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METHYL 2,3,6-TRIDEOXY-2,3-EPIMINO-α-D-ALLOPYRANOSIDE

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ABSTRACT

The reduction of methyl 2-benzamido-2-deoxy-3,4,6-tri-*O*-methanesulphonyl-α-D-glucopyranoside with lithium aluminium hydride gave methyl 2,3,6-trideoxy-2,3-epimino-α-D-allopyranoside. The structure of the epimine was proved by an unequivocal synthesis from methyl 2,3-acetylepimino-4,6-*O*-benzylidene-2,3-dideoxy-α-D-allopyranoside by removal of the benzylidene substituent with *N*-bromosuccinimide, followed by reductive dehalogenation of the resulting 6-bromo derivative and the removal of the 4-*O*-benzoyl and *N*-acetyl substituents.

INTRODUCTION

Carbohydrate epimines, unknown before 1960, are potentially useful intermediates for the synthesis of diamino sugars[1], amino-halo sugars[2,3], aminodideoxy sugars[2], unsaturated sugars[4], etc., by way of ring-opening reactions with various nucleophiles. Several methods are available for their preparation[3,5–8], one of which[7] employs the action of lithium aluminium hydride on a compound containing a benzamido substituent *trans* to a vicinal sulphonyloxy group. We[8] have previously described the preparation of methyl 3,4,6-trideoxy-3,4-epimino-α-L-galactopyranoside from methyl 3-benzamido-3,6-dideoxy-2,4-di-*O*-mesyl-α-L-glucopyranoside by this method, and we now wish to report a related synthesis of an isomeric epimine, methyl 2,3,6-trideoxy-2,3-epimino-α-D-allopyranoside.

RESULTS AND DISCUSSION

The action of lithium aluminium hydride on methyl 2-benzamido-2-deoxy-3,4,6-tri-*O*-methanesulphonyl-α-D-glucopyranoside (**2**) gave a product (20% yield) which possessed the properties expected of a 2,3-epimino-allopyranoside (**3**). In order to confirm this structure, an unequivocal synthesis of epimine **3** from the known[3,7]

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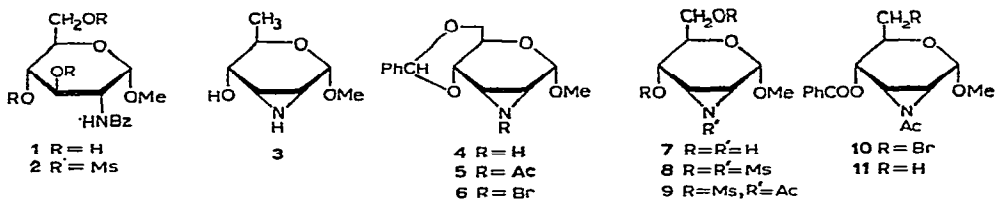
methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-epimino-α-D-allopyranoside (**4**) was pursued. Initially, it was hoped that methyl 2,3-dideoxy-2,3-epimino-α-D-allopyranoside hydrochloride (**7**·HCl), which is readily prepared[3] from compound **4**, could be converted into the 6-deoxy analogue by standard methods. Thus, methanesulphonylation of the hydrochloride of **7** gave the corresponding tri-*O*-methanesulphonyl derivative **8**, but none of the required 6-deoxy-epimine (**3**) could be detected chromatographically when this compound was treated with lithium aluminium hydride. We have recently found[9] that, whereas the epimine ring is resistant to ring-opening by lithium aluminium hydride, the methanesulphonylepimino ring is readily opened. In an alternative approach, the epimine hydrochloride (**7**·HCl) was *N*-acetylated[10], and then methanesulphonylated. Treatment of the resulting disulphonate **9** with lithium aluminium hydride gave mainly methyl 2,3-dideoxy-2,3-epimino-α-D-allopyranoside (**7**) (identified chromatographically), and only a trace of the required 6-deoxy derivative could be detected. Selective replacement of the 6-sulphonyloxy group of compound **9** by thiocyanate, which might provide an alternative route to the 6-deoxy-epimine **3**, was also unsuccessful.



A recent method of removing 4,6-*O*-benzylidene substituents from hexopyranosides involves treatment with *N*-bromosuccinimide to give the corresponding 4-*O*-benzoyl-6-bromo-6-deoxyhexopyranosides and thence[11] the 6-deoxy derivatives. When this reaction was applied to the free epimine **4** with about 1 mole of reagent, the benzylidene ring was not ruptured; instead, *N*-bromination took place to give methyl 4,6-*O*-benzylidene-2,3-bromoepimino-2,3-dideoxy-α-D-allopyranoside (**6**) in 25% yield. This product was more conveniently formed (73% yield) when the epimine **4** was treated with sodium hypobromite. When the reaction was applied to the acetylepimine **5**, however, it followed the normal course to give the required methyl 2,3-acetylepimino-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-allopyranoside (**10**) as a syrup. Reductive dehalogenation of the bromo derivative with Raney nickel in ethanol yielded the crystalline 6-deoxy-4-benzoate **11**, which, on treatment with sodium methoxide, gave methyl 2,3,6-trideoxy-2,3-epimino-α-D-allopyranoside (**3**) identical with the product obtained from the 3,4,6-trimethanesulphonate **2**.

The structures of the 6-bromo-4-benzoate **10** and the derived 6-deoxy derivative (**11**) were proved by their 100 MHz n.m.r. spectra. Previous n.m.r. data for epiminopyranosides[8,12] have shown (*i*) that protons situated at the bridgehead positions of the three- and six-membered rings are coupled to adjacent protons on the pyranoside ring only if they are *cis* and (*ii*) that these protons are to high field of most other ring-protons (τ 6.9–7.9). The bromo derivative **10** showed (Fig. 1) a

complex 2-proton multiplet at τ 6.76 associated with the epimine ring. The low-field multiplet at τ *ca.* 5 was assigned to H-1 and H-4, and this was clearly demonstrated by irradiating at the frequency of H-2,3, when the multiplet collapsed to a broad doublet (H-4; J 9.5 Hz) and a broad singlet (H-1). The H-5 resonance was clearly observed at τ 5.9 as a septet, and the C-6 protons as the AB part of an ABX system (Fig. 1). The 6-deoxy-4-benzoate **11** had a similar spectrum, except that the C-6 protons occurred as a doublet at τ 8.78. H-2 and H-3 were observed at τ 6.82, and H-1 and H-4 as overlapping multiplets at τ *ca.* 5.16; H-5 gave an octet at τ 6.0 similar to that observed for H-5 in methyl 3,4,6-trideoxy-3,4-epimino-α-D-galacto-pyranoside[8] and its derivatives. Irradiation at the frequency of H-2,3 collapsed the multiplet at τ 5.16 into a singlet (H-1) and a doublet (H-4; J 9.0 Hz), and irradiation at the frequency of H-6 collapsed the H-5 octet into what was almost a doublet (J 9.0 Hz).

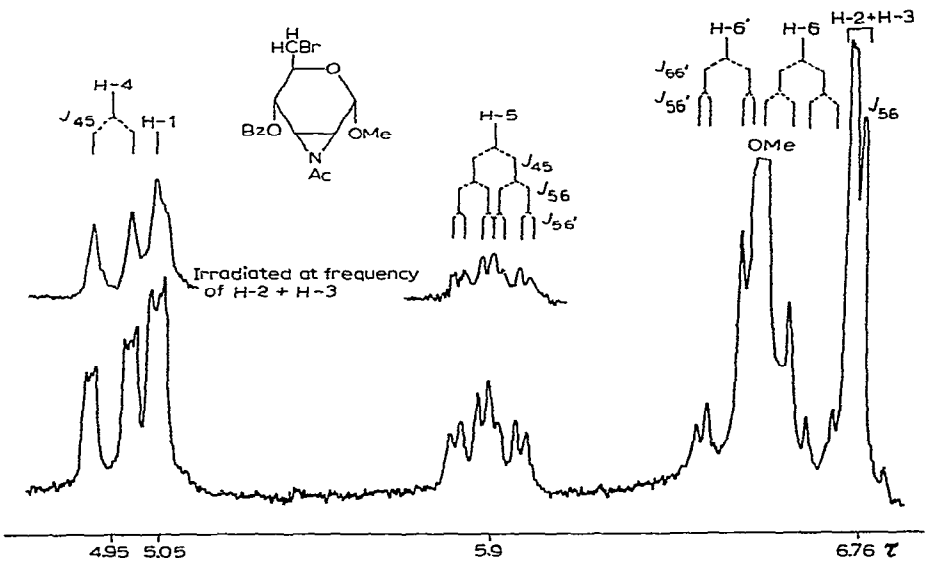


Fig. 1. The 100 MHz n.m.r. spectrum of methyl 2,3-acetylepimino-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-allopyranoside (**10**) with the results of decoupling experiments.

EXPERIMENTAL

M.p.s. were measured on a Kofler microstage. Optical rotations were determined at 20° in chloroform on a Perkin–Elmer 141 polarimeter, unless otherwise stated. P.m.r. spectra were measured on a Varian HA-100 spectrometer with tetramethylsilane as internal reference.

Methyl 2-benzamido-2-deoxy-3,4,6-tri-O-methanesulphonyl-α-D-glucopyranoside (**2**). — A solution of 17 g of methyl 2-benzamido-2-deoxy-α-D-glucopyranoside[13] (**1**) in dry pyridine (300 ml) was cooled in an ice bath, and methanesulphonyl chloride (50 g) was added slowly (5 min) with mechanical stirring. The solution was left

for 6 h at room temperature and cooled, and ice (50 g) was then added. After 1 h at room temperature, the mixture was evaporated to a thick slurry which was extracted with chloroform (5 × 100 ml). The chloroform extract was washed with water (100 ml), dried ($CaSO_4$), and evaporated. The residue crystallised from a mixture of methanol (100 ml) and ethanol (30 ml) as two crops. The trisulphonate (17.6 g, 58%) had m.p. 151° (decomp.) and $[\alpha]_D$ +85° (*c* 0.3) (Found: C, 38.4; H, 4.8; N, 2.65; S, 18.1. $C_{17}H_{25}NO_{12}S_3$ calc.: C, 38.4; H, 4.7; N, 2.65; S, 18.1%).

*Methyl 2,3,6-trideoxy-2,3-epimino-α-*D*-allopyranoside* (**3**). — To a solution of 8 g of the trimethanesulphonate **2** in dry tetrahydrofuran (350 ml) was cautiously added lithium aluminium hydride (11.2 g), and the solution was heated under reflux for 3.5 h. The reaction mixture was cooled to 0°, and a saturated solution (100 ml) of Rochelle salt was added slowly. The precipitate was filtered off, and washed with boiling chloroform, and tetrahydrofuran. The combined filtrate and washings were evaporated to a syrup which was distilled at 125°/0.2 mm. The distillate was dried *in vacuo* over phosphorus pentaoxide, and crystallised from ether–light petroleum, to yield the epimine **3** (0.48 g, 20%), m.p. 123–125°, $[\alpha]_D$ +177° (*c* 0.4) (Found: C, 52.4; H, 8.6; N, 8.1. $C_7H_{13}NO_3$ calc.: C, 52.8; H, 8.2; N, 8.8%).

*Methyl 2,3-dideoxy-4,6-di-*O*-methanesulphonyl-2,3-methanesulphonylepimino-α-*D*-allopyranoside* (**8**). — To a solution of 1.1 g of methyl 2,3-dideoxy-2,3-epimino-α-D-allopyranoside hydrochloride[3] (**7**·HCl) in dry pyridine (10 ml), was added methanesulphonyl chloride (2 ml), and the solution was left for 18 h at room temperature. Ice–water was added to precipitate the product which was collected, dried *in vacuo*, and dissolved in hot acetone, and the solution was filtered. Addition of ether, with cooling, caused crystallisation of the trisulphonate **8** (1 g, 50%), m.p. 173–174°, $[\alpha]_D$ +156° (*c* 0.5) (Found: C, 29.5; H, 4.6; N, 3.5. $C_{10}H_{19}NO_{10}S_3$ calc.: C, 29.3; H, 4.65; N, 3.5%). The infrared spectrum showed strong absorption at 1170 cm^{-1} and a broad band at 1310–1360 cm^{-1}, and no band assignable to NH stretching.

*Methyl 2,3-acetylepimino-2,3-dideoxy-4,6-di-*O*-methanesulphonyl-α-*D*-allopyranoside* (**9**). — A solution of methyl 2,3-dideoxy-2,3-epimino-α-D-allopyranoside hydrochloride[3] (1 g) in methanol–acetic anhydride (3:1, 250 ml) was shaken overnight with silver acetate (2 g). The filtered solution was evaporated to a syrup which was co-concentrated twice with toluene and twice with dry ethanol. The resulting, syrupy *N*-acetylepimine, although pure by t.l.c., could not be crystallised. To a solution of this syrup in pyridine (4 ml), was added methanesulphonyl chloride (2 ml) with cooling, and the solution was kept for 24 h at room temperature. To the resulting black solution was added ice–water, and the mixture was extracted with chloroform (3 × 10 ml). The chloroform extract was washed with aqueous sodium carbonate and water, boiled with decolourising charcoal, and evaporated. On cooling, an ethanolic solution of the residue deposited a syrup which crystallised on standing at room temperature to yield the product **9** (0.6 g, 34%), m.p. 102–105°, $[\alpha]_D$ +160° (*c* 2) (Found: C, 35.5; H, 5.0; N, 3.7. $C_{11}H_{19}NO_9S_2$ calc.: C, 35.4; H, 5.1; N, 3.8%). Attempts to recrystallise the compound always produced a syrup which crystallised on standing.

Methyl 4,6-O-benzylidene-2,3-bromoepimino-2,3-dideoxy-α-D-allopyranoside (**6**). — (*a*) To the epimine **4** (25 mg) in carbon tetrachloride (1 ml) was added *N*-bromosuccinimide (18.6 mg, 1.1 mol.) and barium carbonate (30 mg). The suspension was heated under reflux for 1 h, when t.l.c. (chloroform–ether, 1:1 v/v) indicated that reaction was complete, giving one major, fast-moving product. Recrystallisation from ethanol gave a white powder, but caused considerable decomposition to give back starting material, which remained in the mother liquors. Further recrystallisation from ethyl acetate yielded the product (8 mg, 25%), m.p. 174–175°, $[\alpha]_D$ +99° (*c* 0.6) (Found: C, 49.0; H, 4.6; Br, 23.5; N, 4.1. $C_{14}H_{16}BrNO_4$ calc.: C, 49.1; H, 4.7; Br, 23.5; N, 4.1%).

Attempts to repeat this reaction on a larger scale led to mixtures which could not be crystallised.

(*b*) A solution of sodium hypobromite was prepared by the addition of bromine (6.1 g) to a solution of sodium hydroxide (3 g) in water (10 ml). Portions of this solution were added dropwise with shaking to a solution of the epimine **4** (100 mg) in chloroform (0.5 ml) until a distinct yellow colour remained. More chloroform was added to redissolve the precipitated product, and an equal volume of water was added. The organic layer was washed twice with water and evaporated at room temperature to give a white solid, which was triturated with light petroleum and collected (crude yield, 95 mg, 73%). Recrystallisation from ethyl acetate afforded fine needles, m.p. 174–175°, identical (i.r. and mixed m.p.) with the product obtained above.

The compound was unstable in solution, an undried chloroform solution becoming discoloured after about 30 min.

Methyl 2,3-acetylepimino-4-O-benzoyl-6-bromo-2,3,6-trideoxy-α-D-allopyranoside (**10**). — Methyl 2,3-acetylepimino-4,6-*O*-benzylidene-2,3-dideoxy-α-D-allopyranoside (**5**) (2.5 g), *N*-bromosuccinimide (3 g), and barium carbonate (5 g) were suspended in carbon tetrachloride (100 ml), and the mixture was heated under reflux in the presence of broken glass for 15 min. The solution, which contained bromine, was filtered and evaporated to a syrup. T.l.c. indicated that reaction was complete, yielding a faster moving product together with considerable proportions of slow-moving impurities. Separation on a column of silica gel, with chloroform–ether (1:1, v/v) as eluent, yielded the 6-bromo derivative as a syrup which was dried *in vacuo* over silica gel and paraffin wax. Crystallisation from ethanol–light petroleum, with seeding, afforded granular crystals, m.p. 88–89°, $[\alpha]_D$ +144° (*c* 1) (Found: C, 50.2; H, 4.8; Br, 20.7; N, 3.6. $C_{16}H_{18}BrNO_5$ calc.: C, 50.0; H, 4.7; Br, 20.8; N, 3.6%).

The use of equimolar proportions of the acetylepimine and *N*-bromosuccinimide led to incomplete reaction, and, owing to the similarity in mobilities of the product and starting material, chromatographic purification of the product was not practicable in this case.

Methyl 2,3-acetylepimino-4-O-benzoyl-2,3,6-trideoxy-α-D-allopyranoside (**11**). — The 6-bromo-4-benzoate **10** (600 mg) was dissolved in ethanol (10 ml), and silver

carbonate (300 mg) and Raney nickel (2 spatula loads) were added. The mixture was heated under reflux for about 6 h, and then filtered and evaporated to a syrup. The product and starting material could not be distinguished chromatographically. After purification by column chromatography with chloroform–ether (1:1, v/v), the resulting syrup crystallised spontaneously. Recrystallisation from ethanol–light petroleum yielded the product (200 mg, 40%), m.p. 107–108°, $[\alpha]_D$ +182° (*c*, 0.6) (Found: C, 62.6; H, 6.3; N, 4.6. $C_{16}H_{19}NO_5$ calc.: C, 63.0; H, 6.2; N, 4.6%).

*Methyl 2,3,6-trideoxy-2,3-epimino-α-*D*-allopyranoside* (**3**) *from* **11**. — To a solution of compound **11** (84 mg) in methanol (2 ml), was added a solution of sodium (10 mg) in methanol (2 ml), and the mixture was heated under reflux for 5 min, when chromatography (chloroform–methanol, 4:1 v/v) indicated the presence of a product that was co-incident with the product obtained previously by lithium aluminium hydride reduction of compound **2**.

The solution was evaporated to half its original volume, and an equal amount of chloroform was added. The mixture was passed through a short column of silica gel, by using chloroform–methanol (1:1), to remove excess of sodium methoxide. After evaporation of the solvent, the residue was crystallised from ether, yielding a sample (15 mg, 35%) identical (i.r. and mixed m.p.) with that obtained from the reaction of lithium aluminium hydride with the trimethanesulphonate **2**.

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