ARYLAZO-GLYCENOSIDES

PART III[1]. CONVERSION OF METHYL 4,6-*O*-BENZYLIDENE-3-DEOXY-α-D-*erythro*-HEXOPYRANOSIDULOSE INTO 4,6-*O*-BENZYLIDENE-3-DEOXY-D-*erythro*-HEXOSULOSE 2-PHENYLHYDRAZONE*

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ABSTRACT

It has been shown that the phenylhydrazone of methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosidulose, on treatment with mild base, affords 4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hexosulose 2-phenylhydrazone. This conversion is considered to involve 1,4-elimination of methanol to give 4,6-*O*-benzylidene-2,3-dideoxy-3-phenylazo-D-*erythro*-hex-1-enopyranose as an intermediate, which is then hydrolysed with overall 1,4-addition of water. The existence of this phenylhydrazone in the *aldehydo*-form is discussed, and a comparison made with some other aldose derivatives which possess an sp^2 hybridised carbon atom at position 2.

INTRODUCTION

Previously, we reported[1] that glycopyranosidulose phenylhydrazones, substituted at the α-position to the anil carbon atom with residues that function as good leaving-groups, can be converted into azoalkene derivatives. This transformation involves mild, base-catalysed 1,4-elimination of a carboxylic acid or sulphonic acid from, respectively, a phenylhydrazone benzoate or toluene-*p*-sulphonate. Others have reported similar transformations[2]. An examination of the behaviour of a glycopyranosidulose phenylhydrazone which possesses no adjacent ester substituent is now reported.

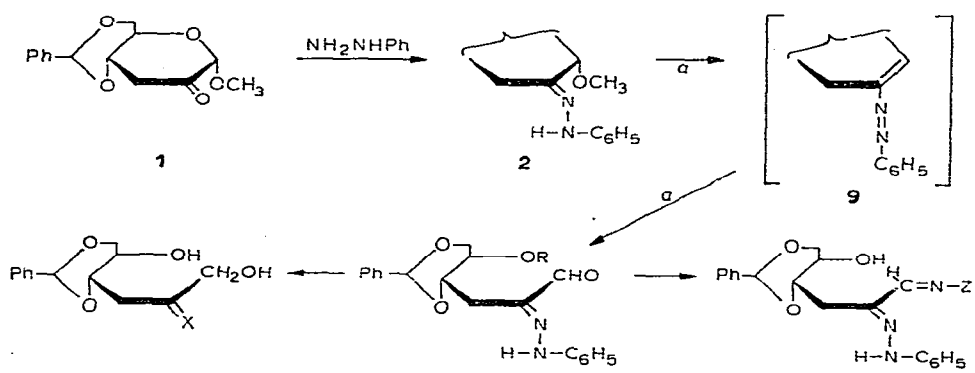
RESULTS AND DISCUSSION

Treatment of methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosidulose (**1**) with phenylhydrazine hydrochloride in pyridine at room temperature for one hour gave the phenylhydrazone derivative **2** (46%), which was identical with the product obtained from the reduction[1] of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-phenylazo-α-D-*erythro*-hex-2-enopyranoside with sodium borohydride. In an effort to improve

*Dedicated to Professor M. Stacey, C.B.E., F.R.S., in honour of his 65th birthday.

the yield of the phenylhydrazone **2**, the reaction period was extended (12 h) but, surprisingly, this reaction afforded only a trace of **2**, as shown by t.l.c. Instead, another compound, less mobile on t.l.c., was formed in high yield. It was easily isolated, as bright-yellow crystals, and identified from its elemental analysis and spectral characteristics as 4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hexosulose 2-phenylhydrazone (**3**). In particular, the infrared spectrum indicated that OH, NH, and O=C–C=N–NPh functional groups were part of the structure. The presence of the last-mentioned group was also indicated by three u.v. absorption maxima at 238, 296, and 345 nm, the positions and intensities of which were very similar to those reported by Henseké and Winter[3] for the structurally similar 1-phenylhydrazones of methyl-glyoxal and D-*arabino*-hexosulose. The n.m.r. spectrum of the phenylhydrazone **3** exhibited two high-field quartets due to the C-3 methylene protons. The signals for the other chain-protons (H-4,5,6) appeared, together with the signal for the hydroxyl proton, as a complex multiplet. The most significant signal was the sharp singlet arising from the aldehydic proton which appeared at very low field (τ 0.5), just above the imino-proton singlet.

The reactions exhibited by compound **3** provide additional evidence for the proposed structure. The presence of the free hydroxyl group was confirmed by the formation of an acetyl derivative (**4**) which gave a n.m.r. spectrum containing a three-proton singlet due to the acetyl methyl group but otherwise similar to that of **3**. Chemical evidence for a carbonyl group was obtained by the formation of oxime and phenylosazone derivatives (**5** and **6**). The latter compound, produced by treating the phenylhydrazone **3** with one mol. of phenylhydrazine, was the same as 4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hexosulose bis(phenylhydrazone) prepared by Micheel and his co-workers[4] by an independent route. Reduction of the phenylhydrazone **3** with sodium borohydride, followed by hydrolysis of the reduced product (**7**) with aqueous, ethanolic acetic acid containing pentane-2,4-dione, gave 4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hexulose (**8**). The ease with which the phenylhydrazone residue was removed from this reduced compound contrasts markedly with the resistance to



1 2 9

7 X=NNHPh
8 X=O

3 R=H
4 R=Ac

5 Z=OH
6 Z=NHPh

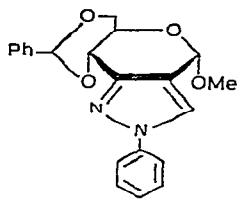
Scheme 1

hydrolysis shown by the hexosulose derivative **3**. Even prolonged treatment of this compound with aqueous acetic acid gave no free hexosulose.

The alternative structure for compound **3**, with the phenylhydrazone residue at the aldehydic (C-1) position, rather than the keto (C-2) position as proposed, can be excluded because compound **3** has a melting point different from that of 4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hexosulose 1-phenylhydrazone prepared by Micheel and his co-workers[4].

A possible route to the hexosulose phenylhydrazone **3** from the glycopyranosidulose **1** is shown in Scheme 1 (path *a*). Base-catalysed elimination of methanol from the pyranosidulose phenylhydrazone **2**, involving either phenylhydrazine or pyridine as catalyst, would give rise to the intermediate unsaturated compound **9** which would be hydrolysed readily, either in the reaction medium or during work-up for product isolation.

It is noteworthy that Paulsen and Stoye[5] have found that the aglycon methoxyl group can be eliminated from the hydrazone of the pyranosidulose **1**. However, this transformation requires strong base and the reaction differs from that reported here, since elimination is accompanied by disproportionation which leads to nitrogen and 4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hex-1-eno-pyranose. It is noteworthy that hydrolysis of the pyrazole **10** gives an acylic sugar derivative[6], probably by a similar mechanism.



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The existence of compound **3** in the open-chain form is noteworthy. It would appear from these results, and reports in the literature, that certain aldose derivatives with unsaturated functional groups at position 2 tend to exist in the open-chain aldehydo-form rather than as the pyranoid structure. This tendency probably arises from the resonance energy possessed by such conjugated structures. Fraser-Reid[7] has found, for example, that 4,6-*O*-benzylidene-2,3-*C*-cyclomethylene-2,3-dideoxy-D-allose exists in the open-chain form, as does 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-*trans*-hex-2-enose.

EXPERIMENTAL

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 ethanolic solutions with a Perkin–Elmer Spectrophotometer 402; mass spectra were measured on an A.E.1. MS 902 instrument operated with an ionising potential of 70 eV and a probe inlet temperature of 150°; and the 60- and 100-MHz n.m.r. spectra were determined with Varian Associates A-60D or HA-100D instruments.

*Methyl 4,6-O-benzylidene-3-deoxy-α-*D-erythro-*hexopyranosidulose* (**1**).—Methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside (7.0 g), prepared according to the method of Prins[8], was oxidised[9] in methyl sulphoxide (70 ml) containing acetic anhydride (35 ml) to give compound **1** (4.4 g, 64%), m.p. 110–111°, $[\alpha]_D$ +94° (chloroform), which was identical with material prepared previously in our laboratory by oxidation[10] of the same *arabino*-glycoside with ruthenium tetroxide.

*Methyl 4,6-O-benzylidene-3-deoxy-α-*D-erythro-*hexopyranosidulose phenylhydrazone* (**2**). — The methyl glycopyranosidulose **1** (0.2 g) was dissolved in pyridine (1.5 ml), phenylhydrazine hydrochloride (0.13 g) was added, and the mixture was left in the dark, at room temperature, for 1 h. Water was added and the solid which separated was collected and recrystallised from ethanol to afford the phenylhydrazone **2** as cream-coloured needles (0.12 g, 46%), m.p. 175–180°, λ_{max} 275 nm (ε 27,800); ν_{max} 3300 (NH), 1600 and 1500 cm^{-1} (C=N–NPh); lit.[1] m.p. 177–179°.

*4,6-O-Benzylidene-3-deoxy-*D-erythro-*hexosulose 2-phenylhydrazone* (**3**). — The pyranosidulose **1** (4.0 g) was treated with phenylhydrazine hydrochloride (2.5 g), as described above, but for 12 h. Work-up of the reaction mixture afforded the phenylhydrazone **3** as bright-yellow plates (3.8 g, 74%), m.p. 197–198°, $[\alpha]_D$ −737° (chloroform), λ_{max} (ε) 238 (7800), 296 (2000), 345 nm (21000); ν_{max} 3400 (OH), 3200 (NH), 1650 (CO, conj.), 1600, 1560, and 1500 cm^{-1} (C=N–NPh). The 100-MHz n.m.r. spectrum measured in $CDCl_3$ showed 20 protons at τ 0.3 (s, NH); 0.5 (s, CHO); 2.5~3.4 (cm, Ph_2); 4.48 (s, PhC*H*); 5.75 (q), 6.0 (o), 6.3~6.6 (cm, 5H) (H-4,5,6,6′, and OH); 6.7 (q, $J_{3,4}$ 4 and $J_{3,3'}$ 12.5 Hz, H-3); 7.3 (q, $J_{3',4}$ 3 Hz, H-3′). The mass spectrum had peaks at *m/e* 340 (M^+, 19%), 322 (15%), 105 (51%), 91 (32%), 77 (85%), and 93 which was the base peak.

Anal. Calc. for $C_{19}H_{20}N_2O_4$: C, 67.0; H, 5.9; N, 8.2. Found C, 66.9; H, 6.0; N, 8.0.

*Reactions of 4,6-O-benzylidene-3-deoxy-*D-erythro-*hexosulose 2-phenylhydrazone* (**3**).—(*a*) *Acetylation.* The phenylhydrazone **3** (0.2 g) was treated with acetic anhydride (0.2 ml) in dry pyridine (1 ml) at room temperature for 2 h. Water was added and the cream-coloured solid which separated was recrystallised from ethanol to yield the acetate **4** as yellow needles (0.15 g, 67%), m.p. 122°; ν_{max} 3200 (NH), 1730 (AcO), 1680 (CHO), 1600, 1560, and 1500 cm^{-1} (C=N–NPh). The n.m.r. spectrum measured at 60 MHz in $CDCl_3$ showed 22 protons at τ 0.43 (s, NH), 0.7 (s, CHO), 2.4~3.5 (cm, Ph_2), 4.46 (s, PhC*H*), 5.0–6.6 (cm, 4H, H-4,5,6,6′), 7.0~7.2 (d, H-3,3′), 7.85 (s, CH_3CO_2).

Anal. Calc. for $C_{21}H_{22}N_2O_5$: C, 66.0; H, 5.8; N, 7.3. Found: C, 65.8; H, 5.7; N, 7.1.

(*b*) *Oximation.* The phenylhydrazone **3** (0.2 g) in pyridine (1 ml) was treated with hydroxylamine hydrochloride (0.08 g) for 2 h at room temperature. The orange solid which separated upon addition of water (5 ml) was recrystallised from ethanol to afford the oxime **5**, m.p. 135–137°; ν_{max} 3300 and 3250 (broad), 1600, 1560, and 1500 cm^{-1} (C=N–NPh).

Anal. Calc. for $C_{19}H_{21}N_3O_4$: C, 64.2; H, 6.0. Found: C, 64.4; H, 5.9.

(*c*) *Phenylosazone formation.* The phenylhydrazone **3** (0.2 g) in pyridine (2 ml) was treated with phenylhydrazine hydrochloride (0.1 g) for 1 h at room temperature. Water (5 ml) was then added and the solid which separated was recrystallised from ethanol to give 4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hexosulose bis(phenylhydrazone) (**6**) as yellow needles (0.16 g, 64%), m.p. 188–189°; *lit.*[4] m.p. 185–190°; ν_{max} 3450 (NH), 3350 (OH), 1610, 1580, 1570, 1520, and 1500 cm^{-1}. The n.m.r. spectrum showed 26 protons at τ 1.0 (s, NH), 2.35~3.5 (cm, Ph_3, NH, and HC=N), 4.45 (s, PhC*H*), 5.7~7.0 (cm, 7H).

Anal. Calc. for $C_{25}H_{26}N_4O_3$: C, 69.8; H, 6.1; N, 13.0. Found: C, 70.1; H, 6.5; N, 12.9.

(*d*) *Reduction.* The phenylhydrazone **3** (0.3 g) was suspended in methanol (10 ml) and sodium borohydride (0.1 g) was added. After 0.5 h at room temperature, water was added to the reaction mixture and the solid which separated was recrystallised from ethanol–water to afford 4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hexulose phenylhydrazone (**7**) (0.25 g, 82%), m.p. 139–141°, $[\alpha]_D$ +84° (methanol); ν_{max} 3300 and 3200 (OH and NH), 1600, 1550, and 1500 cm^{-1} (C=N–NPh). The n.m.r. spectrum measured at 60 MHz in $CDCl_3$ showed 21 protons at τ 1.47 (s, NH), 2.5~3.5 (cm, Ph_2), 4.52 (s, PhC*H*), 5.6–5.9 (d, 2H), 6.0~6.7 (cm, 6H), 7.15~7.3 (m, H-3,3'); the NH signal and two proton resonances in the region 6.0–6.7 were lost on deuteriation.

Anal. Calc. for $C_{19}H_{22}N_2O_4$: C, 66.7; H, 6.5; N, 8.2. Found: C, 66.8; H, 6.6; N, 8.1.

4,6-O-Benzylidene-3-deoxy-D-erythro-*hexulose* (**8**). — The phenylhydrazone **7** (0.1 g) was stirred with 60% aqueous ethanol (5 ml) containing pentane-2,4-dione (0.05 ml) and acetic acid (0.2 ml) for 2 h at 50°. The solution was evaporated to dryness, water (2 ml) was then added, and the solution was re-evaporated. This procedure was repeated three times. The residue was recrystallised from ethanol to yield the title compound (**8**) (0.05 g, 61%), m.p. 114–114.5°; ν_{max} 3475, 3400 (OH), 1750 cm^{-1} (CO). The n.m.r. spectrum measured at 60 MHz in $CDCl_3$ showed 16 protons at τ 2.5–2.8 (cm, Ph), 4.52 (s, PhC*H*), 5.6–6.5 (cm, 6H), and 6.8–7.4 (cm, 4H); deuteriation with D_2O caused the loss of 2 protons in the region τ 6.8–7.4.

Anal. Calc. for $C_{13}H_{16}O_5$: C, 61.9; H, 6.4. Found: C, 62.1; H, 6.4.

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