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SYNTHESIS OF MEDIUM HETEROCYCLIC RINGS FROM 6-DEOXY-D-ALLOSE

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ABSTRACT

The synthesis of di-(6-deoxy-β-D-allofuranose) 1,5′:1′,5-dianhydride (**8**) from 6-deoxy-D-allose is described. Periodate oxidation of **8**, followed by borohydride reduction and acetylation, yielded a crystalline 2,4,7,9-tetra(acetoxymethyl)-5,10-dimethyl-1,3,6,8-tetraoxecane (**3**).

INTRODUCTION

There is considerable interest at the present time in the conformational analysis of heterocyclic systems[1]. In recent years, we[2,3] have been concerned with the conformational properties of medium heterocyclic rings, most of which have been derived from carbohydrate precursors. The tetraoxecane derivatives **1** and **2** have been prepared[2], for example, from di-β-D-ribofuranose 1,5′:1′,5-dianhydride (**6**)[2,4,5]. Thus, when compound **6** was subjected to periodate oxidation, followed by borohydride reduction and acetylation, a 2,4,7,9-tetra(acetoxymethyl)-1,3,6,8-tetraoxecane (**2**) was obtained as a crystalline compound. De-*O*-acetylation of **2** yielded the corresponding 2,4,7,9-tetra(hydroxymethyl)-1,3,6,8-tetraoxecane (**1**), which is also a crystalline compound. Compound **1** is of potential interest in connection with studies[6] on cyclic polyethers and their complexes. We report now the synthesis of di-(6-deoxy-β-D-allofuranose) 1,5′:1′,5-dianhydride (**8**), which yielded a 2,4,7,9-tetra(acetoxymethyl)-5,10-dimethyl-1,3,6,8-tetraoxecane (**3**) by the route described for the conversion of **6** into **2**.

RESULTS AND DISCUSSION

6-Deoxy-D-allose was prepared by way of the reaction[7] of 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-L-mannofuranose with methanolic sodium methoxide. Treatment of 6-deoxy-D-allose with benzaldehyde, zinc chloride, and

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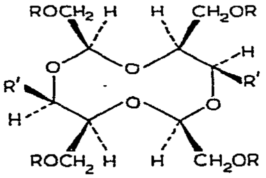
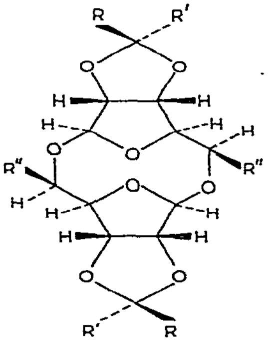
glacial acetic acid for 1 h at 80° gave a syrup, which was revealed by t.l.c. as a complex mixture. A solution of the syrup in methanol, kept at 5°, afforded in low yield a crystalline material, which was identified as a mixture of the two diastereoisomers (**11a** and **11b**) of 1,5-anhydro-2,3-*O*-benzylidene-6-deoxy-β-D-allofuranose. The n.m.r. spectrum in chloroform-*d* of this product showed two singlets at τ 4.33 and τ 3.83, whose integration corresponded to one proton in a ratio of approximately 10:1. These signals have been assigned (*cf.* Ref. 8), respectively, to the *exo* benzylidene-methine proton of the *syn* isomer **11a** and to the *endo* benzylidene-methine proton of the *anti* isomer **11b**. The H-1 signal was a broadened singlet, an observation consistent[9] with the β-D configuration for the group on C-1. It was reported[8] previously that benzylidenation of D-ribose under the same conditions as described for 6-deoxy-D-allose also yields, amongst other products, the *syn* isomer (**10a**) and the *anti* isomer (**10b**) of 1,5-anhydro-2,3-*O*-benzylidene-β-D-ribofuranose; in the n.m.r. spectra of **10a** and **10b**, the signals for the benzylidene-methine protons were observed at τ 4.32 and τ 3.84, respectively. Hydrogenation over 10% palladium-on-carbon of the mixture of **11a** and **11b** yielded crystalline 1,5-anhydro-6-deoxy-β-D-allofuranose (**12**).

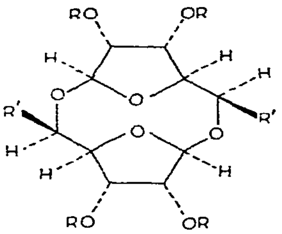


1 R = H, R' = H
2 R = Ac, R' = H
3 R = Ac, R' = Me

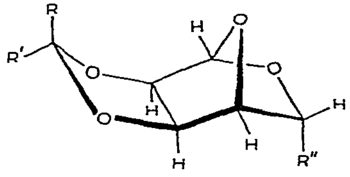


4a R = Ph, R' = H, R'' = H
4b R = H, R' = Ph, R'' = H
5a R = Ph, R' = H, R'' = Me
5b R = H, R' = Ph, R'' = Me

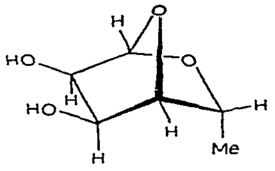
The preponderant component in the methanolic mother liquors from the crystallization of **11a** and **11b** was isolated as syrup by way of column chromatography on silica gel, and has been identified as di-(2,3-*O*-benzylidene-6-deoxy-β-D-allofuranose) 1,5':1',5-dianhydride. For di-(2,3-*O*-benzylidene-6-deoxy-β-D-allofuranose) 1,5':1',5-dianhydride, three diastereoisomers are possible, namely, the two with both benzylidene-methine protons either *endo* (**5a**) or *exo* (**5b**), and that with one benzylidene-methine proton *endo* and the other *exo*. The n.m.r. spectrum in chloroform-*d* of the syrupy product showed two singlets at τ 4.06 and τ 4.32, of equal intensities; these signals are assigned to *endo* and *exo* benzylidene-methine protons, respectively. The product is thus a mixture of diastereoisomers. At least the two diastereoisomers, **4a** and **4b**, of di-(2,3-*O*-benzylidene-β-D-ribofuranose) 1,5':1',5-dianhydride are also obtained[8] on benzylidenation of D-ribose under the same conditions as employed in the present work for 6-deoxy-D-allose. Hydrogenation over 10% palladium-on-carbon of the mixture of diastereoisomers of di-(2,3-*O*-benzylidene-6-deoxy-β-D-allofuranose) 1,5':1',5-dianhydride gave crystalline di-(6-deoxy-β-D-allofuranose) 1,5′:1′,5-dianhydride (**8**), which afforded the tetraacetate **9** in crystalline form on treatment with acetic anhydride–pyridine. The n.m.r. spectrum of **9** in chloroform-*d* was analogous to that previously obtained[2] for di-(2,3-di-*O*-acetyl-β-D-ribofuranose) 1,5′:1′,5-dianhydride (**7**). In the spectrum of **9**, a 2-proton singlet at τ 5.04 was assigned to H-1,1′, an assignment consistent with the β-D configuration at both glycosidic centers; the corresponding signal for compound **7** had been observed at τ 4.87. As in the case of **7** (*cf.* Ref. 2), the magnitudes of the couplings between the other protons for **9** (see Experimental section) are consistent with $^3T_2$ conformations for the furanoid rings and an "up-down-up-down" arrangement of the four oxygen atoms within the ten-membered ring, which also displays a two-fold (simple) axis of symmetry. Although a molecular ion was not observed in the mass spectrum of either compound **8** or the acetylated derivative **9**, several peaks were observed in each case at *m/e* values higher than that for the potential molecular ion of a monomeric structure*. The integrity of the configurations of C-5 and C-5′ in **8** was confirmed by the fact that only 6-deoxy-D-allose was obtained on acid-catalyzed hydrolysis of **8**.



6 R = H, R′ = H
7 R = Ac, R′ = H
8 R = H, R′ = Me
9 R = Ac, R′ = Me



10a R = Ph, R′ = H, R″ = H
10b R = H, R′ = Ph, R″ = H
11a R = Ph, R′ = H, R″ = Me
11b R = H, R′ = Ph, R″ = Me



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Treatment of compound **8** with sodium metaperiodate, followed by reduction of the oxidized product with sodium borohydride, and then acetylation with acetic anhydride–pyridine, afforded a crystalline 2,4,7,9-tetra(acetoxymethyl)-5,10-dimethyl-1,3,6,8-tetraoxecane (**3**). The elemental analysis, and i.r. and n.m.r. spectra, were all in agreement with structure **3**.

EXPERIMENTAL

General methods. — Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter at 23±3°. I.r. spectra were

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*Mass spectral data for a mixture of diastereoisomers of di-(2,3-*O*-benzylidene-β-D-ribofuranose) 1,5′:1′,5-dianhydride, compounds **6**–**9**, and the mixture of **11a** and **11b** obtained in the present work are reported in Ref. 10.

recorded with a Beckman IR5A spectrophotometer. N.m.r. spectra were recorded at 60 MHz in chloroform-*d* or in acetone-d_6 with tetramethylsilane (τ 10.00) as internal standard, or in deuterium oxide with sodium 4,4-dimethyl-4-silapentane-1-sulfonate (τ 10.00) as internal standard. High-resolution mass spectra were determined with a JEOL JMS-OISC double-focusing spectrometer at an ionizing potential of 75 eV. T.l.c. was performed with Silica Gel G as the adsorbent; the developed plates were air-dried, sprayed with 5% ethanolic sulfuric acid, and heated at about 150°. The term "petroleum ether" refers to the fraction of b.p. 60–80°. Hydrogenations were performed with a Parr apparatus at a pressure of approximately 28×10^3 kg m^{-2}.

*Benzylidenation of 6-deoxy-*D*-allose*. — 6-Deoxy-D-allose[7] (3 g) was treated with benzaldehyde (150 ml), zinc chloride (15 g), and glacial acetic acid (15 ml) for 1 h at 80°, by the procedure described by Wood *et al.*[5] for the benzylidenation of D-ribose at 80° (see also Ref. 8). T.l.c. (1:4, v/v, ethyl acetate–petroleum ether) of the resultant syrupy product (4.05 g) showed the presence of several components; the preponderant one had R_F 0.50. A solution of the syrup in methanol, kept at 5°, deposited a crystalline material (402 mg), m.p. 140–148°, which was identified as an approximately 10:1 mixture of the two diastereoisomers (**11a** and **11b**, respectively) of 1,5-anhydro-2,3-*O*-benzylidene-6-deoxy-β-D-allofuranose; n.m.r. data (chloroform-*d*): τ 2.62 (5-proton singlet, Ph group), 4.33, 3.83 (2 singlets corresponding in intensity to 1 proton, *exo* and *endo* benzylidene-methine protons, respectively, in the approximate proportion 10:1), 4.85 (1-proton broadened singlet, H-1), 5.30–5.68 (3-protons, H-2, H-3, and H-4), 5.83–6.25 (1-proton multiplet, H-5), and 8.80 (3-proton doublet, $J_{5,6}$ 7 Hz, C-6 Me). The i.r. spectrum (Nujol) did not show any absorption attributable to an hydroxyl group. The molecular formula of the crystalline product was confirmed as $C_{13}H_{14}O_4$ by mass spectrometry: $M^{+\cdot}$ 234.087±0.002 (Calc. for $C_{13}H_{14}O_4$: 234.0892).

The methanolic mother liquors were evaporated, and a portion (830 mg) of the syrupy residue was applied to a column of silica gel (mesh 60–120). Elution with 1:5, v/v, ethyl acetate–petroleum ether afforded the component, which had R_F 0.50 in t.l.c. in 1:4 ethyl acetate–petroleum ether, as a syrup (224 mg), $[\alpha]_D^{23}$ $-87°$ (*c* 2.51, chloroform). This component was identified as a mixture of diastereoisomers of di-(2,3-*O*-benzylidene-6-deoxy-β-D-allofuranose) 1,5′:1′,5-dianhydride. The i.r. spectrum (smear) did not show any absorption attributable to an hydroxyl group; n.m.r. data (chloroform-*d*): τ 2.57 (10 protons, Ph groups), 4.06, and 4.32 (2 singlets corresponding in intensity to 2 protons, *endo* and *exo* benzylidene-methine protons, respectively, in the approximate proportion 1:1).

*1,5-Anhydro-6-deoxy-β-*D*-allofuranose* (**12**). — Hydrogenation over 10% palladium-on-carbon of the mixture (180 mg) of diastereoisomers **11a** and **11b** in ethanol afforded a crystalline product (38 mg). Recrystallization from ethyl acetate gave pure **12**, m.p. 122.5–124.5°; $[\alpha]_D^{23}$ $-51.5°$ (*c* 1.93, methanol), $[\alpha]_{365}^{23}$ $-169°$; n.m.r. data (acetone-d_6 containing one drop of deuterium oxide): τ 4.87 (1-proton singlet, $J_{1,2}$ <0.5 Hz, H-1), 5.63 (1-proton doublet, $J_{3,4}$ <0.5 Hz, $J_{4,5}$ 3.6 Hz, H-4), 5.76 (1-proton doublet, $J_{2,3}$ 6.0 Hz, H-2 or H-3), 6.17 (1-proton doublet, partial overlap with H-5 signal, H-3 or H-2), 6.28 (1-proton, 8-line multiplet, $J_{5,6}$ 6.5 Hz, H-5), and 8.85 (3-proton doublet, C-6 Me). The product did not reduce Fehling's solution.

Anal. Calc. for $C_6H_{10}O_4$: C, 49.3; H, 6.9. Found: C, 49.4; H, 6.9.

*Di-(6-deoxy-β-*D*-allofuranose) 1,5′:1′,5-dianhydride* (8). — Hydrogenation over 10% palladium-on-carbon of the mixture (200 mg) of diastereoisomers of di-(2,3-*O*-benzylidene-6-deoxy-β-D-allofuranose) 1,5′:1′,5-dianhydride in ethanol (50 ml) afforded crystalline **8** (21 mg, 42%). Recrystallization from 19:1, v/v, acetone–water gave an analytically pure sample as needles, m.p. 253–255°, $[\alpha]_D^{23}$ $-84.3°$ (*c* 1.09, water); n.m.r. data (deuterium oxide): τ 5.02 (2-proton broadened singlet, H-1,1′), 5.36–5.61 (2 protons, doublet of doublets, $J_{2,3} = J_{2',3'} = 4.5$ Hz, $J_{3,4} = J_{3',4'} =$ 7.3 Hz, H-3,3′), 5.91–6.39 (6 protons, H-2,2′, H-4,4′, and H-5,5′), and 8.81 (6-proton doublet, $J_{5,6} = J_{5',6'} = 7.0$ Hz, C-6,6′ Me groups).

Anal. Calc. for $C_{12}H_{20}O_8$: C, 49.3; H, 6.9. Found: C, 49.2; H, 6.9.

In a separate experiment, an almost doubled, overall yield of **8** was isolated by way of hydrogenation of the syrupy mixture directly obtained by benzylidenation of 6-deoxy-D-allose. The hydrogenation product was a crystalline material, which was then dissolved in 19:1, v/v, acetone–water. Seeding of this solution with a crystal of **8** obtained above, afforded analytically pure **8** as needles.

*Di-(2,3-di-O-acetyl-6-deoxy-β-*D*-allofuranose) 1,5′:1′,5-dianhydride* (9). — Compound **8** (28 mg) was acetylated in the usual manner with acetic anhydride–pyridine to give a crystalline product. Recrystallization from ethanol afforded analytically pure **9** (25 mg, 55%), m.p. 166–167°, $[\alpha]_D^{23}$ $+16°$ (*c* 1.08, chloroform); t.l.c. (1:1, v/v, ethyl acetate–petroleum ether): R_F 0.33; n.m.r. data (chloroform-*d*): τ 5.04 (2-proton singlet, H-1,1′), 4.67–4.76 (2-proton doublet, $J_{2,3} = J_{2',3'} = 5.0$ Hz, H-2,2′), 4.26–4.50 (2 protons, doublet of doublets, $J_{3,4} = J_{3',4'} = 6.9$ Hz, H-3,3′), 5.85–6.26 (4-proton multiplet, $J_{4,5} = J_{4',5'} = 1.3$ Hz, $J_{5,6} = J_{5',6'} = 7.1$ Hz, H-4,4′ and H-5,5′), 8.92 (6-proton doublet, C-6,6′ Me groups), 7.89, and 7.96 (12 protons, OAc groups on C-2,2′ and C-3,3′). Spin-decoupling was used to verify the assignments of H-3,3′, H-4,4′, H-5,5′, and of the C-6,6′ methyl protons.

Anal. Calc. for $C_{20}H_{28}O_{12}$: C, 52.2; H, 6.1. Found: C, 51.9; H, 6.1.

*Acid-catalyzed hydrolysis of di-(6-deoxy-β-*D*-allofuranose) 1,5′:1′,5-dianhydride* (8). — Compound **8** (19 mg) in M aqueous trifluoroacetic acid (6 ml) was heated on a steam bath for 4 h; t.l.c. (1:1, v/v, chloroform–ethanol) indicated that all of the dianhydride (R_F 0.73) had been converted into a slower-moving component (streak, R_F 0.25–0.50). Evaporation of the solvent gave a slightly-colored, crystalline residue, m.p. 130°. The product was washed with cold ethanol to afford white needles, m.p. 138–141°; an authentic sample of 6-deoxy-D-allose had m.p. 140–143°. The hydrolysis product also migrated as a homogeneous component, at the same rate as authentic 6-deoxy-D-allose, on Whatman No. 1 filter paper in 3:1:1, v/v, butanol–ethanol–water (alkaline silver nitrate[11] and sodium metaperiodate–potassium permanganate[12] spray reagents); the presence of 6-deoxy-L-talose ($R_{6\text{-deoxyallose}}$ 1.18; authentic sample obtained from methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside[13]) in the hydrolyzate was not detected by paper chromatography.

2,4,7,9-Tetra(acetoxymethyl)-5,10-dimethyl-1,3,6,8-tetraoxecane (3). — Compound **8** (308 mg) was dissolved in water (8 ml) and a solution of sodium metaperiodate (300 mg) in water (4 ml) was added; the reaction mixture was kept for 9 h at room temperature. After the excess of periodate and iodate had been precipitated with a 10% aqueous barium chloride solution, sodium borohydride (170 mg) was added to the filtered solution; the reaction mixture was kept for 16 h at room temperature. The excess of borohydride was destroyed by the addition of solid carbon dioxide, and the solution was evaporated. The solid residue was treated with acetic anhydride (10 ml) in dry pyridine (30 ml) in the usual manner. The acetylation mixture was poured into ice–water (100 ml), and the mixture was kept for 1 h before being extracted several times with chloroform. The combined chloroform extracts were washed with an aqueous solution of sodium hydrogen carbonate and then with water, dried (sodium sulfate), and evaporated to give a syrup (150 mg) which was shown by t.l.c. (1:1, v/v, ethyl acetate–petroleum ether) to consist of two components having R_F values of 0.4 and 0.2. The slower-moving component was isolated as a solid (65 mg) by column chromatography on silica gel, and was identified as **3**. Recrystallization from ether–petroleum ether gave an analytically pure sample of **3** as colorless crystals (40 mg, 10%), m.p. 97–98°, $[\alpha]_D^{23}$ +28.6° (*c* 0.52, chloroform); λ_{max}^{KBr} 5.78 μm (OAc), no absorption attributable to an hydroxyl group; n.m.r. data (chloroform-*d*): τ 5.40 (2-proton triplet, $J\sim5.5$ Hz, H-2,7), 5.8–6.6 (12 protons), 7.40, 7.66 (2 singlets corresponding in intensity to 12 protons, OAc groups on C-2,4,7,9), and 8.83 (6-proton doublet, $J\sim6.5$ Hz, Me groups on C-5,10).

Anal. Calc. for $C_{20}H_{32}O_{12}$: C, 51.72; H, 6.90. Found: C, 51.75; H, 6.99.

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