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SYNTHESIS OF DL- AND D-*gluco*-HEPT-3-ULOSE

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ABSTRACT

DL-*gluco*-Hept-3-ulose was synthesised by oxidation of tri-*O*-isopropylidene-*meso*-*glycero*-*gulo*-heptitol with methyl sulphoxide–phosphorus pentaoxide, and subsequent hydrolysis. D-*gluco*-Hept-3-ulose (**3**) was synthesised by oxidation of one of the two isopropylidene derivatives from perseitol (D-*glycero*-D-*galacto*-heptitol), which is presumed to have the 1,2:4,5:6,7 structure, followed by hydrolysis. The crude product from the reduction of DL-*gluco*-hept-3-ulose with sodium borohydride showed two peaks corresponding to *meso*-*glycero*-*gulo*-heptitol and perseitol on g.l.c. of the trimethylsilyl derivatives. Isolation and acetylation of the latter heptitol revealed it to be racemic perseitol. Oxidation of DL-*gluco*-hept-3-ulose with oxygen in alkali followed by treatment with ferric acetate–hydrogen peroxide gave products with chromatographic behaviour characteristic of arabinonolactone and erythrose. Treatment of DL-*gluco*-hept-3-ulose with 2,4-dinitrophenylhydrazine gave a 1-deoxy-2,4-dinitrophenylosazone.

INTRODUCTION

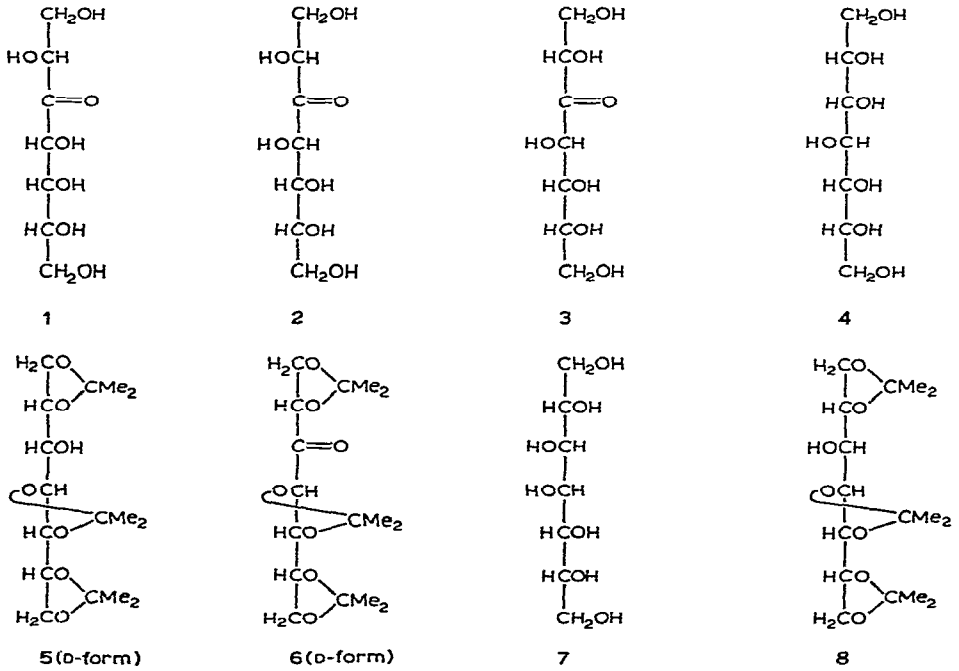
In addition to coriose (**1**, D-*altro*-hept-3-ulose), a naturally occurring hept-3-ulose[1], D-*manno*-hept-3-ulose (**2**) has been synthesised[2] and D-*gluco*-hept-3-ulose (**3**) was reported to be produced from D-glucose 6-phosphate in the presence of a digest of rat-liver supernatant[3]. We now report syntheses of DL-*gluco*-hept-3-ulose and D-*gluco*-hept-3-ulose.

RESULTS AND DISCUSSION

D-*glycero*-D-*gulo*-Heptonolactone, which was produced by the Kiliani synthesis from D-glucose[4], was reduced with sodium borohydride to *meso*-*glycero*-*gulo*-heptitol[5] (**4**) which was converted into a crystalline, racemic triacetonide (DL-**5**) that gave a crystalline *p*-nitrobenzoate. Oxidation of DL-**5** with methyl sulphoxide–

*Part VIII of the Series "Coriose and Related Compounds". For Part VII, see ref. 7*b*.

phosphorus pentaoxide afforded crystalline, racemic 1,2:4,5:6,7-tri-*O*-isopropylidene-D-*gluco*-hept-3-ulose (DL-**6**), which gave a crystalline *p*-nitrophenylhydrazone. Hydrolysis of DL-**6** in 0.05M sulphuric acid gave an optically inactive syrup with an elemental analysis appropriate for a hydrate of DL-*gluco*-hept-3-ulose. In paper chromatography, the ketose gave a greyish brown colour with the orcinol reagent which was closely similar to those given by coriose and D-*manno*-hept-3-ulose and readily distinguishable from that given by hept-2-uloses.



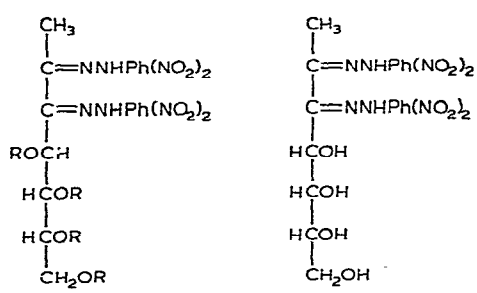
Reduction of DL-*gluco*-hept-3-ulose with sodium borohydride at ~0° yielded a crude product which, on g.l.c. of the trimethylsilyl derivative, showed two peaks corresponding to **4** and perseitol (**7**). Fractional crystallization of the mixture from methanol gave crystalline **4** and another heptitol (m.p. 211–212°), which differed from **7** (m.p. 187–188°) in melting point and i.r. spectrum (Nujol). The latter heptitol gave a crystalline hepta-acetate (m.p. 140–141°), for which the i.r. spectrum of a chloroform solution was identical with that of perseitol hepta-acetate[6] (m.p. 118–119°). The hepta-acetate had the same retention times in g.l.c. as did trimethylsilyl ethers of the racemic heptitol and perseitol. Thus, the racemic heptitol is DL-perseitol. The foregoing results establish the structure of DL-*gluco*-hept-3-ulose and support the structures assigned to DL-**5** and DL-**6**. The purity of DL-*gluco*-hept-3-ulose was shown by reduction with sodium borohydride in the cold which gave only two products; coriose shows similar behaviour[1a].

Oxidation of DL-*gluco*-hept-3-ulose with oxygen in 2M potassium hydroxide yielded a product having the chromatographic properties of arabinonolactone which, on treatment with ferric acetate–hydrogen peroxide, was converted into a further product having the chromatographic mobility of erythrose. The results of this degradation sequence are analogous to those reported for coriose[1a] and further indicate the structure of the synthetic hept-3-ulose.

D-*gluco*-Hept-3-ulose was synthesized from perseitol (D-*glycero*-D-*galacto*-heptitol). Acetonation of perseitol gave a two-component product mixture (t.l.c.). The component of higher mobility was isolated by chromatography and shown to be a tri-*O*-isopropylidene derivative (m.p. 58–60°). On oxidation with methyl sulphoxide–phosphorus pentaoxide, it gave an optically active ketone which had properties (t.l.c. mobility, i.r.spectra in chloroform, and n.m.r. spectra) identical to those of DL-**6**. The ketone was therefore 1,2:4,5:6,7-tri-*O*-isopropylidene-D-*gluco*-hept-3-ulose (**6**) and its precursor was 1,2:4,5:6,7-tri-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (**8**). The second product of the acetonation of perseitol was isolated as a syrup and was not readily oxidized with methyl sulphoxide–phosphorus pentaoxide.

Hydrolysis of **6** yielded a syrup which had an R_F value in paper chromatography identical to that of DL-*gluco*-hept-3-ulose. D-*gluco*-Hept-3-ulose was purified by preparative paper chromatography, and g.l.c., after trimethylsilylation, revealed four peaks (*e.g.*, OV-17, 180°; R_{GLC} 1.50, 1.56, 1.91, and 2.50); the DL-heptose gave the same four peaks. Both crystalline coriose and D-*manno*-hept-3-ulose give[7] more than two peaks on g.l.c. after trimethylsilylation. The four peaks shown by DL- and D-*gluco*-hept-3-ulose are probably due to pyranose, furanose, and keto forms.

The behaviour of DL-*gluco*-hept-3-ulose and of coriose[8] were analogous in that, although reaction with phenylhydrazine gave no crystalline product, treatment with 2,4-dinitrophenylhydrazine in 2M hydrochloric acid yielded a crystalline osazone (**9**), m.p. 258–260°, which analyzed as $C_{19}H_{20}N_8O_{12}$. A methyl signal at δ 2.38 in the n.m.r. spectrum (methyl sulphoxide-d_6), and the u.v. absorptions, λ_{max} 402 (4.68) and 438 nm (4.67), are analogous to those of 1-deoxycoriose 2,4-dinitrophenylosazone[8] (**10**). The acetate **11** ($C_{27}H_{28}N_8O_{16}$, m.p. 234–236°) of **9** gave an n.m.r. spectrum (deuteriochloroform) containing four acetyl signals in addition to those for vinyl methyl protons (δ 1.7–2.4), and H-4,5,6,7 [7.01 (d, J 3 Hz), 5.76 (dd, J_1 9, J_2 3 Hz),



5.6–5.3 (m), and 4.4–4.2 (m)]; the assignments were confirmed by double-resonance experiments. These data show the structure of the osazone produced from DL-*gluco*-hept-3-ulose to be racemic **9**.

Although Nigam *et al.*[3] reported that acid treatment of their enzymically produced D-*gluco*-hept-3-ulose gave a heptulosan which yielded a crystalline tetrabenzoate[3], coriose and synthetic DL-*gluco*-hept-3-ulose were recovered in high yield after similar acid treatment, and significant dehydration was not detected by p.c. and g.l.c. The enzymic product obtained by Nigam *et al.* was also reported to give a positive colour reaction for heptulose with the orcinol–trichloroacetic acid reagent, although the colour was not described. However, only hept-2-uloses were known at that time, and it was later found[2] that hept-2- and -3-uloses give different colours with the orcinol reagent. The structure assigned to the enzymic product[3] therefore requires further experimental confirmation.

EXPERIMENTAL

General. — Paper chromatography (p.c.) was carried out by the ascending method with *A* 1-butanol–pyridine–water (6:4:3), *B* 1-butanol–ethanol–water (4:1.2:1), or *C* 1-butanol–acetic acid–water (4:1:5). Heptuloses were detected with orcinol–trichloroacetic acid–1-butanol (saturated with water) (1:30:240). Preparative p.c. was carried out on Toyo filter paper No. 526 with solvent *B*; separated components were extracted with methanol. T.l.c. was performed on Silica Gel G (Merck) and detection was effected with conc. sulphuric acid.

Trimethylsilyl derivatives were prepared with chlorotrimethylsilane–hexamethyldisilazane–pyridine (1:2:10). G.l.c. was carried out with a Shimadzu 5A gas chromatograph equipped with a flame-ionization detector and a glass column (2 m × 3 mm i.d.) packed with 3% of OV-17 or 1.5% of SE-52 on 80–100 mesh Chromosorb W treated with hexamethyldisilazane (HMDS), and 1.5% of SE-30 on 60–80 mesh Chromosorb W treated with HMDS. R_{GLC} is the retention time relative to that of α-D-glucose.

1,2:4,5:6,7-Tri-O-*isopropylidene*-D(L)-glycero-D(L)-gulo-*heptitol* (DL-**5**). — A mixture of **4** (1.35 g), dry acetone (100 ml), cupric sulphate (2 g), and conc. sulphuric acid (0.5 ml) was stirred at room temperature. The heptitol dissolved within 4 h, and stirring was continued for an additional 12 h. The resulting, dark-yellow solution was neutralized with anhydrous sodium carbonate, filtered, and concentrated under reduced pressure at 40°. The residual syrup crystallised from hexane (10 ml) to give, after recrystallisation from hexane, DL-**5** (1.59 g), m.p. 42–43°, $\nu_{max}^{CHCl_3}$ 3520 cm^{-1} (OH). N.m.r. data (90 MHz, CCl_4, internal Me_4Si): δ 4.2–3.3 (9H, H-1/H-7), 1.26 (s, 6H, 2 Me), 1.33 (s, 12H, 4 Me).

Anal. Calc. for $C_{16}H_{28}O_7$: C, 57.81; H, 8.49. Found: C, 57.90; H, 8.69.

The *p*-nitrobenzoate of DL-**5** had m.p. 155–157° (from ether). N.m.r. data ($CDCl_3$): δ 8.29 (s, 4H, $-C_6H_4-NO_2$), 5.65 (dd, 1 H, J_1 5, J_2 2 Hz, H-3), 4.60–3.58 (m, 8H, H-1,2, H-4/H-7), 1.41–1.27 (6 Me).

Anal. Calc. for $C_{23}H_{31}NO_{10}$: C, 57.37; H, 6.49; N, 2.91. Found: C, 57.16; H, 6.43; N, 3.13.

*1,2:4,5:6,7-Tri-O-isopropylidene-*DL-gluco-*hept-3-ulose* (DL-**6**). — To a stirred solution of DL-**5** (2.2 g) in methyl sulphoxide (20 ml), phosphorus pentaoxide (2 g) was added at 0°. After being stirred for 18 h at room temperature, the mixture was poured into ice–water (50 ml) and extracted with dichloromethane. The extract was washed with 10% aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), filtered, and concentrated under reduced pressure at 40°. The syrupy residue crystallized from hexane (10 ml) to give, after recrystallization from hexane, DL-**6** (1.08 g), m.p. 39–40°, $\nu_{max}^{CHCl_3}$ 1730 cm^{-1} (C=O). N.m.r. data (CCl_4): δ 4.46 (t, 1H, J 6 Hz, H-2), 4.52 (d, 1H, J 6 Hz, H-4), 4.27–3.67 (m, 6H, H-1 and H-5/H-7), 1.36–1.23 (6 Me).

Anal. Calc. for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 58.12; H, 8.01.

*1,2:4,5:6,7-Tri-O-isopropylidene-*DL-gluco-*hept-3-ulose* p-*nitrophenylhydrazone*. — A solution of DL-**6** (56 mg) and *p*-nitrophenylhydrazine (26.7 mg) in ethanol (2 ml) was warmed in a boiling water-bath for 1 h. After cooling, dichloromethane was added to the mixture, and the solution was washed successively with 5% hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated. The syrupy residue crystallized from ether to give, after recrystallization from ether, yellow needles of the title compound (59.5 mg), m.p. 119–121°. N.m.r. data ($CDCl_3$): δ 8.16 (d, 2H, J 4.5 Hz), 7.02 (d, 2H, J 4.5 Hz), 10.24 (s, 1H, –NH–), 4.93 (t, 1H, H-2), 4.6–3.9 (7H, H-1 and H-4/H-7), 1.65–1.33 (6 Me).

Anal. Calc. for $C_{22}H_{31}N_3O_8$: C, 56.76; H, 6.71; N, 9.03. Found: C, 56.66; H, 6.75; N, 9.34.

DL-gluco-*Hept-3-ulose* (**3**). — The ketone DL-**6** (2 g) was hydrolysed with 0.05M sulphuric acid (25 ml) for 7 h at 55°, and the hydrolysate was extracted with dichloromethane. The aqueous layer was neutralized with aqueous barium hydroxide, filtered through Celite 545, and evaporated under reduced pressure at 35°. P.c. of the syrupy residue (1.08 g) revealed **3**, which gave a greyish brown spot with the orcinol reagent at R_F 0.44, 0.41, and 0.20 for solvents *A–C*, respectively. G.l.c. data (R_{GLC} at 180°): OV-17 1.50, 1.56, 1.91, and 2.50; SE-52, 1.70, 2.18, and 2.35; SE-30 1.83 and 2.50.

Anal. Calc. for $C_7H_{14}O_7 \cdot H_2O$: C, 36.84; H, 7.07. Found (after lyophilization): C, 36.69; H, 6.74.

To a stirred, ice-cold solution of **3** (310 mg) in water (3 ml), 2M potassium hydroxide (5 ml) was added and oxygen was absorbed (15.6 ml). The solution was passed through a column of Amberlite IR-120(H^+) resin (2 ml), and then concentrated under reduced pressure at 40°. The syrupy residue (213 mg) had chromatographic behaviour (p.c., solvent *B*, detection with alkaline hydroxylamine–ferric chloride, R_F 0.28; g.l.c., SE-30, 150°, R_{GLC} 0.28 and 0.32) identical to that of arabinonolactone; gluconolactone was not detected.

Calcium hydroxide (15 mg), barium acetate (6 mg), ferric sulphate (3 mg), and water (1.5 ml) were added to the foregoing lactone (60 mg), and the mixture was refluxed for 10 h. The ice-cold, filtered mixture was treated with 30% hydrogen peroxide (5 ml). Another 5-ml portion of 30% hydrogen peroxide was added after 2 h,

and the mixture was stored overnight at room temperature, then filtered and passed through a column of Amberlite IR-120(H^+) resin (20 ml), and concentrated under reduced pressure. The syrupy product (23.4 mg), which was purified by preparative p.c. (solvent *B*, R_F 0.36), had R_{GLC} 0.16, 0.18, and 0.24 (g.l.c., OV-17, 155°). These data were identical with those for erythrose.

Reduction of DL-gluco-*hept-3-ulose with sodium borohydride* (**3**). — To an ice-cold solution of **3** (100 mg) in water (10 ml) a solution of sodium borohydride (13 mg) in water (5 ml) was added with stirring, and the mixture was stored overnight in a refrigerator. Acetic acid was added (to pH 5–6), and the solution was passed through a column of Amberlite IR-120(H^+) resin (15 ml) and then concentrated under reduced pressure. Boric acid was removed from the syrupy residue by repeated distillation of methanol therefrom under reduced pressure. G.l.c. (OV-17, 170°) of the syrupy residue after trimethylsilylation revealed only components with R_{GLC} 3.19 and 3.31, corresponding to *meso-glycero-gulo*-heptitol and perseitol. Fractional crystallisation of the syrup from methanol gave first a product (57 mg, after recrystallisation from methanol), m.p. 211–212°, the i.r. spectrum (Nujol) of which showed some differences from that of perseitol in the fingerprint region.

Anal. Calc. for $C_7H_{16}O_7$: C, 39.62; H, 7.60. Found: C, 39.37; H, 7.67.

Concentration of the mother liquor gave a second product (36 mg, after recrystallisation from methanol), m.p. 127–128°, which was identified as *meso-glycero-gulo*-heptitol by mixture m.p., i.r. spectrum, and g.l.c. of the trimethylsilyl ether.

The heptitol, m.p. 211–212°, gave a hepta-acetate (acetic anhydride–pyridine), m.p. 140–141° (from ether), the i.r. spectrum ($CHCl_3$) and g.l.c. behaviour (SE-52, 210°, R_{GLC} 3.66) of which were identical with those of perseitol hepta-acetate.

Anal. Calc. for $C_{21}H_{30}O_{14}$: C, 49.80; H, 5.93. Found: C, 49.78; H, 6.00.

Isopropylidene derivatives of perseitol. — To a vigorously stirred suspension of perseitol (3.55 g) in dry acetone (80 ml), conc. sulphuric acid (0.5 ml) and anhydrous cupric sulphate (4 g) were added, and stirring was continued for 12 h. The mixture was neutralised with sodium carbonate (2 g), filtered, and concentrated *in vacuo*. T.l.c. (chloroform–methanol, 96:4) of the resulting, thick syrup (4.22 g) revealed a minor (R_F 0.4) and a major component (R_F 0.3). The syrup (4-g portion) was eluted from a column of Silicic acid (Mallinckrodt, 100 mesh, 100 g) with chloroform. The fractions which contained the product having R_F 0.4 were combined and concentrated *in vacuo*. Crystallization of the syrupy residue from hexane and recrystallisation of the product (604 mg) from hexane gave **8** (513 mg), m.p. 58–60°, $[\alpha]_D^{20}$ −7° (*c* 2.4, chloroform).

Anal. Calc. for $C_{16}H_{28}O_7$: C, 57.81; H, 8.49. Found: C, 57.63; H, 8.40.

The fractions which contained the component having R_F 0.3 were combined and concentrated *in vacuo* to afford a syrup (2.8 g), $[\alpha]_D^{20}$ −6.6° (*c* 5.3, chloroform).

Anal. Found: C, 57.39; H, 8.44.

D-gluco-*Hept-3-ulose* (**3**). — To a stirred solution of **8** (200 mg) in methyl sulphoxide (2 ml), phosphorus pentaoxide (150 mg) was added at 0°. After being stirred for 15 h at room temperature, the reaction mixture was poured into ice–water, and the resulting solution was washed with 10% aqueous sodium hydrogen carbonate

and water, dried ($MgSO_4$), and concentrated *in vacuo*. The syrupy residue (128 mg) showed the same R_F value (t.l.c., chloroform–methanol, 96:4) as 1,2:4,5:6,7-tri-*O*-isopropylidene-DL-*gluco*-hept-3-ulose. The syrup was hydrolysed with 1% sulphuric acid (5 ml) at 50° for 18 h, and the hydrolysate was neutralized with aqueous barium hydroxide, filtered through Celite, and concentrated under reduced pressure at 40°. Preparative p.c. (solvent *B*) of the syrupy residue (92.8 mg) gave syrupy **3** (57 mg), $[\alpha]_D^{17}$ −24° (*c* 2.2, water), which on p.c. afforded a greyish brown spot with the orcinol reagent (R_F values 0.44, 0.41, and 0.20, in solvents *A*–*C*, respectively) identical with those of DL-*gluco*-hept-3-ulose. The trimethylsilyl ether of this syrup showed the same gas chromatogram as that of the trimethylsilyl ether from DL-*gluco*-hept-3-ulose.

Anal. Calc. for $C_7H_{14}O_7 \cdot H_2O$: C, 36.84; H, 7.07. Found: C, 36.91; H, 6.91.

A solution of DL-*gluco*-hept-3-ulose (51.3 mg) in 0.5M hydrochloric acid (3 ml) was kept at 97° for 1 h, and then passed through a column of Amberlite IR-45(HO^-) resin (2 ml). Concentration of the effluent *in vacuo* gave a syrupy residue (41.4 mg), which was identified as starting material by p.c. (solvent *A*, orcinol reagent and potassium metaperiodate–benzidine[9]) and g.l.c. (OV-17 and SE-30) of the trimethylsilyl derivative.

1-Deoxy-DL-gluco-*hept-3-ulose 2,4-dinitrophenylosazone* (**9**). — DL-*gluco*-hept-3-ulose (56 mg) was added to a warm solution of 2,4-dinitrophenylhydrazine (190 mg) in a mixture of 2M hydrochloric acid (8.3 ml) and ethanol (1.2 ml). The resulting solution was warmed in a boiling water-bath for 2 h, and the crystalline precipitate (90 mg) was filtered off from the warm solution. An additional crop (10 mg) was obtained from the mother liquor. The combined product was recrystallized from ethyl acetate to yield orange needles of **9** (27 mg), m.p. 258–260°.

Anal. Calc. for $C_{19}H_{20}N_8O_{12}$: C, 41.12; H, 3.61; N, 20.29. Found: C, 41.09; H, 3.77; N, 20.48.

The tetra-acetate **11** of **9** was obtained as orange crystals, m.p. 234–236° (from hexane).

Anal. Calc. for $C_{27}H_{28}N_8O_{16}$: C, 45.01; H, 3.92; N, 15.56. Found: C, 45.18; H, 3.98; N, 15.41.

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