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SYNTHESIS OF METHYL 4,6-*O*-METHYLENE-D-GLYCOPYRANOSIDES*†

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ABSTRACT

Methyl 4,6-*O*-methylene-D-glycopyranosides having the α-D-*altro*, α- and β-D-*gluco*, α-D-*manno*, and α-D-*galacto* configurations were prepared in 3.4 to 27.4% yields by condensing formaldehyde from 1,3,5-trioxane with the methyl glycosides in anhydrous 1,4-dioxane at 95° with boron trifluoride as the catalyst. A crystalline methyl 2,3:4,6-di-*O*-methylene-α-D-mannopyranoside was also isolated. Crystalline methyl 4,6-*O*-methylene 2,3-di-*O*-*p*-tolylsulfonyl-α-D-galacto- and α-D-glucopyranosides were prepared in 78 and 54.4% yields. N.m.r. coupling constants of the 2,3-di-*O*-acetyl derivatives of the 4,6-*O*-methylene glycosides were used to establish the *C1*(D) conformation for each derivative.

INTRODUCTION

Various aldehydes and ketones have been condensed with sugars and glycosides to form many cyclic acetal derivatives. However, the reviews of De Belder[1] and Brady[2] indicate that few formaldehyde (methylene) acetals of sugars and glycosides have been structurally characterized. Condensations with formaldehyde have produced complex mixtures containing mono- and di-methylene acetals, having either 1,3-dioxane or 1,3-dioxolane rings, or both, and oxidodimethylene acetals having seven-membered rings[1–4].

To elucidate the stereochemical requirements for a glycol system that elicits a sweet taste, we have prepared five new, crystalline, water-soluble, methyl 4,6-*O*-methylene-D-aldohexopyranosides. Correlations between the structures of these glycosides and their sweet and bitter taste-responses will be reported elsewhere.

RESULTS AND DISCUSSION

Several variations of the preparative procedure were investigated. The complexity of the reaction mixtures was decreased by using 1,3,5-trioxane instead of para-

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TABLE I

CHEMICAL-SHIFT DATA[a] (τ-VALUES) FOR SOLUTIONS OF METHYL 2,3-DI-*O*-ACETYL-4,6-*O*-METHYLENE-D-GLYCOPYRANOSIDES AND METHYL 2,3:4,6-DI-*O*-METHYLENE-α-D-MANNOPYRANOSIDE IN BENZENE-d_6

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*H-7*	*H-7'*	*2,3-OCH$_2$O–*		*OCH$_3$*	*OCOCH$_3$*	
										H-8	*H-8'*			
8	5.18 (5.01)[b]	5.75q	6.28c		6.02q	6.44q		5.14d (4.97)	5.77d (5.37)	5.02d (4.78)	5.31d (5.50)	7.11s		
9	5.17d	5.01q	4.11q	6.85q	6.30c	6.06q	6.86q	5.26d	5.84d			7.11s	8.26s	8.35s
10	5.89d	4.79q	4.58q		6.05c			5.23d	5.86d			6.84s	8.25s	
11	5.59d	4.44c	4.30c		6.69c			5.12d	5.70d			7.15s	8.27s	8.32s
12	4.92d	4.33q	4.54q				6.70c	5.03d	5.74d			7.00s	8.27s	8.32s
13	5.47	4.80c	4.57q	5.72c	5.95c	6.36q	6.75q	5.13d	5.70d			7.00s	8.26s	8.44s

[a]From spectra measured at 100 MHz; peak multiplicities: s, singlet; d, doublet; t, triplet; q, quartet, and c, complex multiplet. [b]Spectral assignments in chloroform-*d*.

formaldehyde or formalin. Pure, dry 1,4-dioxane[5] proved to be a more suitable reaction-medium than diethyl ether[6], dimethyl sulfoxide[7], or acetonitrile. Among the catalysts examined with 1,3,5-trioxane, boron trifluoride etherate[7] gave higher yields of the desired 4,6-methylene acetals than did concentrated sulfuric acid or ethanesulfonic acid. In 1,4-dioxane, the optimum reaction-temperature was 95°; at the refluxing temperature, much of the formaldehyde distilled and polymerized in the condenser. Reactions prolonged for more than 5 h at 95° produced more by-products and polymers with no increase in yield of the desired monoacetal. Methyl 4,6-*O*-methylene-α-D-altropyranoside (7) was prepared from the corresponding glucoside by adopting Richtmyer's procedure for the analogous 4,6-*O*-benzylidene derivatives[8].

TABLE II

FIRST-ORDER COUPLING CONSTANTS (Hz)[a] OF METHYL 2,3-DI-*O*-ACETYL-4,6-*O*-METHYLENE-D-GLYCOPYRANOSIDES AND METHYL 2,3:4,6-DI-*O*-METHYLENE-α-D-MANNOPYRANOSIDE IN BENZENE-d_6

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{6,6'}$	$J_{7,7'}$
8	<0.4	7.4	—	—	10.0	6.2
9	3.8 (3.6)[b]	10.0 (9.8)	10.0 (8.5)	9.7	—	6.0
10	7.8	—	—	—	—	6.0
11	1.4 (1.2)[b]	—	—	—		6.0
12	3.6 (3.5)[c]	10.8	—	—	9.0	6.4
13	<0.4 (0.9)[b]	3.0 (2.9)	3.0 (2.9)	—	10.0	6.0

[a]From spectra measured at 100 MHz. [b]Reported by B. Coxon[9]. [c]Reported by N. Baggett *et al.*[14].

Coxon[9] compared n.m.r. spectra of 36 methyl 4,6-*O*-benzylidene-α-D-glycopyranosides and reported that the pyranoid rings existed exclusively in the *C1*(D) conformation. Our n.m.r. data (Tables I and II) on methyl 2,3-di-*O*-acetyl-4,6-*O*-methylene-D-glycopyranosides agree closely with corresponding data of Coxon; hence, our compounds can be concluded to have the *C1*(D) conformation and a corresponding 4,6-*O*-substitution of hydroxyl groups. I.r. absorptions in carbon tetra-

TABLE III

I.R. ABSORPTION FREQUENCY (cm^{-1}) AND INTRAMOLECULAR HYDROGEN-BONDING PARAMETER $\Delta\nu$ (cm^{-1}) OF METHYL 4,6-*O*-METHYLENE-D-GLYCOPYRANOSIDES IN CARBON TETRACHLORIDE

Configuration	*Free-OH*	*Bonded-OH*	$\Delta\nu$
α-altro	3630 (3630)[a]	3600 (3601), 3550 (3556)	30, 80
α-galacto	3640 (3617)	3610[b] (3591)	30
α-gluco	3610 (3609)	3580 (3578)	30
β-gluco	3615 (3614)	3575 (3603)	40
α-manno	3615 (3611)	3580 (3597)	35

[a]Values in parentheses were reported by H. Spedding[10]. [b]Weak shoulder at *ca.* 3605 cm^{-1}.

chloride (Table III) of the free and hydrogen-bonded hydroxyl groups also corresponded closely to those reported by Spedding[10] for methyl 4,6-*O*-benzylidene-hexopyranosides in the *C1*(D) conformation.

Only the galactopyranoside derivative would be expected to have an axially oriented 1,3-dioxane ring. The chemical shift of H-7 (the acetal methylene group) in **12** (Table I) is farther downfield than that of H-7 in the other derivatives, and the difference in chemical shifts of H-7 and H-7′ ($\Delta = 0.71$), is significantly different from the corresponding differences (av. $\Delta = 0.575$) for the other α-D-hexopyranosides **9**, **10**, **11**, and **13** having equatorially oriented 1,3-dioxane rings.

Tosylation of the methyl 4,6-*O*-methylene-α-D-gluco- and- α-D-galactopyranosides under the same conditions showed a much faster reaction for the galactoside. After 3 days at 25°, the 2,3-di-*O*-tosyl galactoside was isolated in 78% yield, whereas the glucoside gave equal amounts of mono and 2,3-di-*O*-tosyl derivatives. Even after 9 days, only a 42% yield of the 2,3-di-*O*-tosyl glucoside could be isolated. This difference in rates probably can be attributed to decreased steric hindrance in the galactoside derivative because of the axially oriented 1,3-dioxane ring.

Chromatographic evidence for 2,3:4,6-di-*O*-methylene derivatives was found in each of the reaction mixtures; however, only methyl 2,3:4,6-di-*O*-methylene-α-D-mannoside (**8**) crystallized spontaneously from the mother liquors. Assignments for the anomeric (τ 5.01) and 2,3-*O*-methylene protons of **8** at τ 4.78 and 5.50, respectively, differ from those previously reported by Bhattacharjee and Gorin[11]. A low coupling-constant ($J_{8,8'}$ 0.7 Hz) for the geminal methylene protons in the fused 1,3-dioxolane ring on C-2 and C-3 of **8** was observed. Crabb and Cookson[12] reported coupling constants of this order for the methylene protons in fused 1,3-dioxolane rings. The n.m.r. data for compound **8** (Tables I and II) also indicate a *C1*(D) conformation for the pyranoside ring.

EXPERIMENTAL

General. — All reactions were monitored, and purity of all derivatives was established by t.l.c. T.l.c. was performed on EM Reagent Silica Gel G (Brinkmann Instruments Inc.) with air-dried plates of 0.25 mm thickness. The spots were detected by spraying with 5% ethanolic sulfuric acid and charring. I.r. spectra were determined in dilute carbon tetrachloride solutions ($c < 1\%$) with a Perkin–Elmer Model 621 spectrophotometer. N.m.r. spectra were recorded with a Varian Model HA-100 spectrometer; chemical shifts were assigned by spin-decoupling experiments and referred to internal tetramethylsilane. Samples were dried in the presence of phosphorus pentaoxide under diminished pressure for 24–48 h at room temperature before analysis. The melting points, determined in capillary tubes, are not corrected.

Methyl 4,6-O-methylene-D-glycopyranosides (**1–4**). — The methyl D-glycopyranosides (0.2 mole) were finely powdered in a mortar and stirred with 1,3,5-trioxane (10.5 g; 0.35 mole of formaldehyde) and purified (dry) 1,4-dioxane (400 ml) in a reflux apparatus. Boron trifluoride etherate (2 ml) was added, and

the stirred slurry was heated for 5 h at 95°. Sodium hydrogen carbonate was added and the slurry was stirred overnight. Solids, including insoluble polymeric material, were filtered off and washed twice with fresh 1,4-dioxane; the combined filtrates were evaporated under diminished pressure. T.l.c. examination of the syrupy mixtures [acetone–petroleum ether (b.p. 37.6–51.2°)–toluene, 7:3:2] disclosed only one major component, several minor components, and unreacted starting material. The syrupy mixture was dissolved in water and continuously extracted (36 h) with chloroform. The chloroform extract containing methyl 4,6-*O*-methylene derivatives and several minor components was dried with anhydrous sodium sulfate (powder) and evaporated under diminished pressure. The methyl 4,6-*O*-methylene derivatives were crystallized from ethyl acetate and ethyl acetate–hexane.

*Methyl 4,6-*O*-methylene α-*D*-glucopyranoside* (**1**). — A 5.6 g (13.6%) yield of product was obtained by crystallization from ethyl acetate, m.p. 127–128°, $[\alpha]_D^{20}$ +120.5° (*c* 1, water); n.m.r. data (chloroform-*d*): τ 5.78, $J_{1,2}$ 3.8 Hz (H-1), 6.57 (OMe), 5.04 and 5.43, $J_{7,7'}$ 6.2 Hz (4,6-*O*-methylene ring protons), and 7.57 (hydroxyl protons).

Anal. Calc. for $C_8H_{14}O_6$: C, 46.6; H, 6.84. Found: C, 46.9; H, 6.92.

*Methyl 4,6-*O*-methylene β-*D*-glucopyranoside* (**2**). — A 5.4 g (13.2%) yield was obtained by crystallization from ethyl acetate–hexane, m.p. 171–172°, $[\alpha]_D^{25}$ −77° (*c* 0.5, water); n.m.r. data (0.1 acetone-d_6:3CD_3CN): τ 5.78, $J_{1,2}$ 7.8 Hz (H-1), 6.57 (OMe), 5.04 and 5.43, $J_{7,7'}$ 6.2 Hz (4,6-*O*-methylene ring protons), and 7.57 (hydroxyl protons).

Anal. Calc. for $C_8H_{14}O_6$: C, 46.6; H, 6.84. Found: C, 46.6; H, 6.95.

*Methyl 4,6-*O*-methylene α-*D*-mannopyranoside* (**3**). — Crystallization from ethyl acetate–hexane produced 4.5 g (10.9%), m.p. 122–123°, $[\alpha]_D^{20}$ +58° (*c* 1, water); n.m.r. data (chloroform-*d*): τ 5.30, $J_{1,2}$ 1.7 Hz (H-1), 6.65 (OMe), 4.94 and 5.36, $J_{7,7'}$ 6.0 Hz (4,6-*O*-methylene ring protons), and 6.38 (hydroxyl protons).

Anal. Calc. for $C_8H_{14}O_6$: C, 46.6; H, 6.83. Found: C, 46.7; H, 6.90.

*Methyl 4,6-*O*-methylene α-*D*-galactopyranoside* (**4**). — A 1.6 g (3.4%) yield was obtained by crystallization from ethyl acetate–hexane, m.p. 222–223°, $[\alpha]_D^{20}$ +182° (*c* 1, water); n.m.r. data (dimethyl sulfoxide-d_6): τ 5.36, $J_{1,2}$ 3.6 Hz (H-1), 6.74 (OMe), 5.03 and 5.37, $J_{7,7'}$ 6.0 Hz (4,6-*O*-methylene ring protons); and 6.39 (hydroxyl protons).

Anal. Calc. for $C_8H_{14}O_6$: C, 46.6; H, 6.90. Found: C, 46.6; H, 6.84.

*Methyl 4,6-*O*-methylene-2,3-di-*O*-p-tolylsulfonyl-α-*D*-glucopyranoside* (**5**). — Fifty g of methyl 4,6-*O*-methylene-α-D-glucopyranoside in 350 ml of dry pyridine, with a 50% excess of *p*-toluenesulfonyl chloride (100 g) was boiled for 24 h under reflux. The product was obtained by pouring the mixture onto ice, extracting with chloroform, and removing pyridine by repeated evaporation of toluene from the nonvolatile product. The residue was redissolved in chloroform and treated with activated charcoal and Celite 535 to give a yield of 67.8 g (54.4%) of **5** after crystallization from chloroform–hexane; m.p. 188–189°, $(\alpha]_D^{20}$ +60° (*c* 1, chloroform). N.m.r. data (chloroform-*d*): τ 5.09, $J_{1,2}$ 4.0 and $J_{1,3}$ 1.4 Hz (second-order multiplets[13],

H-1), τ 6.68 (OMe), 5.22 and 5.66, $J_{7,7'}$ 6.0 Hz (4,6-*O*-methylene ring protons), 7.59 (tolyl methyl protons), and 2.30–2.74 (aromatic protons).

Anal. Calc. for $C_{22}H_{24}O_{10}S_2$: C, 51.6; H, 4.72. Found: C, 51.6; H, 4.95.

*Methyl 2,3-anhydro-4,6-*O*-methylene α-*D*-allopyranoside* (**6**). — By the procedure of Richtmyer[8], an 18 g (72%) yield was obtained from **5**, by crystallization from chloroform–hexane; m.p. 162–163°, $[\alpha]_D^{20}$ +127° (*c* 5, chloroform); n.m.r. data (chloroform-*d*): τ 5.18, $J_{1,2}$ 1.8 and $J_{1,3}$ 1.3 Hz (second-order multiplets[13], H-1), 6.59 (OMe), 4.93 and 5.36, $J_{7,7'}$ 6.0 Hz (4,6-*O*-methylene ring protons).

Anal. Calc. for $C_8H_{12}O_5$: C, 50.8; H, 6.83. Found: C, 51.1; H, 6.53.

*Methyl 4,6-*O*-methylene α-*D*-altropyranoside* (**7**). — By the procedure of Richtmyer[8], a 5.36 g (27.4%) yield was obtained after crystallization from ethyl acetate; m.p. 114–115°, $[\alpha]_D^{20}$ +124° (*c* 0.5, water); n.m.r. data (dimethyl sulfoxide-d_6): τ 5.59 (broad singlet, $J_{1,2}$ <0.4 Hz, H-1), 6.76 (OMe), 4.76 and 5.46 (OH), 5.06 and 5.38, $J_{7,7'}$ 6.0 Hz (4,6-O-methylene ring protons).

Anal. Calc. for $C_8H_{14}O_6$: C, 46.6; H, 6.84. Found: C, 46.6; H, 6.99.

*Methyl 2,3:4,6-di-*O*-methylene-α-*D*-mannopyranoside* (**8**). — A 13.8 mg (0.62%) yield of product was obtained after crystallization from ethyl acetate. The dimethylene acetal was obtained from the mother liquors of crystallization of the monomethylene acetal. The crystallization solvent (mother liquor) was evaporated and the syrup redissolved in water, to afford a crude, crystalline product. The crude product was recrystallized from ethyl acetate; m.p. 144–145°, $[\alpha]_D^{20}$ +19.4° (*c* 0.33, chloroform); the i.r. spectrum indicated the absence of hydroxyl groups.

Anal. Calc. for $C_9H_{14}O_6$: C, 49.6; H, 6.46. Found: C, 49.3; H, 6.49.

TABLE IV

METHYL 2,3-DI-*O*-ACETYL-4,6-*O*-METHYLENE-D-GLYCOPYRANOSIDES[a]

Product configuration	*Yield* (%)	*M.p.* (°C)	$[\alpha]_D^{20}$ (*CHCl*$_3$)	*Found*	
				C	*H*
9 α-*gluco*[b]	59.3	118–119	+132°, *c* 0.5	49.8	6.25
10 β-*gluco*	56.0	169–170	−65°, *c* 0.5	49.7	6.16
11 α-*manno*	47.3	168–169	+43.8°, *c* 1	49.9	6.38
12 α-*galacto*[b]	57.9	109–110	+192°, *c* 0.5	50.0	6.21
13 α-*altro*[c]	79.2	137–138	+74°, *c* 0.5	49.5	5.98

[a] *Anal.* Calc. for $C_{12}H_{18}O_8$: C, 49.7; H, 6.25. [b] Ethyl acetate–hexane. [c] Crystallized from ethyl acetate–petroleum ether.

Peracetylation (see Table IV). — One gram of each (0.5 g of altroside) methyl 4,6-*O*-methylene-D-glycopyranoside was dissolved in 25 ml of dried pyridine containing acetic anhydride (2 ml), and the solutions were heated for 10 min on a steam bath, and kept overnight at room temperature. The solutions were then concentrated by evaporation with toluene under diminished pressure.

*Methyl 4,6-*O*-methylene-2,3-di-*O*-p-tolysulfonyl-α-D-galactopyranoside* (**14**). — By the procedure of Richtmyer[8], after 3 days, a 1.95 g (78%) yield of product was obtained by crystallization from chloroform–hexane; m.p. 167–168°, $[\alpha]_D^{20}$ +99° (*c* 1, chloroform); n.m.r. data (benzene-d_6): τ 4.86, $J_{1,2}$ 3.4 and $J_{1,3}$ 1.6 Hz (second-order multiplets[13], H-1), 7.03 (OMe), 5.19 and 5.85, $J_{7,7'}$ 6.0 Hz (4,6-*O*-methylene ring protons), 8.13 (tolyl methyl protons), and 2.30–3.25 (aromatic protons).

*Methyl 4,6-*O*-methylene-2,3-di-*O*-p-tolylsulfonyl-α-D-glucopyranoside* (**5**). — T.l.c. monitoring (10% acetone–toluene) of the reaction, conducted exactly as for **14**, showed approximately equal amounts of mono- and 2,3-di-*O*-tosyl derivatives after 4 days. After 9 days at room temperature, these products remained and were separated by dry-column chromatography on Silica Gel G (3% water) with 10% acetone–toluene as eluant. A mono-*O*-tosyl derivative (95.2 mg, 5%) was crystallized from chloroform–hexane; m.p. 181–182°, $[\alpha]_D^{20}$ +84° (*c* 1, chloroform); the i.r. spectrum showed a strong hydroxyl band at 3600 cm^{-1}, whereas the 2,3-di-*O*-tosyl derivative **5**, 1.2 g (42%) showed no hydroxyl band.

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REFERENCES

1 A. N. De Belder, *Advan. Carbohyd. Chem.*, 20 (1965) 219.
2 R. F. Brady, Jr., *Advan. Carbohyd. Chem. Biochem.*, 26 (1971) 197.
3 P. Andrews, L. Hough, and J. K. N. Jones, *J. Amer. Chem. Soc.*, 77 (1955) 125.
4 R. L. Nelson and E. Percival, *J. Chem. Soc.*, (1957) 2191.
5 K. B. Wiberg, *Laboratory Technique in Organic Chemistry*, McGraw–Hill, New York, 1960, p. 245
6 D. M. Hall and O. A. Stamm, *Carbohyd. Res.*, 12 (1970) 421.
7 C. Boffi and L. Ferrari, *Staerke*, 21, No. 4 (1969) 100.
8 N. K. Richtmyer, *Methods Carbohyd. Chem.*, 1 (1962) 107.
9 B. Coxon, *Tetrahedron*, 21 (1965) 3481.
10 H. Spedding, *J. Chem. Soc.*, (1961) 3617.
11 S. S. Bhattacharjee and P. A. J. Gorin, *Can. J. Chem.*, 47 (1969) 1195.
12 T. A. Crabb and R. C. Cookson, *Tetrahedron Lett.*, 12 (1964) 679.
13 D. H. Buss, L. Hough, L. D. Hall, and J. F. Manville, *Tetrahedron*, 21 (1965) 69.
14 N. Baggett, J. M. Duxbury, A. B. Foster, and J. M. Webber, *Carbohyd. Res.*, 1 (1965) 22.