[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF KANSAS]

THE OXIDATION OF SOME β-SUBSTITUTED PYRIDINE ALKIODIDES[1]

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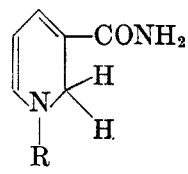
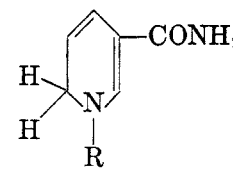
Received July 5, 1950

Although the role of the nicotinamide moeity in Coenzymes I and II has long been known (1), there still exists doubt as to whether the structure of the reduced form of the coenzyme is I or II, *i.e.*, whether the 2- or the 6-position is the active one.



I



II

On the basis of biochemical oxidation experiments, Knox and Grossman (2) suggested the 6-position as the active center. They were able to isolate 1-methyl-2-pyridone-5-carboxamide from the urine of volunteers who had ingested nicotinamide methochloride. The same compound was also obtained by the action of a rabbit liver quinine-oxidizing enzyme on nicotinamide methochloride. Huff (3) provided further support for this argument when he found that both trigonelline acid sulfate and 1-methylnicotinamide salts could be oxidized to 1-methyl-2-pyridone-5-carboxylic acid by ferricyanide in alkaline solution.

The present work was then undertaken to determine whether the nature of the β-substituent would affect the orientation of the chemical oxidation. While our investigation was in progress Wiegand and Holman (4) reported that the low temperature oxidation of nicotinamide methiodide by ferricyanide gave 1-methyl-2-pyridone-3-carboxamide. We therefore extended our investigation to include a study of the apparent discrepancy between the results of Huff and those of Wiegand and Holman.

RESULTS

We found that the chemical oxidation of 3-methylpyridine methosulfate, 3-methylpyridine ethiodide, nicotinamide methiodide, and probably 3-bromopyridine methiodide occurred predominantly in the 2-position. 3-Cyanopyridine methiodide appeared to be oxidized in both positions, whereas nicotinic acid methosulfate was oxidized predominantly in the 6-position.

The structure of the product obtained by oxidation of the last-named com-

[1] One of us, H. L. B., is indebted to the U. S. Public Health Service for a fellowship during 1947 and 1948.

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pound by the ferricyanide procedure of Huff (3) or with alkaline hydrogen peroxide was established by melting point and by conversion to the amide, which showed no depression in melting point when mixed with authentic samples generously provided by Drs. Knox and Holman.

Evidence that the product obtained by the low-temperature oxidation of 3-cyanopyridine methiodide by the method of Decker and Kaufmann (5) was a mixture of cyanopyridones was afforded by the fact that it boiled and melted over a wide range. Repeated recrystallization did not resolve the mixture into the isomeric forms. Attempted hydrolysis of the mixture to the amide by the method of Späth and Koller (6) was unsuccessful. Hydrolysis to the acid by the procedure of the same authors gave a fair yield of pure 1-methyl-2-pyridone-5-carboxylic acid. None of the 2,3-isomer could be isolated from the mother liquors despite the wide melting range of the original nitrile. By analogy with the results obtained by us in other cases, however, it appears probable that 1-methyl-3-cyano-2-pyridone was the principal contaminant in the original oxidized mixture.

Oxidation of nicotinamide methiodide at 0° gave 1-methyl-2-pyridone-3-carboxamide, as reported by Wiegand and Holman (4). Identity of the compound was confirmed by mixed melting point with an authentic sample prepared from 2-hydroxynicotinic acid and with one kindly supplied by Dr. Holman, and by depression of the melting point upon admixture with 1-methyl-2-pyridone-5-carboxamide.

β-Picoline methiodide, when oxidized by the method of Fargher and Furness (7), gave 1,3-dimethyl-2-pyridone. The product was identified by comparison of its boiling point and the melting point of its hydrochloride with those of authentic samples of the two isomeric dimethylpyridones, prepared by alkylation of the corresponding hydroxypicolines, according to the general procedure of Binz and Rath (8). The method of von Pächmann and Baltzer (9), in which the hydroxy compound is heated under pressure with an alkyl halide, failed to give isolable amounts of product. Treatment of the hydroxypicolines with diazomethane gave only the starting material, although Meyer (10) has reported obtaining 2-methoxypyridine, rather than 1-methyl-2-pyridone, from 2-pyridone.

β-Picoline ethiodide, treated according to the method of Decker and Kaufmann (5), gave a low yield of 1-ethyl-3-methyl-2-pyridone. Most of the product was a high-boiling material of unknown composition, perhaps an iodinated product, inasmuch as 1-ethyl-3-methyl-2-pyridone is readily iodinated in acid solution.[3] The identity of the oxidation product was confirmed by comparison of the boiling point and ultraviolet absorption spectrum (Figure I) with those of authentic samples of 1-ethyl-3-methyl-2-pyridone and 1-ethyl-5-methyl-2-pyridone prepared from the corresponding hydroxypicolines.

A fair yield of a product tentatively identified as 1-methyl-3-bromo-2-pyridone, boiling over a range, was obtained by oxidation of 3-bromopyridine methiodide in the same manner. The boiling point, melting point, and the ultraviolet absorption spectrum (Figure II) of the compound differed markedly from the values obtained for an authentic sample of the 2,5-isomer, prepared in the usual manner from

[3] Unpublished work, University of Kansas, 1948.

2-amino-5-bromopyridine. In this connection, a more convenient procedure than that of Case (11) was developed for the preparation of the amine, which is a useful intermediate. Bromination of the oxidation product gave the known 1-methyl-3,5-dibromo-2-pyridone. The brominated product did not depress the melting point of the compound obtained by the bromination of 1-methyl-5-bromo-2-pyridone. The rates of bromination of the two monobromides, however, differed markedly.

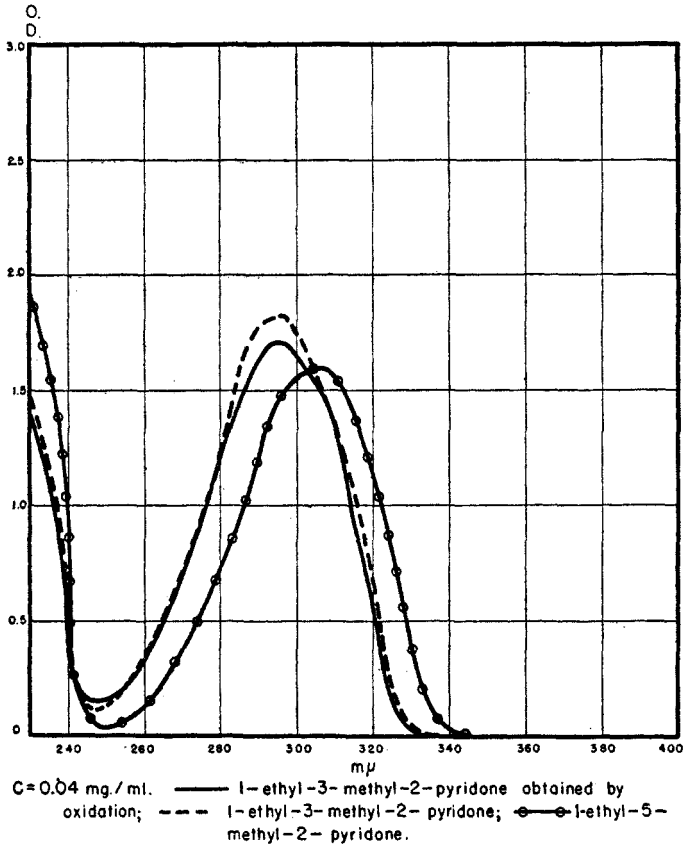

FIG. I

Attempts to prepare 1-methyl-3-bromo-2-pyridone by independent synthesis failed. Methyl 3-bromocoumalate, prepared in equally poor yield by the method of von Pechmann (12) and by diazomethane esterification, was converted quantitatively to 1-methyl-3-bromo-5-carbomethoxy-2-pyridone with excess methylamine solution. The acid obtained by alkaline hydrolysis could not be decarboxylated to the desired 1-methyl-3-bromo-2-pyridone, either by pyrolysis in the presence of copper, as described by Case (11), or by vacuum pyrolysis, even though evolution of carbon dioxide did occur in both cases. Possibly at elevated temperatures the molecule enters into condensation reactions at the halogenated position.

DISCUSSION

The results at first glance are rather confusing. A consideration of the mechanism, however, provides a possible explanation. Knox and Grossman (2) have pointed out that the reaction probably proceeds in two steps: 1. formation of the pseudo-base and 2. dehydrogenation of the pseudo-base to the pyridone (Figure III). The orientation of pseudo-base formation should, then, be the principal factor in the determination of the position at which oxidation occurs.

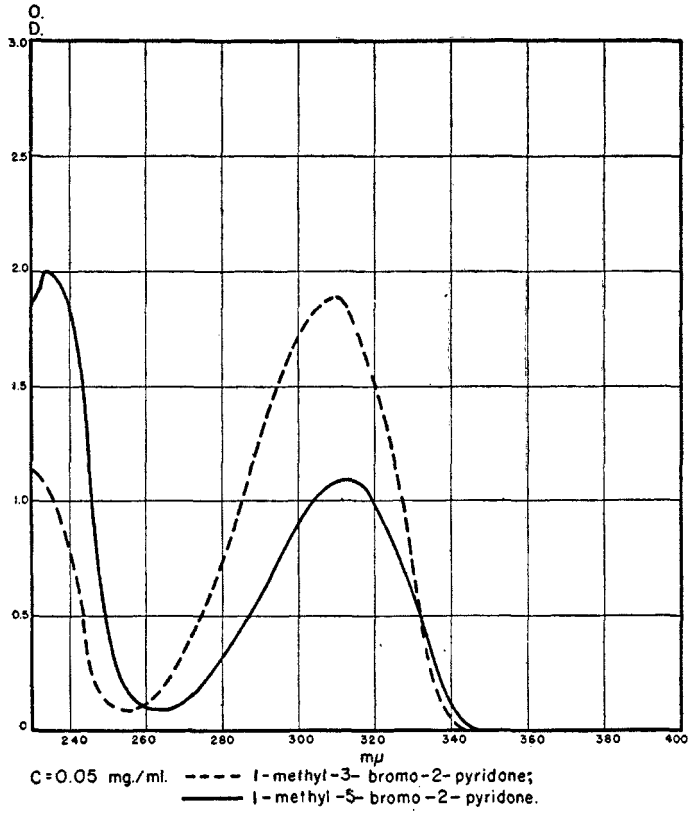

FIG. II

On the other hand, if the presence of a certain substituent renders one of the pseudo-bases less reactive than the other, the relative ease of formation of the two pseudo-bases might not be the decisive factor.

As a result of resonance interaction of the β-substituent with the two double bonds of the ring, more resonance structures can be written for the pseudo-base (Figure IV) formed by addition of the hydroxide ion at the 2-position than for the isomeric pseudo-base (Figure V) formed by addition at the 6-position. This is true whether the resonance involves electron donation to the ring (type A) or electron withdrawal from the ring (type B). Hence, the effect of any β-substituent which is capable of resonance interaction with the double bonds of the

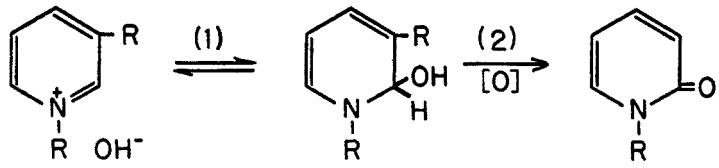

FIG. III

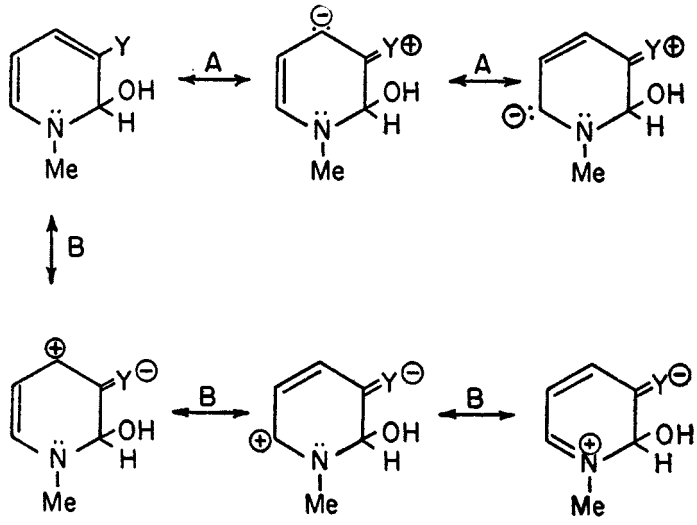

FIG. IV

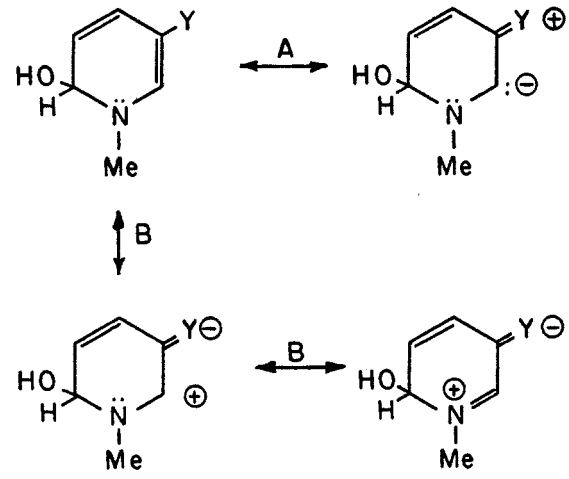

FIG. V

ring might be expected to lend added resonance stabilization to the pseudo-base shown in Figure IV, thereby favoring the formation of this pseudo-base and, ultimately, oxidation at the 2-position. The β-methyl group is capable of interacting in resonance of Type A *via* the Baker-Nathan effect. Type A resonance of a

bromine atom with a system of double bonds is generally accepted. The ability of a carbonyl group such as that present in the nicotinamide derivative to interact through resonance of type B is well known. Hence, it might be expected that the methyl and carboxamide groups and the bromine atom at the β-position would favor oxidation at the 2-position.

A possible explanation of the two cases in which oxidation occurred at the 6-position follows from a critical examination of the mechanism proposed in Figure VI. If Y is capable of interacting with the hydroxyl hydrogen so as to decrease its acidity, then step A would be hindered. Accordingly, formation of the 2,3-substituted pyridone would be inhibited and oxidation to the 2,5-substituted pyridone would be favored.

In the case of nicotinic acid methosulfate, a study of the Fisher-Hirschfelder models of the two pseudo-bases suggests that spatially such electrostatic inter-

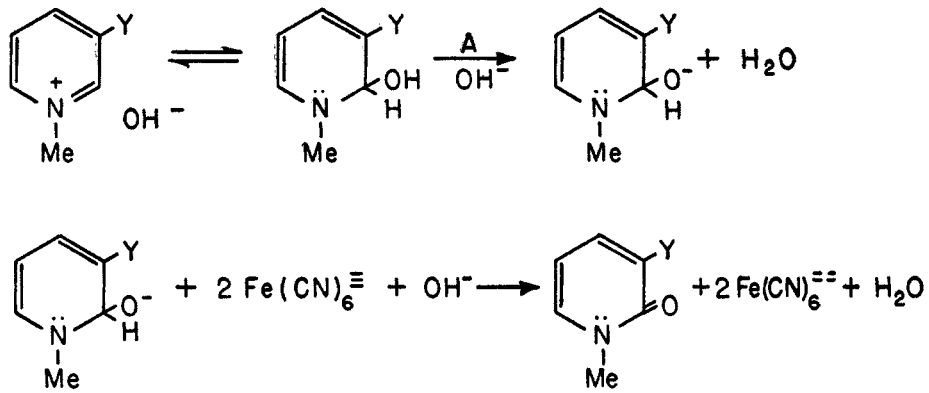

FIG. VI

action could occur easily between the oxygen atoms of the carboxylate ion (formed in basic solution) and the hydrogen atom of the hydroxyl group in the 2-hydroxylated compound, but not, of course, in the pseudo-base with the hydroxyl group at the 6-position.[4] In addition, the ionic charge would tend to block pseudo-base formation at the 2-position because of its electrostatic repulsion on the approaching hydroxide ion. These combined effects are perhaps sufficient to explain the absence of 1-methyl-2-pyridone-3-carboxylic acid in the product obtained by chemical oxidation of nicotinic acid methosulfate in basic solution.

Similarly, an examination of the models of the pseudo-bases of 1-methyl-3-cyanopyridine hydroxide suggests that the highly negative nitrile nitrogen is favorably situated spatially to interact with the hydrogen of the hydroxyl in the 2-position to decrease its acidity, and thereby to inhibit oxidation at the 2-position and to favor formation of the 2,5-substituted product.

[4] The interaction in this case is not classified as hydrogen bonding with chelation because the system of two conjugated double bonds ordinarily considered as required for chelation is lacking.

On the basis of these results it is suggested that considerable caution should be exercised in applying the results of purely chemical studies to problems of biochemical reactivity. In particular, steric effects which may not be critical in these chemical studies might very well be decisive in determining the orientation of products obtained by enzymatic action.

EXPERIMENTAL[5,6]

1-Methyl-2-pyridone-5-carboxylic acid. A mixture of 50 g. of nicotinic acid and 75 ml. of redistilled methyl sulfate was heated at 100° for one hour with stirring. The mixture was then cooled, diluted with 100 ml. of water, and extracted with chloroform.

A. One half of the solution was neutralized to *p*H 6, and then 10 g. of sodium hydroxide was added. After ¼ hour, a solution of 182 g. of potassium ferricyanide in 550 ml. of water was added dropwise over the course of one hour. After an additional ¾ hour, the solution was adjusted to *p*H 3.4 with sulfuric acid and cooled. A crude yield of 12 g. was obtained. A small amount of blue inorganic material could not be conveniently removed by recrystallization from water, but only by extraction of the finely ground acid with anhydrous ether in a Soxhlet apparatus. After removal of the ether, the residue was recrystallized from water to give pure 1-methyl-2-pyridone-5-carboxylic acid, m.p. 239.5–240.5°.

B. The other half of the solution was neutralized with sodium hydroxide and mixed with 100 ml. of alcohol and 50 ml. of 50% sodium hydroxide solution. The resulting deep red solution was warmed to 50° and 200 ml. of 30% hydrogen peroxide was added over a period of ¾ hour. A vigorous exothermic reaction occurred. The solution was then acidified to *p*H 3.5 with sulfuric acid and chilled overnight. The voluminous precipitate was filtered, dried, ground finely, and extracted with ether in the Soxhlet. A 7-g. yield of acid, m.p. 240.5–241.5°, was isolated.

1-Methyl-2-pyridone-5-carboxamide. A mixture of 1.36 g. of the above acid and 15 ml. of thionyl chloride was refluxed for one hour. The thionyl chloride was removed *in vacuo* and the residue shaken with 3 ml. of cold concentrated ammonia solution. After cooling for one hour, the precipitate was filtered and recrystallized from water; its melting point (211.0–211.5°) was essentially undepressed when it was mixed with an authentic sample (m.p. 209.0–211.5°) kindly furnished by Dr. Knox or with one (m.p. 204.0–206.5°) sent us through the courtesy of Dr. Holman.

1-Methyl-3- and 5-cyano-2-pyridones. To an ice-cooled solution of 72.5 g. of 3-cyanopyridine methiodide[3] in 200 ml. of water, solutions of 200 g. of potassium ferricyanide in 550 ml. of water and 90 g. of potassium hydroxide in 100 ml. of water were added simultaneously over a one-hour period with vigorous stirring. The resulting solution was saturated with potassium carbonate in the cold. After removal of the precipitated potassium ferrocyanide, the solution was exhaustively extracted with 1:1 ether-chloroform. The combined extracts were washed, dried, and concentrated. The residue was distilled *in vacuo* to give 5 g. (14%) of a yellow mixture of 1-methylcyano-2-pyridones, b.p. 180–200°/2 mm. Späth (6) reported b.p. 243°/18 mm. for 1-methyl-3-cyano-2-pyridone. The same results were obtained when sodium chloride was used as the saturating agent. After recrystallization from alcohol, the product sintered at 112–114°, semi-melted at 117–125°, and gave a clear melt at 142°. Repeated recrystallization gave a very small amount of material melting at 159.0–159.8°. Analysis indicated a very low nitrogen content.

Attempted hydrolysis to the amide by the method of Späth and Koller (6) gave only a small amount of the compound melting at 159°. Hydrolysis to the acid, on the other hand, was successful. The crude product (2 g.), added to 10 g. of sodium and 200 ml. of anhydrous methyl alcohol, was refluxed for 72 hours while a stream of nitrogen was bubbled through the

[5] All melting points are corrected. Boiling points are uncorrected.

[6] Analyses are by Clark Microanalytical Laboratory, Urbana, Illinois, except those indicated by an asterisk, which are by Microchemical Specialties Co., Berkeley 3, Calif.

solution. The solution was concentrated *in vacuo*, acidified, and evaporated to dryness *in vacuo*. The powdered residue was extracted repeatedly with anhydrous alcohol. The extract was concentrated and the residue recrystallized from water to give 0.6 g. of crude 1-methyl-2-pyridone-5-carboxylic acid, m.p. 220–230°. After recrystallization from water it melted at 239.5–240.8°. Mixing with an authentic sample of acid did not depress the melting point. Recrystallization of the residue gave only a small additional amount of 2,5-substituted acid.

1-Methyl-2-pyridone-3-carboxamide. A solution of 61 g. of nicotinamide methiodide in 175 ml. of water was cooled to 0° and stirred vigorously. Solutions of 60 g. of potassium hydroxide in 70 ml. of water and 175 g. of potassium ferricyanide in 500 ml. of water were added simultaneously over a 1½-hour period. The solution was stirred for an additional ¾ hour, saturated with salt, and filtered. The filtrate was extracted exhaustively with chloroform. The extract was washed, dried, and concentrated to dryness. The crude material (5.3 g., 15%), after recrystallization from water, melted at 217.1–218.2°; mixed with an authentic sample, m.p. 219.5–220.1°. A sample of Dr. Holman's material, m.p. 217–218°, gave the same mixed melting point with the authentic sample.

Preparation of an authentic sample of the above amide. A solution of 5 g. of 2-hydroxynicotinic acid (13) and 4.4 g. of potassium hydroxide in 20 ml. of water was evaporated to dryness. The residue was powdered and heated with 50 ml. of anhydrous methyl alcohol and 6 ml. of methyl iodide at 90° for five hours in a pressure bottle (12). The solution was cooled, filtered, and concentrated on the steam-bath. The residue was hydrolyzed by refluxing with 13 ml. of 10% sodium hydroxide solution for two hours. The solution was then cooled and acidified with hydrochloric acid. The mixture was cooled overnight and filtered to give 4 g. of crude acid. A sample recrystallized from water melted at 184.5–185.1°. Späth (6) reported m.p. 183°. A mixture of 1.2 g. of the acid and 15 ml. of thionyl chloride was refluxed for one hour. Excess thionyl chloride was removed *in vacuo*, the residue shaken with 3 ml. of concentrated ammonium hydroxide, and cooled for one hour. The precipitate (1 g.) was recrystallized from water to give short needles, m.p. 219.0–219.5°. After a second recrystallization the pure 1-methyl-2-pyridone-3-carboxamide melted at 219.5–220.1°.

1,3-Dimethyl-2-pyridone. A mixture of 25 g. of β-picoline and 50 g. of methyl sulfate was heated on the steam-bath overnight and then diluted with 150 ml. of water. A solution of 170 g. of potassium ferricyanide in 350 ml. of water was cooled in ice and stirred vigorously, while the methosulfate solution and a solution of 90 g. of potassium hydroxide in 100 ml. of water were added simultaneously over the course of one hour. The solution was stirred for an additional ¾ hour, saturated with potassium carbonate, and filtered. The precipitate was washed thoroughly and the filtrate extracted repeatedly with benzene. The extract was washed, dried, and concentrated and the residue distilled to give 13.8 g. (41%) of 1,3-dimethyl-2-pyridone, b.p. 86–88°/1.45 mm., n_D^{25} 1.5538.[7]

The *hydrochloride*, prepared by passing anhydrous hydrogen chloride into an ether solution of the base, melted at 120.1–121.2° after recrystallization from anhydrous alcohol-ether. The melting point was not depressed when the compound was mixed with the hydrochloride of an authentic sample of the 2,3-isomer, but dropped to 75–83° when the hydrochloride of the 2,5-isomer was added.

Authentic 1,3-dimethyl-2-pyridone. The compound was prepared by the alkylation of 2-hydroxy-3-methylpyridine, which was obtained in quantitative yield by the method of Seide (14), except that evaporation of the solution to dryness before extraction with chloroform was found unnecessary. Attempted alkylation with methyl iodide at 90°, or with diazomethane in ether-dioxane solution, gave only starting material. The method of Binz and Räth (8) on the other hand, proved successful. To a refluxing solution of 15.9 g. of 2-hydroxy-3-methylpyridine and 9.7 g. of potassium hydroxide in 200 ml. of anhydrous ethanol, an excess of methyl iodide in ethanol solution was added dropwise over a two-hour period with stirring. The solution was stirred for an additional two hours, then cooled, filtered, and

[7] It should be noted that this procedure was not satisfactory for the oxidation of N-methylated 3-bromopyridine and nicotinamide derivatives.

concentrated on the steam-bath. The residue was diluted with chloroform, refiltered to remove additional potassium iodide, and again concentrated. Vacuum distillation of the final residue gave 12 g. (68%) of 1,3-dimethyl-2-pyridone, b.p. 83–84°/1.3 mm., n_D^{25} 1.5525. The *hydrochloride*, prepared as described above, melted at 120.2–121.6°.

Anal. Calc'd for C_7H_9NO: N, 11.4. Found: N, 11.3.

Authentic 2,5-isomer. Crude 2-hydroxy-5-methylpyridine was prepared by Seide's (14) method from 2-amino-5-methylpyridine (Reilly Tar & Chemical Corp.) in 87% yield. Methylation as described above gave 13.8 g. (75%) of 1,5-dimethyl-2-pyridone, b.p. 109–111°/1.7 mm., n_D^{25} 1.5565, and m.p. 36.8° (cooling curve). The *hydrochloride* melted at 159.5–160.2°.

Anal. Calc'd for C_7H_9NO: N, 11.4. Found: N, 11.4.

1-Ethyl-3-methyl-2-pyridone. A mixture of 24 g. of β-picoline and 75 ml. of ethyl iodide was heated overnight at 90° in a pressure bottle. The mixture was cooled, filtered, and the precipitate washed with ether. The residue (61 g.) was taken up in 200 ml. of water and cooled to 0°. Solutions of 150 g. of potassium ferricyanide in 350 ml. of water and 60 g. of potassium hydroxide in 70 ml. of water were then added simultaneously with vigorous stirring over the course of one hour. The mixture was stirred for an additional ¾ hour and then saturated with potassium hydroxide. The precipitate was removed by filtration, and both the solution and the precipitate were extracted thoroughly with chloroform. The extract was washed, dried, and concentrated. The residue was distilled to give 8.0 g. (23.8%) of 1-ethyl-3-methyl-2-pyridone, b.p. 95–96°/2.5 mm.

Authentic 1-ethyl-3-methyl-2-pyridone. A solution of 15.9 g. of 2-hydroxy-3-methylpyridine and 9.7 g. of potassium hydroxide in 200 ml. of absolute ethanol was treated with excess ethyl iodide as described above. Vacuum distillation gave 12.6 g. (62%) of 1-ethyl-3-methyl-2-pyridone, b.p. 92°/2.2 mm., n_D^{25} 1.5411.

Anal. Calc'd for $C_8H_{11}NO$: N, 10.2. Found: N, 10.5.

Authentic 1-ethyl-5-methyl-2-pyridone. Exactly 15.9 g. of 2-hydroxy-5-methylpyridine was treated as described above to give 12.4 g. (60%) of 1-ethyl-5-methyl-2-pyridone, b.p. 104–106°/1.7 mm., n_D^{25} 1.5415.

Anal. Calc'd for $C_8H_{11}NO$: N, 10.2. Found: N, 10.5.

1-Methyl-3-bromo-2-pyridone. A mixture of 33 g. of 3-bromopyridine and 50 ml. of methyl iodide was heated overnight at 90°. A quantitative yield of crude material was obtained. The product was dissolved in 175 ml. of water, cooled to 0°, and stirred vigorously. Solutions of 133 g. of potassium ferricyanide in 400 ml. of water and 60 g. of potassium hydroxide in 70 ml. of water were added simultaneously over a 2½-hour period. The solution was stirred for several additional hours, saturated with potassium carbonate, and filtered. Both the precipitate and the solution were thoroughly extracted with chloroform. The extract was washed, dried, and concentrated. Vacuum distillation yielded 10.6 g. (27%) of material, careful fractionation of which gave a small fraction boiling between 110–118°/0.45 mm. and a much larger fraction boiling at 122–127°/0.45 mm. On refractionation the latter boiled at 120–125°/0.5 mm.

*Anal.** Calc'd for C_6H_6BrNO: N, 7.5; Br, 42.5.
Found: N, 7.5; Br, 42.5.

Preparation of an authentic sample of 1-methyl-5-bromo-2-pyridone. A. Preparation of 2-amino-5-bromopyridine. To a solution of 20 g. of 2-aminopyridine in 100 g. of 20% sulfuric acid, was added 13 ml. of bromine over a period of one hour. The solution was stirred overnight, diluted with 150 ml. of water, and neutralized with solid sodium carbonate. After cooling, the precipitate (38 g.) was removed, dried, extracted twice with Skellysolve B, and recrystallized from benzene to give 21.7 g. of 2-amino-5-bromopyridine, m.p. 132–135°. Case (11) reported m.p. 138°.

B. 2-Hydroxy-5-bromopyridine. The 2-amino-5-bromopyridine prepared above was treated by the method of Seide (14) to give 11.0 g. (50%) of 2-hydroxy-5-bromopyridine, m.p. 162–166° after one recrystallization from water. Tschitschibabin (15) reported m.p. 177–178°.

C. Exactly 15.0 g. of 2-hydroxy-5-bromopyridine was methylated as described above to

give 12.3 g. (73%) of 1-methyl-5-bromo-2-pyridone, b.p. 126–131°/1.6 mm., which solidified at once to a solid, m.p. 62.1–63.0°. Räth (8) reported m.p. 53°. Methylation with diazomethane in ether-dioxane solution failed.

*Anal.** Calc'd for C_6H_6BrNO: N, 7.5; Br, 42.5.

Found: N, 7.6; Br, 42.4.

1-Methyl-3,5-dibromo-2-pyridone. A. Preparation from the oxidation compound. To a cooled solution of 2.2 g. of 1-methyl-3-bromo-2-pyridone in 10 ml. of glacial acetic acid, 0.7 ml. of bromine was added with stirring. The product began to precipitate after 45 mins. After an additional hour, 30 ml. of water was added with vigorous shaking. The white precipitate (1.7 g.) was removed by filtration, washed thoroughly, and recrystallized from alcohol-water; m.p. 182.1–183.2°. No depression resulted upon admixture with a sample of the dibromide prepared from 1-methyl-5-bromo-2-pyridone. Decker (5) reported m.p. 178°.

B. Preparation from 1-methyl-5-bromo-2-pyridone. A solution of 2.0 g. of the 2,5-derivative was treated as described above to give 1.3 g. of the same product, m.p. 182.1–183.2°. Precipitation began after 10 seconds.

Attempted preparation of an authentic sample of 1-methyl-3-bromo-2-pyridone. Methyl 3-bromocoumalate was prepared in 31% yield by the method of von Pechmann (12) or in 29% yield by esterification with diazomethane in alcohol solution. In both cases a considerable amount of an intractable oil was formed.

1-Methyl-3-carbomethoxy-5-bromo-2-pyridone. To 200 ml. of 18% methylamine solution, exactly 50 g. of finely powdered methyl 3-bromocoumalate was added with shaking. A quantitative yield of the pyridone compound precipitated within a few minutes and was separated by filtration. The crude ester was hydrolyzed by refluxing for four hours with excess sodium hydroxide in 50-50 water-alcohol solution. The solution was concentrated, filtered, and acidified. The crude acid (48 g.), m.p. 290°, was removed and dried. Attempted decarboxylation as described by Case (11) led only to a chloroform-insoluble resin. Attempted vacuum pyrolysis gave a very high-melting solid.

SUMMARY

1. The structure of the products of the oxidation of a series of N-alkylated β-substituted pyridines has been investigated.

2. The nature of the β-substituent in N-alkylated pyridines has been shown to affect the orientation of the chemical oxidation of these compounds.

3. A mechanism has been proposed which accounts for the differences observed in the orientation of the oxidation products.

4. The danger in the application of the results of purely chemical studies to problems of biochemical reactivity is pointed out.

LAWRENCE, KANSAS

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