ALKYLATION OF METHYL 4,6-O-BENZYLIDENE-α-D-GALACTOPYRANOSIDE

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The partial alkylation of methyl 4,6-O-benzylidene-α-D-galactopyranoside in dimethylformamide and dimethyl sulfoxide in the presence of barium oxide and hydroxide is described. It has been shown that methylation and benzylation lead predominantly to the 3-alkyl derivatives with yields of 30-40%, benzylation taking place more selectively than methylation. The compounds synthesized have been characterized by their melting points and specific rotations.

The known methods for the synthesis of the methyl ethers of galactose are fairly complicated in many cases, since they include the introduction and removal of a large number of protective groupings. In view of this, the selective alkylation of carbohydrate derivatives containing several free hydroxy groups is of considerable interest for the synthesis of methyl and benzyl ethers of monosaccharides. Definite advances have been achieved in this direction [1-4]. The most suitable method has proved to be that of Kuhn [3] — alkylation by methyl iodide or benzyl bromide in dimethylformamide (DMFA) in the presence of barium oxide and hydroxide. In a number of cases, the selectivity of alkylation is fairly high and the possibility of the practical utilization of the method is determined only by the choice of a convenient means of isolating the desired product from the reaction mixture.

The present paper described the alkylation of methyl 4,6-O-benzylidene-α-D-galactopyranoside (I), which leads with yields of about 30% to the 3-O-alkyl derivatives. These compounds may be the starting materials for a standard production of 2-O- and 3-O-methyl-D-galactoses, which are necessary as markers in the study of the carbohydrate structures by the methylation method. Previous attempts at the partial methylation of compound I with the aid of Haworth's and Purdie's methods proved to be unsuccessful [5].

To achieve a solution of the problem set, a solution of (I) in DMFA or dimethyl sulfoxide (DMSO) in the presence of BaO and $Ba(OH)_2 \cdot 8H_2O$ was treated with 1.2 equivalents of methyl iodide or benzyl bromide. As a result, all the theoretical possible methyl and benzyl ethers of (I) have been isolated and characterized. Methylation of the diol (I) gave a mixture of products consisting of monomethyl ethers with small amounts of dimethyl ethers and of the starting material. Among the monomethyl ethers, 3-O-methyl-(I) (II) predominated.

It must be mentioned that the isomeric 3-O-methyl- and 2-O-methyl-(I)'s (as also the 3-O-benzyl- and 2-O-benzyl-(I)'s) are chromatographically separable in the form of the corresponding 2-O- and 3-O-acetyl derivatives.

To isolate (II), the reaction mixture after appropriate working up and subsequent acetylation was recrystallized from ethanol, as a result of which 2-O-acetyl-(II) (III) was obtained with a yield of 40%. The deacetylation of (III) gave compound (II) quantitatively, this being additionally characterized in the form of the 2-O-tosyl and 2-O-benzyl derivatives. From the mother liquors by chromatography on SiO_2 and subsequent deacetylation, (I), 2-O-methyl)(I), 3-O-methyl-(I), and 2,3-di-O-methyl-(I) were isolated.

The benzylation of (I) in DMSO gave a mixture with a considerable predominance of monobenzyl ethers the main component of which was 3-O-benzyl-(I) (IV). After appropriate working up and the recrystallization of the mixture of ethers from benzene the yield of (IV) was 30%. The position of the benzyl group in the ether (IV) was shown by methylation, which led to the known 3-O-benzyl-2-O-methyl-(I) (V). The mother liquors, after acetylation, chromatography on SiO_2, and subsequent deacetylation tielded 2,3-di-O-benzyl-(I), 3-O-benzyl-(I), and (I).

Thus, the reactivity of the hydroxy group at C-3 in compound (I) on alkylation in aprotic bipolar solvents using BaO and $Ba(OH)_2 \cdot 8H_2O$ as the base is higher than that of the hydroxy group at C-2, and benzylation takes place more effectively than methylation.

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It is possible that the reason for the different reactivities of the hydroxy groups is the formation of an intramolecular hydrogen bond [6-7], which raises the nucleophilicity of the corresponding hydroxy group.

EXPERIMENTAL

Melting points were determined on a heated stage with an accuracy of ±1°C. Specific rotations were measured on a CM-1 polarimeter (Na lamp) with an accuracy of ±2%.

Chromatography was performed on silica gel L (40-100), and thin-layer chromatography on Woelm TLC silica gel.

The following solvent systems were used. For thin-layer and column chromatography: 1) benzene–ethyl acetate (2:8); 2) benzene–ethyl acetate (8:3); 3) CCl_4–acetone (8:2); 4) CCl_4–acetone (9:1).

The spots of the sugars on the plates were revealed by the application of a 5-10% ethanolic solution of H_2SO_4 followed by heating.

A. Methylation of Methyl 4,6-O-Benzylidene-α-D-galactopyranoside (I). 2-O-Acetyl-4,6-O-benzylidene-3-O-methyl-α-D-galactopyranoside (III). Over 10 min, with vigorous stirring, 4.2 ml of CH_3I was added to a solution of 14.1 g (0.05 mole) of (I) in 70 ml of DMFA containing 18 g of BaO and 7 g of $Ba(OH)_2 \cdot 8H_2O$. The reaction was monitored in system 1. The reaction mixture was stirred for another 10 h and was then diluted with 350 ml of $CHCl_3$ and centrifuged. The solution was washed with water to a weakly alkaline reaction, dried over Na_2SO_4, and evaporated to dryness. The residue (10 g) was acetylated with 50 ml of a mixture of pyridine and acetic anhydride (1:1) at room temperature for 12 h. The solution was evaporated in vacuum and the viscous syrup so obtained was recrystallized from 50 ml of ethanol, giving 5.5 g of (III). A second recrystallization from 25 ml of ethanol gave 5 g of pure product with mp 137-138°C, $[\alpha]_D$ +171° (c 1.7; chloroform). Found, %: C 60.30; H 6.84. $C_{17}H_{22}O_7$, %: C 60.35; H 6.55.

Methyl 4,6-O-Benzylidene-3-O-methyl-α-D-galactopyranoside (II). A solution of 5 g of (II) in 50 ml of absolute methanol was treated with two drops of a 10% solution of sodium methanolate in methanol. The mixture was kept at 40°C for 10 h and was then neutralized with KU-2 cation-exchange resin and was evaporated to dryness. The residue was recrystallized from 50 ml of a mixture of ethanol and chloroform (9:1), to give 4.5 g of pure (II) with mp 170°C, $[\alpha]_D$ +187° (c 1.2; chloroform). According to the literature; mp 174°C, $[\alpha]_D$ +189° [5]. Found, %: C 60.45; H 6.91. $C_{15}H_{20}O_6$, %: C 60.86; H 6.80.

Methyl 4,6-O-Benzylidene-3-O-methyl-2-O-tosyl-α-D-galactopyranoside (VI). The tosylation of 1 g of (III) was carried out with 1 g of p-TsCl in 5 ml of pyridine at 38°C for three days. The reaction mixture was poured, with stirring, into 100 ml of water. The solid product (1.5 g) was filtered off and recrystallized from ethanol–chloroform (9:1) to give 1.1 g of (VI) with mp 186°C, $[\alpha]_D$ +166° (c 1.3; chloroform). According to the literature [5], mp 187°C, $[\alpha]_D$ +168°.

Methyl 2-O-Benzyl-4,6-O-benzylidene-3-O-methyl-α-D-galactopyranoside (VIII). Compound (II) (5 g) was benzylated with 2.5 ml of benzyl bromide in 25 ml of DMFA in the presence of 2 g of sodium hydride. The excess of NaH was decomposed with methanol, and the mixture was poured into water and extracted with chloroform. The organic layer was washed with water to neutrality, dried with anhydrous Na_2SO_4, and evaporated to dryness. The residue was recrystallized from 25 ml of ethanol to give 5 g of pure (VIII) with mp 109°C, $[\alpha]_D$ +72° (c 1.8; chloroform). Found, %: C 67.90; H 6.71. $C_{22}H_{26}O_6$, %: C 68.38; H 6.78.

To isolate the reaction products, the mother solution after the isolation of (III) was evaporated to a dry residue (4 g), which was dissolved in 10 ml of CCl_4 and chromatographed on 100 g of SiO_2. On elution with solvent system 3, the following were isolated:

a) 0.2 g of methyl 2,3-di-O-acetyl-4,6-O-benzylidene-α-D-galactopyranoside, mp 117°C, $[\alpha]_D$ +199° (c 2.0; chloroform). Found, %: C 58.51; H 6.48. $C_{18}H_{22}O_8$, %: C 59.01; H 6.05;

b) 0.5 g of methyl 3-O-acetyl-4,6-O-benzylidene-2-O-methyl-α-D-galactopyranoside, the Zemplen deacetylation of which gave 0.35 g of methyl 4,6-O-benzylidene-2-O-methyl-α-D-galactopyranoside with mp 149-150°C, $[\alpha]_D$ +130° (c 1.0; chloroform). According to the literature [5]: 152°C, $[\alpha]_D$ +132°;

c) 0.6 g of methyl 2-O-acetyl-4,6-O-benzylidene-3-O-methyl-α-D-galactopyranoside, mp 137°C, $[\alpha]_D$ +170° (c 1.5; chloroform); and

d) 0.2 g of methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-galactopyranoside with mp 122°C, $[\alpha]_D$ +166° (c 1.3; chloroform). According to the literature [10]: mp 123-124°C, $[\alpha]_D$ +173°.

B. Benzylation of Methyl 4,6-O-Benzylidene-α-D-galactopyranoside. Methyl 3-O-Benzyl-4,6-O-benzylidene-α-D-galactopyranoside (IV). Over 10 h, with vigorous stirring, 7 ml of benzyl bromide was added to a solution of 14.1 g (0.05 mole) of (I) in 70 ml of DMSO containing 18 g of BaO and 7 g of $Ba(OH)_2 \cdot 8H_2O$. The reaction was monitored in system 2. The reaction mixture was stirred for another 10 h and was then diluted with 350 ml of $CHCl_3$ and centrifuged. The solution was washed with water to a weakly alkaline solution, dried with Na_2SO_4, and evaporated to dryness. The residue (12 g) was recrystallized from 60 ml of benzene to give 5 g of (IV). Recrystallization from 50 ml of ethanol yielded the pure product with mp 195°C, $[\alpha]_D$ +185° (c 1.5; chloroform). Found, %: C 67.34; H 6.69. $C_{21}H_{24}O_6$, %: C 67.73; H 6.50. After the isolation of the (IV), the mother solution was evaporated to a dry residue (6 g) and this was recrystallized from 60 ml of ethanol to give gave 1.5 g of methyl 2,3-di-O-benzyl-4,5-O-benzylidene-α-D-galactopyranoside with mp 174-175°C, $[\alpha]_D$ +75° (c 2.9; chloroform). Found, %: C 72.68; H 6.55. $C_{28}H_{30}O_6$, %: C 72.71; H 6.54.

The remaining mother solution was evaporated to dryness and the residue was acetylated with 50 ml of a mixture of acetic anhydride and pyridine (1:1). The mixture of acetates (4 g) was dissolved in 15 ml of CCl_4 and chromatographed on 350 g of SiO_2 in system 4. The following compounds were isolated:

a) 0.2 g of methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside, mp 174-175°C, $[\alpha]_D$ +75°;

b) 0.5 g of methyl 3-O-acetyl-2-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside, the Zemplen deacetylation of which gave 0.2 g of methyl-2-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside (VII) with mp 101-103°C, $[\alpha]_D$ +63° (c 1.0; chloroform). Found, %: C 66.83; H 6.42. $C_{21}H_{24}O_6$, %: C 67.73; H 6.50. The methylation of (VII) gave the above-described methyl 2-O-benzyl-4,6-O-benzylidene-3-O-methyl-α-D-galactopyranoside, mp 108°C, $[\alpha]_D$ +70°;

c) 0.3 g of methyl 2-O-acetyl-3-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside, the Zemplen deacetylation of which gave 0.25 g of methyl-3-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside, mp 194°C $[\alpha]_D$ +185°; and

d) 0.2 g of methyl 2,3-di-O-acetyl-4,6-O-benzylidene-α-D-galactopyranoside, mp 116°C, $[\alpha]_D$ +199°.

Methyl 3-O-Benzyl-4,6-O-benzylidene-2-O-methyl-α-D-galactopyranoside (V). The methylation of 5 g of (IV) was carried out with an excess of methyl iodide in 25 ml of DMFA in the presence of 2 g of sodium hydride. The excess of NaH was decomposed with ethanol, and the mixture was poured into water and extracted with chloroform. The extract was washed with water to neutrality dried with Na_2SO_4, and evaporated to dryness. The residue (6 g) was recrystallized from 30 ml of ethanol, giving 5 g of pure (V) with mp 130-131°C, $[\alpha]_D$ +158° (c 1.0; chloroform). According to the literature [11], mp 130-131°C, $[\alpha]_D$ +158°.

CONCLUSIONS

1. Simple syntheses of 3-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside and 4,6-O-benzylidene-3-O-methyl-α-D-galactopyranosides have been proposed.

2. It has been shown that the hydroxy group at C-3 possesses increased reactivity in Kuhn alkylation reactions.

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MASS SPECTROMETRY OF COMPLETELY ACETYLATED MONOSACCHARIDE FORMATES

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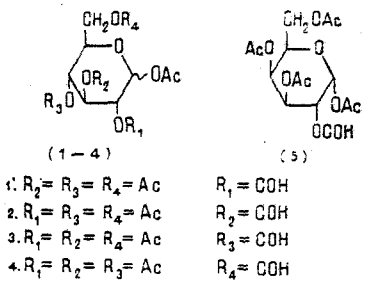
The mass-spectrometric fragmentation of model samples of fully acetylated monoformates of D-glucose and D-galactose has been studied. It has been shown that it is similar to the fragmentation of the full acetates of the hexoses, is characteristic, and permits the position of a formyl group in a monosaccharide to be determined.

We have previously developed a method for determining the positions of sulfate groups in sulfated carbohydrates through their replacement by formyl groups with the subsequent mass-spectrometric identification of the compounds formed. In this connection, it is a matter of interest to study the mass spectra of formyl derivatives of monosaccharides. In the present paper we consider the interpretation of the mass spectra of the peracetates of formyl derivatives of D-glucose (compounds 1-4) and of D-galactose (compound 5).



Fully acetylated monosaccharide formates

The mass-spectrometric characteristics for these compounds, which are given in Table 1, enable us to judge that the decomposition of the fully acetylated monosaccharide formates is similar to the decomposition of fully acetylated hexoses [2]. The mass spectra contain two main series of fragments, B and C (using Heyns and Muller's symbols [2]).

Series B (scheme 1, next page) begins by the elimination of the glycosidic acetoxy group (ion with m/z 317), and the subsequent ejection of formic or acetic acid and a molecule of ketene leads to fragments with m/z 211 (compounds 1, 3-5), 197 (1, 2, 4, 5), 169 (1-3, 5), and 155 (4). The ion with m/z 271 is absent from the spectra of 1, 3-5 and is characteristic for 2. The ion with m/z 211 is observed only in the mass spectra of compounds (1), (3), (4), and (5) and is strongest for (1) and (5).

Series C (scheme 2, next page) begins with fragment C_1, which is formed by the cleavage of the C_1—C_2 bond. The elimination of a Ac_2O molecule leads to the fragment C_2 with m/z 274 (1, 3-5). The following fragment, C_3, is formed by the ejection of formic acid. The peak with m/z 274 is present in the spectra of compounds (1, 3-5), and an ion with m/z 242 only in the spectrum of (2). Table 1 gives information on the relative intensities of the peaks observed in

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