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METHYL 4,6-*O*-BENZYLIDENE-*O*-ETHYL- AND -*O*-VINYL-α-D-GLUCOPYRANOSIDES

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ABSTRACT

Methyl 4,6-*O*-benzylidene-3-*O*-vinyl-α-D-glucopyranoside (**2**), methyl 4,6-*O*-benzylidene-2,3-di-*O*-vinyl-α-D-glucopyranoside (**6**), and methyl 4,6-*O*-benzylidene-2,3-di-*O*-ethyl-α-D-glucopyranoside (**7**) have been prepared and characterized. The 2-vinyl ether (**3**) rearranges on alumina chromatography to methyl 4,6-*O*-benzylidene-2,3-*O*-ethylidene-α-D-glucopyranoside (**4**).

INTRODUCTION

Studies of the synthesis, optimum conditions for preparation, and structure of vinyl ethers of carbohydrates have been the subject of previous papers[1–4]. It was found that these vinyl ethers are usually quite hydrophilic, and, when polymerized, do not yield products having the desired properties. The vinyl ethers of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside appeared more suitable as monomers, and their synthesis by vinylation with acetylene was undertaken.

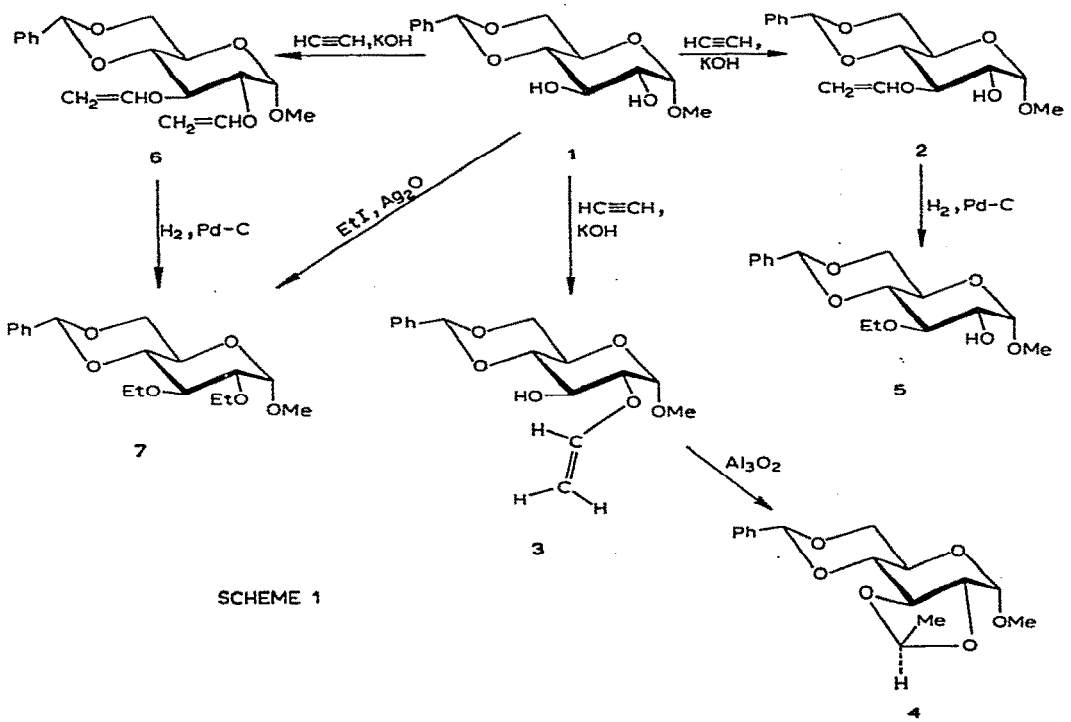
DISCUSSION

Mono-*O*-vinylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) was accomplished by using a *p*-dioxane–water solvent system and relatively mild reaction conditions[2,5], and a crude mixture (a) was obtained by recrystallization from ether. T.l.c. showed two widely separated spots, the faster-moving of which probably contained two compounds having R_F values almost identical with that of methyl 4,6-*O*-benzylidene-3-*O*-ethyl-α-D-glucopyranoside (**5**), and the slower-moving spot corresponded to the starting material (**1**).

When a portion of the original reaction mixture was recrystallized repeatedly from ether, a mixture (b), m.p. 107–109°, was obtained, which showed only the faster-moving spot on t.l.c. From the n.m.r. spectra of this mixture, obtained in methyl sulfoxide-d_6 and chloroform-*d*, it was possible to estimate the ratio of free 3-OH and 2-OH present. This estimate was based on the area under the 3-OH and 2-OH lines, and their field position and line-width, by analogy with the spectra of methyl 4,6-*O*-benzylidene-2- and -3-*O*-ethyl-α-D-glucopyranosides[5] (**3** and **2**). The chemical

shifts of the 2-OH and -3-OH in the starting material (**1**) appear as doublets at τ 5.35 (J 2.3 Hz) and τ 5.08 (J 6.7 Hz) respectively, whereas the 3-ethyl ether (**5**) exhibits a doublet at τ 5.35 (J 1.8 Hz) attributed to the 2-OH resonance. The total line-widths are 6 and 12 Hz., respectively, and this is assumed to be the case for compounds **2** and **3**.

Chromatography of mixture (a), and subsequent recrystallization of the eluted solid from ether, yielded pure methyl 4,6-*O*-benzylidene-3-*O*-vinyl-α-D-glucopyranoside (**2**), m.p. 134–134.5°, $[\alpha]_D^{22}$ +95.6° (*c* 1, chloroform). The n.m.r. spectra in chloroform-*d* and methyl sulfoxide-d_6 confirmed the position of the vinyl group. Satisfactory chemical evidence for the identity of this compound was obtained by hydrogenation of **2** to methyl 4,6-*O*-benzylidene-3-*O*-ethyl-α-D-glucopyranoside (**5**), which was identical in all respects with an authentic sample.

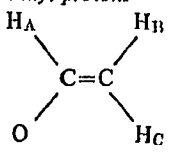


SCHEME 1

Concentration of the mother liquors from which mixture (a) had crystallized gave a crude solid (mixture c). The n.m.r. spectrum in methyl sulfoxide-d_6 indicated that c was a mixture of starting material with the 2- and 3-vinyl ethers (**3** and **2**). The last two were present in the ratio of 3 to 2. Chromatography of mixture (c) on Woelm alumina gave three fractions, A, B, and C. The most polar component (C) was the starting material **1**. Fraction B was a mixture of several compounds that was not examined further. Fraction A, the least polar, was a single compound, m.p. 139–140°. Its i.r. spectrum indicated that there was no hydroxyl group in the molecule.

TABLE I

N.M.R. SPECTRA OF METHYL 4,6-*O*-BENZYLIDENE-*O*-VINYL-α-D-GLUCOPYRANOSIDES[a]

Compound	*Ph*	*Low-field Vinyl protons* 	*PhCH*	*H-1*	*H-2, H-3, H-4, H-5, H-6, vinyl protons*	*OMe*	*2-OH or 3-OH*
1[b]	2.53 s		4.42 s	4.87 d, $J_{1,2}$ 4	5.8–6.6 e	6.70 s	5.35 d, $J_{2,OH}$ 2.3, 5.08 d, $J_{3,OH}$ 6.7
2[c]	2.48 e	3.47 q, $J_{A,B}$ 6.5, $J_{A,C}$ 14	4.38 s	5.05 d, $J_{1,2}$ 3.4	5.2–6.5 e	6.53 s	7.23 s
2+3[b]	2.68 e	3.56 q, $J_{A,B}$ 7 3.64 q, $J_{A,C}$ 14	4.54 s 4.57 s	5.20 d, $J_{1,2}$ 3.0	5.25–6.65 e	6.67 s 6.70 s	5.4 e 5.1 e
4[c]	2.80 s	(ethylidene H) 4.91 q, *J* 5	4.54 s	5.06 d, $J_{1,2}$ 3.0	5.8–6.8 e	6.93 s	(ethylidene CH_3) 8.97 d, *J* 5
5[b]	2.63 s		4.39 s	5.00 d, $J_{1,2}$ 3.8	5.8–6.6 e	6.92 s	5.35 d, $J_{2,OH}$ 1.8
6[c]	2.60 s	3.59 q, $J_{A,B}$ 6.5 3.70 q, $J_{A,C}$ 14	4.47 s	5.12 d, $J_{1,2}$ 3.6	5.42–6.5 e	6.58 s	
7[c]	2.56 s		4.45 s	5.20 d, $J_{1,2}$ 3.1	5.68–6.80 e	6.55 s	$2CH_3$ 8.43, 8.47, *J* 7

[a]Chemical shifts are on the τ-scale relative to external Me_4Si (Me_2SO-d_6) or internal Me_4Si ($CDCl_3$); s, singlet; d, doublet; q, quartet; e, envelope; *J* values are in Hz. [b]In Me_2SO-d_6; [c]In $CDCl_3$.

The n.m.r. spectrum of A in chloroform-*d* showed a high-field, methyl doublet (τ 8.98, *J* 5 Hz) in addition to the usual features of methyl 4,6-*O*-benzylidenehexopyranosides[9]. These data support a structural assignment as methyl 4,6-*O*-benzylidene-2,3-*O*-ethylidene-α-D-glucopyranoside (**4**). The stereochemistry of **4** is probably that shown, since models of the alternative structure showed considerable steric crowding between the 1-methoxyl group and the ethylidene methyl groups. Orthoesters[10–12], which form during acyl migration, show similar structural configurations.

Based upon t.l.c. evidence, the vinylation reaction-mixture contained some 30–50% of starting material, together with both monovinyl ethers. No divinyl ether was present, nor did the crude mixture (a) contain any *O*-ethylidene derivative (0.5% could have been detected by n.m.r.). Crystallization and chromatography on Woelm alumina gave only the 3-vinyl ether (**2**), the 2,3-ethylidene acetal (**4**), the starting material **1**, and a mixture of products that, according to the i.r. spectrum, contained no benzylidene group.

Recoveries of 90% indicated that the 3-vinyl ether **2** is reasonably stable to chromatography, and thus did not give rise to the ethylidene acetal **4**. The formation of the latter thus appears to have been due to the cyclization of the 2-vinyl ether **3** on the alumina column.

The *O*-benzylidene di-*O*-vinyl derivative **6** was prepared easily by using *p*-dioxane alone as the solvent for the vinylation reaction. No hydroxyl groups were apparent in the i.r. spectrum of **6**, and both the i.r. and n.m.r. spectra were consistent with the structure assigned (see Table I). Confirmation of the structure was obtained by hydrogenation of **6** to the corresponding diethyl ether (**7**), and comparison of this product with the diethyl ether synthesized independently from **1**.

EXPERIMENTAL

Melting points are uncorrected. T.l.c. was performed on Silica Gel G (E. Merck, Germany), with benzene–ethanol or benzene–butyl alcohol. The plates were developed by spraying the dried chromatogram with a 10% (w/v) solution of phosphomolybdic acid, followed by heating for 5 min at approximately 100°. I.r. spectra were recorded on a Perkin–Elmer Infracord spectrometer, Model 137, and optical rotations were measured on a Bendix Automatic polarimeter or a Rudolph polarimeter Model 80. N.m.r. spectra were measured on a Varian Associates A-60 spectrometer (60 MHz), and tetramethylsilane ($\tau = 10.00$) was used as the internal or external standard. Methyl sulfoxide-d_6 and 1% tetramethylsilane in chloroform-*d* (Silanor) were obtained from Merck, Sharp and Dohme, Ltd., Canada, and were used without purification. Most of the samples for n.m.r. were degassed. All peaks assigned to hydroxyl groups were confirmed by deuterium oxide exchange. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Mono-O-vinylation of methyl 4,6-O-benzylidene-α-D-glucopyranoside (**1**). — A mixture of 20 g (0.07 mole) of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, 2 g of potassium hydroxide, 100 ml of redistilled *p*-dioxane, and 100 ml of water was placed

in a 300-ml, stirred autoclave. The autoclave was flushed with nitrogen and heated to 150°. Acetylene gas, compressed to 400 p.s.i.g., was admitted and maintained at that pressure for 6 h. The cooled autoclave was then vented, and carbon dioxide was used to carbonate the reaction mixture. After filtration, the filtrate was evaporated to dryness, and the residue was recrystallized twice from ethyl ether. This mixture (a) showed two spots on t.l.c. (0.25 mm silica gel G, 3% BuOH in benzene). The slower-moving spot corresponded to starting material. The faster-moving spot appeared to contain two substances having R_F values close to that of compound **5**.

When a portion of the reaction mixture was recrystallized five times from ether, a mixture (b) was obtained; m.p. 107–109°, $[\alpha]_D^{22}$ +86.8° (*c* 1, chloroform). T.l.c. showed only the faster-moving spot. The n.m.r. spectra of this mixture (b) indicated that it contained methyl 4,6-*O*-benzylidene-3- and -2-*O*-vinyl-α-D-glucopyranosides (**2** and **3**) (see Table I).

Anal. Calc. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.49. Found: C, 62.18; H, 6.59.

Mixture (a) (3.3 g) was dissolved in benzene and chromatographed on Woelm alumina, activity I (60 g) with benzene as the eluent. After the first 50 ml of eluate had been discarded, the next 150 ml was evaporated, to give 2.65 g of crystalline product which showed one spot on t.l.c. After three recrystallizations from ether, the pure monovinyl ether **2** was obtained and dried; m.p. 134–134.5°, $[\alpha]_D^{25}$ + 95.6° (*c* 1, chloroform); n.m.r. and i.r. spectral data are given in Tables I and II.

Anal. Calc. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.49. Found: C, 62.12; H, 6.40.

*Identification of the pure methyl 4,6-*O*-benzylidene-mono-*O*-vinyl-α-D-glucopyranoside.* — Compound **2** (200 mg, 6.5 mmoles) was hydrogenated in 95% ethanol, with 5% Pd/C as catalyst. Three recrystallizations from ethanol gave 150 mg (74%) of crystalline product, m.p. 168–169°, $[\alpha]_D^{22}$ +111.1° (*c* 0.99, chloroform). On admixture with authentic methyl 4,6-*O*-benzylidene-3-*O*-ethyl-α-D-glucopyranoside (**5**), this product showed no depression of m.p. The n.m.r. and i.r. spectra of the product could be superimposed on those of the authentic sample (see Tables I and II).

*Formation and isolation of methyl 4,6-*O*-benzylidene-2,3-*O*-ethylidene-α-D-glucopyranoside* (**4**). — The mother liquors from which mixture (a) had been removed were evaporated, to give 16 g of crude solid. This was dissolved in benzene, and chromatographed over Woelm aluminum oxide, activity I (300 g). Fraction A (2.5 g) was obtained by eluting with 1.8 liters of benzene; and fraction B (5.8 g) with 2 liters of 5% of ether in benzene. The column was then washed with 5% of methanol in benzene to give 7.2 g of fraction C, which was identified as methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**). (Fraction B was a mixture of at least four compounds, and was not characterized further. The i.r. spectrum of B showed hydroxyl bands and a band at 1680 cm^{-1} (PhCHO), but no vinyl bands.) Fraction (a) was identified as methyl 4,6-*O*-benzylidene-2,3-*O*-ethylidene-α-D-glucopyranoside (**4**), m.p. 139-140°. The arguments in favor of this assignment are outlined in the Discussion.

Anal. Calc. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.49. Found: C, 62.21; H, 6.35.

*Methyl 4,6-*O*-benzylidene-2,3-*di*-O-vinyl-α-D-glucopyranoside* (**6**) — A mixture of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (20 g, 0.07 mole), 10 g of powdered

potassium hydroxide, and 200 ml of redistilled *p*-dioxane was placed in a 300-ml autoclave and stirred. The autoclave was flushed with nitrogen, and acetylene gas was admitted and maintained at 400 p.s.i.g. for 6 h. The autoclave was cooled, and vented, and carbon dioxide was introduced to carbonate the reaction mixture. After filtration, the filtrate was evaporated to dryness, the residue was extracted with ethyl ether, and the extract was dried (anhydrous potassium carbonate), and evaporated. The resulting crude solid was mixed with a minimal volume of Skellysolve B, the suspension was filtered, the filtrate was evaporated, the residue was dissolved in a large volume of ether, and the solution was treated with charcoal. The solid resulting after filtration and evaporation was recrystallized four times from ether; m.p. 92–93°, $[\alpha]_D^{20}$ +87.3° (*c* 1, chloroform), $\nu_{max}^{CCl_4}$ 3050, 2950, 1640, 1625 (sh), 1465, 1410 (sh), 1385 (sh), 1370, 1350 (sh), 1325, 1310, 1280, 1200 (sh), 1190, 1170, 1150 (sh), 1120, 1105, 1090, 1055, 1030, 995, 970, 940, 915, 878, 835, 690 cm^{-1}. N.m.r. spectral data are given in Table I.

Anal. Calc. for $C_{18}H_{22}O_6$: C, 64.67; H, 6.58. Found: C, 64.51; H, 6.39.

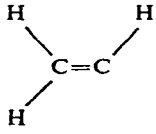
Preparation of methyl 4,6-O-benzylidene-2,3-di-O-ethyl-α-D-glucopyranoside (7) *from* (6). — To a suspension of 0.5 g of 5% Pd/C in 100 ml of 95% ethanol was added 1 g (~ 3 mmoles) of methyl 4,6-*O*-benzylidene-2,3-di-*O*-vinyl-α-D-glucopyranoside; after 3 h, the theoretical amount of hydrogen had been absorbed. The reaction conditions were maintained for a further 2 h, but no more hydrogen was taken up. The product was recrystallized three times from absolute ethanol; m.p. 91–92°, $[\alpha]_D^{25}$ +86.2° (*c* 1, chloroform).

Anal. Calc. for $C_{18}H_{26}O_6$: C, 63.90; H, 7.69. Found: C, 64.08; H, 7.90.

Methyl 4,6-O-benzylidene-2,3-di-O-ethyl-α-D-glucopyranoside (7). — To a solution of 2.82 g (10 mmoles) of **1** and 6.0 ml (75 mmoles) of ethyl iodide in 50 ml of *N*,*N*-dimethylformamide was added 10.5 g (45 mmoles) of dry silver oxide, and the suspension was stirred for 28 h at room temperature. The silver oxide was then removed by filtration, and the filtrate was evaporated to dryness. The crude product was recrystallized to constant optical rotation, yield 2.1 g (62%), m.p. 91–92°, $[\alpha]_D^{25}$

TABLE II

CHARACTERISTIC INFRARED ABSORPTION BANDS[a] OF THE METHYL 4,6-*O*-BENZYLIDENE-*O*-VINYL-α-D-GLUCOPYRANOSIDES

Compound	*OH*		*CH*	*Ring vibrations*	*Type 2a bands*
2+3	3550, 3450	3085, 1640, 1620, (1601)	2930, 2860	913	835
3	3600, 3400	3100, 1645, 1625, (1605)	2950, 2870	919	842
4		(1605)	2950	918	832
6		3080, 1640, 1625 (sh), (1608)	2940, 2850	918	840
7		(1601)	2995, 2950, 2850	917	

[a] In $CHCl_3$ solution (polystyrene calibration); frequencies in cm^{-1}.

+86.2° (*c* 1, chloroform). The product proved to be identical in all respects (m.p., i.r., and n.m.r. spectra, and behavior on t.l.c.) with the hydrogenation product prepared from the divinyl compound.

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