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THE SYNTHESIS OF SOME METHYL 4,6-*O*-BENZYLIDENE-α-D-*erythro*-HEXOPYRANOSID-2,3-DIULOSE DERIVATIVES

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ABSTRACT

Methyl 4,6-*O*-benzylidene-3-deoxy-3-phenylazo-α-D-glucopyranoside (**1**) has been oxidised with the Pfitzner–Moffat reagent to the 2,3-diulose 3-phenylhydrazone derivative (**2**) which has been characterised as the phenylosazone (**3**) and oxime (**4**). An unstable 2-imino derivative (**10**) of the same diulose has been produced by base-catalysed elimination of nitrogen from methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranosid-3-ulose (**8**). The imino intermediate was trapped as a quinoxaline derivative (**9**). The base-catalysed reactions of certain other hydrazone derivatives of methyl hexosiduloses have also been examined.

INTRODUCTION

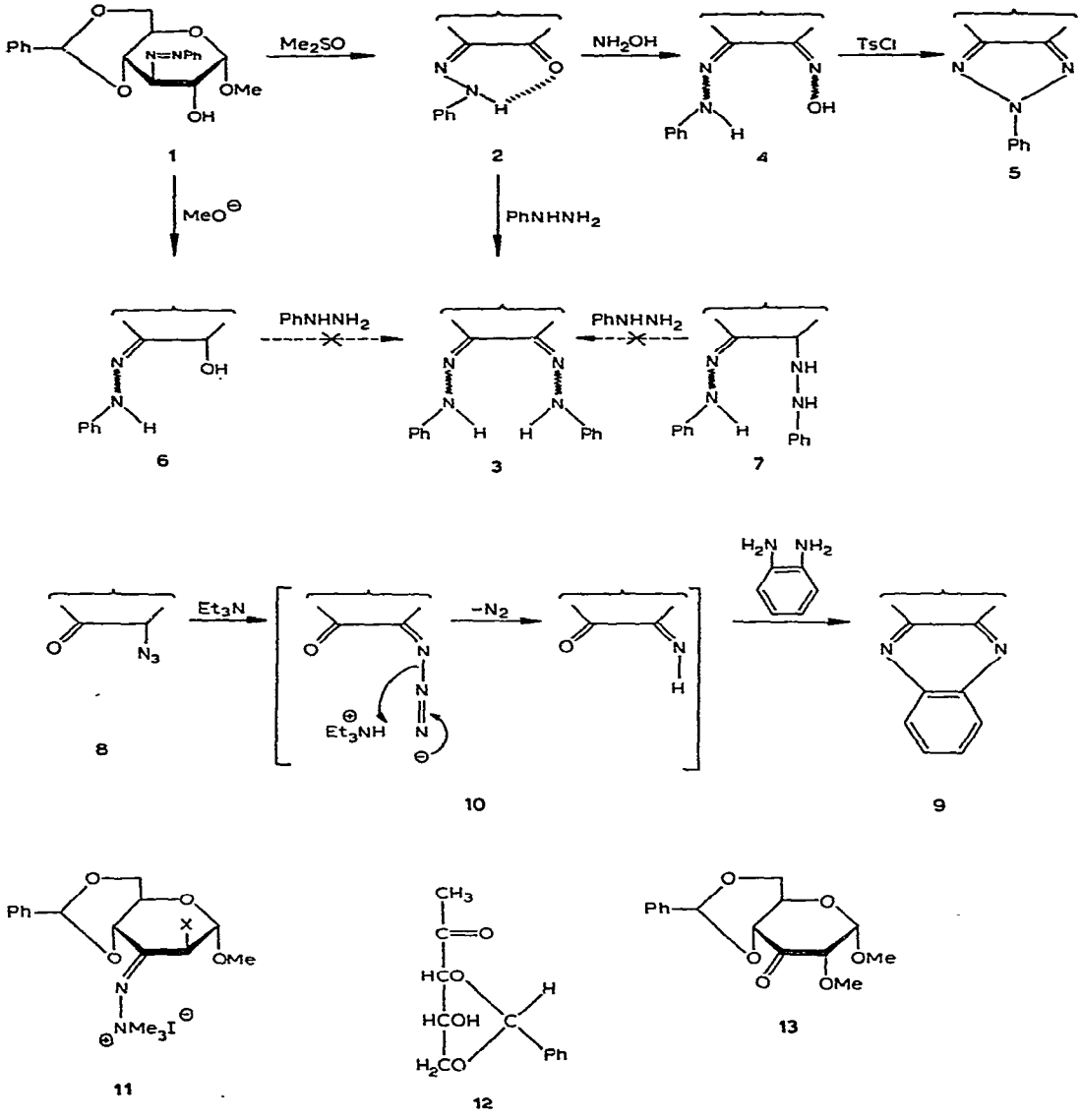
Glycopyranosid-diulose derivatives that contain an α-diketone structural unit are rare. The few preparations of this class of compounds that have been reported[1–3] usually employ rearrangement reactions, at least in the final step of the syntheses, rather than direct, oxidative methods. When diuloses are formed in these reactions, they are usually isolated as their anil derivatives.

We report here some approaches to the synthesis of anil derivatives of methyl 4,6-*O*-benzylidene-α-D-*erythro*-hexopyranosid-2,3-diulose.

RESULTS AND DISCUSSION

Direct oxidation of the vicinal, free-hydroxyl groups in methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was attempted with several reagents. Ruthenium tetraoxide in carbon tetrachloride[4] oxidised the glucoside derivative rapidly, but the product(s) formed were strongly complexed with the ruthenium dioxide precipitate, and a solvent which would extract the organic component was not found. Methyl sulphoxide with dicyclohexylcarbodi-imide and phosphoric acid[5] failed to give the required product, and in the presence of acetic anhydride[6], this oxidant gave only trace amounts of the diulose, as indicated by a low yield of the quinoxaline **9** isolated after the crude oxidation product had been treated with 1,2-diaminobenzene. It was

concluded that, in the oxidation stage, extensive methylthiomethyl ether formation had occurred.



The 3-phenylazo derivative[7] (**1**) of the glucopyranoside underwent smooth reaction with the Pfitzner–Moffat reagent to give a bright-yellow, crystalline product, which was identified from its elemental analysis, spectral characteristics, and reactions as the methyl hexopyranosid-2,3-diulose 3-phenylhydrazone derivative **2**. In particular, the ultraviolet spectrum indicated[8] that the O=C–C=NNHPh group was part

of the structure and this was confirmed by the infrared spectrum; it also exhibited an NH absorption band. The n.m.r. spectrum showed that the molecule contained an *O*-benzylidene residue, another phenyl group, an aglycon methyl group, an anomeric proton, four ring protons which gave unresolved signals, and an NH group which appeared as a broad singlet at very low field (*i.e.*, δ 14.03). We attribute the deshielding of this proton to the presence of the six-membered, chelated ring-system as shown in **2**. Presumably, compound **2** is formed from **1** by oxidation at C-2 followed by acid-catalysed isomerisation of the phenylazo group at C-3.

Compound **2** undergoes reaction with the usual ketonic reagents; for example, with phenylhydrazine, the known phenylosazone **3** was formed in quantitative yield, and with hydroxylamine, a crystalline product was obtained, which was shown by t.l.c. to contain two components. These were assumed to be geometric isomers since the mixture had the correct elemental analysis for the oximes depicted as **4** and, furthermore, treatment of the crude product with an excess of *p*-tolylsulphonyl chloride in pyridine gave the phenylosotriazole **5** in very high yield.

It should be possible to convert the α-hydroxyphenylazo compound **1**, *via* its tautomeric hydrazone form **6**, into a diulose derivative by the Fischer osazone synthesis. Chittenden and Guthrie[9] have shown that **1** is tautomerised in methanolic sodium methoxide to the *syn*-modification of **6**, which undergoes mutarotation in chloroform ($[\alpha]_D$ $+50 \rightarrow +157°$) to the *anti*-isomer. They also found that when either of these isomers was treated with phenylhydrazine under a variety of conditions, only on one occasion (with sodium ethoxide) did osazone formation occur, and even this reaction was not repeatable.

The *syn*-phenylhydrazone **6** isolated in this work had a different m.p. from the reported[9] value, but it mutarotated in a similar fashion ($[\alpha]_D$ $+55 \rightarrow +157°$) and the *anti*-isomer isolated was identical to that obtained by the earlier workers[9]. Its elemental analysis and n.m.r. spectrum showed that our *syn*-isomer (**6**) contained the additional elements of methanol, and it is probably this which accounts for the difference in m.p.

Attempts to convert compound **6** into the osazone **3** with phenylhydrazine in acetic acid failed and, furthermore, even the 2-phenylhydrazino-3-phenylhydrazone (**7**) could not be oxidised with this reagent. The failure of this oxidant, particularly in the latter case, was surprising since there are a number of precedents where oxidation proceeded readily for both five-[10] and six-membered ring[11] phenylhydrazino-phenylhydrazones.

A novel route to mono-imino derivatives of 1,2-diketones is the base-catalysed elimination of nitrogen from α-azido ketones[12]. This reaction has now been applied to methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranosid-3-ulose[15] (**8**). When **8** was treated with triethylamine in methanol, a gas, presumably nitrogen, was evolved but the only detectable organic product was benzaldehyde. However, when the reaction was conducted in the presence of 1,2-diaminobenzene, the known quinoxaline derivative **9** was isolated in 67% yield. This indicated that the α-imino-ketone **10** was formed in the reaction, probably by the mechanism shown. Attempts

to trap this intermediate with phenylhydrazine or hydroxylamine led only to the formation of the 3-phenylhydrazone or 3-oxime derivative, respectively, of the azide **8**. However, when **8** was treated with triethylamine in methyl sulphoxide containing pyridine and then treated with phenylhydrazine, the osazone **3** was isolated.

The base-catalysed reactions of other hydrazone derivatives of methyl hexosiduloses have also been examined.

Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose was prepared by the oxidation of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside with methyl sulphoxide and acetic anhydride. The product was identical with that obtained when the oxidant was ruthenium tetraoxide[4] or the chromium trioxide–pyridine complex[13], but the yield was relatively poor owing to the formation (up to 60%) of methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methylthiomethyl-α-D-*arabino*-hexopyranoside. Addition of dichloromethane (up to 67% by volume) to the oxidation mixture marginally increased the amount of the hexopyranosid-3-ulose. With the Pfitzner–Moffatt reagent, the amount of the methylthio derivative was reduced.

Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose reacted with 1,1-dimethylhydrazine to give the dimethylhydrazone which, on treatment with methyl iodide, gave a water-soluble trimethylhydrazone iodide (**11**, X = H). Both of these solid derivatives were difficult to purify. When **11** (X = H) was treated with aqueous sodium hydroxide and the product extracted into ether by vigorous stirring, it was found that, in the early part of the reaction, the parent methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose was detectable together with a second product. As the reaction proceeded, the hexopyranosidulose diminished in amount and the other product increased. When only one product was finally detectable, work-up gave a nitrogen-free solid which, on the basis of its elemental analysis and infrared and n.m.r. spectral properties, is considered to be 3,5-*O*-benzylidene-1-deoxy-D-*erythro*-pentulose (**12**). Attempts to carry out the same conversion by treatment of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose with aqueous sodium hydroxide in *p*-dioxane gave decreased yields of compound **12** and gave other unidentified, and apparently unstable, products. The improved yields of **12** from **11** (X = H) may simply reflect the greater water-solubility of this compound compared with the parent 3-ulose. When the trimethylhydrazone iodide of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-*arabino*-hexopyranosid-3-ulose (**11**, X = OMe) was treated with aqueous sodium hydroxide as previously described, a single, crystalline, nitrogen-free product was isolated. It showed i.r. absorption for carbonyl but not for hydroxyl. The n.m.r. spectrum indicated the presence of two methoxyl groups and was consistent with the compound's being methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-*ribo*-hexopyranosid-3-ulose (**13**), *i.e.*, loss of the trimethylhydrazone iodide grouping and epimerisation at C-2 had occurred. No evidence of the occurrence of an elimination product was obtained. Subsequently, compound **13** (OMe equatorial) was obtained directly, and in high yield, by treatment of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-*arabino*-hexopyranosid-3-ulose (OMe axial) with triethylamine in 96% aqueous ethanol[14].

EXPERIMENTAL

Methods. — Unless stated otherwise, infrared spectra were measured on solid samples dispersed in KBr, with a Perkin–Elmer Infracord model 137; ultraviolet spectra were obtained for ethanol solutions with a Perkin–Elmer Spectrophotometer model 402; optical rotations were measured on chloroform solutions with a Bellingham and Stanley Polarimeter, and n.m.r. spectra were obtained with a Varian A-60 instrument.

*Methyl 4,6-O-benzylidene-α-*D-erythro-*hexopyranosid-2,3-diulose 3-phenylhydrazone* (**2**). — Phosphoric acid (4 ml) was added dropwise to a stirred solution of methyl 4,6-*O*-benzylidene-3-deoxy-3-phenylazo-α-D-glucopyranoside (**1**, 10.5 g) and dicyclohexylcarbodi-imide (12.5 g) in methyl sulphoxide (100 ml) at room temperature. The reaction mixture was left for 18 h and then the mixture was worked-up in the usual way[5] to give, after recrystallisation from ethanol, **2** (6.8 g, 65%), m.p. 193–195°, $[\alpha]_D^{24}$ −438° (*c* 0.6); ν_{max} 1655, 1610, and 1500 cm^{-1} (O=C–C=NNHPh); λ_{max} 228 and 385 nm. N.m.r. data: δ 4.79 (*s*, H-1), 4.80–3.80 (complex *m*, H-4,5,6,6'), 3.52 (*s*, OMe), 5.72 (*s*, PhC*H*), 7.70–6.90 (complex *m*, Ph), 14.04 (*s*, N*H*).

Anal. Calc. for $C_{20}H_{20}N_2O_5$: C, 65.2; H, 5.5; N, 7.6. Found: C, 65.1; H, 5.2; N, 7.7.

*Methyl 4,6-O-benzylidene-α-*D-erythro-*hexopyranosid-2,3-diulose bisphenylhydrazone* (**3**). — The phenylhydrazone **2** (0.9 g) was heated with phenylhydrazine (1.5 g) in methanol (20 ml) until dissolution was complete. Cooling then gave the yellow bisphenylhydrazone (**3**) (1.0 g, 90%), m.p. 219–220° (dec.), $[\alpha]_D^{24}$ −592° (*c* 1.0); lit.[2] m.p. 210° (dec.), $[\alpha]_D^{26}$ −557°.

Anal. Calc. for $C_{26}H_{26}N_4O_4$: C, 68.1; H, 5.7; N, 12.2. Found: C, 68.2; H, 5.6; N, 12.3

*Methyl 4,6-O-benzylidene-α-*D-erythro-*hexopyranosid-2,3-diulose 2-oxime 3-phenylhydrazone* (**4**) *and phenylosotriazole* (**5**). — The phenylhydrazone **2** (4 g) and hydroxylamine hydrochloride (0.8 g) were dissolved in pyridine (10 ml) and left at room temperature for 24 h. The solution was then poured into water to give a solid (4 g, 96%), which t.l.c. showed contained the *syn-* and *anti*-isomers of the oxime-hydrazone **4**.

Anal. Calc. for $C_{20}H_{21}N_3O_5$: C, 62.7; H, 5.5; N, 11.0. Found: C, 63.1; H, 5.7; N, 11.1.

A dried sample of compound **4** (3.5 g) was dissolved with *p*-tolylsulphonyl chloride (3 g) in pyridine (25 ml) and left at 0° for 3 days. The solution was then poured into water (100 ml) and the resulting precipitate was filtered off to give the phenylosotriozole **5** (2.9 g, 87%), m.p. 242–243°, $[\alpha]_D^{24}$ −33.6° (*c* 2.0), ν_{max} 1605 and 1505 cm^{-1}. N.m.r. data (C_5D_5N): δ 6.07 broad (*s*, H-1), 5.99 (*s*, PhC*H*), 5.5–4.1 (complex *m*, H-4,5,6,6'), 3.57 (*s*, OMe), 8.4–7.1 (2Ph).

Anal. Calc. for $C_{20}H_{19}N_3O_4$: C, 65.7; H, 5.2; N, 11.5. Found: C, 65.4; H, 5.3; N, 11.3.

Methyl 4,6-O-benzylidene-α-D-ribo-hexopyranosid-3-ulose syn-*phenylhydrazone* (**6**). — Compound **1** (3.5 g) was heated in boiling, methanolic sodium methoxide (0.08M, 100 ml) for 2 h under nitrogen. The yellow colour of the solution faded quickly and colourless needles formed after ~15 min. Cooling and storage in a refrigerator for several hours gave **6** as colourless crystals (3.35 g), m.p. 149–152° (with some darkening and evolution of gas); the product then re-solidified and re-melted with decomposition at 187–190°; **6** had $[\alpha]_D^{24}$ +55→ +156.5° in 18 h (*c* 1.0). Chittenden and Guthrie[9] reported m.p. 163–165°, $[\alpha]_D$ +49.8→ +156.8° for this compound.

Anal. Calc. for $C_{20}H_{22}N_2O_5 \cdot CH_3OH$: C, 62.7; H, 6.5, N, 7.0. Found: C, 62.4; H, 6.3; N, 7.3.

This phenylhydrazone (2.5 g) was isomerised to the *anti* form by treatment with hot methanol (100 ml) containing glacial acetic acid (a few drops). It was obtained as fine, white needles (2.4 g), m.p. 198–200° (dec.), $[\alpha]_D$ +158° (*c* 1.0); lit.[9] m.p. 208–210°, $[\alpha]_D^{23}$ +157°.

Anal. Calc. for $C_{20}H_{22}N_2O_5$: C, 64.8; H, 6.0; N, 7.6. Found: C, 64.9; H, 6.1; N, 7.5.

Treatment of either of the above phenylhydrazones with phenylhydrazine and acetic acid in boiling methanol or 2-methoxyethanol under nitrogen gave only the *anti*-phenylhydrazone; insignificant amounts of the osazone **3** were obtained.

Treatment of methyl 2-azido-4,6-O-benzylidene-2-deoxy-α-D-ribo-hexopyranosid-3-ulose (**8**) *with triethylamine.* — (*a*) *In ethanol.* Triethylamine (0.5 ml) was added to a warm solution of methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranosid-3-ulose[15] (**8**) (0.3 g) and 1,2-diaminobenzene (0.6 g) in ethanol (25 ml). A reaction occurred from which nitrogen gas was evolved; it was taken to completion by heating for 10 min under reflux. After cooling, the reaction solution was poured into water and the quinoxaline derivative **9** separated as needles (0.24 g, 70%), m.p. 246–248° (dec.), $[\alpha]_D^{24}$ −94.7° (*c* 1.0); lit.[1] m.p. 230–240° (dec.), $[\alpha]_D^{18}$ −90°. N.m.r. data: δ 5.89 (*s*, H-1), 5.0 (*d*, $J_{4,5}$ 9.0), 4.8–3.9 (complex *m*, H-5,6,6'), 3.71 (*s*, OMe), 5.75 (*s*, PhC*H*), 8.4–3.2 (complex *m*, Ph).

Anal. Calc. for $C_{20}H_{18}N_2O_4$: C, 68.6; H, 5.2; N, 8.0. Found: C, 68.2; H, 5.0; N, 8.0.

(*b*) *In methyl sulphoxide.* Triethylamine (0.8 ml) was added to a solution of the azido-ulose **8** (0.3 g) in methyl sulphoxide (3 ml) and pyridine (3 ml) at 40°. When the evolution of nitrogen ceased, phenylhydrazine hydrochloride (0.3 g) was added and the mixture was left at room temperature overnight. The product was precipitated with water and shown to be the bisphenylhydrazone **3** (0.1 g, 22%), identical with that isolated previously.

Methyl 4,6-O-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose. — Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside (10.6 g) was dissolved in a mixture of methyl sulphoxide (120 ml), acetic anhydride (80 ml), and dichloromethane (400 ml), and the solution was stored at room temperature for 24 h. After heating under reflux for a further 24 h, the solution was cooled and poured into water (1 litre). Potassium carbonate (120 g) was added portionwise with vigorous stirring.

The organic layer was separated, washed thrice with water (250-ml portions), dried (Na_2SO_4), filtered, and concentrated to a semi-solid mass which contained two components. Extraction with light petroleum (b.p. 60–80°) and recrystallisation of the solid residue from ethanol gave methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (4.5 g, 42%), m.p. 167–169°; lit.[13] m.p. 177–178°, lit.[4] m.p. 171–172°.

The light petroleum extract was concentrated to a colourless syrup which slowly solidified. Repeated recrystallisation from light petroleum (b.p. 60–80°) gave methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methylthiomethyl-α-D-*arabino*-hexopyranoside as long, colourless needles, m.p. 64–66°, $[\alpha]_D^{24}$ +145° (*c* 4), which had no i.r. absorption for C=O or OH. The n.m.r. spectrum resembled that of the starting material but lacked the hydroxyl proton peak and showed an additional 2-proton singlet at δ 4.81 and a 3-proton singlet at δ 2.12.

Anal. Calc. for $C_{16}H_{22}O_5S$: C, 58.9; H, 6.8; S, 9.8. Found: C, 58.9; H, 6.6; S, 9.3.

3,5-O-Benzylidene-1-deoxy-D-erythro-*pentulose* (**12**). — Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (2.6 g) in 1,1-dimethylhydrazine (10 ml), ethanol (50 ml), and glacial acetic acid (0.2 ml) was stored at room temperature for 20 h. Concentration of the mixture afforded a thick syrup which solidified. Recrystallisation from light petroleum (b.p. 60–80°) gave the dimethylhydrazone (3.0 g, 96%), m.p. 98–100°. This product was not purified further, but a portion (2.4 g) in acetonitrile (15 ml) and benzene (10 ml) was treated with methyl iodide (5 ml) at ambient temperature for 22 h. Removal of the solvent gave a semi-solid mass which was triturated with ethanol. The almost colourless solid (3.1 g) was collected by filtration and washed with benzene. Freshly prepared methiodide (6.6 g) in water (250 ml) was added to 2M aqueous sodium hydroxide (7.5 ml) and ether (150 ml). The mixture was stirred vigorously and the ethereal layer examined periodically by t.l.c. After 0.3 h, the parent hexosidulose and a second mobile component were observed in approximately equal amounts. After 3 h, the new product was the sole component in the ethereal layer, which was then separated, dried ($MgSO_4$), filtered, and concentrated to a syrup that crystallised. This product (2 g) was recrystallised thrice from light petroleum (b.p. 60–80°) to give the title compound (1.35 g), m.p. 76.5–78.5°, $[\alpha]_D^{24}$ +38.7° (*c* 2); ν_{max} 3500, 1720, 755, and 700 cm^{-1}. N.m.r. data: δ 7.65–7.10 (5H, Ph), 5.50 (*s*, 1H, C_6H_5CH), 2.29 (3H, Me), 3.46 (1H exchangeable with D_2O, OH), 4.5–3.5 (4H, complex multiplet).

Anal. Calc. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.6; H, 6.4.

*Methyl 4,6-O-benzylidene-2-O-methyl-α-*D-ribo-*hexopyranosid-3-ulose* (**13**). — Methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-*arabino*-hexopyranosid-3-ulose was converted into its dimethylhydrazone methiodide as described above. The crude methiodide (2 g) in water (40 ml) was extracted twice with benzene to remove coloured material and then was treated with 2M aqueous sodium hydroxide (1.5 ml) and benzene (40 ml). After 5 days, the benzene layer was separated, washed with water, dried ($MgSO_4$), filtered, and concentrated to a syrup, from which crystalline material

was obtained by trituration with dichloromethane and light petroleum. When recrystallised from the same solvent, the title compound (0.2 g) was obtained with m.p. 195–199°, $[\alpha]_D^{24}$ +45° (*c* 1.0); ν_{max} 1745 cm^{-1} (C=O). N.m.r. data: δ 3.57 and 3.47 (each 3H, *s*, OMe) and 5.23 (*d*, H-1, $J_{1,2}$ 4.5 Hz).

Anal. Calc. for $C_{15}H_{18}O_6$: C, 61.2; H, 6.2. Found: C, 61.2; H, 5.8.

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