41a] m.p. 72.5°), was 358 g. (70.3%). In a subsequent run, using the same procedure but employing only 0.70 mole of phenylacetyl chloride, a yield of 76.7% was achieved.

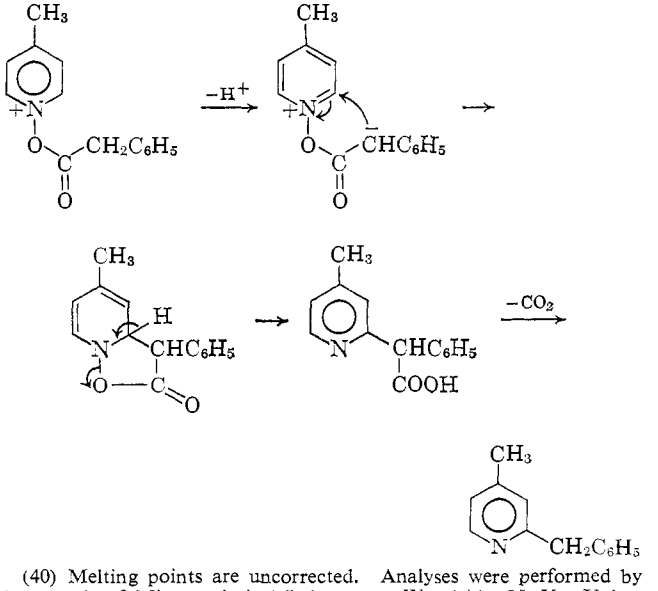
Reaction of Phenylacetic Anhydride with 2-Picoline N-Oxide. The first run was performed on a large scale for the purpose of isolating and identifying products. The next two runs were performed for the purpose of yield comparisons under standard conditions.

Run 1. Large-Scale Run in Benzene at Variable Temperature. A solution of 127.0 g. (0.500 mole) of phenylacetic anhydride in 500 ml. of benzene was added rapidly at 25° to a solution of 54.5 g. (0.500 mole) of 2-picoline N-oxide in 500 ml. of benzene. Nitrogen ebullition of the system had been started 5 min. prior to the addition of the anhydride. After standing at room temperature overnight with a slow nitrogen purge, the mixture was heated at reflux (82°) for 8 hr. (Preliminary runs indicated that the heating period was necessary for completion of the reaction.) The gain in weight of the Caroxite tube was 3.50 g., indicating that 0.0795 mole of carbon dioxide was formed.

After the removal of 50 ml. of the reaction mixture for possible future examination, most of the benzene (786.5 g.) was distilled at atmospheric pressure. When vacuum distillation was begun in order to obtain the higher boiling fractions, a Dry Ice trap was placed in the system so that no distillate would be lost. The following fractions were obtained: A, 41.5 g., b.p. 25–35° (10 mm.); B, 129.0 g., b.p. 115–160° (0.5 mm.); C, 9.8 g., b.p. 160–240° (0.5 mm.). The nondistillable residues amounted to 13.0 g. The large benzene fraction (786.5 g.) collected during the initial distillation of the reaction mixture was found by gas chromatography to contain neither toluene nor 2-picoline.

Fraction A was redistilled through an 18-in. Vigreux column at atmospheric pressure to give three fractions,

(39) For example



(40) Melting points are uncorrected. Analyses were performed by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y. Unless otherwise specified, gas chromatographic analyses were performed on a Perkin-Elmer Model 154-D vapor fractometer.

(41) (a) R. Anschütz and W. Berns, *Ber.*, **20**, 1389 (1887); (b) W. S. Denham, *J. Chem. Soc.*, 1235 (1909); (c) G. Eglinton, E. R. H. Jones, B. L. Shaw, and M. C. Whiting, *ibid.*, 1860 (1954).

boiling from 80 to 129°, each of which was examined by quantitative gas chromatography [2-m. × 0.25-in. column packed with FLEXOL NP-27 (Union Carbide Corp.) (25%) on Chromosorb W operated at a temperature of 100°], utilizing a peak-height calibration chart. The amount of toluene was calculated to be 0.25 g. (0.0027 mole) while that of 2-picoline was 12.5 g. (0.134 mole).

One of the cuts from the redistillation of fraction A was shown to be 2-picoline, b.p. 127–129° (lit.[42] b.p. 129.5°). Its infrared spectrum was identical with that of an authentic sample (Reilly Tar and Chemical Corp.), and its picrate, from ethanol, had m.p. 167–168.5° (lit.[43] m.p. 165°).

The still residue (3.1 g.) from the redistillation of fraction A was found by quantitative v.p.c. (200°) to contain 0.93 g. of benzaldehyde. The latter was isolated by distillation, b.p. 177–178° (lit.[44] b.p. 178.3°), and identified by comparison of its retention time and infrared spectrum with those of an authentic specimen. An additional 0.32 g. was detected in the first distillate from the work-up of fraction B. The yield of benzaldehyde was 1.31 g. (0.0124 mole).

Fraction B was dissolved in ether, washed with 5% aqueous sodium bicarbonate (six 100-ml. portions) to remove phenylacetic acid, and distilled through an 18-in. Vigreux column to give three fractions: D, 1.6 g., b.p. 90–96° (0.3 mm.); E, 5.2 g., b.p. 96–100° (0.3 mm.); F, 37.1 g., b.p. 121–123° (0.3 mm.). Fraction D contained some benzaldehyde, as mentioned above; the remainder consisted of benzylpicolines (see E).

Fraction E was identified as a mixture of benzylpicolines on the following basis. Titration of the material with perchloric acid gave an equivalent weight of 187 (calculated for benzylpicoline, 183). The infrared spectrum as a film showed the absence of carbonyl absorption and was consistent with that to be expected of a benzylpicolines mixture (total yield 0.068 mole). Gas chromatographic examination was performed with an F and M Model 500, using a column (8.5 ft. × 0.25 in.) packed with Versamid 900 (2%) on Chromosorb W operated at a temperature of 200°. Four components were noted, with retention times and approximate relative percentages as follows: (1) 3.2 min., 8%; (2) 4.5 min., 85%; (3) 5.1 min., 6%; (4), 5.8 min., 1%. The major component (2) was collected (41 mg.) and methyl group absorption was found to be absent from its infrared spectrum. A *picrate* was obtained as yellow needles, m.p. 124.5–126.5° [lit.[45] m.p. for the picrate of 2-(β-phenylethyl)pyridine (XI) 125.5–127.0°].

Fraction F was identified as 2-pyridinemethanol phenylacetate (X, 0.164 mole) on the basis of (1) the carbonyl band at 1740 cm.$^{-1}$ in its infrared spectrum (carbon disulfide), (2) its smooth saponification to 2-pyridinemethanol (Aldrich Chemical Co.) and phenylacetic acid, and finally (3) by the identity of its infrared spectrum and gas chromographic retention time (fraction F gave a single sharp peak at 3.7 min. when a 10-ft. Versamid column at 245° and a flow rate of 38 cc./min. was used) with those of an authentic sample (see below).

The bicarbonate washings from fraction B were acidified with hydrochloric acid and extracted with ether; the solvent was removed to give 68.5 g. of phenylacetic acid, identified by comparison of its infrared spectrum with that of an authentic sample. An additional 1.5 g. of this acid was recovered by a similar treatment of fraction C, affording a total recovery of 70.0 g. (total yield, 73.5 g., 0.54 mole).

The acidified bicarbonate washing from fraction B, from which the phenylacetic acid had been removed, was saturated with sodium carbonate and extracted several times with ether. Evaporation of the ether gave a white solid (0.3 g.), which, after recrystallization from benzene, had m.p. 163–165°. The material was characterized as a pyridinol on the basis of the bright red ferric chloride test and the broad absorption (due to hydrogen bonding) in the 2700–2500-cm.$^{-1}$ region, typical of pyridinols, in its infrared spectrum.

Fraction C was dissolved in ether, washed with aqueous sodium bicarbonate, and distilled through a 6-in. Vigreux column to give 5.0 g. of an amber liquid, b.p. 160–170° (0.5 mm.), which partially crystallized. By recrystallization from ether, 2.1 g. of pale yellow needles, m.p. 156–157°, were obtained. This material was identified as diphenylmaleic anhydride (DPMA, XII) on the basis of its ultraviolet fluorescence,[46] melting point,[47] infrared (1761 and 1840 cm.$^{-1}$) and n.m.r. (τ 2.62) spectra, and by its chemical properties,[47c] including the preparation of its N-phenylimide, m.p. 174.5–175.5° (lit. m.p. 174–175°,[48] m.p. 172°[49]).

Examination of the bicarbonate washing of fraction C in the same manner as that of fraction B did not reveal the presence of any pyridinols.

Run 2. In Refluxing Benzene. With nitrogen ebullition, a mixture of 25.4 g. (0.100 mole) of phenylacetic anhydride and 400 ml. of benzene, contained in a 1-l., four-necked flask, was heated to 50°. 2-Picoline N-oxide (10.9 g., 0.100 mole) was added rapidly, and the temperature was raised to 82° (reflux) within a 10-min. period and maintained at that temperature for 8 hr. The total carbon dioxide evolution was 1.38 g. (0.0313 mole). The reaction mixture was then worked up, using the following procedure developed especially for the quantitative analysis of such mixtures.

(1) The Basic Fraction. A portion (341.0 g.) of the reaction mixture (374.5 g.) was washed with 10% aqueous hydrochloric acid and with water in order to remove all basic components. When dry sodium carbonate was added to the combined aqueous extracts, in a 2-l. beaker until the solution was definitely alkaline, a dark brown second phase separated. This mixture was extracted with ether, and the solvent was removed from the dried (sodium sulfate) extract at atmospheric pressure. The remainder of the ether and all (v.p.c.) of the 2-picoline were removed at the water pump on a steam bath. The residue (9.58 g.) was analyzed for benzylpicolines and 2-pyridine-

(42) F. C. Garrett and J. A. Smythe, *J. Chem. Soc.*, **81**, 449 (1902).
(43) A. Ladenburg, *Ann.*, **247**, 7 (1888).
(44) G. W. A. Kahlbaum, *Ber.*, **27**, 1386 (1894).
(45) F. W. Bergstrom, T. R. Norton, and R. A. Seibert, *J. Org. Chem.*, **10**, 452 (1945).
(46) C. A. Bischoff and P. Walden, *Ann.*, **279**, 118 (1894).
(47) (a) C. L. Reimer, *Ber.*, **13**, 742 (1880); (b) L. Rugheimer, *ibid.*, **15**, 1625 (1882); (c) G. Heller, *Ann.*, **358**, 349 (1908); (d) L. Denivelle and D. Razavi, *Compt. rend.*, **237**, 570 (1953).
(48) R. Anschütz and P. Bendix, *Ann.*, **259**, 65 (1890).
(49) F. Bergmann, *J. Am. Chem. Soc.*, **64**, 176 (1942).

methanol phenylacetate by quantitative v.p.c., using a 10-ft. column packed with Versamid 900 (2%) on Chromosorb W, at a temperature of 245°. Under these conditions, the benzylpicolines fraction appeared as a major peak [2-(β-phenylethyl)pyridine] and several minor adjacent peaks at 1.5- to 2.1-min. elution time. The pyridyl ester eluted as a single peak at 3.7 min. No other peaks were discernible.

In calculating the benzylpicolines yield, the assumption was made that the basic portion isolated as described above contained only benzylpicolines and pyridyl ester. The weight of ester was then subtracted from the total weight of the fraction to give the weight of benzylpicolines (3.35 g., 0.0183 mole) by difference. The validity of the assumption that the basic fraction contained only benzylpicolines and pyridyl ester, *i.e.*, that all the components were eluted, was tested by comparing the detector response of a distilled benzylpicolines fraction (having approximately the same isomer distribution as the benzylpicolines in the basic fraction under discussion) with the detector response of the benzylpicolines in the basic fraction. By this method, the benzylpicolines concentration in the basic fraction was calculated to be 33.2% (compared with 35.0% by the subtraction method).

(*2*) *The Acidic Fraction.* The reaction mixture, after having been extracted with hydrochloric acid as described above, was extracted with 5% aqueous sodium bicarbonate and with water. The extracts were combined, filtered, made strongly acidic with hydrochloric acid, and thoroughly extracted with ether. Concentration of the dried (sodium sulfate) extract produced phenylacetic acid as a white solid, m.p. 75.0–76.5°

(*3*) *The Neutral Fraction.* The reaction mixture, after having been subjected to both acidic and alkaline extractions, was dried (sodium sulfate) and filtered; the benzene was removed *in vacuo*. The quantity of diphenylmaleic anhydride (DPMA, XII) was determined by quantitative infrared spectroscopy using the peak at 775 $cm.^{-1}$.

(*4*) *2-Picoline and Benzaldehyde.* These were determined by examining another sample of the original reaction mixture directly by v.p.c. using the 10-ft. Versamid 900 column at 150°.

Run 3. In Refluxing Benzene with Inhibitor. The conditions for this reaction were identical with those for the preceding run, with the exception that 1.09 g. (10.0% by weight of the 2-picoline N-oxide) of *m*-dinitrobenzene was charged to the reaction flask before heating was commenced. At the end of 8 hr. at reflux, the carbon dioxide evolution was 1.33 g. (0.302 mole). The reaction mixture was worked up, following the analytical scheme described above.

2-Pyridinemethanol Phenylacetate (X). A mixture of 10.9 g. (0.100 mole) of freshly distilled 2-pyridinemethanol (Aldrich Chemical Co.), 40.8 g. (0.300 mole) of phenylacetic acid, and 350 ml. of xylene was heated at reflux (142°) for 16 hr., with azeotropic removal of the water produced. The dark brown reaction mixture was washed with 10% aqueous hydrochloric acid. The aqueous extract was made alkaline with sodium carbonate and extracted with ether; the extract was distilled through a semimicro column to give 19.6 g. (86.5%) of 2-pyridinemethanol phenylacetate, b.p. 122° (0.4 mm.). Its infrared spectrum in carbon disulfide showed strong carbonyl absorption.

Anal. Calcd. for $C_{14}H_{13}O_2N$: C, 73.98; H, 5.77; N, 6.12. Found: C, 73.78; H, 5.77; N, 6.02.

Reaction of Phenylacetic Anhydride with 4-Picoline N-Oxide. The initial run was made on a large scale in order to facilitate the isolation and identification of products. The two small-scale runs were performed for the purpose of yield comparisons under standard conditions.

Run 1. Reaction in Benzene at Variable Temperature. A mixture of 254 g. (1.00 mole) of phenylacetic anhydride, 109 g. (1.00 mole) of 4-picoline N-oxide, and 200 ml. of benzene was subjected to nitrogen ebullition at room temperature for 20 hr., gradually heated to reflux, and held at that temperature for 13 hr. The carbon dioxide evolved was 12.5 g. (0.284 mole).

The procedure employed for working up the reaction mixture was, in general, the same as for the corresponding 2-picoline N-oxide reaction. After 100 ml. of the reaction mixture had been set aside for possible future examination, the remainder was distilled, first at atmospheric pressure to remove the bulk of the solvent and, later, under high vacuum to separate the volatiles from the nonvolatiles. Four fractions were obtained from the initial distillation: A, 1590 g., b.p. 79–80° (1 atm.), recovered benzene; B, 196.9 g., b.p. 25–50° (10 → 1 mm.); C, 193.0 g., b.p. 110–200° (0.4 mm.); D, 49.0 g., b.p. 200–280° (0.2 mm.). The nondistillable residues (24.5 g.) cooled to a black, brittle, resinous-looking solid.

No toluene was detected by v.p.c. in fraction A. Fraction B was carefully redistilled through a 24-in. Vigreux column to give 10 fractions (total weight, 189.0 g.), b.p. 80–176° (1 atm.). Each fraction was examined by quantitative v.p.c., using a 10-ft. Versamid 900 column at a temperature of 100°. The following results were obtained: toluene, 0.32 g. (0.0035 mole); 4-picoline, 59.9 g. (0.645 mole); benzaldehyde, 8.6 g. (0.081 mole). In addition to the identification of 4-picoline on the basis of its retention time, the infrared spectrum (thin film) of the appropriate distillate fraction matched that of an authentic sample.

Fraction C was dissolved in 700 ml. of ether, and the phenylacetic acid was removed by extractions with saturated aqueous sodium bicarbonate (eight 200-ml. portions). Ether was added from time to time to keep the volume at 700 ml. This was followed by a water wash (three 100-ml. portions). The ether solution was dried (sodium sulfate), the ether removed *in vacuo*, and distillation continued, through an 18-in. Vigreux column, to give seven fractions (total weight 22.0 g.), b.p. 95–130° (0.3 mm.). On standing, some of these fractions partially solidified, while others remained liquid even after prolonged cooling at 0°.

Application of infrared spectrometry and gas chromatography showed these fractions to be complex mixtures, containing four major components altogether. The five lower-boiling fractions (b.p. 95–120° (0.3 mm.), 15.7 g.) consisted of a mixture of three components, none of which contained carbonyl groups. On a 10-ft. Versamid column at a temperature of 245° and a flow rate of 50 cc./min., these components had retention times as follows: (1) 2.2 min.; (2) 2.4 min.; (3) 2.9 min. Component 3 was isolated as a solid by

filtration of one of the partially solidified distillate fractions. Recrystallization of the solid from ethanol–water gave white needles, m.p. 69–71° [lit.[50] m.p. for 4-(β-phenylethyl)pyridine (XV) 69–71°]. The material had an equivalent weight of 184 (calculated 183) as determined by titration with perchloric acid. The infrared spectrum (carbon disulfide) showed no carbonyl absorption.

A *picrate* had m.p. 162–164° (lit.[50] m.p. for the picrate of XV 162–163°).

Gas chromatographic examination of one of the distillate fractions, b.p. 105–107° (0.3 mm.), derived from fraction C showed that it consisted mainly of components 1 and 2 in nearly equal proportion. Titration of this liquid fraction gave an equivalent weight of 187 (calculated for benzylpicoline 183), indicating that it was probably a mixture of benzylpicolines. Separation and collection of the individual components by v.p.c. was not possible in this case because the two peaks were not sufficiently resolved. However, a similar fraction, obtained from the reaction of 4-picoline N-oxide with phenylacetyl chloride[51] was shown, by gas chromatography and infrared spectrometry, to contain components 1 and 2 in approximately 20:1 ratio. By preparative v.p.c., 100 mg. of component 1 was collected as a pale yellow oil. By titration with perchloric acid, the material was found to have an equivalent weight of 184. The infrared spectrum (CS_2) differed from that of the mixture of components 1 and 2 mainly in the relative intensities of the bands rather than in their positions. Component 1 was identified as 2-benzyl-4-picoline (XVI) [and differentiated from 3-benzyl-4-picoline (XVII), undoubtedly component 2] on the basis of its n.m.r. spectrum.[52] The material was examined as a 10% solution in carbon tetrachloride with a Varian A-60 spectrometer. Integration of the signals for the α- and β-hydrogen atoms of the pyridine ring, at τ 1.72 and 3.23, respectively, gave a 1:2 ratio of α- to β-hydrogen, and demonstrated substitution in the 2-position. Signals for methyl (τ 7.80) and methylene (τ 5.98) hydrogen in 3:2 ratio were in accord with the assigned structure.

The two highest boiling fractions, b.p. 120–130° (0.3 mm.), derived from fraction C each contained a carbonyl group as shown by an infrared peak at 1747 cm.$^{-1}$. Those fractions (total weight 6.3 g.) were combined. By preparative gas chromatography (Versamid 900 column at 245°), a pale yellow oil was collected (retention time 6.0 min.), the infrared spectrum of which was identical with that of an authentic (see below) sample of 4-pyridinemethanol phenylacetate (XIV). By v.p.c., the yield of the 4-ester was calculated to be 0.025 mole.

The bicarbonate washing from fraction C was acidified, extracted with ether to remove the phenylacetic acid, saturated with sodium carbonate, and extracted several times with ether. Evaporation of the ether yielded 0.2 g. of 4-methyl-3-pyridinol, identified by comparison of its infrared spectrum with that of an authentic sample.[8]

When fraction D, 49.0 g., b.p. 200–280° (0.2 mm.), a dark viscous liquid, was diluted with ether, a voluminous yellow solid precipitated. This material (8.0 g.) was isolated by filtration and recrystallized by diluting its acetone solution with water. A pale yellow solid, m.p. 176–178° (6.8 g.), was obtained. Work-up of the mother liquor from fraction D provided an additional 4.1 g. of the solid. The infrared spectrum (CS_2) possessed a strong carbonyl band at 1771 cm.$^{-1}$. As discussed in the Results section, the material is probably 5-oxo-3,4-diphenyl-2-benzaldihydrofuran (XVIII) (lit.[28] m.p. 175–176°).

Run 2. Reaction in Refluxing Benzene without Inhibitor. With nitrogen ebullition, a mixture of 25.4 g. (0.100 mole) of phenylacetic anhydride and 400 ml. of benzene was heated to 50°. 4-Picoline N-oxide (10.9 g., 0.100 mole) was added rapidly, and the temperature was raised to reflux within a 10-min. period. The mixture was then heated at gentle reflux for 8 hr., after which it was quantitatively analyzed as described for the corresponding 2-picoline N-oxide reaction.

Run 3. In Refluxing Benzene with Inhibitor. The conditions for this reaction were identical with those for the preceding run, with the exception that 1.09 g. (10.0% by weight of the 4-picoline N-oxide) of *m*-dinitrobenzene was charged to the reaction flask before heating was started.

Control Experiment to Determine Stability of Products under Reaction Conditions. The following materials were charged to a 1-l. four-necked flask: 25.4 g. (0.100 mole) of phenylacetic anhydride, 10.9 g. (0.100 mole) of 4-picoline N-oxide, 400 ml. of benzene, 1.06 g. (0.0100 mole, 10 mole %) of benzaldehyde, 0.45 g. (0.0020 mole, 2 mole %) of 4-pyridinemethanol phenylacetate, 1.65 g. (0.0090 mole, 9 mole %) of benzylpicoline isomers. With nitrogen ebullition, the mixture was heated at reflux for 8 hr. The carbon dioxide evolution was 1.74 g. (0.0395 mole). The mixture was worked up using the analytical procedure previously described. The results have been presented in Table II.

4-Pyridinemethanol Phenylacetate (XIV). A mixture of 21.8 g. (0.200 mole) of 4-pyridinemethanol (Aldrich Chemical Co.), 55.9 g. (0.220 mole) of phenylacetic anhydride, and 400 ml. of benzene was heated at reflux for 4 hr. The reaction mixture was extracted with 10% aqueous hydrochloric acid and the aqueous extract was filtered, made alkaline with sodium carbonate, and extracted with ether. The dried ether extract was distilled through a 15-in. Vigreux column to give 35.0 g. (77.1%) of a pale, straw-colored liquid, b.p. 134–136° (0.3 mm.). The infrared spectrum (CS_2) had a strong carbonyl band at 1747 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{13}O_2N$: C, 73.98; H, 5.77; N, 6.12. Found: C, 73.75; H, 5.75; N, 6.00.

Effect of Temperature and Nitrogen Ebullition on the Composition of the Benzylpicoline Fraction in the Reaction of 4-Picoline N-Oxide with Phenylacetic Anhydride. The composition of the benzylpicoline fraction obtained in this reaction performed in refluxing benzene with nitrogen ebullition (Table I)

(50) B. Fels, *Ber.*, 37, 2137 (1904).

(51) This reaction also produced carbon dioxide and the ester, but the conditions proved inferior to those outlined above.

(52) H. J. Bernstein, and W. G. Schneider, *J. Chem. Phys.*, **24**, 469 (1956); V. J. Kowalewski and D. G. de Kowalewski, *ibid.*, **36**, 266 (1962); W. Brügel, *Z. Elektrochem.*, **66**, 159 (1962); C. B. Rao and V. Venkateswarlu, *Proc. Indian Acad. Sci.*, **A54**, 305 (1961).

was compared with those obtained in similar reactions performed at room temperature in the same solvent. In both room temperature runs, a solution of phenylacetic anhydride (50.8 g., 0.200 mole) and 4-picoline N-oxide (21.8 g., 0.200 mole) in 800 ml. of benzene was allowed to stand at room temperature for 12 days. In only one of the runs was nitrogen ebullition used (with consequent sweeping away of the evolved carbon dioxide). The results in Table III indicate that although the total yield of benzylpicolines does not vary appreciably as conditions are changed, the composition of the benzylpicoline fraction is greatly influenced by the reaction conditions. The reason for this behavior is not clear.

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Aromatic N-Oxides. V. The Reaction of 4-Picoline N-Oxide with Various Anhydrides[1,2]

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A product study of the reactions of 4-picoline N-oxide with acetic, isobutyric, and pivalic anhydrides is reported. The product categories include carbon dioxide, esters (4-acyloxymethylpyridine and 3-acyloxy-4-methylpyridine), and alkylpyridines (4-alkylpyridines, 3,4-dialkylpyridines, and 2,4-dialkylpyridines). A rationalization of these results is made utilizing an intramolecular radical-pair mechanism via the intermediate anhydro base.

The various mechanisms which have been suggested to explain the formation of 4-pyridylmethyl acetate (VI, R = CH_3) and 3-acetoxy-4-methylpyridine (VII, R = CH_3) from the reaction of 4-picoline N-oxide and acetic anhydride have been reviewed in a recent report by Oae.[4] In the generally accepted mechanistic scheme, as outlined above, both the initial step leading to the formation of 1-acyloxy-4-methylpyridinium ion (III) and its conversion, by proton abstraction with the acid anion IV, to the anhydro base V have been based on analogy with similar reactions, particularly the comparable reaction of 2-picoline N-oxide and acid anhydrides.[2] Recently, we have obtained evidence for III by isolation of this cation as its perchlorate and the conversion of III perchlorate by base to a mixture of esters VI and VII.[5] In addition, spectroscopic evidence is available for the anhydro base V and will be reported in the near future.[5]

A controversy still exists over step 3, the transformation of V to the ester mixture VI and VII. The intermolecular mechanism requires attack of the acid anion (IV) on the exocyclic methylene group of V with expulsion of the acid anion attached to nitrogen (path A) and the formation of ester VI. Ester VII would arise by attack of IV at the C-3 position of V and expulsion of the N acid anion (path B) followed by an allylic rearrangement of VIII to regenerate the pyridine ring. The alternate mechanism involves an intramolecular rearrangement of V which may occur *via* a concerted, ion-pair or radical-pair process. Evidence in favor of

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(2) For paper IV in this series, see V. J. Traynelis and P. L. Pacini, *J. Am. Chem. Soc.*, 86, 4917 (1964).

(3) (a) Department of Chemistry, West Virginia University, Morgantown, W. Va.; (b) abstracted from the Ph.D. dissertation of A. I. G. submitted Oct. 1964.

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

(5) V. J. Traynelis and A. I. Gallagher, unpublished results.