

James H. Looker and Michael D. Clifton

Department of Chemistry, University of Nebraska-Lincoln,
Lincoln, Nebraska 68588-0304

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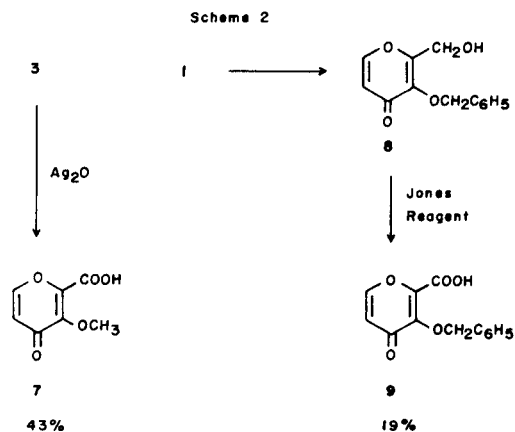
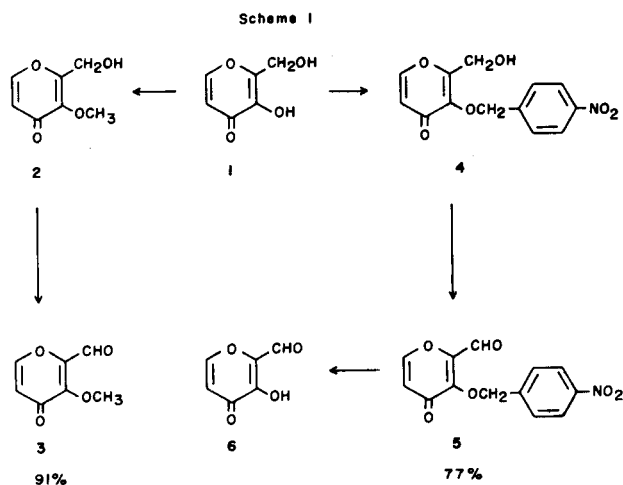
α -Hydroxymaltol (2-hydroxymethyl-3-hydroxy-4*H*-pyran-4-one) (**1**) has been converted to the 3-*O*-methyl ether **2** and 3-*O*-*p*-nitrobenzyl ether **4** by standard methods. The ethers **2** and **4** have been oxidized by barium manganate to the corresponding aldehydes, **3** and **5**, in 91 and 77% yields respectively. Long-term reaction of **5** with hydrogen bromide in acetic acid gives 3-hydroxy-4*H*-pyran-4-one-2-carboxaldehyde (**6**). The aldehyde **3** is readily oxidized by short-term reaction with silver oxide to the corresponding acid **7**.

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The synthesis of comenaldehyde (5-hydroxy-4*H*-pyran-4-one-2-carboxaldehyde) by oxidation of suitably blocked kojic acid derivatives and subsequent deblocking was reported several years ago [1,2]. Comenaldehyde methyl ether (5-methoxy-4*H*-pyran-4-one-2-carboxaldehyde) was prepared in this laboratory [3] by both an oxidative method and by the Kröhnke aldehyde synthesis [4], and by Indian workers by selenium dioxide oxidation [5]. In the present paper, we report synthesis of 3-hydroxy-4*H*-pyran-4-one-2-carboxaldehyde (**6**) by oxidation of the 3-*p*-nitrobenzyl ether **4** of α -hydroxymaltol and subsequent removal of the *p*-nitrobenzyl blocking group. 3-Methoxy-4*H*-pyran-4-one-2-carboxaldehyde (**3**) has been obtained by oxidation of the methyl ether **2** of **1**. Oxidation of **3** to the carboxylic acid **7** is described.

The essential starting material for this study is α -hydroxymaltol (**1**), for which a useful synthesis from pyromeconic acid was described by the Pfizer group [6]. A useful one-pot synthesis of pyromeconic acid from furfuryl alcohol has been developed [7], a synthesis which enhances the importance of **1** as a synthetic intermediate. Selective methylation of **1** was achieved in the present study with dimethyl sulfate in acetone in presence of anhydrous potassium carbonate, with 80-200% excess methylating agent necessary in moderately large runs. The course of the methylation was monitored by analytical thin-layer chromatography on silica gel, which revealed either no dimethyl ether, or only trace quantities. Of several oxidizing agents employed for converting the carbinol **2** to the aldehyde **3**, barium manganate [8] proved to be the oxidant of choice. Reaction of **2** with a large excess of barium manganate in methylene chloride gave the analytically pure 3-methoxy-4*H*-pyran-4-one-2-carboxaldehyde (**3**) in 91% yield. Two oxidants, useful in oxidizing some carbinols to aldehydes, were less satisfactory. Thus, Jones reagent [9] gave a modest yield (30%) of **3**, and pyridinium dichromate [10] an 8% yield of **3**. Deblocking of **3** was not attempted.

Preparation of 2-hydroxymethyl-3-benzyloxy-4*H*-pyran-4-one (**8**) was attempted, since the benzyl block usually is



easily removed by acid cleavage or hydrogenolysis. However, **8** was an oil, resistant to crystallization attempts. A study of the synthesis of 2-hydroxymethyl-4-(*p*-nitrobenzyloxy)-4*H*-pyran-4-one (**4**) then was made. Although **4** was obtained as a crystalline solid, lengthy purification was necessary, including preparative tlc on silica gel in order to obtain analytically pure product. Oxidation of **4** with barium manganate gave the aldehyde **5** in 77% yield. Re-

action of **5** with hydrogen bromide in acetic acid effected cleavage of the *p*-nitrobenzyl blocking group at room temperature, provided a sufficient time of four weeks was allowed. After ten days, tlc indicated appreciable quantities of starting material still to be present. 3-Hydroxy-4*H*-pyran-4-one-2-carboxaldehyde (**6**) was obtained as a crystalline solid. Infrared and proton nuclear magnetic resonance spectra, as well as analytical data, support the assigned structure for **6**.

Aldehyde **3** was converted to 3-methoxy-4*H*-pyran-4-one-2-carboxylic acid (**7**) by short term oxidation with silver oxide [11]. Oxidation of the oily benzyl ether **8** with barium manganate for three days gave no useful result.

Dedication.

This paper is dedicated to Professor Dr. Karl Kratzl, Organic Chemical Institute of the University of Vienna, Vienna, Austria, on the occasion of his seventieth birthday.

EXPERIMENTAL

Melting points were taken in capillary tubes on a Mel-Temp apparatus and are uncorrected. The ¹H nmr spectra were determined with a Varian A-60D spectrometer, with chemical shifts (δ) reported in ppm downfield from internal tetramethylsilane. Infrared spectra were measured on a Beckman Acculab Infrared Spectrometer. Elemental analyses were performed by MicroTech Laboratory, Skokie, Illinois.

2-Hydroxymethyl-3-hydroxy-4*H*-pyran-4-one (α-Hydroxymaltol).

This substance was synthesized from pyromeconic acid by the literature procedure [6] in 75% yield, mp 146-148° (lit [6] mp 148-150°); nmr (DMSO-*d*₆): δ 4.40 (s, 2H, CH₂O), 6.35 (d, 1H, H₃), 8.10 (d, 1H, H₆).

2-Hydroxymethyl-3-methoxy-4*H*-pyran-4-one.

To a solution of 10 g α-hydroxymaltol in 250 ml of reagent acetone, contained in a three-necked flask equipped with condenser and dropping funnel, was added 10 g of anhydrous potassium carbonate. Then 15.9 g of dimethyl sulfate in 50 ml of acetone was added dropwise over a three-hour period. During this addition, the reaction mixture was refluxed and stirred with a magnetic stirrer. Reflux and stirring were continued one hour after addition was complete. Inorganic salts were filtered off, and the filtrate evaporated. The resulting tan, oily, semi-solid residue was dissolved in 100 ml of ethyl acetate and dried over anhydrous magnesium sulfate. After filtering off the drying agent, the ethyl acetate solution was placed in a refrigerator overnight. The title compound crystallized as a tan solid, yield (two crops) 7.6 g (69%). The analytically pure substance was obtained by crystallization from acetone-cyclohexane (1:4 vol), mp 113-115°; nmr (DMSO-*d*₆): δ 3.91 (s, 3H, OCH₃), 4.66 (s, 2H, CH₂O), 6.40 (d, 1H, H₅), 7.74 (d, 1H, H₆); ir (potassium bromide): 3210 (OH), 1640 (CO), 1610, 1270, 1220, 1170, 1050, 1020, 990, 920, 845, 830 cm⁻¹.

Anal. Calcd. for C₇H₈O₄: C, 53.85; H, 5.16. Found: C, 53.97; H, 5.06.

3-Methoxy-4*H*-pyran-4-one-2-carboxaldehyde.

2-Hydroxymethyl-3-methoxy-4*H*-pyran-4-one (700 mg) was dissolved in 50 ml of methylene chloride. Barium manganate (7.5 g) was ground to a fine powder and added immediately to the methylene chloride solution. The mixture was stirred with the aid of a magnetic stirrer for two hours at room temperature. Inorganic by-products were removed by filtration of the reaction mixture through Celite. The Celite was washed with methylene chloride; the latter solution was added to the methylene chloride filtrate previously obtained. Evaporation of methylene chloride *in vacuo* gave a white residue, which was recrystallized from cyclohexane to give 635 mg (92%) of 2-methoxy-4*H*-pyran-4-one-2-carboxaldehyde, mp

85-86°; nmr (deuteriochloroform): δ 4.16 (s, 3H, OCH₃), 6.43 (d, 1H, H₅), 7.73 (d, 1H, H₆), 10.14 (s, 1H, CHO); ir (potassium bromide): 3100 (CH), 1695 (aldehyde CO), 1655 (pyrone CO), 1575, 1460, 1430, 1395, 1275, 1225, 1200, 1175, 1050, 950, 850, 830, 750, 640 cm⁻¹.

Anal. Calcd. for C₇H₈O₄: C, 54.55; H, 3.92. Found: C, 54.58; H, 3.91.

Reaction of 1.48 g of 2-hydroxymethyl-3-methoxy-4*H*-pyran-4-one in 200 ml of acetone with 2.8 ml of Jones reagent (26.72 g chromium trioxide in 23 ml of sulfuric acid, which was added to 100 ml water) at 5-10° for 30 minutes gave 0.82 g of crude product. The latter was chromatographed on silica gel (ethyl acetate as eluent) to give 460 mg (31%) of the aldehyde, mp 85-86°.

Reaction of 1.45 g of 2-hydroxymethyl-3-methoxy-4*H*-pyran-4-one in 75 ml of methylene chloride with 5.4 g of pyridinium dichromate for 24 hours at room temperature gave a dark red reaction mixture. Extensive reaction mixture work-up was necessary, and resulted in 80 mg of aldehyde, which had an ir spectrum identical with that of the aldehyde from barium manganate oxidation.

2-Hydroxymethyl-3-(*p*-nitrobenzyloxy)-4*H*-pyran-4-one.

p-Nitrobenzyl bromide (2.58 g) and 6 g of anhydrous potassium carbonate were added to a solution of 1.5 g of α-hydroxymaltol in 100 ml reagent acetone. The mixture was heated under reflux for 14 hours. After inorganic salts were filtered off, the solvent was evaporated *in vacuo*. The residual red oily semisolid was dissolved in ethyl acetate, and petroleum ether added to turbidity. Cooling in ice gave the tan crystalline product, which was collected by filtration; yield, 1.6 g (55%). Two crystallizations from toluene gave a yellow solid, which was sufficiently pure for oxidation. The yellow solid was purified by tlc on silica gel (chloroform-acetone 10:1 as eluent). Recrystallization from chloroform gave the analytically pure substance, mp 121-123°; nmr (deuteriochloroform): δ 4.55 (s, 2H, CH₂OH), 5.27 (s, 2H, OCH₂Ar), 6.37 (d, 1H, H₅), 7.67 (d, 1H, H₆), 7.53 (d, 2H, aromatic), 8.13 (d, 2H, aromatic); ir (potassium bromide): 3210 (OH), 1635 (CO), 1600, 1560, 1515 (NO₂), 1345, 1300, 1260, 1250, 1195, 1170, 1115, 1040, 1020, 975, 920, 850, 840, 830, 740, 720, 630 cm⁻¹.

Anal. Calcd. for C₁₃H₁₁NO₆: C, 56.32; H, 4.00. Found: C, 56.52; H, 4.02.

3-(*p*-Nitrobenzyloxy)-4*H*-pyran-4-one-2-carboxaldehyde.

To 900 mg of 2-hydroxymethyl-3-(*p*-nitrobenzyloxy)-4*H*-pyran-4-one in 100 ml of methylene chloride was added 9 g of barium manganate. The reaction mixture was stirred with the aid of a magnetic stirrer for three days at room temperature. The mixture was filtered through Celite to remove inorganic products; the Celite was washed with methylene chloride,

which was combined with the initial filtrate. Evaporation of the methylene chloride *in vacuo* gave an off-white crystalline solid. Recrystallization of the latter from 15 ml of toluene gave the analytically pure aldehyde in 700 mg (78%) yield, mp 156-157°; nmr (deuteriochloroform): δ 5.61 (s, 2H, OCH₂Ar), 6.51 (d, 1H, H₅), 7.69 (d, 1H, H₆), 7.58 (d, 2H, aromatic), 8.21 (d, 2H, aromatic); ir (potassium bromide): 1700 (aldehyde CO), 1645 (pyrone CO), 1600, 1570, 1515 (NO₂), 1440, 1355, 1265, 1220, 1205, 1195, 1110, 1055, 965, 955, 865, 850, 835, 740, 695, 625 cm⁻¹.

Anal. Calcd. for C₁₃H₉NO₆: C, 56.72; H, 3.30. Found: C, 56.08; H, 3.54.

3-Hydroxy-4*H*-pyran-4-one-2-carboxaldehyde.

A 1.8 g quantity of 3-(*p*-nitrobenzyloxy)-4*H*-pyran-4-one-2-carboxaldehyde was dissolved in 25 ml of 40% hydrobromic acid-acetic acid solution, without heating, in a glass-stoppered Erlenmeyer flask. The flask was stoppered and allowed to stand at room temperature for four weeks. The crystalline product present was collected by filtration and recrystallized from 20 ml of glacial acetic acid, yield (two crops) 620 mg (61%), mp 113° (marked decomposition); nmr (DMSO-*d*₆): δ 6.48 (d, 1H, H₅), 8.15 (d, 1H, H₆), 10.13 (s, 1H, CHO); ir (potassium bromide): 3090 (OH), 1680 (aldehyde CO), 1635 (pyrone CO), 1480, 1415, 1290, 1200, 1065, 980, 855, 845, 750, 640 cm⁻¹.

Anal. Calcd. for C₆H₆O₄: C, 51.43; H, 2.88. Found: C, 51.32; H, 2.85.

3-Methoxy-4*H*-pyran-4-one-2-carboxylic Acid.

To a solution of 0.49 g silver nitrate in one ml of water was added a

solution of 0.233 g of sodium hydroxide in one ml of water. The resulting silver oxide suspension was cooled in ice, and 205 mg of 3-methoxy-4H-pyran-4-one-2-carboxaldehyde added. After five minutes, the silver salts were filtered off, and the filtrate was acidified with hydrochloric acid. Upon standing at room temperature, there precipitated 97 mg (43%) of 3-methoxy-4H-pyran-4-one-2-carboxylic acid, mp 202-203°, with decomposition at 198°; nmr (DMSO-d₆): δ 3.82 (s, 3H, OCH₃), 6.45 (d, 1H, H₅), 8.12 (d, 1H, H₆); ir (potassium bromide): 3100 (CH), 2850 (OH), 2500 (OH), 1930, 1730 (carboxyl CO), 1635 (pyrone CO), 1590, 1490, 1440, 1305, 1260, 1235, 1165, 975, 855, 825, 800, 735, 650 cm⁻¹.

Anal. Calcd. for C₇H₆O₅: C, 49.42; H, 3.56. Found: C, 49.16; H, 3.53.

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