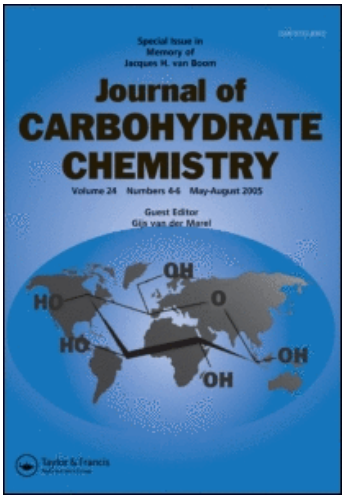

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SYNTHESIS AND CHARACTERIZATION OF THE NATURALLY OCCURRING MONOCYCLIC γ-PYRONE GLUCOSIDES

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ABSTRACT

β-D-Glucosides of pyromeconic acid (3-hydroxy-4-oxo-4H-pyran), maltol (3-hydroxy-2-methyl-4-oxo-4H-pyran) and α-hydroxymaltol (3-hydroxy-2-hydroxymethyl-4-oxo-4H-pyran) were synthesized in one pot by reaction of stoichiometric amounts of acetobromoglucose and preformed hydroxypyrone anion followed by catalytic deacetylation with methanolic KOH. Products were identified and characterized by comparison of mp and molar rotation with literature, and by FAB-MS, negative ferric chloride test, and H-1 and C-13 NMR. All glycosides were levorotatory, beta and gave recognizable pseudo- molecular ions.

INTRODUCTION

Although complex 4-oxo-4H-pyran (4H-pyran-4-one; γ-pyrone) derivatives, e.g. flavonoids,[1] are quite common in nature, simple monocyclic pyrone derivatives are substantially less so.[2] Therefore, it is not surprising that monocyclic pyrone glycosides are equally uncommon. To date only three such materials have been found to occur naturally.

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Pyromeconic acid β-D-glucoside (IUPAC:4-oxo-4-H-pyran-3-yl-β-D-glucopyranoside, C.A. Registry # 5219-76-0), 8, has been found in several species of Erigeron (fleabane, ragweed).[3,4,5] It has an intensely bitter taste[3] and central nervous system activity.[4] The first study[3] also noted the lack of free aglycon in the species that were studied. It was concluded that earlier reports of the free aglycon were due to decomposition of the glucoside during sample handling.

Maltol β-D-glucoside (IUPAC: 2-methyl-4-oxo-4H-pyran-3-yl-β-D-glucopyranoside, C. A. Registry # 20847-13-6), 9,[3,6] has been found in a number of Caryophyllaceae species, particularly Dianthus (pinks).[3] It has also been found in the larch Larix europaea DC and the Canadian fir Tsuga canadensis, in both of which the free aglycon was thought to occur alone.[3] The aglycon and glucoside coexist in several species of Caryophyllaceae.[3]

α-Hydroxymaltol β-D-glucoside (IUPAC:2-hydroxymethyl-4-oxo-4H-pyran-3-yl-β-D-glucopyranoside, C. A. Registry # 66543-09-3), 10, has been found in the fernbrake Petris inaequalis Baker var. aequata (Miq.) Tagawa.[7] This is the first reported occurrence of either α-hydroxymaltol or its glucoside in nature.

One previous effort to synthesize pyromeconic acid β-D-glucoside[8] was unsuccessful under a variety of reaction conditions. One maltol derivative, the β-D-ribofuranoside, has been prepared from tribenzoylribosyl bromide with mercuric cyanide as catalyst.[9]

RESULTS AND DISCUSSION

The experiences of Jerzmanowska and Markiewicz[8] and in this laboratory have demonstrated the sensitivity of hydroxypyrones to oxidizing metals, esterification conditions and competing nucleophiles. Furthermore, chelation of 4- and 6- coordinate metal ions by

hydroxypyrones appears to be preferred over glycosidation using chelating metals as catalysts. In no case was the glycoside obtained when such metals were used as catalysts. Thus, synthesis of the title compounds was possible only by a modififed Michael synthesis inspired by DeBruyne and his co-workers[10] (FIG.1). It involved reaction of stoichiometric amounts of methanolic hydroxypyrone anion (preformed by reaction of the aglycon--1, 2, 3) and acetobromoglucose, 4, under anhydrous conditions. This step was followed directly by catalytic deacetylation of the unisolated tetraacetyl glucoside (5, 6, 7), quenching with ion exchange resin, and gravity column chromatographic purification. On TLC employing silica gel containing a fluorescent indicator desired glucosides 8, 9, and 10 were found to quench the fluorescence due to short wave UV light and char with ethanolic sulfuric acid, whereas the aglycons quenched the fluorescence but did not char, and glycosyl by-products charred but did not quench fluorescence. In this way preliminary identification of both pyrone glucosides and by-products could be made in both the crude reaction mixture and purified fractions. The R_f's of these compounds in 5:2 CH_2Cl_2-MeOH were: 8 = 0.34, 9 = 0.36, 10 = 0.29. All three materials were soluble in water and DMSO, and moderately soluble in lower alcohols.

The synthetic products were further identified by comparison of molar rotations and melting points with literature values.[3,7] In Table 1, experimental melting points of the pyromeconic acid and α-hydroxymaltol derivatives (8 and 10) agree well with literature values. However, the reported melting point of the maltol glucoside, 9, from Dianthus, is quite broad, possibly indicating an impure sample. Thus, comparison with the melting point of the synthetic product has limited utility. However, the molar rotation of synthetic 9 does agree fairly well with the literature value. Similar

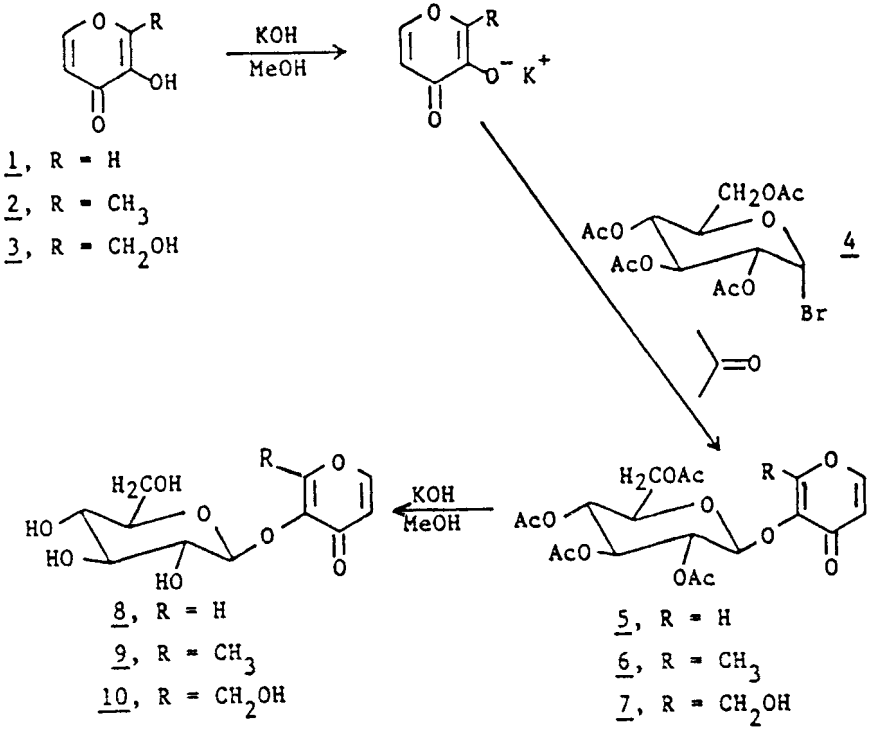


FIG. 1. SYNTHESIS OF MONOCYCLIC PYRONE GLUCOSIDES.

TABLE 1

COMPARISON OF LITERATURE AND EXPERIMENTAL VALUES OF PYRONE GLUCOSIDES

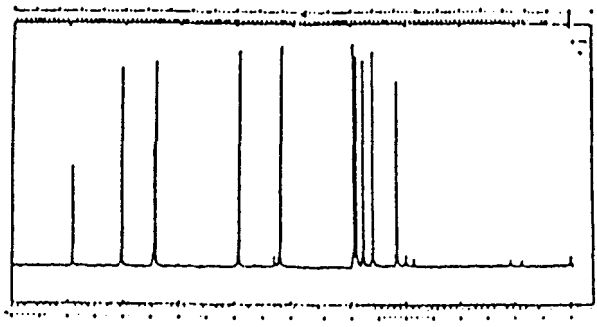
	Melting Point		Molar Rotation		
	Lit.	Exptl.	Literature	Experimental	Ref
8	196-201	195-198	-112°(1.3%,H_2O)	-94.69(4.5%,H_2O)	3
9	120-132	115-118	-52.8°(H_2O)[a]	-54.07(5.2%,H_2O)	3
10	148	149-152	-39.3°(2.9%,H_2O)	-38.8°(4.8%,H_2O)	7

a. concentration not reported

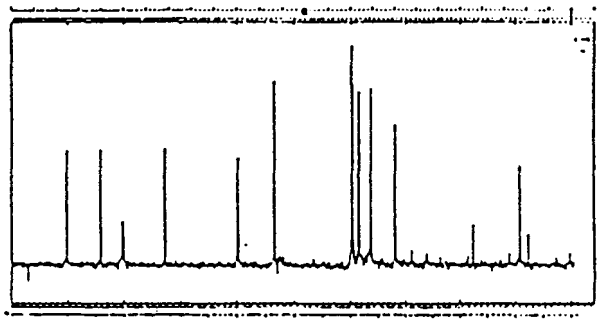
agreement was found between literature and experimental $[\alpha]_D^{20}$ values for 10. The rotation for synthetic 8 agrees with the reported value in direction but is of considerably smaller magnitude, and may be attributable to concentration effects.

Elemental analysis of the synthetic materials was consistent with crystallization of 8 and 9 as hemihydrates. The latter agrees with the literature report.[3] Furthermore, the analysis of α-hydroxymaltol glucoside showed it to crystallize as the monohydrate. The molecular weights of the anhydrous products were confirmed by fast-atom bombardment mass spectrometry (FAB-MS) in a glycerol matrix. All three samples gave readily recognizable pseudomolecular ions. For several samples, this analysis also showed the presence of contaminating methyl β-D-glucoside (MH^+ = 185).

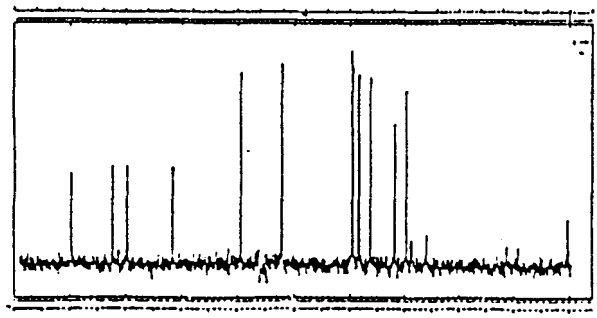
The structure and anomeric configuration of 8, 9, and 10 were confirmed by carbon-13 NMR (FIG.2) The chemical shifts of the pyrone and sugar regions (TABLE 2) agreed quite well with published values for the aglyconic hydroxypyrones[11] and various sugar derivatives.[12,13,14] Comparison with the ^{13}C-NMR spectrum of a 3-hydroxyflavone glucoside[15] also showed distinct similarities, particularly in the sugar region (see FIG.3). As can be seen from FIG. 3a and b., the sugar regions of p-nitrophenyl α- and β-D-glucosides show enough difference, most notably between 70 and 80 ppm, to make determination of anomeric configuration comparatively easy. Furthermore, as can be seen in FIG. 3b., c. & d., the peak pattern in the region from 70 to 80 ppm is not very sensitive to aglycon structure; nearly identical patterns are observed for carbons 2, 3, 4 and 5 of glucose in the p-nitrophenyl β-D-glucoside, kaempferol (3,5,7,4'-tetrahydroxyflavone)-3-O-, and pyromeconic acid β-D-glucosides,[13] as well as in methyl β-D-glucoside (not shown).



a. Pyromeconic acid glucoside. Compound 8.



b. Maltol glucoside. Compound 9.

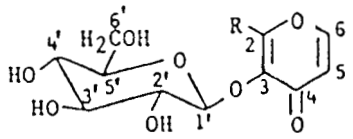


c. α-Hydroxymaltol glucoside. Compound 10.

FIG. 2. Carbon-13 spectra of title compounds.

TABLE 2

CARBON-13 CHEMICAL SHIFT ASSIGNMENTS.



	8		9		10	
C-	ppm	Hz	ppm	Hz	ppm	Hz
2	146.9	7387.3	159.2	8008.5	159.8	8039.4
3	147.6	7426.6	144.2	7253.6	143.6	7221.9
4	176.9	8900.2	179.0	9006.0	179.7	9042.8
5	117.2	6894.2	118.3	5953.9	119.1	5990.0
6	159.6	8025.8	166.9	8396.5	164.9	8928.5
1'	102.9	5177.1	105.7	5319.2	104.8	5772.5
2'	74.8	3762.8	75.9	3820.3	76.0	3824.3
3'	77.2	3880.7	78.1	3930.1	78.2	3933.0
4'	71.1	3576.1	71.6	3601.9	71.9	3616.7
5'	78.1	3929.8	78.8	3960.6	78.7	3960.0
6'	62.5	3143.9	62.9	3163.4	63.1	3172.6
R	-	--	17.7(CH_3)	889.4	58.8(CH_2OH)	2959.6

It is emphasized that, while these are not the first successful syntheses of monocyclic γ-pyrone glycosides, the experimental conditions used in this laboratory give somewhat higher yields of free glycosides than those previously reported[9] for the preparation of maltol riboside (9.96% overall for the riboside *vs.* 12.6% for maltol glucoside and 20.1% for pyromeconic acid glucoside). Prior to obtaining the results described herein, repeated attempts were made to synthesize 8 by reaction of pyromeconic acid with acetobromoglucose in presence of mercuric cyanide as catalyst. Seven to eight products were obtained, which reduced any yield of 8 below acceptable levels. It is possible that competing reaction by mercuric cyanide at $C_{(2)}$ and/or at the enolic hydroxyl group of pyromeconic acid occurs.[16]

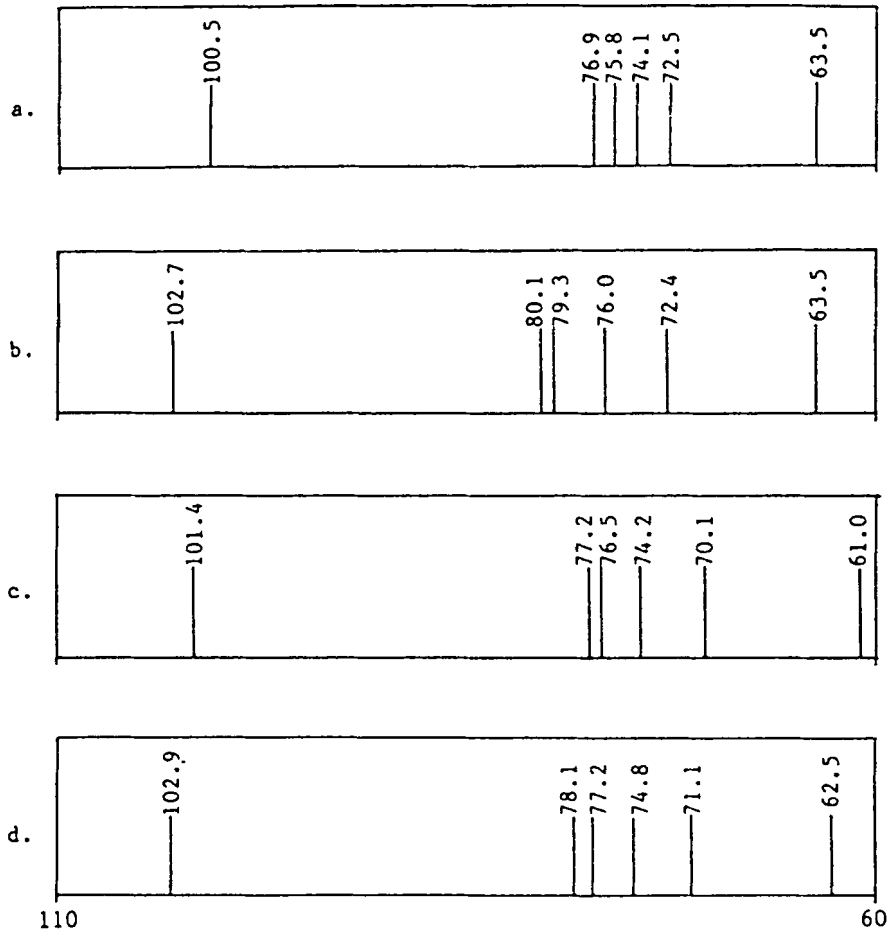


FIG. 3. Carbon-13 chemical shifts of the sugar region of representative glucosides:

a. p-Nitrophenyl-α-D-glucopyranoside;

b. p-Nitrophenyl-β-D-glucopyranoside;

c. Kaempferol-3-O-β-D-glucopyranoside;

d. Pyromeconic acid β-D-glucopyranoside.

EXPERIMENTAL

General Materials and Methods. All solvents were reagent grade, stored over 4 Å molecular sieve. TLC was performed on 10-cm Mylar-backed Merck silica gel $60F_{254}$ plates. Spots were visualized with 10% H_2SO_4 in 95% ethanol, heated for 30 min at 105°C. Purification of

crude reaction mixtures was on a 40 x 2 cm column of Baker or Merck silica gel. Fraction volumes were 20-25 mL, collected with an ISCO Model 1850 fraction collector.

Melting points were taken on a Mel-Temp apparatus, and are corrected. Specific rotations were obtained in water on a Perkin-Elmer 141 Polarimeter. All NMR spectroscopy was done on a Varian XL-200 superconducting instrument, using the 5mm broadband probe. Solvent was D_2O; reference was sodium 3-(trimethylsilyl)-n-propyl sulfate. FAB mass spectra were taken on an AEI MS-50TA instrument.

4-Oxo-4H-pyran-3-yl-β-D-glucopyranoside (Pyromeconic Acid Glucoside). [MW 274 (8)]. A solution of 0.56g pyromeconic acid in 11 mL of 2.5% methanolic KOH (0.00495 mole KOH) was added dropwise to a solution of 2.055g acetobromoglucose (0.555 mole) in 20 mL dry acetone. The resulting mixture was stirred for 8 hours, after which 2.5 mL of 5% methanolic KOH (0.002 mole KOH) was added. The reaction was allowed to proceed for an additional 36 hours, then quenched with Amberlite IR-120H ion-exchange resin. The resin was filtered off, and the solvent removed under reduced pressure when inorganic salts precipitated. The resulting yellow syrup was dissolved in 1.5 mL 1:1 MeOH-CH_2Cl_2, and chromatographed on a 40-cm silica gel column with 10% MeOH in CH_2Cl_2 as eluent. No effort was made to remove the inorganic materials from the loaded solution. The fractions which were identified by TLC with 5:2 CH_2Cl_2-MeOH, R_f = 0.34, as containing the desired glucoside were pooled and the solvent air-evaporated. The off-white material thus obtained was recrystallized from 95% ethanol (this step was found later to be unnecessary), and dried in vacuo over NaOH. Average yield was 275 mg (20.1%); mp 195-198°C, $[\alpha]_D^{20}$ (4.5%, H_2O)-94.6940; MH^+ 275. ^{13}C-NMR data are reported in TABLE 2.

Anal. Calcd for $C_{11}H_{14}O_8 \cdot 1/2\ H_2O$: C, 46.64; H, 5.30. Found: C, 46.67; H, 5.39.

2-Methyl-4-oxo-4H-pyran-3-yl-β-D-glucopyranoside (Maltol Glucoside) [MW 228 (9)]. Maltol (0.63g; 0.005 mole) and 2.055g acetobromoglucose were treated as above, except that 5% MeOH in CH_2Cl_2 was used as column eluent. Solvent from the pooled fractions was air-evaporated to 20% of initial volume, and the remainder removed in a vacuum desiccator over NaOH, then $CaSO_4$. The product, R_f 0.36, mp 115-8°C, solidified during this treatment. The yield was 0.181g, (12.6%); $[\alpha]_D^{20}$ (5.2%, H_2O)-54.074°, MH^+ 289. ^{13}C-NMR data are reported in TABLE 2.

Anal. Calcd for $C_{12}H_{16}O_8 \cdot 1/2\ H_2O$: C, 48.48; H, 5.72. Found: C, 47.91; H, 5.98.

2-Hydroxymethyl-4-oxo-4H-pyran-3-yl-β-D-glucopyranoside (α-Hydroxymaltol Glucoside) [MW 304 (10)]. α-Hydroxymaltol (0.71g; 0.005 mole) and 2.055g acetobromoglucose were treated as above for pyromeconic acid glucoside, using 15% MeOH in CH_2Cl_2 as column eluent. The product crystallized during air-evaporation of the pooled fractions; R_f 0.29; mp 149-52°C. The yield was 0.173g (11.4%); $[\alpha]_D^{20}$ (4.8%, H_2O)-38.81; MH^+ 305. ^{13}C-NMR data are reported in TABLE 2.

Anal. Calcd for $C_{12}H_{16}O_9 \cdot H_2O$: C, 44.72; H, 5.59. Found: C, 44.31; H, 5.46.

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