[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

The Rearrangement of Substituted Pyridine *N*-Oxides with Acetic Anhydride[1,2]

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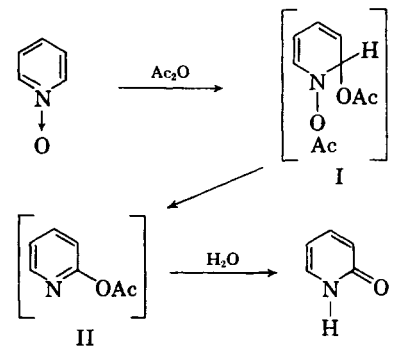
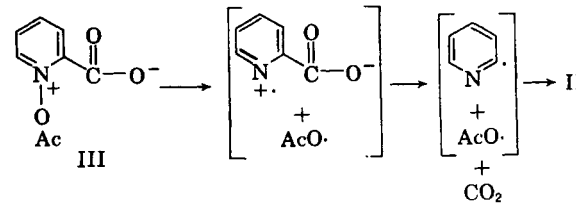
The rearrangement of the 2-, 3-, and 4-substituted carbomethoxypyridine *N*-oxides with acetic anhydride has been studied. These compounds behave normally to give the corresponding 2- or 6-pyridone derivatives.

Since Katada, working in Professor Ochiai's laboratory, first discovered the rearrangement of pyridine *N*-oxide with acetic anhydride,[5,6] much attention has been focused on this reaction both for its theoretical interest and because of its practical synthetic value. With 2- and 4-alkylpyridine *N*-oxides, the rearrangement leads largely to 2- and 4-(acetoxyalkyl)pyridines,[7-13] and it is with these examples that studies of the mechanism have been chiefly concerned. The elegant work of Traynelis and Martello[14,15] has confirmed an earlier suggestion[16] that radicals are generated during the rearrangement. Their studies on the effects of radical inhibitors strongly suggests that the rearrangement of 4-picoline *N*-oxide to 4-(acetoxymethyl)pyridine follows predominantly a radical path.[15] On the other hand, the rearrangement of 2-picoline *N*-oxide to 2-(acetoxymethyl)pyridine must either be predominantly ionic or there is an unusual solvent cage effect rendering radical inhibition ineffective.[14]

Comparable studies have not been made to determine the mechanism of the rearrangement of pyridine *N*-oxides to α-pyridones. In the early work on this rearrangement, Ochiai and Okamoto observed that direct catalytic hydrogenation of the reaction mixture from pyridine *N*-oxide and acetic anhydride gave α-piperidone in nearly quantitative yield.[6] Under comparable conditions α-pyridone in acetic anhydride does not absorb hydrogen. They suggested that the reaction proceeds through the intermediates, I and II, and that it is only on addition of water that α-pyridone is formed.



However, even if I and II are truly intermediates the mechanism for their formation is still obscure and may be closely related to the rearrangements of picoline *N*-oxides with acetic anhydride. In the present study the rearrangement of negatively substituted pyridine *N*-oxides was selected for investigation in the hope that their behavior would provide a basis for distinguishing between predominantly radical or ionic reaction paths. Thus, if the ionic mechanism of Ochiai and Okamoto is correct, it would be expected that negative substituents in the pyridine ring would favor nucleophilic attack and thus promote the rearrangement. On the other hand, if a radical path is predominant, the rearrangement would be expected to take a different course with carboxypyridine *N*-oxides. Thus, with 2-carboxypyridine *N*-oxide, the first intermediate would be expected to be III which, on radical cleavage, might then undergo decarboxylation giving the α-pyridyl radical. Recombination of the α-pyridyl radical and the acetoxy radical would give II and ultimately, on work up, α-pyridone.



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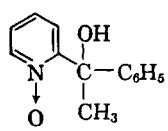
When a solution of 2-carboxypyridine *N*-oxide and acetic anhydride in acetonitrile was warmed to 75–80°, smooth evolution of carbon dioxide occurred in quantitative yield. However, the main product was pyridine *N*-oxide and 2-pyridone was present in relatively small yield. Irradiation in quartz apparatus of a solution of 2-carboxypyridine *N*-oxide and acetic anhydride in acetonitrile with ultraviolet light at room temperature also led to quantitative evolution of carbon dioxide within three hours. In this case the yield of 2-pyridone was somewhat higher but the predominant product was still pyridine *N*-oxide. That the *N*-acyloxypyridinium ion is necessary for easy decarboxylation is evident from the fact that 2-carboxypyridine *N*-oxide undergoes rapid decarboxylation to pyridine *N*-oxide at room temperature on addition of benzoyl chloride. On the other hand, simple protonation does not suffice, as 2-carboxypyridine *N*-oxide is stable in glacial acetic acid at 100°. In an attempt to prepare the zwitter ion III in the absence of a proton donor, a solution of 2-carboxypyridine *N*-oxide in acetonitrile was treated with ketene. Again, rapid decarboxylation occurred when the solution was warmed to 65° and the product was pyridine *N*-oxide.

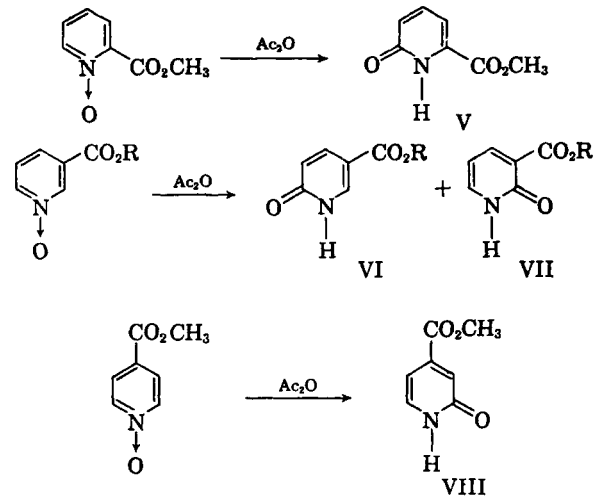
The ease and variety of conditions under which 2-carboxypyridine *N*-oxide undergoes decarboxylation would suggest that the reaction path may be either ionic or radical. If ionic decarboxylation were occurring, it would be expected that 2-carboxypyridine *N*-oxide would undergo the Hammick reaction as does picolinic acid.[17] This was found to be the case. Heating a solution of 2-carboxypyridine *N*-oxide in acetophenone gave a crystalline product having the correct composition for IV.



IV

Finally, the question of the mechanism by which 2-carboxypyridine *N*-oxide undergoes decarboxylation is further confused by the fact that under comparable conditions neither 3- nor 4-carboxypyridine *N*-oxide showed any evidence of decarboxylation or reaction of any type. This would suggest that a cyclic transition state is involved in the case of 2-carboxypyridine *N*-oxide.

In contrast to the behavior of the carboxypyridine *N*-oxides, their methyl esters underwent rearrangement with acetic anhydride in a normal fashion to give the corresponding α-pyridone derivatives. Thus, 2-carbomethoxypyridine *N*-oxide gave 6-carbomethoxy-2-pyridone (V) in 34% yield; 3-carbethoxypyridine *N*-oxide gave a mixture of VI (16%) and VII (28%); and 4-carbomethoxypyridine *N*-oxide yielded VIII in 56% yield. In each case the structure of the product was established either by comparison with known compounds or ultimate degradation to 2-pyridone.



Although all three of these esters underwent rearrangement with acetic anhydride, there was no evidence that the presence of the ester promoted the rearrangement as would be expected for nucleophilic substitution. If anything, the presence of the ester probably retarded the rearrangement. Furthermore, 2-cyanopyridine *N*-oxide was unaffected by boiling with acetic anhydride.

EXPERIMENTAL[18]

Reaction between 2-carboxypyridine N-oxide and acetic anhydride. The preparation of 2-carboxypyridine *N*-oxide was carried out by oxidizing 2-picolinic acid with 30% hydrogen peroxide in glacial acetic acid and the 2-carboxypyridine *N*-oxide was isolated in 70% yield as white crystals, m.p. 166–167° (lit.,[19] m.p. 165–166°). A solution of 1.39 g. of 2-carboxypyridine *N*-oxide and 10 ml. of acetic anhydride in 40 ml. of dry acetonitrile was warmed (75–80°) until vigorous evolution of carbon dioxide began. This was complete in about 1 hr. and corresponded to the theoretical quantity expected for decarboxylation. The solvent and excess acetic anhydride were then removed and the residue was treated with ethanolic picric acid. The yellow solid which separated weighed 2.44 g. (75%) but melted over a range. After several recrystallizations from ethanol, crystals resulted melting at 175–178°, no depression on admixture of the authentic picrate of pyridine *N*-oxide (m.p. 178–179°). When an aliquot of the residue was treated with ethanolic styphnic acid, a styphnate was obtained in 12% yield as yellow needles, m.p. 179–180°. These corresponded in their composition (*Anal.* Calcd. for $C_{13}H_{10}N_4O_{10}$: C, 40.85; H, 2.64. Found: C, 41.20; H, 3.31) to the styphnate of 2-acetoxypyridine and on regeneration of the base, 2-pyridone resulted.[20]

In another experiment a solution of 1.0 g. of 2-carboxypyridine *N*-oxide and 5 ml. of acetic anhydride in 25 ml. of dry acetonitrile was placed in a quartz flask and irradiated

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(18) Analyses by Micro-Tech Laboratories and Miss A. Smith. All melting points are corrected.

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(20) We are indebted to Mr. Roland Scharrer for aiding in this identification.

with an ultraviolet lamp using internal cooling to maintain the solution at room temperature. Carbon dioxide evolution began almost immediately and was complete in 2 hr. 40 min. When the solution was worked up as before, the picrate of pyridine *N*-oxide was isolated in 60% yield and the styphnate of 2-acetoxypyridine in 15% yield.

Hammick reaction with 2-carboxypyridine N-oxide. A solution of 5.0 g. of 2-carboxypyridine *N*-oxide in 60 ml. of acetophenone was heated at 150° until carbon dioxide evolution ceased (1 hr.). The cold solution was then extracted with 50 ml. of 2*N* hydrochloric acid; the aqueous layer was made basic and extracted with ether. Concentration of the dried ether extract gave a yellow oil which, on treatment with a mixture of ether–chloroform–petroleum ether, crystallized to give 2.32 g (30%) of IV as white needles, m.p. 112–113°.

Anal. Calcd. for $C_{13}H_{11}NO_2$: C, 72.54; H, 6.09. Found: C, 72.23; H, 6.25.

Rearrangement of 2-carbomethoxypyridine N-oxide with acetic anhydride. The preparation of 2-carbomethoxypyridine *N*-oxide was carried out following the procedure of Newbold and Spring.[21] An attempt to oxidize methyl 2-picolinate using 30% hydrogen peroxide in glacial acetic acid led to the recovery of methyl 2-picolinate. For characterization, 2 carbomethoxypyridine *N*-oxide was converted to the corresponding *picrate*, m.p. 92–93°.

Anal. Calcd. for $C_{13}H_{10}N_4O_{16}$: C, 40.85; H, 2.64. Found: C, 40.79; H, 2.79, and *styphnate*, m.p. 105–106°.

Anal. Calcd. for $C_{13}H_{10}N_4O_{11}$: C, 39.21; H, 2.53. Found: C, 39.55; H, 2.68.

A solution of 1.9 g. of 2-carbomethoxypyridine *N*-oxide in 10 ml. of acetic anhydride was boiled under reflux for 3.5 hours. After removal of the acetic anhydride under reduced pressure, the residue was made alkaline by addition of a saturated solution of sodium bicarbonate. Then 10 ml. of water was added and the mixture was extracted with benzene. The combined benzene extracts were concentrated to 25 ml. and passed over alumina (activity II). The column was eluted successively with benzene, ether, and mixtures of ether-methanol. From the ether-methanol eluates there was obtained 658 mg. (35%) of a white solid, m.p. 98–100°. After recrystallization from water V was isolated as white crystals, m.p. 109–110°.

Anal. Calcd. for $C_7H_7NO_3$: C, 54.91; H, 4.61. Found: C, 54.90; H, 4.74.

Hydrolysis of a portion of V gave 6-carboxy-2-pyridone as white needles, m.p. 273–275° (lit.,[22,23] m.p. 280, 282°). These, on heating at 285–290°, underwent decarboxylation to give 2-pyridone, identified by infrared spectral comparison and mixture melting point determination with an authentic sample.

Rearrangement of 3-carbethoxypyridine N-oxide with acetic anhydride. A solution of 3-carbethoxypyridine *N*-oxide[24] in 25 ml. of acetic anhydride was boiled under reflux for 12 hr. After removal of the excess acetic anhydride, the residue was treated with benzene and passed over alumina (activity II). From the methanol-ether eluates, two compounds were isolated. The first of these weighed 990 mg. (17%) and melted at 143–144°. This was identified as 5-carbethoxy-2-pyridone, VI (lit.,[25] m.p. 150°) by its melting point and its hydrolysis to 5-carboxy-2-pyridone, m.p. 325° dec. (lit.,[25–27] m.p. 309, 314–316°).

The second compound weighed 1.68 g. (28%) and melted over a range of 132–137°. As its composition indicated it to be a mixture of the methyl and ethyl esters corresponding to VII [*Anal.* Calcd. for $C_8H_9NO_3$ (ethyl ester): C, 57.48; H, 5.43. Calcd. for $C_7H_7NO_3$ (methyl ester): C, 54.90; H, 4.61. Found: C, 55.12; H, 4.92,] presumably resulting from ester interchange during elution, the mixture was hydrolyzed directly to the corresponding acid, 3-carboxy-2-pyridone. This was obtained as white needles, m.p. 246–250° (lit.,[26,28] m.p. 255°, 260°). A portion of the acid was decarboxylated by heating it at 290° for a few minutes and the sublimate was identified as 2-pyridone.

Rearrangement of 4-carbomethoxypyridine N-oxide with acetic anhydride. A solution of 3.0 g. of 4-carbomethoxypyridine *N*-oxide in 30 ml. of acetic anhydride was boiled under reflux for 6 hr. After removal of the excess acetic anhydride, the black tarry residue was taken up in hot methanol, treated with charcoal, and cooled. There separated 1.56 g. (56%) of VIII as white crystals, m.p. 211–212° (lit.,[29] m.p. 209–212°). For characterization, the hydrazide of VIII was prepared and obtained from methanol-water as white crystals, m.p. 254–256° (lit.,[29] m.p. 256–258°). As 3-hydroxy-4-carbomethoxypyridine has been reported to melt at 78.5–80.5°,[30] there can be no doubt that our product has structure VIII.

2-Cyanopyridine N-oxide. The conversion of 2-cyanopyridine to its *N*-oxide was carried out as described for the preparation of 2-carboxypyridine *N*-oxide and proceeded in 70% yield. It was obtained after crystallization from benzene as white crystals, m.p. 120–121°.

Anal. Calcd. for $C_6H_4N_2O$: C, 60.00; H, 3.36. Found: C, 59.78; H, 3.61.

When 2-cyanopyridine *N*-oxide was boiled with excess acetic anhydride for 20 hr., it could be recovered in 82% yield. The stability of 2-cyanopyridine *N*-oxide was also indicated from an attempt to convert it to 2-carbomethoxypyridine *N*-oxide. It was recovered in quantitative yield after boiling for 6 hr. with methanol and concd. sulfuric acid.

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