L-SORBOSE BENZOATES. SYNTHESIS OF 1,3,5-TRI-*O*-BENZOYL-α-L-SORBOPYRANOSE

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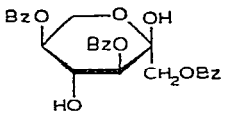
ABSTRACT

Benzoylation of L-sorbose at −10° gave 1,3,5-tri-*O*-benzoyl-α-L-sorbopyranose and 1,3,4,5-tetra-*O*-benzoyl-α-L-sorbopyranose. The structure of the former compound was established by chemical and spectroscopic methods. The preparation of 1,3,5-tri-*O*-benzoyl-4-*O*-methyl-α-L-sorbopyranose, methyl 1,3,5-tri-*O*-benzoyl-4-*O*-methyl-α-L-sorbopyranoside, and methyl 4-*O*-methyl-α-L-sorbopyranoside is described.

RESULTS AND DISCUSSION

Treatment of L-sorbose in dry pyridine at −10° with benzoyl chloride afforded 1,3,5-tri-*O*-benzoyl-α-L-sorbopyranose (**1**, 42.8%) and 1,3,4,5-tetra-*O*-benzoyl-α-L-sorbopyranose (**2**, 23.4%). Compound **2** had been obtained, in 80% yield, by Paulsen *et al.*[1] under the same experimental conditions. Its identity was confirmed by its n.m.r. spectrum, and by conversion into the known methyl 1,3,4,5-tetra-*O*-benzoyl-α-L-sorbopyranoside[1].



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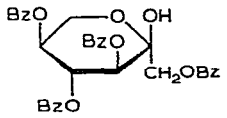

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The principal product of the reaction was compound **1**. Its n.m.r. spectrum (see Fig. 1) in pyridine-d_5 showed H-3 as a doublet at τ 3.65 ($J_{3,4}$ 10 Hz), indicating that the hydroxyl group on C-3 was benzoylated; otherwise, the H-3 signal would be a pair of doublets. The H-5 signal at τ 4.05 appeared as a multiplet unchanged by addition of deuterium oxide, showing that the hydroxyl group on C-5 was benzoylated. At τ 4.74, there was a complex multiplet that, on addition of deuterium oxide, gave a triplet of $J_{3,4}$ and $J_{4,5}$ 10 Hz (see Fig. 1b), which indicated that the 4-hydroxyl group was free.

The high values of the coupling constants ($J_{3,4}$ and $J_{4,5}$ 10 Hz) suggests a *trans*-diaxial arrangement of H-3, H-4, and H-5. This agrees with the *1C* (L) con-

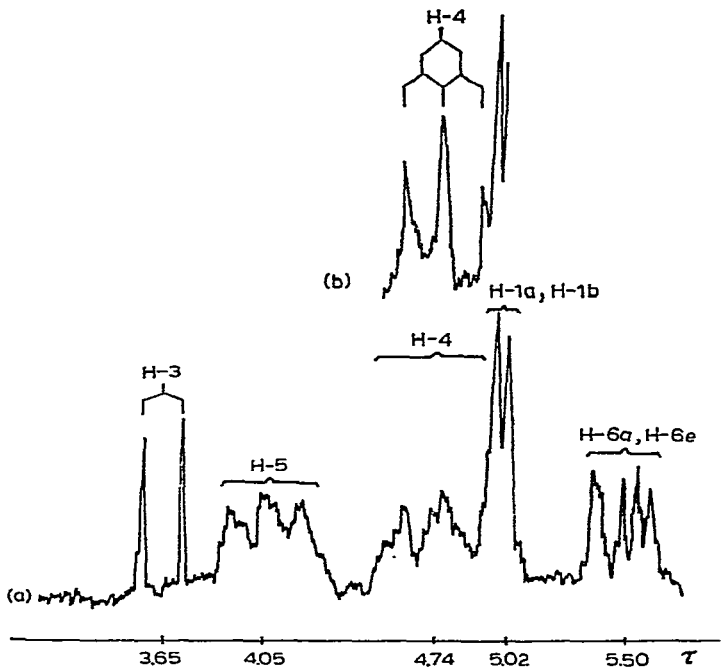
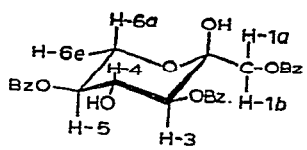


Fig. 1. The 60-MHz n.m.r. spectrum of 1,3,5-tri-*O*-benzoyl-α-L-sorbopyranose (**1**) at 20° in (a) pyridine-d_5, and (b) pyridine-d_5 plus D_2O.

formation (**3**), which, bearing all benzoyl groups in equatorial orientation, is the less-hindered chair conformation.



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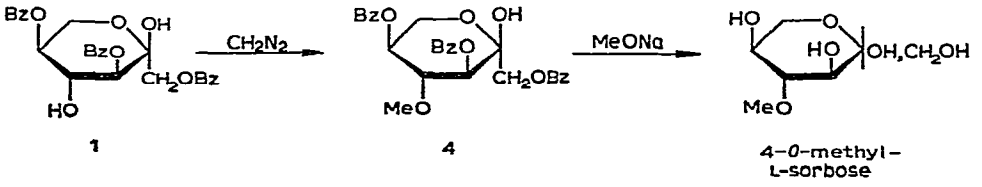
The H-1a and H-1b signals appear as a doublet at τ 5.02, indicating that the 1-hydroxyl group is benzoylated; otherwise, it would appear as a multiplet. The H-6*a* and H-6*e* signals appear as a multiplet at τ 5.50. All of these data show that the hydroxyl groups on C-4 and C-2 are not benzoylated.

The α-L configuration of benzoate **1** was demonstrated by its transformation, by subsequent benzoylation, into 1,3,4,5-tetra-*O*-benzoyl-α-L-sorbopyranose (**2**), whose anomeric configuration had already been established[1]. That the *alpha* configuration is favored can be explained on the basis that the bulky group on C-2 in the equatorial orientation [in the *1C* (L) conformation] presents less steric hindrance than an axial, *beta* group on C-2. This steric factor would be operative in the transition state leading to compound **1**.

The structure assigned to compound **1** was substantiated by methylation with diazomethane in dichloromethane[2]; 1,3,5-tri-*O*-benzoyl-4-*O*-methyl-α-L-sorbopyranose (**4**) was thus obtained; it was debenzoylated with sodium methoxide in methanol,



1 4 4-*O*-methyl-L-sorbose

yielding a monomethyl derivative whose physical constants were identical with those of the 4-*O*-methyl-L-sorbose described by Bosshard and Reichstein[3]. This established that one of the free hydroxyl groups in **1** is situated at C-4.

The n.m.r. spectrum at 60 MHz of **4** (see Fig. 2) in pyridine-d_5 showed H-3 as a doublet at τ 3.90 with $J_{3,4}$ 9.5 Hz. The H-4 signal appears as a triplet at τ 5.39, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz; by irradiation of H-3, this triplet collapses to a doublet arising from the H-4, H-5 interaction. Compared with compound **1** (see Fig. 1), the H-4 upfield shift with regard to its resonance can be ascribed to a higher shielding induced by the methoxyl group on C-4.

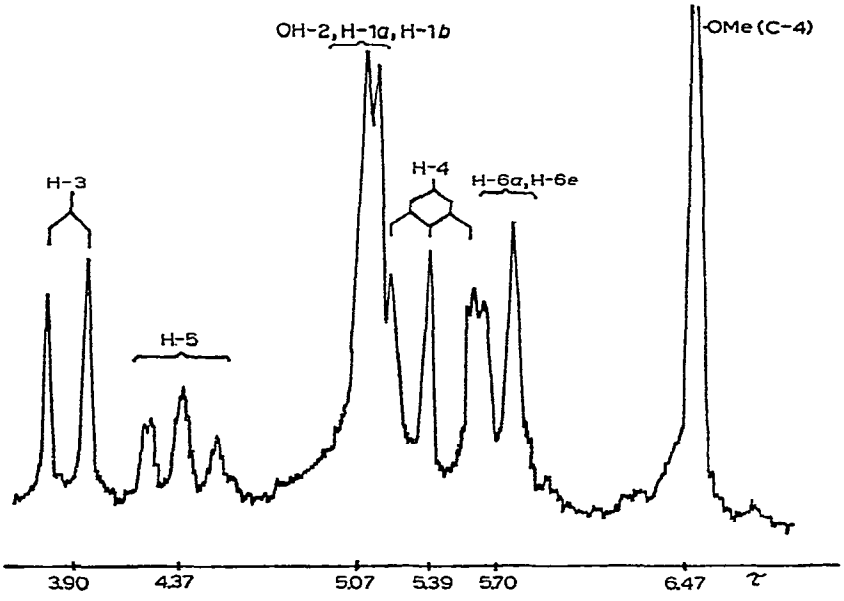


Fig. 2. The 60-MHz n.m.r. spectrum of 1,3,5-tri-*O*-benzoyl-4-*O*-methyl-α-L-sorbopyranose (**4**) at 20° in pyridine-d_5.

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TABLE I

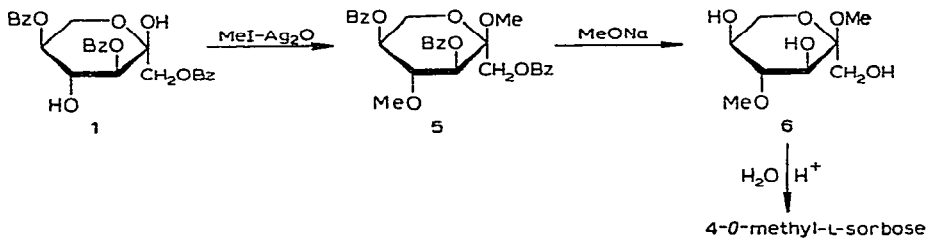
CHEMICAL-SHIFT DATA AND PROTON-PROTON COUPLING-CONSTANTS[a] FOR COMPOUNDS **1**, **2**, **4**, AND **5**, AT 20°

Compound	*No.*	*Solvent*	*Chemical shift of protons* (τ) *and proton-proton coupling-constants* (*Hz*)					
			H-1a H-1b	*H-3*	*H-4*	*H-5*	*H-6a H-6e*	CH_3
1,3,5-Tri-*O*-benzoyl-α-L-sorbopyranose	**1**	pyridine-d_5	5.02	3.65 ($J_{3,4}$ 10)	4.74 ($J_{4,5}$ 10)	4.05	5.50	
1,3,4,5-Tetra-*O*-benzoyl-α-L-sorbopyranose	**2**	$CDCl_3$	5.43	4.25 ($J_{3,4}$ 10)	3.66 ($J_{4,5}$ 10)	4.50	5.82	
1,3,5-Tri-*O*-benzoyl-4-*O*-methyl-α-L-sorbopyranose	**4**	pyridine-d_5	5.07	3.90 ($J_{3,4}$ 9,5)	5.39 ($J_{4,5}$ 9.5)	4.37	5.70	6.47
Methyl 1,3,5-tri-*O*-benzoyl-4-*O*-methyl-α-L-sorbopyranoside	**5**	$CDCl_3$	5.55	4.47 ($J_{3,4}$ 9,5)	5.75–6.33	4.74	5.75–6.33	6.58 6.60

[a]At 60 MHz.

The high values of the coupling constants (9.5 Hz) suggest that H-3, H-4, and H-5 are in a *trans*-diaxial relationship, and, consequently, the molecule has the *1C*(L) conformation. The signal for the 2-hydroxyl group appears superimposed on those for H-1a and H-1b, as a doublet of area equivalent to three protons; this changes to two protons by adding deuterium oxide. In Table I are shown the chemical shifts of the rest of the protons.

On methylation with Purdie's reagents, compound **1** yielded methyl 1,3,5-tri-*O*-benzoyl-4-*O*-methyl-α-L-sorbopyranoside (**5**). Debenzoylation with sodium methoxide in methanol gave methyl 4-*O*-methyl-α-L-sorbopyranoside (**6**), and, on acid hydrolysis, **6** afforded 4-*O*-methyl-L-sorbose[3].



The ready hydrolysis of one methyl group in **6** established its glycosidic character; this, in turn, demonstrated that the other free hydroxyl group in compound **1** is situated at C-2.

The n.m.r. spectrum of **5** in $CDCl_3$ showed H-3 as a doublet at τ 4.47 ($J_{3,4}$ 9.5 Hz). The high value of the coupling constant suggests a *trans*-diaxial arrangement of H-3 and H-4, in the *1C*(L) conformation. The chemical shifts of the rest of the protons are shown in Table I.

EXPERIMENTAL

General procedures. — Paper chromatography was conducted on Whatman No. 1 paper and, on a preparative scale, on Whatman No. 3MM paper. Column chromatography was performed on Whatman cellulose and on Silica Gel (Davison). T.l.c. was conducted on Kieselgel G (Merck); the solvents employed were: (A) 10:2:3 (v/v) butyl alcohol–ethanol–water; (B) 2:3 (v/v) butyl alcohol–water; (C) 97:3 (v/v) benzene–methanol; and (D) 197:3 (v/v) benzene–methanol. The spray reagents were: (F) aniline hydrogen phthalate[4]; (G) alkaline hydroxylamine–ferric nitrate for esters[5]; and (H) urea–hydrochloric acid for ketoses[6]. Melting points are not corrected. N.m.r. spectra were recorded at 20–25° at 60 MHz with a Varian A-60 spectrometer. Tetramethylsilane (τ 10.00) was used as the internal standard. The data on chemical shifts and coupling constants are given in Table I. Optical rotations were determined at 25°.

1,3,5-Tri-O-benzoyl-α-L-sorbopyranose (**1**). — L-Sorbose (18.0 g, 0.1 mole) was dissolved in dry pyridine (300 ml) at room temperature, and the solution was cooled

to −10°, and kept for 1 h at this temperature. Benzoyl chloride (57.6 g, 0.41 mole) was then added dropwise, the temperature of the mixture being kept at −5°. The solution was kept for 1 h at −10° with periodic shaking, and then crushed ice was added at 40-min intervals during 5 h, the temperature being maintained at −10° throughout the operation. The product was extracted with chloroform (4 × 100 ml) at room temperature; the chloroform solution was washed successively with M sulfuric acid, a saturated solution of sodium hydrogen carbonate, and water, dried (calcium chloride), and evaporated to dryness. The residue was dried in a vacuum desiccator; yield 44.3 g. The solid was treated with warm ethyl alcohol, and the extract was used in the next experiment. The precipitate, after recrystallization from ethyl alcohol, had m.p. 190°, $[\alpha]_D$ −20.7° (*c* 0.2, pyridine). T.l.c. with solvent C and detection with reagent G gave only one spot, R_F 0.38.

Anal. Calc. for $C_{27}H_{24}O_9$: C, 65.85; H, 4.87. Found: C, 66.07; H, 4.85.

1,3,4,5-Tetra-O-*benzoyl*-α-L-*sorbopyranose* (**2**). — The mother liquors from compound **1** were diluted with water, yielding a solid that was filtered off, dried, suspended in hot petroleum ether (b.p. 60–80°), and dissolved by adding benzene dropwise to the suspension. On cooling, further amounts (total, 5 g) of compound **1** were obtained. The mother liquors were combined, and evaporated to dryness, and the residue was re-treated with light petroleum–benzene; this procedure was repeated until no more precipitate was obtained. The final residue was suspended in warm water, and dissolved by adding methanol dropwise. On cooling, compound **2** (6.7 g) was obtained, m.p. 134–5°, $[\alpha]_D$ +49° (*c* 0.7, *N,N*-dimethylformamide); lit.[1] m.p. 133–5°, $[\alpha]_D$ +49.8° (*c* 1.0, *N,N*-dimethylformamide). T.l.c. in solvent C (spraying with reagent G) showed only one spot, R_F 0.65.

Anal. Calc. for $C_{34}H_{28}O_{10}$: C, 68.45; H, 4.69. Found: C, 68.75; H, 4.62.

The mother liquors from **2** were evaporated to dryness, and the dried residue (18.2 g) was chromatographed on a column (4.2 × 60 cm) of silica gel, employing benzene with increasing amounts of methanol as the eluant; fractions (50 ml each) were collected. Fractions 37–41 (2.5% methanol in benzene) gave compound **2** (6.3 g). From fractions 42–44, compound **1** (1.2 g) was obtained. The total yield of **1** was 21.1 g (42.8%), and of **2** was 13 g (23.4%). The rest of the fractions gave 10.2 g of colored products that did not crystallize , and were not further investigated.

The identity of compound **2** was confirmed by preparation of its methyl glycoside[1], m.p. 136°, $[\alpha]_D$ +10.9° (*c* 1.3, chloroform); lit.[1] m.p. 134–6°, $[\alpha]_D$ +12.6° (*c* 1.0, chloroform).

1,3,5-Tri-O-*benzoyl-4*-O-*methyl*-α-L-*sorbopyranose* (**4**). — A solution of compound **1** (1.1 g, 2.2 mmoles) in dichloromethane (200 ml) was cooled to 0° and, after addition of two drops of boron trifluoride etherate, a cold solution of diazomethane in dichloromethane (300 ml, obtained from 10 g of nitrosomethylurea[2]) was slowly added. After 4 h at room temperature, the colorless mixture was filtered, and the filtrate was evaporated to dryness. The residual syrup was chromatographed on a column (170 × 15 mm) of silica gel, eluted with benzene (60 ml) and then with 1% (75 ml), 1.5% (45 ml), and 2% (195 ml) methanol in benzene; 25 fractions (15 ml

each) were collected. From fractions 14–16, compound **4** was obtained (680 mg, 61%), m.p. 140°, $[\alpha]_D$ +26.4° (*c* 0.3, chloroform). T.l.c. with solvent D, with spraying with reagent G, gave one spot, R_F 0.27.

Anal. Calc. for $C_{28}H_{26}O_9$: C, 66.39; H, 5.17. Found: C, 66.80; H, 5.49.

4-O-Methyl-L-sorbose. — A solution of compound **4** (550 mg, 1mmole) in 0.01 M sodium methoxide in methanol (100 ml) was kept for 24 h at room temperature, and then made neutral with Zeo-Karb 225 (H^+) ion-exchange resin, and evaporated to dryness. The dried residue was extracted with ethyl acetate (7 × 4 ml) to remove methyl benzoate, and the remaining syrup was chromatographed on a column (35 × 1 cm) of cellulose, with solvent A as the eluant, 10 fractions (5 ml each) being collected. Fraction 4, on paper chromatography with solvent A and spraying with reagent F, gave only one spot, R_{Sorb} 2.00. The compound had m.p. 133°, $[\alpha]_D$ −31.8° (*c* 0.6, water); lit.[3] m.p. 133°, $[\alpha]_D$ −30.9° (*c* 1.85, water).

Anal. Calc. for $C_7H_{14}O_6$: C, 43.29; H, 7.21. Found: C, 43.35; H, 6.95.

Methyl 1,3,5-tri-O-benzoyl-4-O-methyl-α-L-sorbopyranoside (**5**). — Compound **1** (1.0 g, 2 mmoles) was shaken with methyl iodide (7.2 ml, 116 mmoles), and silver oxide (1.87 g) during 5 h at 60°. The suspension was filtered, the filtrate was evaporated, and the residual syrup was dried, and extracted with ethyl ether (10 × 10 ml). Evaporation of the ether extracts gave a crystalline product which, on t.l.c. with solvent E and spraying with reagent G, showed one spot, R_F 0.83; yield 1.0 g (98%). After recrystallization from ethanol, it had, m.p. 185°, $[\alpha]_D$ +26.5° (*c* 0.7, chloroform).

Anal. Calc. for $C_{29}H_{28}O_9$: C, 66.92; H, 5.38. Found: C, 67.15; H, 5.30.

Methyl 4-O-methyl-α-L-sorbopyranoside (**6**). — A solution of compound **5** (500 mg) in 0.01 M sodium methoxide in methanol (100 ml) was kept for 24 h at room temperature, neutralized with Zeo-Karb 225 (H^+) resin, and the solution evaporated to dryness; the residue was extracted with light petroleum (b.p. 60–80°, 3 × 3 ml) to remove methyl benzoate; yield, 170 mg of product. After maceration with ethanol, this gave pure **6**, m.p. 117–118°, $[\alpha]_D$ −77.4° (*c* 0.2, water). Paper chromatography with solvent A and spraying with reagent H (for ketoses) gave one spot, R_{Sorb} 3.41. The n.m.r. spectrum in pyridine-d_5 showed the methoxyl peaks at τ 6.14 and 6.60. The rest of the protons appeared between τ 5.50 and 6.07 as a large multiplet.

Anal. Calc. for $C_8H_{16}O_6$: C 46.15; H 7.74. Found: C 46.55; H 8.07.

Compound **6** (130 mg) was hydrolyzed with 0.5M sulfuric acid for 2 h at 100°, the solution was made neutral with barium carbonate, and filtered, and the filtrate was evaporated to dryness. The residue (100 mg), purified by preparative, descending, paper chromatography, gave 4-*O*-methyl-L-sorbose, m.p. 133°, $[\alpha]_D$ −31.5° (*c* 0.3, water).

Benzoylation of 1,3,5-tri-O-benzoyl-α-L-sorbopyranose (**1**). — Compound **1** (0.200 g, 0.4 mmole) was dissolved in 5 ml of pyridine at room temperature. The solution was cooled to 5°, and 0.1 ml (0.8 mmole) of benzoyl chloride was added. After 24 h at 5°, and 5 h at room temperature the solution was poured into 200 g of crushed ice. The syrup obtained was washed with water (5 × 100 ml), dried, and dis-

solved in ethanol. T.l.c. with solvent C, employing reagent G, gave one spot having the same mobility as compound **2**. The ethanol solution gave a solid (190 mg), m.p. and mixed (with **2**) m.p. 134°, $[\alpha]_D$ +49.5° (*c* 0.34, *N*,*N*-dimethylformamide).

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