The Oxidative Decarboxylation of Carboxylic Acids by Pyridine N-Oxide[1,2]

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Abstract: It is shown that pyridine N-oxide is capable of executing a four-electron decarboxylative oxidation on a number of carboxylic anhydrides or on the corresponding acids in the presence of acetic anhydride, which itself does not undergo this reaction. The major products are aldehydes or ketones, carbon dioxide, and pyridine. Important side products in the case of phenylacetic acid are phenylglyoxylic acid (VI), diphenylmaleic anhydride (VII, DPMA), and, when acetic acid is present, acetylmandelic acid (XII, R = H). These results, in addition to the fact that pivalic anhydride is inert to this oxidation, are interpreted in terms of a novel mechanism which involves nucleophilic substitution of pyridine N-oxide for hydrogen at the α position of the acid *via* mechanisms A, B, or C and subsequent decomposition of the intermediate V to benzaldehyde and phenylglyoxylic acid. The latter, by condensation with phenylacetic acid, yields DPMA. The possibility of each of these steps has been demonstrated experimentally.

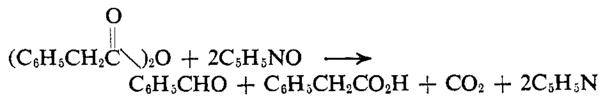
During a study[3] of the reactions of 2- and 4-picoline N-oxide with phenylacetic anhydride, it became evident that, in addition to rearrangement processes proceeding *via* anhydrobase intermediates, there was occurring a redox reaction, the main products of which were picolines, benzaldehyde, and carbon dioxide. A small quantity of diphenylmaleic anhydride (DPMA, VII) produced concurrently was also thought to be a result of the oxidation of the anhydride by the amine oxide. In order to study the scope and mechanism of this novel redox reaction, uncomplicated by processes proceeding from anhydrobase intermediates, a study of the oxidative decarboxylation of various acids and their derivatives by pyridine N-oxide itself was under taken.

Table I. Product Yields in Reactions of Anhydrides and Acids with Pyridine N-Oxide[a]

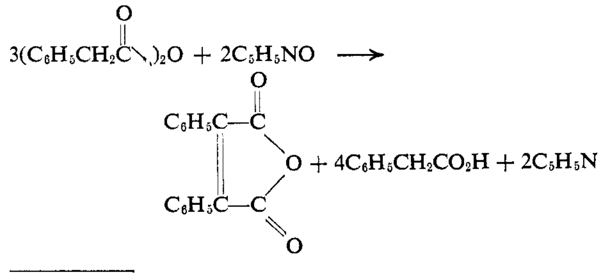
Anhydride or acid	Solvent	Reaction time, hr	Product (yield, %)	Yield of CO_2, %
Phenylacetic anhydride	Benzene	18	Benzaldehyde (69)	76
Phenylacetic acid	Benzene	24	Benzaldehyde (68)	71
Diphenylacetic anhydride	Benzene	10	Benzophenone (68)	83
Diphenylacetic acid	Benzene	10	Benzophenone (62)	86
Isobutyric anhydride	Toluene	48	Acetone (39)	69
Butyric anhydride	Xylene	10	Propionaldehyde (12.4)	19
Acetic anhydride	Xylene	4	2-Acetoxypyridine[b]	Nil
Cyclohexanecarboxylic acid	Toluene	72	*c*	7
Norbornane-2-carboxylic acid	Mesitylene[d]	45	*c*	30
exo-Norborn-5-ene-2-carboxylic acid	Benzene	31	*c*	35

[a] The reactions were carried out in the refluxing solutions until carbon dioxide evolution ceased. [b] Yield not determined. [c] Product not determined; expected ketones absent. [d] In benzene, no carbon dioxide was produced in 24 hr.

As expected, it was found that the yields of redox products from phenylacetic anhydride are greater with pyridine N-oxide than with the picoline N-oxides. The oxidation of this anhydride occurs smoothly in refluxing benzene containing an excess of pyridine N-oxide (Table I) or in benzene containing an equimolar quantity of pyridine N-oxide at 50° for a longer period. A careful examination of the neutral and basic fractions from the lower temperature run revealed that, in addition to benzaldehyde, DPMA (VII) is produced in 11% yield (based on eq 2)[4] and that an equimolar mixture of 2- and 4-benzylpyridine was present in a yield well below 1%.



$$(C_6H_5CH_2\overset{O}{\overset{\|}{C}})_2O + 2C_5H_5NO \longrightarrow C_6H_5CHO + C_6H_5CH_2CO_2H + CO_2 + 2C_5H_5N \quad (1)$$



(2)

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[1] (a) Based in part upon the theses of J. H. F. and I. H. S. submitted to the Department of Chemistry, University of Pittsburgh, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1965 and 1966, respectively. (b) We wish to acknowledge support of this work by Grant PRF-1788-A4 from the Petroleum Research Fund, administered by the American Chemical Society, and by Grant AF-AFOSR 344-63 from the Air Force Office of Scientific Research of the U. S. Air Force.

[2] (a) A preliminary account of much of this work has appeared: T. Cohen, I. H. Song, and J. H. Fager, *Tetrahedron Letters*, 237 (1965). (b) The initial discovery of this type of reaction was announced by T. Cohen and J. H. Fager, Abstracts, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964, p 36C.

[3] T. Cohen and J. H. Fager, *J. Am. Chem. Soc.*, 87, 5701 (1965).

[4] This was determined as a mixture of the DPMA with a compound which is almost certainly a photodimer of DPMA. See Experimental Section.

Diphenylacetic anhydride is oxidized to benzophenone in refluxing benzene containing excess pyridine N-oxide (Table I).

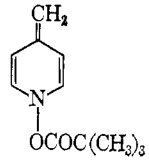
The reaction of acetic anhydride with excess pyridine N-oxide in xylene solution at 100° for 2 hr, at 120° for 2 hr more, and finally at reflux (142°) for 4 hr fails to yield significant quantities of either carbon dioxide or formaldehyde. Instead, the well-known rearrangement to 2-acetoxypyridine occurs.[5,6]

Since acetic anhydride is known[6] to react with pyridine N-oxide very slowly at temperatures below 100°, it seemed likely that carboxylic acid anhydrides, which are used as substrates in the oxidation under discussion, could be replaced with a mixture of the corresponding carboxylic acid and acetic anhydride, thus obviating the frequently time-consuming preparation of the anhydride. This was indeed found to be the case. As indicated in Table I, both phenylacetic and diphenylacetic acids are smoothly oxidized by pyridine N-oxide in the presence of acetic anhydride.

Butyric anhydride fails to react appreciably in refluxing benzene or toluene but is converted to propionaldehyde in poor yield in refluxing xylene. The oxidation is obviously in competition with the rearrangement to 2-butyroxypyridine, the hydrolysis product of which, 2-pyridone, was detected spectroscopically in the reaction mixture.

Isobutyric anhydride is more reactive, being converted to acetone in refluxing toluene. On the other hand, cyclohexanecarboxylic acid produces only 7% carbon dioxide when heated with acetic anhydride and pyridine N-oxide in refluxing toluene for 72 hr. Both bicyclo[2.2.1]heptane-2-carboxylic acid (mixture of *exo* and *endo*) and *exo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid yield about one-third of the theoretical quantity of carbon dioxide when oxidized by pyridine N-oxide but the expected ketones, norcamphor and dehydronorcamphor, could not be detected by gas chromatography in the reaction product.

The failure of pivalic anhydride, at temperatures ranging from the reflux temperature of toluene to that of xylene, to react with pyridine N-oxide is shown by the absence of carbon dioxide production and in one run by the almost quantitative recovery of pyridine N-oxide. Neither does pivalic acid (refluxing benzene) yield carbon dioxide. As will be seen, the nonreactivity of pivalic anhydride provides crucial mechanistic clues only if it is not due to failure of this hindered anhydride to acylate the N-oxide function. That this is not the cause of the nonreactivity is shown by the reaction of pivalic anhydride and 4-picoline N-oxide in refluxing benzene for 71 hr which produces 89% of the theoretical amount of carbon dioxide. The great ease of formation of carbon dioxide in the reaction of 4-picoline N-oxide with pivalic anhydride must certainly be due to the intermediate formation of the anhydrobase I,[3,7] which cannot form in the case of pyridine N-oxide and which decomposes to a radical or ion pair and carbon dioxide. If picoline N-oxide is capable of becoming acylated by pivalic anhydride at such a low temperature then surely pyridine N-oxide must become acylated at the higher reflux temperatures of toluene and xylene.



I

Both glutaric anhydride and cyclohexane-1,2-dicarboxylic anhydride fail to give carbon dioxide in refluxing diethyl Carbitol, bp 195°.

The acid chloride of phenylacetic acid gives a much lower yield (25%) of carbon dioxide upon oxidation by pyridine N-oxide than does the anhydride; this is probably due to dehydrohalogenation to phenylketene.[8,9] No carbon dioxide is produced in the attempted oxidation of phenylacetyl chloride by the weaker base, dimethyl sulfoxide; this is not surprising in view of the rearrangement that occurs when other acid chlorides are heated with dimethyl sulfoxide.[10]

The first step in the decarboxylative oxidation reaction must certainly be nucleophilic attack by the pyridine N-oxide on the anhydride of the acid which is oxidized or on a mixed anhydride with acetic acid. There is a great deal of evidence for this type of acylation.[11] Using the phenylacetic anhydride oxidation as an example, it thus seems likely that the products arise from the N-phenylacetoxypyridinium ion III. Several paths by which this ion may proceed to products will now be considered.

Free-Radical Mechanisms. Although radical mechanisms involving anhydrobase intermediates have frequently been postulated for the reactions of picoline N-oxides,[3,7,12] a reasonable radical path for the present decarboxylative oxidation reaction involving pyridine N-oxide is not immediately obvious since anhydrobase intermediates are not possible. Furthermore, even if the homolytic cleavage of the N–O bond of the N-phenylacetoxypyridinium ion (III) were to occur, to produce a pyridine radical cation, it is very difficult to formulate the mechanism of the oxidation of the resulting benzyl radical by pyridine N-oxide.

A careful search of some of the reaction mixtures in which phenylacetic anhydride and phenylacetic acid were oxidized in benzene solution failed to reveal the presence of the following products which are characteristic of reactions involving benzyl radicals: toluene, 1,2-diphenylethane, and diphenylmethane.[13] On the other hand, the trace of 2- and 4-benzylpyridine produced could result from the attack of benzyl radicals

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[5] M. Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947); *Chem. Abstr.*, **45**, 9536*d* (1951).

[6] J. H. Markgraf, H. B. Brown, Jr., S. C. Mohr, and R. G. Peterson, *J. Am. Chem. Soc.*, **85**, 958 (1963).

[7] V. J. Traynelis and A. I. Gallagher, *ibid.*, **87**, 5710 (1965).

[8] N. Rabjohn and H. M. Molotsky, *J. Org. Chem.*, **23**, 1642 (1958).

[9] Pivalyl chloride gives no carbon dioxide when treated with pyridine N-oxide in any of the following solvents at reflux: benzene, toluene, or xylene. Triphenylacetyl chloride gives no carbon dioxide in refluxing toluene.

[10] F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).

[11] V. J. Traynelis, A. I. Gallagher, and R. F. Martello, *J. Org. Chem.*, **26**, 4365 (1961); C. W. Muth and R. S. Darlak, *ibid.*, **30**, 1909 (1965); S. Furukawa, *J. Pharm. Soc. Japan*, **79**, 492 (1959); *Chem. Abstr.*, **53**, 18029 (1959).

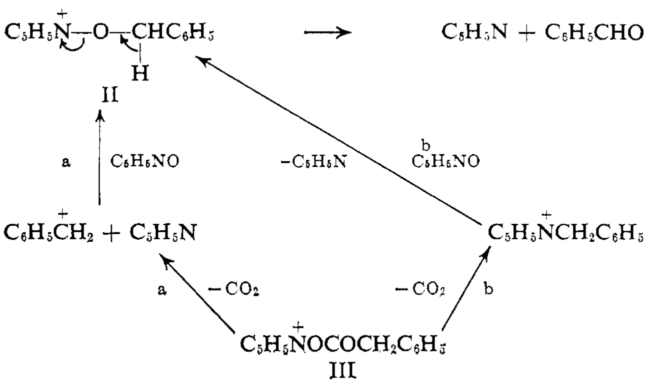
[12] V. Boekelheide and D. L. Harrington, *Chem. Ind.* (London), 1423 (1955); V. J. Traynelis and R. F. Martello, *J. Am. Chem. Soc.*, **80**, 6590 (1958); V. J. Traynelis and R. F. Martello, *ibid.*, **82**, 2744 (1960); S. Oae, T. Kitao, and Y. Kitaoka, *ibid.*, **84**, 3359 (1962); S. Oae, Y. Kitaoka, and T. Kitao, *Tetrahedron*, **20**, 2685 (1964).

[13] This would be expected from the attack of benzyl radicals on benzene: F. D. Greene, H. P. Stein, C. C. Chu, and F. M. Vane, *J. Am. Chem. Soc.*, **86**, 2080 (1964).

on pyridine although other mechanisms are available.[14] Additional evidence against a free-radical path is the absence of propene, one of the disproportionation products of *n*-propyl and isopropyl radicals, in the reaction mixtures from the oxidation of butyric and isobutyric anhydrides.

Several independent observations of Rüchardt, Eichler, and Krätz,[15] whose work was published simultaneously with our own preliminary report,[2a] are also incompatible with the intervention of free benzyl radicals in the oxidation of phenylacetic anhydride.[16]

N-Benzyloxypyridinium Ion (II) as an Intermediate. Since the known N-benzyloxypyridinium ion (II) is converted to benzaldehyde and pyridine in the presence of base,[17] it obviously must be seriously considered as an intermediate in the present reaction. This could arise[15] either by fragmentation of III as shown and combination of the resulting benzyl cation with pyridine N-oxide (path a; this fragmentation is closely analogous to that proposed for the acid-catalyzed decomposition of certain diacyl peroxides and peresters[18]) or by displacement of pyridine by pyridine N-oxide from the N-benzylpyridinium ion produced by loss of carbon dioxide from III (path b).

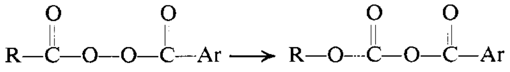


While the reactivity sequence diphenylacetic and phenylacetic > isobutyric > butyric > acetic is quite compatible with path a, the complete lack of reactivity of pivalic anhydride is strong evidence against this fragmentation mechanism.[9] Other evidence is the apparent failure of the proposed benzyl cations to react with carboxylic acids as indicated by the lack of production of benzyl phenylacetate from the oxidation of phenylacetic anhydride in benzene[19] and of benzyl acetate from the oxidation of phenylacetic acid in the presence of excess acetic anhydride in benzene or even in *acetic acid as solvent.*

Path b was eliminated when it was demonstrated that neither benzaldehyde nor pyridine is formed in the attempted reaction of N-benzylpyridinium acetate and pyridine N-oxide in benzene solution.

The Carboxy Inversion Mechanism. Recently, it has been suggested[20,21] that a key step in the conversion of III to products is migration of the benzyl group to the oxygen atom with expulsion of the pyridine molecule. This is similar to the carboxy inversion mechanism observed in a number of diacyl peroxide decompositions.[13,23]

A recent study of Denney and Sherman[23c] has shown that the rate of the rearrangement of acyl aroyl peroxides (IV) to the mixed carbonate depends on the nature of R in IV. The rate decreases substantially in the order tertiary > secondary > primary.

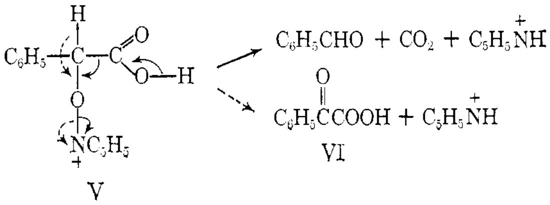


$$R-\overset{O}{\overset{\|}{C}}-O-O-\overset{O}{\overset{\|}{C}}-Ar \longrightarrow R-O-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-Ar$$

IV

While this order is followed with regard to isopropyl, *n*-butyl, and methyl in that isobutyric acid is oxidized much more readily than butyric acid, while acetic acid does not undergo this reaction, the fact that pivalic anhydride is unreactive strongly militates against this type of rearrangement mechanism.

The N-(α-Carboxybenzyloxy)pyridinium Ion (V) as an Intermediate. The fact that acid anhydrides which have an α-hydrogen atom undergo the oxidative decarboxylation reaction with pyridine N-oxide to produce the corresponding aldehydes and ketones while pivalic anhydride is unreactive under these conditions suggests that an α-hydrogen atom is necessary in order for the oxidative decarboxylation to occur. In the phenylactic acid case, a reasonable intermediate which is consistent both with the necessity for an α-hydrogen atom and with the formation of carbon dioxide, pyridine, benzaldehyde, and diphenylmaleic anhydride (VII) is the N-(α-carboxybenzyloxy)pyridinium ion (V) in which the amine oxide has replaced an α-hydrogen atom. The β elimination of a proton and a pyridine nucleus from V (dotted arrows) would yield phenylglyoxylic acid (VI)



in a manner directly analogous to the base-catalyzed decomposition of N-benzyloxypyridinium ion (II).[17] The ion V could also decompose in a carboxylogous fashion[24] (solid arrows) to yield benzaldehyde, carbon dioxide, and the elements of the pyridinium ion. The phenylglyoxylic acid (VI) formed would probably then

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(14) For example, see footnote 39 in ref 3.

(15) C. Rüchardt, S. Eichler, and O. Krätz, *Tetrahedron Letters*, 233 (1965).

(16) While there is no evidence for radicals in any of the low-temperature runs reported in Table I, radicals must have been present in the runs performed in xylene since the same mixture of six isomeric xylylpyridines is produced in both the acetic and butyric anhydride cases. For details, see the thesis of J. H. F.[1]

(17) W. Feely, W. L. Lehn, and V. Boekelheide, *J. Org. Chem.*, **22**, 1135 (1957).

(18) P. D. Bartlett and J. E. Leffler, *J. Am. Chem. Soc.*, **72**, 3030 (1950); H. Hart and R. A. Cipriani, *ibid.*, **84**, 3697 (1962); C. Rüchardt and H. Schwarzer, *Angew. Chem. Intern. Ed. Engl.*, **1**, 217 (1962).

(19) We have no explanation for the production of some of this ester in the same reaction run under somewhat different conditions.[15] This mechanism is not excluded in the oxidation of α-alkoxyacetic acids which produces esters in yields as high as 50%.[20]

(20) C. Rüchardt and O. Krätz, *Tetrahedron Letters*, 5915 (1966).

(21) This type of mechanism had been previously suggested by Koenig[22] for the production of ester in the oxidation of diphenylacetic anhydride.

(22) T. Koenig, *Tetrahedron Letters*, 3127 (1965).

(23) (a) J. E. Leffler, *J. Am. Chem. Soc.*, **72**, 67 (1950); (b) D. Z. Denney, T. M. Valega, and D. B. Denney, *ibid.*, **86**, 46 (1964); (c) D. B. Denney and N. Sherman, *J. Org. Chem.*, **30**, 3760 (1965).

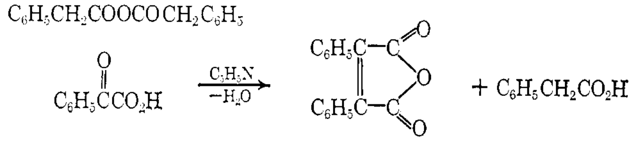
(24) This term has been coined[25] to indicate the analogy between reactions which proceed by loss of a proton and those which proceed by loss of both a proton and carbon dioxide. The latter, which are carboxylogs of the former, invariably occur more rapidly.

(25) T. Cohen and I. H. Song, *J. Org. Chem.*, **31**, 3058 (1966).

be capable of condensing with phenylacetic acid or an anhydride of it in a Perkin reaction to yield the diphenylmaleic anhydride.

These conversions have, in fact, now been realized independently by isolating benzaldehyde (49%) and phenylglyoxylic acid (5%) from the reaction of α-bromophenylacetic acid and pyridine N-oxide in refluxing benzene, a reaction in which V must be an intermediate.[25] The oxidative decarboxylation of α-halo acids is in fact a general reaction which has considerable synthetic and degradative potential.[25]

In a separate experiment, it has also been found that phenylglyoxylic acid reacts with phenylacetic anhydride and pyridine to yield, by condensation, diphenylmaleic anhydride (VII, 46%) and, by decarboxylation, benzaldehyde (6%). The remarkable mechanistic and synthetic implications of this unexpected type of decarboxylation have recently been discussed.[26]



VII

According to the proposed scheme, the detection of phenylglyoxylic acid (VI) might be possible from the reaction of phenylacetic acid with pyridine N-oxide in the presence of acetic anhydride. In fact, the anticipated product, phenylglyoxylic acid (1.2 and 3%, respectively, based on pyridine N-oxide which is the limiting reactant), was isolated in two experiments (Table II) in which an equimolar quantity of pyridine N-oxide and phenylacetic acid was allowed to react (a) in the presence of acetic anhydride in solvent acetic acid at 78° and (b) in benzene containing acetic acid, acetic anhydride, and a small quantity of sodium acetate.

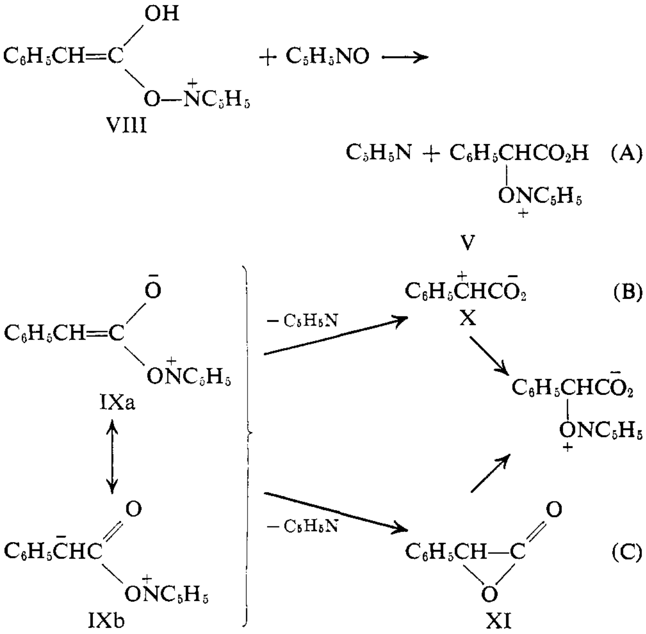
Table II. Product Distributions from the Reactions of Phenylacetic Acid and Pyridine N-Oxide in the Presence of Acetic Anhydride[a]

Product	Yields,[b] %		
	Run 1[c,f]	Run 2[d,g]	Run 3[e,g]
Carbon dioxide	71[h]	j	110[h]
Benzaldehyde	68	7.8	1.3
Diphenylmaleic anhydride	1.4	3.7	10.3
Pyridine	88	16.7	20.4
2- and 4-benzylpyridine	i	i	1.8[k]
Acetylmandelic acid	6.3	6.5	10.5
Phenylglyoxylic acid	Trace	3	1.2

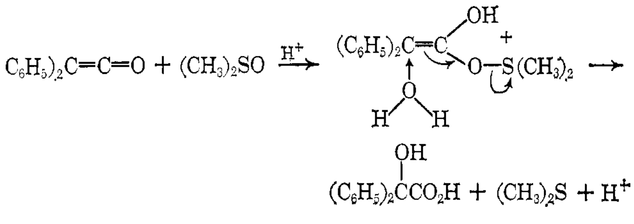
[a] The reactions were carried out until carbon dioxide evolution had ceased. [b] See text for equations on which the yields are based. [c] Four moles of pyridine N-oxide and 2 moles of acetic anhydride/mole of acid, heated at reflux for 24 hr in benzene. [d] Four moles of acetic anhydride, 4 moles of acetic acid, and 0.05 mole of sodium acetate/mole of acid and pyridine N-oxide, heated at reflux for 22 hr. [e] Four moles of acetic anhydride/mole of acid and pyridine N-oxide, heated in acetic acid at 78° for 21 hr. [f] Yields are based on the limiting reactant, phenylacetic acid. [g] Yields are based on the limiting reactant, pyridine N-oxide. [h] Based on eq 3. [i] No attempt was made to analyze for this product. [j] Present, but not determined quantitatively. [k] Infrared estimation indicates that the ratio of 2- and 4-benzylpyridine is about 5:1.

Thus far, it has been demonstrated that the proposed intermediate V could account for the production of carbon dioxide, benzaldehyde, pyridine, phenylglyoxylic acid, and diphenylmaleic anhydride. Turning now to a consideration of the formation of V, at least three reasonable routes are available by which the N-phenylacetoxypyridinium ion (III) could proceed to this intermediate.

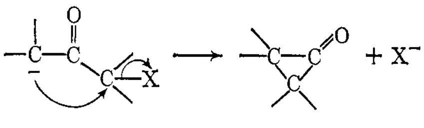
One possible route (A) involves the S_N1' or S_N2' nucleophilic displacement of pyridine from the enol VIII of the ion III. A closely related route (B) involves a similar nucleophilic displacement in the enolate IX derived from III (or VIII) by loss of a proton; the S_N1' version of this mechanism, involving the zwitterion X as an intermediate, has recently been put forth by Koenig.[22] This scheme is in turn closely related to C, in which the intermediate is depicted as an α-lactone (XI).[27]



Adequate analogies are available for the key steps of A and C. The key step in A is similar to the very reasonable reaction path proposed by Lillien[28] to account for the production of benzilic acid in the acid-catalyzed oxidation of diphenylketene by aqueous dimethyl sulfoxide.



Scheme C is somewhat analogous to the key step in the base-catalyzed Favorskii rearrangement of α-halo ketones which appears to proceed by loss of a proton followed by formation of a cyclopropanone ring.[29]



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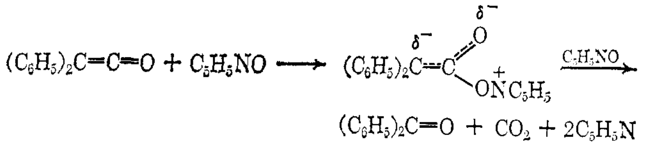
[26] T. Cohen and I. H. Song, *J. Am. Chem. Soc.*, **87**, 3780 (1965).

[27] This possibility was suggested at a recent meeting.[2b]

[28] I. Lillien, *J. Org. Chem.*, **29**, 1631 (1964).

[29] (a) A. S. Kende, *Org. Reactions*, **11**, 261 (1960); (b) E. E. Smissman, T. L. Lemke, and O. Kristiansen, *J. Am. Chem. Soc.*, **88**, 334 (1966).

Koenig[22] has recently provided an elegant demonstration that an enolate species such as IX is indeed capable of oxidative decarboxylation by pyridine N-oxide. He found that diphenylketene is oxidized to benzophenone in the presence of pyridine N-oxide, thus providing a basis for B or C.



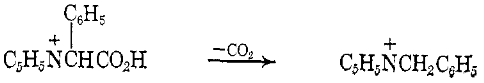
The electrophilic intermediates postulated in A, B, and C would certainly be expected to react with other nucleophilic components of the reaction mixture besides pyridine N-oxide. Thus in the experiments utilizing phenylacetic acid and acetic anhydride, both phenylacetic acid and acetic acid should attack the intermediate to form phenylacetylmandelic acid (XII, R = C_6H_5) and acetylmandelic acid (XII, R = H), respectively.

XII

An attempt was made to detect the latter acid in the product of a reaction in which phenylacetic acid was treated with an excess of pyridine N-oxide and acetic anhydride in benzene solution (run 1 in Table II). Treatment of the acid fraction, which consisted mostly of phenylacetic and acetic acid, with diazomethane, and distillation of the resulting ester mixture produced a fraction which was very rich in the methyl ester of acetylmandelic acid (6.3% yield) according to its infrared and nmr spectra and its gas chromatographic behavior on three different columns. The yield of benzaldehyde was 68%. By the use of a deficiency of pyridine N-oxide in benzene containing added acetic acid, the ratio of acetylmandelic acid to benzaldehyde produced is increased substantially (run 2, Table II). Presumably, the acetic acid can now compete effectively with pyridine N-oxide for capture of the electrophilic intermediate.[30] When the reaction is performed in acetic acid as solvent (run 3) the yield of acetylmandelic acid is increased to 10.5% while the yield of benzaldehyde drops to about 1%.[30]

The yields of acetylmandelic acid recorded in Table II are minimum yields for we have found that this acid (XII, R = H) itself is oxidized by pyridine N-oxide in the presence of acetic anhydride to produce benzaldehyde in 49% yield. Thus, both of the side products, acetylmandelic acid and phenylglyoxylic acid, are capable of conversion to the major product, benzaldehyde.

We have also succeeded in capturing the electrophilic intermediate with pyridine. The reaction of phenylacetic acid–acetic anhydride with pyridine N-oxide in pyridine solution leads to the production of the N-benzylpyridinium ion (XIV) in a yield (nmr) of 43% of the carbon dioxide evolved. The ion was also identified as its crystalline picrate salt. Our previous work[26] has shown that the initial product (XIII), expected from the attack of pyridine on the electrophilic intermediate, is rapidly decarboxylated to XIV.

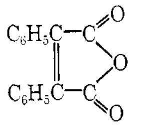


XIII XIV

The yields in Table II are based on the following equations.

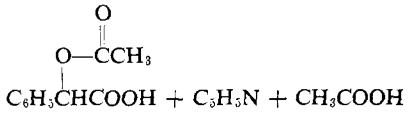
$$C_6H_5CH_2COOH + (CH_3CO)_2O + 2C_5H_5NO \longrightarrow C_6H_5CHO + CO_2 + 2C_5H_5N + 2CH_3COOH \quad (3)$$

$$2C_6H_5CH_2COOH + 3(CH_3CO)_2O + 2C_5H_5NO \longrightarrow$$



$$+ 6CH_3COOH + 2C_5H_5N \quad (4)$$

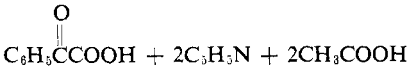
$$C_6H_5CH_2COOH + (CH_3CO)_2O + C_5H_5NO \longrightarrow$$



$$C_6H_5\underset{\displaystyle C_6H_5CHCOOH}{O{-}\overset{\overset{O}{\|}}{C}CH_3} \ \text{}$$

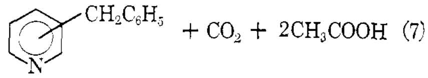
$$C_6H_5CH(O\overset{O}{\overset{\|}{C}}CH_3)COOH + C_5H_5N + CH_3COOH \quad (5)$$

$$C_6H_5CH_2COOH + (CH_3CO)_2O + 2C_5H_5NO \longrightarrow$$



$$C_6H_5\overset{\overset{O}{\|}}{C}COOH + 2C_5H_5N + 2CH_3COOH \quad (6)$$

$$C_6H_5CH_2COOH + (CH_3CO)_2O + C_5H_5NO \longrightarrow$$



$$+ CO_2 + 2CH_3COOH \quad (7)$$

It would be very difficut to explain the production of acetylmandelic acid without invoking intermediates which are subject to *nucleophilic* attack at a position α to a carboxyl group. There is considerable novelty in such an attack since the α positions of carboxylic acids are usually subject only to *electrophilic* attack. The possible synthetic utility of this concept is now under investigation.

On the basis of recent experiments by Rüchardt and Krätz,[20] scheme C involving an α-lactone intermediate appears unlikely at least in the case of diphenylacetic anhydride. The appropriate lactone, generated independently, apparently behaves similarly in the presence and absence of pyridine N-oxide. In general, schemes A and B are thus preferred.[31] Both are compatible with the deuterium scrambling reported[22] to occur in the case of partially α-deuterated phenylacetic anhydride provided that the enolization or enolate formation is reversible.[32] The claim[22] that the oxidation rate is inversely proportional to the concentration of phenylacetic acid is also compatible with schemes A and B. The acid could act

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[30] The low yield of benzaldehyde and pyridine in runs 2 and 3 along with the high yield of carbon dioxide in run 3 (it was not determined in run 2) is probably due to the fact that pyridine can now compete effectively with pyridine N-oxide for capture of the electrophilic intermediate. See below.

[31] We find unconvincing the arguments recently brought forth against schemes A and B.[20] For example, evidence for the lack of isomerization in the oxidation of anhydrides of the type $(RCH_2CH{=}CHCO)_2O$, was not given. The isomerized products would be of the type $RCOCH{=}CHCO_2H$ and would be found in the acid fraction, mixed with a large amount of acid $RCH_2CH{=}CHCO_2H$. Furthermore, the two possible positions of nucleophilic attack on the allylic systems are extremely different electronically, and one of these might be much preferred over the other.

[32] The scrambling could also have occurred at an earlier stage; for example, the anhydride itself was not reported to be inert toward exchange with product acid.

so as to decrease the equilibrium concentration of the enolate ion IX, as suggested,[22] or it could decrease the activity of pyridine N-oxide (toward acylation) by hydrogen bonding with it.[32a]

Experimental Section

The reactions, involving pyridine N-oxide which occurred in refluxing solvents were performed under a stream of nitrogen which was conducted out of the reaction vessel *via* the reflux condenser, through a drying tube containing Drierite, and finally through two Caroxite (Fisher Scientific Co.) tubes where carbon dioxide was quantitatively absorbed. All solvents were dried before use.

Diphenylacetic Anhydride. Potassium diphenylacetate was prepared as follows. A solution of 28.0 g (0.500 mole) of potassium hydroxide pellets in 100 ml of anhydrous ethanol was added dropwise, with stirring, at 20° to a mixture of 106 g (0.500 mole) of diphenylacetic acid and 300 ml of anhydrous ethanol. The white solid which precipitated was removed by filtration at 5°, washed sparingly with ethanol, and dried in an oven for 2 hr at 110°. The yield was 82 g (66%).

To a suspension of 25.0 g (0.100 mole) of potassium diphenylacetate in 200 ml of dioxane was added dropwise at room temperature a solution of 9.5 g (0.050 mole) of *p*-toluenesulfonyl chloride in 100 ml of dioxane. The mixture was heated at reflux (102°) with stirring for 2 hr. When the cooled mixture was poured into 2 l. of water, an oil separated and gradually crystallized to a white solid. The solid was removed by filtration, washed with water, and air dried. The crude product (20 g) was dissolved in acetone, and small amounts of insoluble potassium chloride were removed by filtration. Diphenylacetic anhydride was precipitated by diluting the filtrate with water until an 80:20 water–acetone mixture was obtained. The white crystals were removed by filtration, washed thoroughly with water, and dried in a vacuum desiccator for 20 hr to yield 10.9 g (54%) of pure material, mp 97–99° (lit.[33] mp 98°).

Reaction of Phenylacetic Anhydride with Pyridine N-Oxide. A. In Refluxing Benzene with Excess Amine Oxide. A mixture of 25.4 g (0.100 mole) of phenylacetic anhydride,[3] 38.0 g (0.400 mole) of pyridine N-oxide, and 800 ml of dry benzene was heated at reflux for 18 hr. The weight of carbon dioxide absorbed by the Caroxite was 3.35 g (76%). By gas chromatographic examination (Versamid column at 150°) of the reaction mixture, the yields of benzaldehyde (retention time 2.2 min) and pyridine (1.2 min) were calculated to be 69 and 79%, respectively. Both pyridine and benzaldehyde were isolated from the reaction mixture and identified by comparison with authentic samples.

The neutral fraction containing benzaldehyde was examined by gas chromatography (Versamid column at 225°) to determine whether or not it contained benzyl phenylacetate, 1,2-diphenylethane, and/or diphenylmethane, possible reaction products. These materials were not detected; chromatograms prepared from authentic samples indicated that yields of benzyl phenylacetate (retention time 3.6 min), 1,2-diphenylethane (1.7 min), or diphenylmethane (1.5 min) of as little as 0.5% should have been detectable.

B. At 50° with Equimolar Quantities of Reactants. A mixture of 25.4 g (0.100 mole) of phenylacetic anhydride, 9.5 g (0.100 mole) of pyridine N-oxide, and 400 ml of benzene was heated at 50° for 5 days, and then at reflux for 8 hr. The heating period resulted in increasing the carbon dioxide evolution from 30.3 to 32.9%.

The light orange needles which had formed in the flask during the 5-day heating period were removed by filtration, washed with acetone, and dried in an oven at 100°. There was obtained 0.521 g, mp 325°. This material was identified[34] as a photodimer of DPMA.

By appropriate extraction techniques three fractions were isolated from the clear brown filtrate: A, basic fraction (0.23 g); B, phenylacetic acid (13.82 g); C, neutral fraction (4.90 g). By preparative gas chromatography (Versamid column at 200°), two components were collected from fraction A (these were present in nearly equal amounts but constituted only a minor portion of this fraction) and were identified as 2- and 4-benzylpyridine by comparison of their retention times and infrared spectra with authentic materials (Reilly Tar and Chemical Corp.). Treatment of a portion of fraction C with boiling aqueous potassium hydroxide, extraction of the clear aqueous solution with ether to remove benzaldehyde, and acidification of the aqueous solution, followed by extraction with ether, resulted in the isolation of pale yellow crystals, mp 153.5–155.0°, from the ether extract. The material was identified by previously described methods[3] as diphenylmaleic anhydride (DPMA). Quantitative infrared analysis of fraction C indicated the total yield of DPMA, taking into account that converted to photodimer, to be 0.037 mole/mole of reactant or 11%, based on eq 2. Gas chromatographic examination (Versamid column at 225°) of another portion of fraction C showed that neither benzyl phenylacetate, nor 1,2-diphenylethane, nor diphenylmethane was present in detectable amounts.

Reaction of Diphenylacetic Anhydride with Pyridine N-Oxide. The procedure was similar to A above. The benzophenone was identified by comparison with an authentic sample. The yields (vpc) are shown in Table I.

Reaction of Butyric Anhydride with Pyridine N-Oxide. A. In Xylene. An exploratory run in refluxing benzene indicated that higher temperatures were required for decarboxylation to proceed at an appreciable rate. Accordingly, a mixture of 15.8 g (0.100 mole) of butyric anhydride, 38.0 g (0.400 mole) of pyridine N-oxide, and 400 ml of xylene was heated at reflux (142°) for 10 hr. The propionaldehyde formed in the reaction was carried by the effluent nitrogen stream to a trap containing 50 ml of ice-cold water where it was absorbed. The effluent from this trap was dried with Drierite before being conducted into the Caroxite tube where carbon dioxide (0.81 g, 19%) was absorbed. By gas chromatographic examination (Reoplex 400 column at 75°) of the dilute aqueous solution of propionaldehyde taken from the water trap, the quantity of propionaldehyde (retention time 1.0 min) absorbed was determined to be 0.72 g (12.4%). Acetone (1.2 min) was not detected. In a separate experiment, positive identification of the trapped material as propionaldehyde was obtained by the preparation of its 2,4-dinitrophenylhydrazine derivative, light orange crystals from ethanol, mp 156–158° (lit.[35] mp 154.5–155°), undepressed when mixed with an authentic sample. A test for propylene, by passing the effluent through a bromine–carbon tetrachloride mixture, was negative.

The butyric anhydride–pyridine N-oxide reaction mixture was washed with water. The water extract was saturated with sodium carbonate and back-extracted with chloroform to give, after evaporation, a light tan solid (4.1 g) which, by infrared examination, was shown to be mainly unreacted pyridine N-oxide. However, a band at 1667 cm^{-1} indicated that a pyridone (most likely 2-pyridone from the hydrolysis of 2-butyroxypyridine) was also present. A xylylpyridine fraction was also isolated.[16]

B. In Toluene. A mixture of 15.8 g (0.100 mole) of butyric anhydride, 76.0 g (0.800 mole) of pyridine N-oxide, and 400 ml of toluene was heated at reflux (112°) for 24 hr. The carbon dioxide evolved weighed 0.367 g (8%). This amount is in marked contrast to the 57% of carbon dioxide evolved in a 24-hr period in the corresponding isobutyric anhydride reaction (see below).

Reaction of Isobutyric Anhydride with Pyridine N-Oxide. A mixture of 15.8 g (0.100 mole) of isobutyric anhydride, 76.0 g (0.800 mole) of pyridine N-oxide, and 400 ml of toluene was heated at reflux (112°) for 48 hr. The carbon dioxide evolved weighed 3.05 g (69%). The acetone produced in the reaction was absorbed in a water trap, as previously described for the propionaldehyde case. By gas chromatography (Reoplex 400 column at 75°) the quantity of acetone (retention time 1.2 min) absorbed was determined to be 2.3 g (39%). Identification of the absorbed material as acetone was based on its relative retention time on the Reoplex column and on the preparation of a 2,4-dinitrophenylhydrazine derivative, orange crystals from ethanol, mp 127–128° (lit.[35] mp 125.0–126.5°), alone or mixed with an authentic sample. A bromine–carbon tetrachloride test for the presence of propylene was negative. A run made in refluxing xylene afforded acetone in lower yield (*ca.* 20%).

Reaction of Acetic Anhydride with Pyridine N-Oxide. This run was made with great care in order to detect and measure formaldehyde, even if it were formed in minute quantities. A mixture of 95.0 g (1.00 mole) of pyridine N-oxide, 25.5 g (0.250 mole) of acetic anhydride, and 800 ml of xylene was heated at 100° for 2 hr, at 120° for 2 hr more, and, finally, at vigorous reflux (142°) for 4 hr. Although the reaction mixture was dark and opaque at the end of

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[32a] Note Added in Proof. In Koenig's most recent contribution to this field [T. Koenig, *Tetrahedron Letters*, 2751 (1967)] the possibility of rate retardation by such hydrogen bonding has also been recognized. This paper also provides independent evidence against the carboxy inversion route to benzaldehyde.

[33] H. Staudinger, *Ann.*, **356**, 51 (1907).

[34] For details of this identification, see the thesis of J. H. F.[1a]

[35] J. D. Roberts and C. Green, *J. Am. Chem. Soc.*, **68**, 214 (1946).

the heating period, the total gain in weight of the Caroxite tube was 0.006 g, indicating that carbon dioxide evolution was not significant. No formaldehyde (retention time 0.5 min) was detectable by gas chromatographic examination (Reoplex column at 75°) of water from the trap. Distillation of the reaction mixture *in vacuo* gave a fraction, bp 45–47° (0.2 mm) (presumably, 2-acetoxypyridine, the expected N-oxide rearrangement product), which, upon methanolysis, gave a white solid which was identified as 2-pyridone by its melting point, mp 105–107° (lit.[36] mp 106°), undepressed when mixed with an authentic sample. A xylylpyridine fraction was also isolated.[16]

Reaction of Diphenylacetic Acid with Pyridine N-Oxide. A mixture of 38.0 g (0.400 mole) of pyridine N-oxide, 21.2 g (0.100 mole) of diphenylacetic acid, 15.3 g (0.150 mole) of acetic anhydride, and 400 ml of benzene was heated at reflux for 10 hr. Carbon dioxide evolution was rapid and copious, amounting to 3.7 g (86%). Gas chromatographic examination (Versamid column at 225°) of the reaction mixture (421 g) showed that it contained 2.68% by weight of benzophenone (62%).

Reactions of Phenylacetic Acid with Pyridine N-Oxide. Run 1. Reaction for 24 Hr in Refluxing Benzene. A solution of 10.2 g (75.0 mmoles) of phenylacetic acid, 11.5 g (130 mmoles) of acetic anhydride, and 28.5 g (300 mmoles) of pyridine N-oxide in 300 ml of benzene was heated at reflux for 24 hr. The yields are shown in Tables I and II. Benzaldehyde, DPMA, and pyridine were determined by vpc analyses of the neutral and basic fractions. The former contained no benzyl acetate, toluene, or 1,2-diphenylethane. The ether extract containing the acid fraction was treated with diazomethane as follows. To a 500-ml erlenmeyer flask containing a mixture of 60 ml of 40% sodium hydroxide and 200 ml of ether was added with magnetic stirring 7.1 g (5.0 g active) of EXR-101 (N,N′-dinitroso-N,N′-dimethylteraphthalamide, E. I. du Pont de Nemours and Co.) at the temperature of an ice-salt bath. The bath was removed and the stirring was continued for 1 hr at room temperature. The yellow ether layer containing diazomethane was separated by decantation, dried over potassium hydroxide pellets for 2 hr, and slowly added to the ethereal acidic fraction. The reaction mixture was magnetically stirred for 10 min, and the excess diazomethane was destroyed by the addition of acetic acid. The solution was extracted several times with aqueous 10% sodium bicarbonate, washed with water, and dried over sodium sulfate. The ether was evaporated on a steam bath, and the residue was shown by vpc to contain methyl esters of phenylacetic and acetylmandelic (retention time 19 min on an SE-30 column at 150°) acids and of a trace amount of phenylglyoxylic acid (retention time 14 min). A control experiment indicated that acetylmandelic acid is quantitatively methylated by this procedure.

The methyl ester of acetylmandelic acid (0.25 g) was isolated by distillation and identified by comparison with an authentic sample. From the acid fraction of the original reaction mixture the following derivatives of phenylglyoxylic acid were prepared: 2,4-dinitrophenylhydrazone, mp 195–196° (lit.[37] mp 196–197°); phenylhydrazone, mp 152–153° (lit.[37] mp 153°); mercuric salt, mp 165–166° (lit.[38] mp 164°). The melting point of each derivative was undepressed upon admixture with an authentic sample.

Run 2. Reaction for 22 Hr in Refluxing Benzene with a Deficiency of Pyridine N-Oxide. A solution of 28.5 g (0.300 mole) of pyridine N-oxide, 40.8 g (0.300 mole) of phenylacetic acid, 122.5 g (1.200 moles) of acetic anhydride, 72 g (1.2 moles) of glacial acetic acid, and 4.2 g (0.05 mole) of sodium acetate in 300 ml of benzene was heated at reflux for 22 hr. The yields, based on the limiting reagent pyridine N-oxide, are given in Table II.

Run 3. Reaction for 21 Hr in Acetic Acid at 78°. A vigorously stirred solution of 40.8 g (0.300 mole) of phenylacetic acid, 122.5 g (1.200 moles) of acetic anhydride, 28.5 g (0.300 mole) of pyridine N-oxide, and 72.0 g (1.200 moles) of acetic acid was heated at 78 ± 1° for 21 hr. The yields, based on pyridine N-oxide, are given in Table II.

A vpc examination of the neutral fraction on a silicone rubber column at 150° showed a small peak (0.15%, vpc estimate) for a substance having the same retention time (5 min) as that of an authentic sample of benzyl acetate. However, no attempt was made to identify this substance definitely.

Run 4. Reaction in Pyridine. A solution of 1.67 g (17.4 mmoles) of pyridine N-oxide dissolved in 25 ml of pyridine was added to a solution which had been preheated at 100° for 2 hr under nitrogen, consisting of 3.63 g (26.7 mmoles) of phenylacetic acid and 4.42 g (42.9 mmoles) of acetic anhydride in 25 ml of pyridine. After 30 min at 100°, the evolved carbon dioxide weighed 0.27 g (0.35 mole of carbon dioxide/mole of pyridine N-oxide). The solvent was evaporated from a small aliquot of the cooled reaction mixture and the residue was dissolved in 10% aqueous hydrochloric acid. The aqueous solution was evaporated to dryness, and the residue was dissolved in deuterium oxide containing sodium *p*-toluenesulfonate as an internal standard for quantitative nmr analysis. By using the integrated area of the methylene peak (also present in the authentic bromide salt) at τ 4.22 ppm (DSS as standard), the yield of N-benzylpyridinium chloride was found to be 43% of that of the evolved carbon dioxide. The solvent was evaporated from the remainder of the reaction mixture, and the residue was treated with 50 ml of ethereal hydrogen bromide. The ether solution was washed several times with water, and the combined aqueous wash was made basic with concentrated ammonia and extracted with ether. The aqueous phase containing the N-benzylpyridinium bromide was treated with 50 ml of ammonium picrate solution containing excess ammonia. The resulting yellow crystalline solid, after drying in a vacuum desiccator, had mp 118–119° (lit.[39] mp 116–118°) and was equivalent to 30% of the evolved carbon dioxide. The infrared spectrum was identical with that of an authentic sample of N-benzylpyridinium picrate prepared in the same way from the corresponding bromide salt (see next experiment).

Attempted Reaction of Pyridine N-Oxide with N-Benzylpyridinium Acetate in Refluxing Benzene. A. Preparation of N-Benzylpyridinium Acetate. A sample of N-benzylpyridinium bromide[40] (2.5 g, 10 mmoles), which was obtained by the reaction of equimolar quantities of pyridine and benzyl bromide in acetone, was treated with 3.0 g (18 mmoles) of silver acetate in 35% aqueous ethanol for 1 hr at room temperature. The silver bromide was eliminated by filtration and the aqueous solution was evaporated *in vacuo*. The dark brown residue was dissolved in 10 ml of ethanol and allowed to stand for 2 days at room temperature. The coagulated excess silver acetate was removed by filtration. This procedure was repeated once more. Evaporation of the solution gave a brown oily residue, the nmr spectrum of which, in water solution, was similar to that of N-benzylpyridinium bromide except for the additional proton peak for the acetate, at τ 8.03 ppm The integrated proton area ratio by nmr was 4.8:5.2:2.2:2.9 (theory, 5:5:2:3), for pyridine, phenyl, benzylic, and acetate protons.

Direct vpc examination of this residue showed that no pyridine and benzaldehyde were present. This residue was used for the attempted reaction with pyridine N-oxide.

B. Reaction with Pyridine N-Oxide. A heterogeneous mixture of 1.1 g (4.6 mmoles) of N-benzylpyridinium acetate, 1.3 g (61 mmoles) of pyridine N-oxide, and 300 ml of benzene was heated at reflux with vigorous magnetic stirring for 22 hr. Direct vpc examination of the reaction mixture showed that benzaldehyde and pyridine were both absent.

Reaction of Pyridine N-Oxide with Acetylmandelic Acid in the Presence of Acetic Anhydride. A solution of 20.0 g (210 mmoles) of pyridine N-oxide, 9.70 g (50.0 mmoles) of acetylmandelic acid,[41] and 10.2 g (100 mmoles) of acetic anhydride in 215 ml of benzene was heated at reflux for 6.5 hr, during which time there was observed 45.5% of carbon dioxide evolution. Vpc analysis showed that the solution contained a 48.5% yield of benzaldehyde, a 55.7% yield of pyridine, and a trace amount of a substance having the same retention time as that of diphenylmaleic anhydride. No reaction occurred in the absence of acetic anhydride. The quantitative determination of phenylglyoxylic acid as the mercuric salt[38] was attempted twice but only a trace amount of the mercuric salt was obtained (less than 2% of theory). The light tan solid had mp 165–166° (lit.[38] mp 164°), undepressed when mixed with an authentic sample.

Reaction of Phenylglyoxylic Acid, Pyridine, and Phenylacetic Anhydride in Benzene. A solution of 2.57 g (17.0 mmoles) of phenylglyoxylic acid, 4.35 g (17.0 mmoles) of phenylacetic anhydride,[3] 0.67 g (8.05 mmoles) of pyridine, and 90 ml of benzene was

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heated at reflux for 7 hr. The yields were: carbon dioxide, 40%; benzaldehyde, 5.8%; and diphenylmaleic anhydride, 45.7% (vpc).

Attempted Reaction of Pivalic Anhydride and Pivalic Acid with Pyridine N-Oxide. A solution of 0.0613 g (0.645 mmole) of pyridine N-oxide and 0.471 g (2.45 mmoles) of pivalic anhydride[42] in 10 ml of mesitylene was heated at 113° for 4.5 hr under a nitrogen atmosphere. No carbon dioxide and no isobutylene was produced. The reaction mixture was extracted with ether (five 10-ml portions) and the aqueous phase diluted to 100 ml. A portion (2.00 ml) of this solution was diluted to 100 ml and submitted to quantitative ultraviolet analysis using the pyridine N-oxide absorption at 254 $\mathrm{m}\mu$. This analysis indicated that 98% of the pyridine N-oxide was recovered.

Carbon dioxide was not produced in a similar reaction for 6 hr in refluxing xylene nor by the use of pivalic acid, acetic anhydride, and pyridine N-oxide in refluxing benzene for 16 hr.

Reaction of 4-Picoline N-Oxide and Pivalic Anhydride in Benzene. A solution of 8.7 g (80 mmoles) of 4-picoline N-oxide, 3.7 g (20 mmoles) of pivalic anhydride,[42] and 180 ml of benzene was heated at reflux for 71 hr. The yield of carbon dioxide was 88.6%.

Reaction of Phenylacetyl Chloride with Pyridine N-Oxide. To a mixture of 38.0 g (0.400 mole) of pyridine N-oxide and 400 ml of chloroform (ethanol-free) was added, dropwise and with stirring, at 30–35°, 15.4 g (0.100 mole) of phenylacetyl chloride. The temperature of the mixture was then raised to the reflux point (65°). The carbon dioxide evolution was, at first, fairly rapid, 1.10 g (25.0% of the theoretical amount) being evolved in the first 1.5 hr. After that, it slowed considerably and, during the final 24 hr of heating, only 0.62 g of additional carbon dioxide was evolved, for a total of 1.72 g (39.1%). The conversion to benzaldehyde was determined by gas chromatographic examination of the reaction mixture (Versamid column at 150°) to be 18.6%.

Reaction of Bicyclo[2.2.1]heptane-2-carboxylic Acid (Mixture of *exo* and *endo*) with Pyridine N-Oxide in Mesitylene. An exploratory run in refluxing benzene indicated that a higher temperature was required for decarboxylation (no carbon dioxide evolution was observed during 24 hr). Accordingly, a solution of 3.5 g (25 mmoles) of norbornane-2-carboxylic acid,[43] 9.80 g (100 mmoles) of pyridine N-oxide, and 7.1 g (70 mmoles) of acetic anhydride in 75 ml of mesitylene was heated at reflux for 45 hr. Carbon dioxide evolution (yield, 30%) appeared to be complete after 35 hr of heating.

Direct vpc analysis on a polyphenyl ether column at 100° showed that norcamphor was not present in the reaction mixture. The possible products norbornane and norbornene could not be determined by vpc since they have the same retention time as mesitylene. No evidence could be found for the presence of an unsaturated acid in the acid fraction of the product.

Reaction of *exo*-Bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid and Pyridine N-Oxide. A solution of 19.3 g (200 mmoles) of pyridine N-oxide, 6.9 g (50 mmoles) of *exo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid,[43] 15.4 g (100 mmoles) of acetic anhydride, and 100 ml of benzene was heated at reflux for 31 hr. The yield of carbon dioxide was 35.4%. The neutral fraction of the product gave negative ketone tests with several reagents and exhibited an infrared spectrum of a mixed anhydride of the starting acid and acetic acid.

Similar runs made in refluxing toluene, xylene, dioxane, and diglyme afforded carbon dioxide and mixed anhydrides, but no condensable material was deposited in ice-cooled traps.

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The Wallach Rearrangement. II.[1] Kinetics of the Rearrangement of Azoxybenzene and Its Derivatives in Strongly Acidic Solution[2]

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Cincinnati, Ohio 45221. Received March 7, 1967

Abstract: A kinetic study of the rearrangement of azoxybenzene and α- and β-4-bromo- and α- and β-4-methylazoxybenzene into the corresponding hydroxyazobenzenes in 20 vol. % ethanol and 80 vol. % aqueous sulfuric acid–water solutions has been undertaken by ultraviolet spectrophotometry. The rate constants obtained show that the rearrangement is an acid-catalyzed pseudo-first-order reaction. The activation parameters of the rearrangement were obtained and several steps in the mechanism of the rearrangement are elucidated.

The investigation of the Wallach rearrangement, the conversion of azoxybenzene and its derivatives into 4-hydroxyazobenzene and the corresponding substituted hydroxyazobenzenes in the presence of strong acid, has recently been approached by two methods. One of these has focused on the position to which the azoxy oxygen atom migrates.[1,3,4] The other method has involved mechanistic studies of the rearrangement using isotopic tracers.[5,6] By the former method, Hahn and Jaffé found that the oxygen atom in the azoxy group of a 4-monosubstituted azoxybenzene migrates to the unsubstituted ring, depending neither on the nature of the substituent already present in the other ring, nor on the relation between the oxygen atom and the available position. It was found,

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(1) Part I in the series: C. S. Hahn and H. H. Jaffé, *J. Am. Chem. Soc.*, **84**, 946 (1962).

(2) (a) This investigation was financially supported by the United Board for Christian Higher Education in Asia and the Graduate School of Yonsei University. (b) This paper comprises a portion of the dissertation submitted by K. W. Lee in partial fulfillment of the requirements for the M.S. degree in the Graduate School of Yonsei University, Seoul, Sept 1966. (c) Presented at the 16th and 17th Annual Meeting of the Korean Chemical Society, 1965 and 1966.

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