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# An Alternative Preparation of *O*-Benzylidene Acetals

PER J. GAREGG, LAJOS MARON and CARL-GUNNAR SWAHN

*Institutionen för organisk kemi, Stockholms Universitet, S-104 05 Stockholm, Sweden*

A novel synthesis of *O*-benzylidene acetals containing 1,3-dioxane as well as 1,3-dioxolane rings is described. It involves the reaction of benzal chloride in pyridine with glycosides.

The standard method for preparing benzylidene acetals of carbohydrates involves the condensation of the carbohydrate with benzaldehyde in the presence of an acidic catalyst, zinc chloride being the usual choice.[1] Buchanan and Schwarz have described the use of formic acid in benzaldehyde as being particularly useful for the preparation of alkyl 4,6-*O*-benzylidene hexosides in which the formation of 2,3- as well as 4,6-benzylidene acetals is possible.[2] These reactions are thermodynamically controlled and thus invariably yield 1,3-dioxane derivatives with an equatorial phenyl group (*e.g.* alkyl 4,6-*O*-benzylidene-hexopyranosides). In dioxolane rings, however, the energy difference between the stereoisomers is smaller. In consequence, two stereoisomers may be observed in five-membered cyclic benzylidene acetals.[1] Thus two stereoisomeric forms of methyl 3,4-*O*-benzylidene-β-L-arabinopyranoside have been reported.[3] Baggett and coworkers have described the synthesis of 2-phenyl-1,3-dioxane derivatives of sugars under irreversible conditions. Treatment of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside and the corresponding α-D- and β-D-galactopyranosides, with benzal bromide and potassium *t*-butoxide yielded about 30 % of 4,6-benzylidene derivatives with the phenyl group situated axially as well as equatorially in the 1,3-dioxane ring.[4,5] The preparation has recently been modified as exemplified by the reaction, under basic conditions, of benzaldehyde with methyl 2,3-di-*O*-methyl-6-*O*-*p*-tolylsulphonyl-α-D-glucopyranoside.[6]

In the present communication an alternative to the above methods is presented. The carbohydrate is treated with 1.2 mol of benzal chloride in pyridine at reflux temperature. Following cooling to room temperature, the product is acetylated by the addition of acetic anhydride and then worked up.

The various compounds made, the yields obtained and other pertinent data, including analyses for new compounds, are given in Table 1.

It will be noted that the preparation gives the thermodynamically controlled product. Thus methyl 2,3-di-*O*-methyl-α-D-glucopyranoside yields the

*Table 1.* Preparation of *O*-benzylidene acetals. Solvent for rotation, $CHCl_3$.

| Run No. | Starting material | Product | Yield % | M.p. | $[\alpha]_D$ | Ref. | Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Found | | | Calculated | | |
| | | | | | | | C | H | O | C | H | O |
| 1 | Methyl α-D-gluco-pyranoside | Methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (I) | 50 | 101–104° | +75° | 8 | | | | | | |
| 2 | Methyl 2,3-di-*O*-methyl-α-D-gluco-pyranoside | Methyl 2,3-di-*O*-methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (II) | 26 | 123.5–124.5° | +97° | 3 | | | | | | |
| 3 | Benzyl α-D-arabinopyranoside | Benzyl 3,4-*O*-benzylidene-α-D-arabinopyranoside [a] (two isomers in ratio – 1:1), (IIIa and IIIb) | 51 | 148–149 | +10° | | 69.4 | 6.02 | 24.5 | $C_9$ 69.5 | $H_{20}$ 6.14 | $O_5$ 24.4 |
| | | | | 116–117° | +8° | | 69.4 | 5.97 | 24.7 | 69.5 | 6.14 | 24.4 |
| 4 | D-Ribono-1,4-lactone | 2,3-*O*-Benzylidene-D-ribono-1,4-lactone [b] (IV) | 24 | 164–166° | −85° | | 61.1 | 5.07 | 33.9 | $C_{12}$ 61.0 | $H_{12}$ 5.12 | $O_5$ 33.9 |
| 5 | Methyl α-D-manno-pyranoside | Monobenzylidene derivatives, GLC: 2,3-:4,6-acetal 3:7 (Va) | 40 | | | | | | | | | |
| | | Methyl 2,3-4,6-di-*O*-benzylidene-α-D-manno-pyranoside (Vb, Vc) | 11 | 176–179° | 0° | 9, 10 | | | | | | |
| | | | | 99–101° | −58° | | | | | | | |

[a] Deacetylated product of standard procedure.
[b] Worked up directly after acetalization, without acetylation.

4,6-acetal with an equatorial phenyl group only, and none of the axial isomer. All crude reaction mixtures which could contain 4,6-benzylidene acetals with axial phenyl groups were carefully examined by TLC, GLC, and by NMR; only acetals with equatorially situated phenyl groups were, however, found. This was confirmed by the isomerization of IIIa into a mixture of IIIa and IIIb under the reaction conditions. The method seems particularly suited for the preparation of five-membered, dioxolane acetals, of which two stereoisomers may be obtained.

The yields are acceptable and the method may be useful in the synthesis of benzylidene acetals in the presence of acid-labile protecting groups present in the starting material.

The identity of the various new compounds follows from the analytical and NMR data. For the two 3,4-*O*-benzylidene acetals of benzyl α-D-arabinopyranoside, IIIa and IIIb respectively, the NMR spectra indicate that IIIa, with the high-field signal for the benzylic acetal proton has this proton in the *exo* configuration.[7]

Only one isomer of 2,3-*O*-benzylidene-D-ribono-1,4-lactone was observed. In the absence of NMR data for its configurational isomer no prediction of the configuration at the acetalic carbon atom of IV can be made.

The acetalization of methyl α-D-mannopyranoside yielded a complex mixture of monobenzylidene and dibenzylidene derivatives. The monobenzylidene fraction resisted attempts at preparative TLC separations. Examination of this fraction by NMR and chromatography and comparison to reference methyl 4,6-*O*-benzylidene-α-D-mannopyranoside revealed that the 4,6-acetal predominated in the mixture. The two 2,3-acetals were found in approximately equal amounts. Of these latter two, that with the signal for the acetal proton at the lowest field ($\delta$ 6.27) probably has an *endo* acetal hydrogen. The dibenzylidene derivatives Vb and Vc [8,9] in all probability both have dioxane acetal proton in an axial position ($\delta$ 5.70 and 5.58, respectively) and an *endo* dioxolane acetal proton ($\delta$ 6.34) in Vb while that in Vc ($\delta$ 6.03) is given by an *exo* dioxolane acetal proton.

The observed stereochemistry of the products may be due to epimerization of the reaction products *via* carbanion intermediates. This is currently under investigation.

## EXPERIMENTAL

Concentrations were performed at reduced pressure. Melting points are corrected. Optical rotations were determined at room temperature (20 – 22°) with a Perkin-Elmer 141 polarimeter. NMR spectra were recorded with a Varian A-60A spectrometer using tetramethylsilane as internal reference. Chemical shifts ($\delta$) are given in ppm downfield from tetramethylsilane. Pertinent parts of the various NMR spectra are given in Table 2. The remainder of the spectra were invariably in accordance with the presumed structures. TLC was performed on silica gel (Merck DC-Fertigplatten Kieselgel $F_{254}$ for analytical and 2 mm PSC-Fertigplatten Kieselgel $F_{254}$ for preparative separations). The various benzylidenations were followed by TLC using ethyl acetate as solvent throughout. The reactions were not, however, optimized. GLC was run on a Perkin-Elmer F 11 instrument fitted with a 3 % ECNSS-M on Gas Chrom Q glass column. The nitrogen flow rate was 30 ml/min.

The following represents a typical preparation.

Methyl α-D-glucopyranoside (7.6 g) in dry pyridine (100 ml) and benzal chloride (7.6 g) was refluxed with a calcium chloride tube fitted to the top of the condenser for

*Table 2.* Chromatographic and pertinent NMR data.

| Run No. | Product | Solvent used in TLC examination of product | Temp. for GLC | NMR parameters | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | δ, aromatic H | δ, methine H | δ, methoxyl | δ, methylene in benzyl | δ, *O*-acetyl | Solvent |
| 1 | I | | 180–200° | 7.33 | 5.42 | 3.40 | | 2.00<br>2.03 | $CCl_4$ |
| 2 | II | Chloroform | – | 7.40 | 5.44 | 3.39<br>3.47<br>3.57 | | | $CCl_4$ |
| 3 | IIIa | Chloroform-diethyl ether 7:3 | 210° | 7.42 | 5.97 | | 4.68<br>4.85 | | $CDCl_3$ |
| | IIIb | Chloroform-diethyl ether 7:3 | | 7.47 | 6.28 | | 4.75<br>4.93 | | |
| 4 | IV | Chloroform-diethyl ether 6:4 | – | 7.48 | 6.03 | | | | $CDCl_3$ |
| 5 | Va | Chloroform-diethyl ether 7:3 | 180–200° | 7.45 | 5.93 [a]<br>5.62 [b]<br>6.27 [a] | 3.38 | | 2.02 [a]<br>2.05 [a] 1.98 [b]<br>2.08 [a] 2.13 [b] | $CDCl_3$ |
| | Vb | Chloroform-diethyl ether 9:1 | 210° | 7.48 | 5.70<br>6.34<br>5.58 | 3.44 | | | $CDCl_3$ |
| | Vc | | | 7.51 | 6.03 | 3.44 | | | |

[a] 2,3-Acetal. [b] 4,6-Acetal.

7.5–9 h. After cooling to room temperature, acetic anhydride (20 ml) was added and the solution allowed to stand overnight. Excess water was added and the mixture extracted with benzene. The benzene layer was washed with, in turn, ice-cold 1 M sulphuric acid, saturated aqueous sodium bicarbonate, and finally water. The benzene solution was dried over magnesium sulphate, filtered and concentrated. The dark-coloured residue crystallized to yield methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside, 7.3 g, m.p. 101–104°, $[\alpha]_D + 75°$ (*c*, 1.0, chloroform).[1] Part of the material was deacetylated with 1.67 % ammonia in methanol to yield methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, m.p. 161–163° undepressed on admixture with an authentic sample. The various preparations are summarized in Table 1, chromatographic and NMR data in Table 2.

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