Note

Improved preparation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

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Preparation of the title compound, a much used intermediate, was first described by van Ekenstein and Blanksma[1] who heated a mixture of methyl α-D-glucopyranoside and benzaldehyde in the presence of anhydrous sodium sulfate to obtain a product having m.p. 158°. Irvine and Scott[2] considered the sodium sulfate unnecessary; merely heating (145–160°, several hours) the two reactants together also gave a product having the correct analysis for the title compound, although the m.p. (148–149°) was low. Freudenberg[3] suggested that this anomalous substance was a mixture of diastereoisomers arising from the asymmetry of the acetal carbon atom. These early procedures gave inferior products in low yield. By including an acidic catalyst, Freudenberg[3] markedly improved the reaction. Upon shaking a mixture of methyl α-D-glucopyranoside, benzaldehyde, and anhydrous zinc chloride at room temperature for a brief period (3 h) he obtained a single product in good yield. Freudenberg's method has subsequently become accepted as the method of choice. Unfortunately, the product obtained is impure[4]; several recrystallizations are often necessary for purification[5]. These recrystallizations are not only time-consuming but they may seriously decrease the yield.

Bergonzi *et al.*[6] condensed methyl α-D-glucopyranoside and benzaldehyde, dissolved in dimethyl sulfoxide, in the presence of boron trifluoride etherate as an acetalation catalyst. The product, purportedly pure title compound, had m.p. 164–165°, $[\alpha]_D^{20}$ +71° (methanol). However, its low specific rotation has cast doubt on the purity of this preparation, for which no elemental analyses were given.

Presented herein are two rapid methods of preparing the title compound: (*A*) an acetalation procedure that uses *p*-toluenesulfonic acid as catalyst (in the presence of Drierite), and (*B*) a modified Freudenberg procedure. Both give the title compound analytically pure and in good yield, directly, in 1 day.

EXPERIMENTAL

General. — All evaporations were performed under diminished pressure (water aspirator) at 50–60° (bath). Melting points were determined with a Fisher–Johns*

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*The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

melting-point apparatus and are uncorrected. Steam distillations were performed at 100°.

Reagents. — The methyl α-D-glucopyranoside (finely divided, m.p. 167–168°) was dried *in vacuo* for 1 h at 60–70° (bath) before use. The benzaldehyde was freshly distilled. The commercial zinc chloride (anhydrous granular; assay, 95% $ZnCl_2$), was fused and the resulting solid, while still hot, was ground under dry benzene or petroleum ether and added immediately to the benzaldehyde. The powdered Drierite was either (*a*) minus 20-mesh Drierite as received from the manufacturer (W. A. Hammond Drierite Co., Xenia, Ohio, U. S. A.) or (*b*) prepared by grinding in a mortar freshly regenerated[7], nonindicating, granular Drierite. Indicating Drierite was unsatisfactory since it contaminated the product with cobalt salt. Granular Drierite, used directly without grinding, gave inferior yields as did partially exhausted Drierite.

A. p-Toluenesulfonic acid–Drierite method. — *p*-Toluenesulfonic acid monohydrate (7 g) was dissolved in benzaldehyde (70 ml) by gentle heating (35–40°) and agitation. To the solution was added methyl α-D-glucopyranoside (28 g) and powdered Drierite (100 g). The mixture was shaken for exactly 1 h (longer shaking resulted in a lower yield), and then was diluted with chloroform (250 ml). The flask was swirled vigorously, the heavier sediment allowed to settle, and the extract, containing some finely divided Drierite in suspension, was separated by careful decantation. To the extract was added chloroform washings (3 × 150 ml) of the Drierite sediment. The combined chloroform extract and washings were worked up as described in section *C*.

B. Modified Freudenberg (zinc chloride) method. — To a solution of anhydrous zinc chloride (15 g) in benzaldehyde (70 ml) was added methyl α-D-glucopyranoside (28 g) and the mixture was shaken for 1 h. It was then poured, in a thin stream, with rapid stirring into chloroform (750 ml). The zinc chloride and unreacted methyl glucoside formed a gummy mass from which the chloroform extract and subsequent chloroform washings (containing some suspended material) were separated by decantation. The combined chloroform extracts and washings were worked up as in section *C*.

Neither use of a larger proportion of zinc chloride, as specified by others[3–5], nor longer periods of shaking[3–5], increased the yield. Most of the zinc chloride could be dissolved in the benzaldehyde by gentle warming (35–40°) and agitation for 15–20 min; a slight, undissolved residue did not affect the subsequent yield. Occasionally the zinc chloride–benzaldehyde complex precipitated during the warming, but this occurrence also did not affect the subsequent yield of the title compound.

C. Work-up of chloroform extracts. — The combined chloroform extracts from Method A or B were shaken with cold water (2 × 100 ml), and then with saturated aqueous sodium hydrogen carbonate (100 ml), and filtered through a medium porosity, sintered-glass funnel (85 mm). (The extraction with water resulted in quantitative transfer of the finely divided Drierite (Method *A*) from chloroform suspension to aqueous suspension. The first 100 ml of cold-water washing, which contained most of the Drierite, tended to solidify in ~30 min. Consequently, it was advisable to remove it immediately from the separatory funnel.) To the filtrate was added water (250 ml) and sodium hydrogen carbonate (5 g) and the whole was evaporated until most of the chloroform had been removed. The mixture was then vigorously steam distilled until no more benzaldehyde appeared in the distillate (odor). The benzaldehyde-free mixture was then diluted with water to 1000 ml, steam distilled for a further 3–4 min, and filtered hot through a large, coarse porosity, sintered-glass funnel. (The pink-colored mixture from Method A contained a small amount of an insoluble oil, most of which settled to the bottom of the flask; the (hot) supernatant liquid was separated from it by careful decantation before filtration.) The cloudy filtrate was reheated (steam jet) to 95°, treated with activated charcoal (Darco G-60, 15 g), and rapidly filtered hot through a Celite bed that had been prepared by filtering a slurry of Celite (5 g) in water (100 ml) through a medium porosity, sintered-glass funnel (85 mm). Crystallization, which began immediately in the cooling filtrate, was continued overnight at room temperature. The filtered product was washed in the funnel by resuspending it in cold water (2 × 200 ml); it was then pressed out and dried on a porous tile. (For yields and physical constants, see Table I.) The original cloudy filtrate (Method B), if not charcoaled, produced (two crops) 20–23 g (50–56% yield) of crude, crystalline product 96–97% pure as determined from its specific optical rotation. This yield was approximately that originally reported by Freudenberg[3] for his (crude) product.

TABLE I

DATA ON METHYL 4,6-*O*-BENZYLIDENE-α-D-GLUCOPYRANOSIDE[a]

Method of preparation	*Yield (two crops)*		*M.p. °C*	$[\alpha]_D^{20}$		*Analyses[b] found*	
	g	*%*		c 2, $CHCl_3$	c 2, CH_3OH	*% C*	*% H*
A[c]	19–20	48–50	166–167	+110°	+92°	59.7	6.5
B	15–16	38–40	166–167	+110°	+93°	59.6	6.5

[a] Richtmyer and Hudson[5] reported m.p. 163–164° and $[\alpha]_D^{20}$ +110° (*c* 2, $CHCl_3$) for the pure title compound as did Richtmyer[4]; they reported yields (crude product obtained by the Freudenberg method) of 60–70% and 70%, respectively.
[b] Calc. for $C_{14}H_{18}O_6$: C, 59.6; H, 6.4.
[c] Mixed m.p. (with product from Method *B*), 166–167° (no depression).

A small second crop could be obtained by concentrating the combined mother liquor and washings to 500 ml, heating to 90°, treating with activated charcoal (5 g), and filtering rapidly, as before, through a Celite bed. The crystalline product, on cooling, was separated by filtration, washed with cold water as before, and dried on a porous tile. This product had the same m.p. and specific rotation as the first crop.

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