[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

STUDIES ON γ-PYRONES. I. DERIVATIVES OF KOJIC ACID[1]

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The varied reactivities of γ-pyrones (1,2), together with the ready availability of some of them such as kojic acid and maltol make these substances interesting starting materials for synthesis. In this paper we are reporting several syntheses based on kojic acid, as shown in the Flow Sheet.

Yabuta (3) and Armit and Nolan (4) found that selective methylation of the phenolic hydroxyl group of kojic acid could be achieved by the use of diazomethane, but Yabuta reported that methyl sulfate attacked both hydroxyl groups and led to the dimethyl ether. We have reinvestigated this reaction and found that even with methyl sulfate the phenolic hydroxyl group is attacked first, and good yields of the monomethyl ether, II, can be obtained if an excess of methyl sulfate is avoided.

2-Chloromethyl-5-methoxy-4-pyrone (III) is obtained easily and in good yield from kojic acid monomethyl ether. Although the chlorine atom in III is reactive, the compound does not undergo most replacement reactions normally. Thus treatment with alkali cyanides (4) causes tar formation, and similar results were obtained in the present work when cuprous cyanide was used. When attempts were made to prepare a Grignard reagent from III the magnesium dissolved, but on hydrolysis only an intractable gum was obtained. The chloro compound does react normally with tertiary aliphatic amines to give quaternary salts (VI) in good yield, but attempts to react it with N-β-dimethylaminoethylaniline were unsuccessful. The halogen atom of III can be replaced by hydrogen by use of zinc and acetic acid (5) or tin and hydrochloric acid, but catalytic hydrogenation of III over Raney nickel is not selective.

2-Chloromethyl-5-methoxy-4-pyridone (VIII) was prepared from 2-hydroxymethyl-5-methoxy-4-pyridone (VII) by the action of thionyl chloride in chloroform. The structure of VIII was established by hydrogenation to 2-methyl-5-methoxy-4-pyridone (V), identical with the substance prepared from 2-methyl-5-methoxy-4-pyrone (IV) and ammonia. The m.p. of V (105–106°) and its picrate (180°) found in this work are not in agreement with those reported by Yabuta (3) (115° and 200°, respectively); this discrepancy may be due to varying degrees of hydration.[4] 2-Chloromethyl-5-methoxy-4-pyridone gave only tars on treatment with sodium cyanide, cuprous cyanide, and sodioacetoacetic ester. It re-

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[1] The material in this paper is abstracted, in part, from the Ph.D. Dissertation of Joseph F. Ackerman, University of Notre Dame, June, 1949.

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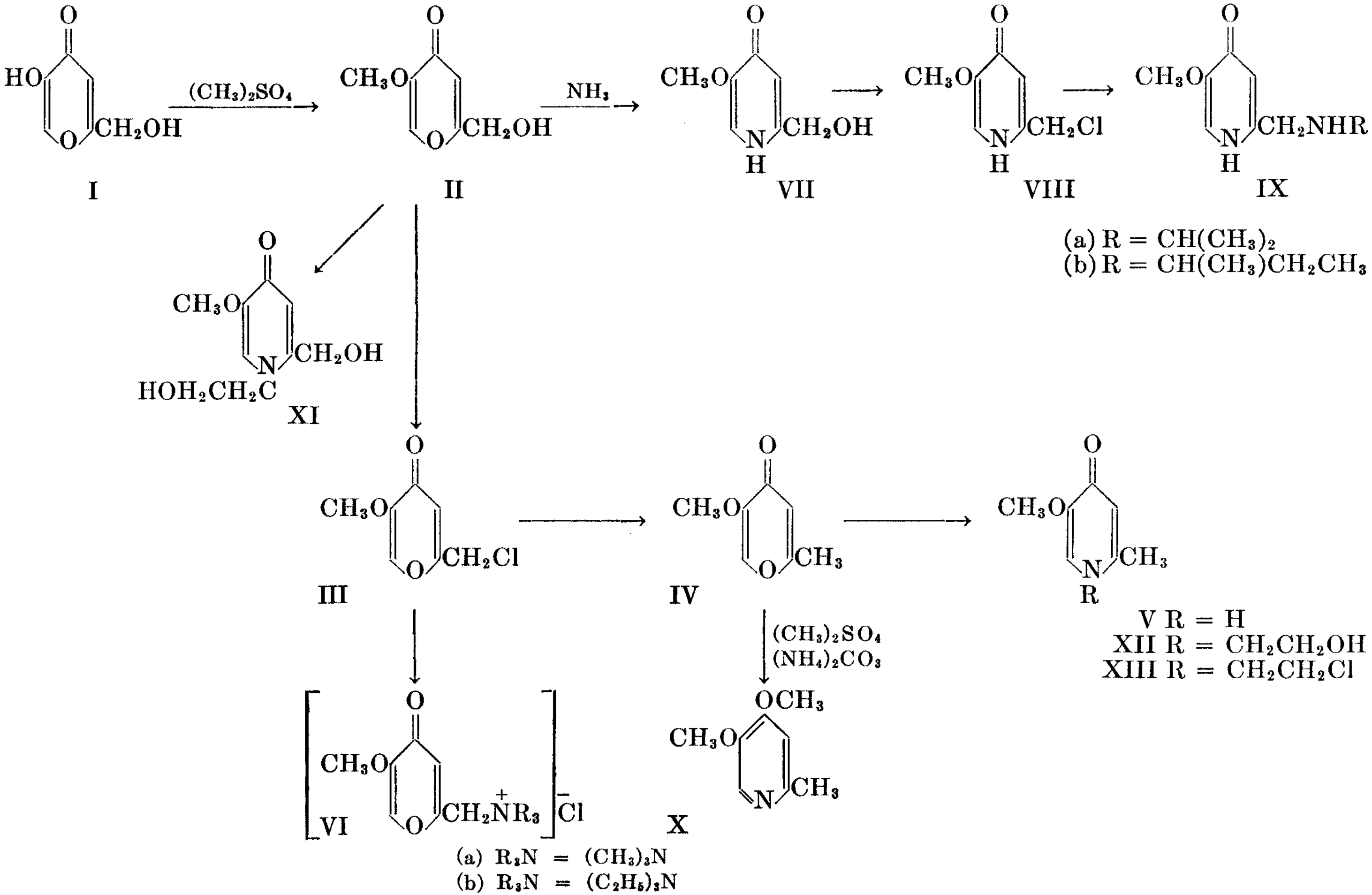
[4] The 4-pyrones and 4-pyridones form hydrates very readily, and other cases of discrepancies in melting points due to hydration have been observed; thus, 5-methoxy-2-hydroxymethyl-4-pyridone has been reported to melt at 95°, 111°, and 173–175° (2).

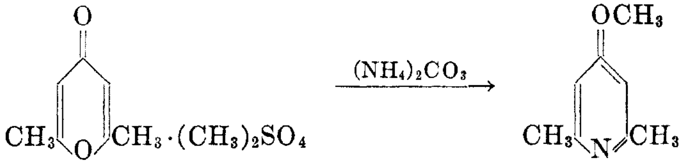
FLOW SHEET


I
(CH₃)₂SO₄
II
NH₃
VII
VIII
IX
(a) R = CH(CH₃)₂
(b) R = CH(CH₃)CH₂CH₃
XI
III
IV
V R = H
XII R = CH₂CH₂OH
XIII R = CH₂CH₂Cl
(CH₃)₂SO₄
(NH₄)₂CO₃
VI
X
(a) R₃N = (CH₃)₃N
(b) R₃N = (C₂H₅)₃N

acted normally with primary amines, however, to form the 2-alkylaminomethyl-5-methoxy-4-pyridones (IX).

5-Methoxy-2-hydroxymethyl-4-pyrone and 5-methoxy-2-methyl-4-pyrone on treatment with ethanolamine gave the corresponding 1-(β-hydroxyethyl)pyridones, but pyridones were not obtained when the ethyl ester of glycine was used as the amine. 5-Methoxy-2-methyl-N-(β-hydroxyethyl)-4-pyridone (XII) was converted to the β-chloro compound (XIII) with thionyl chloride, but when this same reaction was applied to 5-methoxy-2-hydroxymethyl-N-(β-hydroxyethyl)-4-pyridone (XI) only one of the two hydroxyl groups was replaced.

Von Baeyer (6) observed that when 2,6-dimethylpyrone methyl methosulfate was treated with perchloric acid and then with ammonium carbonate it formed 2,6-dimethyl-4-methoxypyridine rather than the N-methylpyridone:



We have found that this reaction can also be carried out on 5-methoxy-2-methyl-4-pyrone, to give 4,5-dimethoxy-2-methylpyridine. Attempts to replace the perchloric acid with other strong acids such as *p*-toluenesulfonic acid or trichloroacetic acid were unsuccessful and neither the pyrone methiodide nor the methosulfate could be converted to the pyridine by treatment with ammonium carbonate.

EXPERIMENTAL[5,6]

2-Hydroxymethyl-5-methoxy-4-pyrone (II). To a well-stirred solution of 114 g. (0.8 mole) of kojic acid[7] in 500 ml. of 10% potassium hydroxide there was added 101 g. (0.8 mole) of redistilled dimethyl sulfate in portions over a period of thirty minutes. The temperature was kept below 25° by occasional cooling in an ice-bath. Stirring was continued for an additional fifteen minutes and the mixture was cooled in an ice-bath and filtered. The product weighed 90 g. (72%) and after recrystallization from methanol melted at 157–158° and was pure enough for subsequent reactions. Recrystallization from a 1:1 mixture of ethanol and ether raised the melting point to 161°, in agreement with Yabuta's value (3).

2-Methyl-5-methoxy-4-pyrone (IV). 2-Chloromethyl-5-methoxy-4-pyrone (III) was prepared from the hydroxy compound (II) and thionyl chloride, as described by Yabuta (3) for 2-chloromethyl-5-hydroxy-4-pyrone. Yield about 65%, m.p. 118°. Attempts were made to remove the halogen by catalytic hydrogenation over Raney nickel, but the reaction was not sufficiently selective. Reduction of III by tin and conc'd hydrochloric acid gave a 40% yield of IV.

The best results were obtained when the chloro compound was reduced with zinc and acetic acid, essentially as described by Yabuta (5). The average yield was 87%, m.p. 69–70°.

2-(Trimethylaminomethyl)-5-methoxy-4-pyrone chloride (VIa). A mixture of 6 g. (0.035 mole) of 2-chloromethyl-5-methoxy-4-pyrone, 18 g. (0.08 mole) of 30% aqueous trimethyl-

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[5] Analyses for C, H, and N by Clark Microanalytical Laboratory, Urbana, Ill.

[6] All melting points are uncorrected.

[7] We wish to thank the Northern Regional Laboratory and the Corn Products Refining Co. for their generous gifts of kojic acid.

amine, and 50 ml. of ethanol was heated at 90° for 2½ hours in a closed container. Evaporation of the resulting solution under reduced pressure yielded a brown, oily residue which was triturated with dry acetone until crystallization occurred. Recrystallization from a methyl alcohol-acetone mixture yielded 5 g. (63%) of the quaternary salt, m.p. 209° (dec.).

Anal. Calc'd for $C_{10}H_{16}ClNO_3$: C, 51.39; H, 6.90; N, 5.99; Cl, 15.20.
Found: C, 51.84; H, 7.11; N, 5.75; Cl, 15.32.

2-(Triethylaminomethyl)-5-methoxy-4-pyrone chloride (VIb). A mixture of 5 g. (0.028 mole) of 2-chloromethyl-5-methoxy-4-pyrone and 6 g. (0.06 mole) of triethylamine in 50 ml. of 95% ethanol was refluxed for four hours. Evaporation of the reaction mixture under reduced pressure left a brown oil which crystallized on trituration with dry acetone. Recrystallization from a methyl alcohol-acetone mixture yielded 5 g. (65%) of hygroscopic plates, m.p. 72–74°.

Anal. Calc'd for $C_{13}H_{22}ClNO_3 \cdot \frac{1}{2} H_2O$: C, 54.82; H, 8.14; N, 4.92; Cl, 12.45.
Found: C, 54.91; H, 8.29; N, 4.98; Cl, 12.86.

2-Methyl-5-methoxy-4-pyridone (V). 2-Methyl-5-methoxy-4-pyrone (2 g.) was heated with 10 ml. of conc'd ammonium hydroxide at 90° for two hours. The product after recrystallization from a mixture of acetone and ethyl acetate melted at 105–106° and formed a picrate, m.p. 178°. Yabuta (3) who made V by this same reaction reported the m.p. as 115°, and that of the picrate as 200°.

5-Methoxy-2-chloromethyl-4-pyridone hydrochloride (VIII). 5-Methoxy-2-hydroxymethyl-4-pyridone (VII) was prepared by treating pyrone II with ammonia at 90°, as described by Armit and Nolan (4); the yield of material with m.p. 171–172° was 75%. Redistilled thionyl chloride (15 ml.) was added in portions to a solution of 5 g. of VII in 20 ml. of chloroform, cooled in an ice-bath, and the mixture was refluxed for an hour to complete the reaction. The product separated on cooling and was recrystallized from an absolute alcohol-acetone mixture. Yield of product with m.p. 152–153°, 70%.

Anal. Calc'd for $C_7H_9Cl_2NO_2$: C, 40.02; H, 4.32; N, 6.67.
Found: C, 40.09; H, 4.41; N, 6.90.

Reduction of 5-methoxy-2-chloromethyl-4-pyridone. A solution of 0.01 mole of VIII in 50 ml. of absolute ethanol containing 0.02 mole of potassium hydroxide was shaken with hydrogen in the presence of Raney nickel. The calculated amount of hydrogen (0.01 mole) was absorbed in forty-five minutes and absorption then ceased. The product (V) isolated from the solution melted at 102–103° after recrystallization from ethyl acetate, and formed a picrate, m.p. 180°. These substances did not depress the melting points of V and its picrate prepared from 2-methyl-5-methoxy-4-pyrone.

2-Isopropylaminomethyl-5-methoxy-4-pyridone dihydrochloride (IXa). To 10 g. (0.047 mole) of 2-chloromethyl-5-methoxy-4-pyridone hydrochloride (VIII) dissolved in 50 ml. of absolute ethanol there was added 15 g. (0.25 mole) of isopropylamine and the mixture was heated for 3 hours at 100° in a closed container. After cooling, the solution was evaporated to dryness under reduced pressure and 50 ml. of 18% hydrochloric acid was added. The solution was again evaporated to dryness and the residue after washing with 50 ml. of cold *n*-propyl alcohol was recrystallized from a methyl alcohol-acetone mixture. Colorless plates weighing 9.4 g. (75%) were obtained, m.p. 235° (dec.).

Anal. Calc'd for $C_{10}H_{18}Cl_2N_2O_2$: C, 44.62; H, 6.74; N, 10.41; Cl, 26.34.
Found: C, 44.95; H, 6.64; N, 10.94; Cl, 26.21.

2-sec-Butylaminomethyl-5-methoxy-4-pyridone dihydrochloride (IXb). This was prepared as described above, using 8 g. of IV and 10 g. of *sec*-butylamine. The product weighed 7.5 g. (70% yield) and melted at 231° (dec.).

Anal. Calc'd for $C_{11}H_{20}Cl_2N_2O_2$: C, 46.65; H, 7.12; N, 9.89; Cl, 25.04.
Found: C, 46.87; H, 7.26; N, 9.74; Cl, 24.87.

1-(β-Hydroxyethyl)-2-methyl-5-methoxy-4-pyridone. A solution of 13 g. (0.21 mole) of ethanolamine in 25 ml. of water was added with stirring to 30 g. (0.21 mole) of 2-methyl-5-methoxy-4-pyrone (IV) in 150 ml. of water over a period of fifteen minutes. The reaction mixture was refluxed for 3 hours and then evaporated under reduced pressure. The residue was dissolved in a small amount of absolute ethanol and again evaporated under vacuum. An oil remained which crystallized upon trituration with isopropanol. The product after recrystallization from isopropanol had m.p. 166° and weighed 21 g. or 58% of the theoretical.

Anal. Calc'd for $C_9H_{13}NO_3$: C, 58.99; H, 7.15; N, 7.64.

Found: C, 58.69; H, 7.15; N, 7.58.

1-(β-Hydroxyethyl)-2-hydroxymethyl-5-methoxy-4-pyridone. To a solution of 29 g. (0.186 mole) of II in 100 ml. of water was added 10.2 g. (0.20 mole) of ethanolamine. The mixture was stirred for two hours at room temperature and was then refluxed for one hour and evaporated under reduced pressure. Trituration of the residue with a small amount of isopropanol gave cream-colored crystals; m.p. 167–168° after recrystallization from absolute ethanol yield 15 g.

Anal. Calc'd for $C_9H_{13}NO_4$: C, 54.25; H, 6.58; N, 7.03.

Found: C, 54.04; H, 6.49; N, 7.18.

1-(β-Chloroethyl)-2-methyl-5-methoxy-4-pyridone hydrochloride. To 5 ml. of purified thionyl chloride there was added in small portions, 8 g. of 1-(β-hydroxyethyl)-2-methyl-5-methoxy-4-pyridone. A vigorous reaction occurred and after the evolution of gas had ceased, the excess thionyl chloride was removed under reduced pressure. The residue solidified to a buff-colored powder on trituration with acetone. The product was treated with propanolic hydrogen chloride and 6.5 g. of buff-colored plates were obtained, m.p. 208° (dec.).

Anal. Calc'd for $C_9H_{13}Cl_2NO_2$: C, 45.40; H, 5.50; N, 5.88.

Found: C, 45.81; H, 5.49; N, 5.94.

Reaction of 1-(β-hydroxyethyl)-2-hydroxymethyl-5-methoxy-4-pyridone with thionyl chloride. To 2 ml. of purified thionyl chloride was added one gram of the pyridone. A vigorous reaction occurred and when the evolution of gas had stopped, the excess thionyl chloride was removed by evaporation. The residue was triturated with acetone and colorless crystals, m.p. 121–122° were obtained. Analysis indicated that one of the hydroxyl groups had been replaced by chlorine.

Anal. Calc'd for $C_9H_{13}Cl_2NO_3$: C, 42.56; H, 5.16; N, 5.52.

Found: C, 42.59; H, 5.11; N, 5.34.

2-Methyl-4,5-dimethoxypyridine (X). A mixture of 30 g. (0.21 mole) of 2-methyl-5-methoxy-4-pyrone and 31 g. (0.25 mole) of dimethyl sulfate was heated for two hours at 50°. The resulting oily, red liquid was cooled in an ice-bath and added to a twofold excess of cold 20% perchloric acid. After standing for two hours, the mixture was filtered and the crystalline methoperchlorate was added in portions to 175 ml. of cold 10% ammonium carbonate solution. The mixture was allowed to warm to room temperature and after saturation with ammonium sulfate, the solution was extracted with ethyl acetate. The extract yielded 20 g. of reddish-brown oil which was distilled *in vacuo*, b.p. 78–80°/1 mm. The *hydrochloride* melted at 164°.

Anal. Calc'd for $C_8H_{12}ClNO_2 \cdot \frac{1}{2}H_2O$: C, 48.35; H, 6.59; N, 7.05.

Found: C, 48.18; H, 6.64; N, 6.82.

SUMMARY

1. A new procedure has been developed for the preparation of kojic acid monomethyl ether.

2. Several derivatives of 5-methoxy-2-chloromethyl-4-pyrone and the corresponding pyridone have been prepared.

3. 5-Methoxy-2-methyl-4-pyrone has been converted to 4,5-dimethoxy-2-methylpyridine by the Baeyer reaction.

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