A NEW SYNTHESIS OF 1-DEOXY-D-*manno*-HEPTULOSE*

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ABSTRACT

Reaction of 4-*O*-benzoyl-2,3:5,6-di-*O*-isopropylidene-D-mannononitrile with methylmagnesium iodide produced 1-benzamido-1-deoxy-2,3:5,6-di-*O*-isopropylidene-1,1-*C*-dimethyl-D-mannitol (7) (25.4%) and 1-deoxy-3,4:6,7-di-*O*-isopropylidene-*keto*-D-*manno*-heptulosimine (3) (51.3 %). The structure of the first compound was established by hydrolysis to 1-benzamido-1-deoxy-1,1-*C*-dimethyl-D-mannitol subsequently degraded to 2-benzamido-2-methylpropanal. Hydrolysis of the second compound gave 1-deoxy-D-*manno*-heptulose.

INTRODUCTION

1-Deoxy-2-keto sugars have been synthesized by several routes from aldoses[1], *O*-acylated glycopyranosyl halides[2], *O*-acylated *aldehydo*-aldoses[3], and *O*-acylated aldonyl halides[4] by reaction with a one-carbon compound or a one-carbon donor. The methyl-carbon atoms of the 1-deoxy-2-keto sugars were derived, in these syntheses, from the carbon atoms of nitromethane[1], cyanide ion[2], and diazomethane[3,4], and from the methylene carbon-atom of malonic acid[5]. Ohle and Dambergis[6] extended the sugar carbon-chain by treatment of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranuronic acid with methylmagnesium iodide or ethylmagnesium iodide, and subsequently obtained 7-deoxy-D-*galacto*-heptos-6-ulose and 6,6-*C*-dimethyl-D-galactose or the respective ethyl derivatives.

Attempts to synthesize ketose derivatives by treatment of 2-anilino-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-gluconpremonitrile with Grignard reagents or with alkyllithiums yielded 1-*C*-alkyl(or aryl)-1-anilino-1-deoxy-D-arabinitols[7], products of replacement of the cyanide group by alkyl or aryl residues. This reaction seems to be characteristic of cyanohydrins and α-aminonitriles (see Ref. 7 and references therein).

Zhdanov *et al.*[8] have recently obtained 3,4:6,7-di-*O*-cyclohexylidene-1-deoxy-D-*manno*-heptulose from 2,3:5,6-di-*O*-cyclohexylidene-D-mannono-1,4-lactone, ethyl bromoacetate, and zinc, followed by alkaline hydrolysis and decarboxylation of the product.

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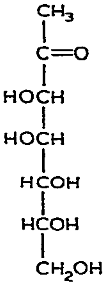
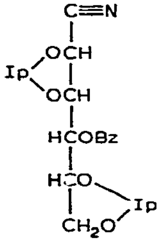
*Preliminary accounts of part of this work have been presented [*Israel J. Chem.*, 7 (1969) 28; 8 (1970) 136].

1-Deoxy-D-*manno*-heptulose (**1**) has been obtained from D-mannose by the nitromethane synthesis[1], and has also been recently synthesized from 2,3,4,5,6-penta-*O*-benzoyl-D-mannonyl chloride and diazomethane[9]. Both syntheses are time-consuming, and the final product is obtained in low yield. Interest in **1** as a substrate for biological studies led us to attempt its synthesis from 4-*O*-benzoyl-2,3:5,6-di-*O*-isopropylidene-D-mannononitrile (**2**) and methylmagnesium iodide via 1-deoxy-3,4:6,7-di-*O*-isopropylidene-*keto*-D-*manno*-heptulosimine (**3**), although the concomitant formation of 1-amino-1-deoxy-2,3:5,6-di-*O*-isopropylidene-1,1-*C*-dimethyl-D-mannitol (**5**) was expected.



1



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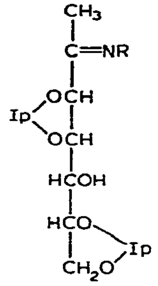
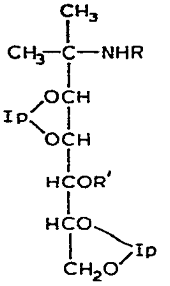


3 R = H

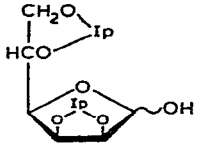
4 R = $NHC_6H_3Cl_2$



5 R = R′ = H

6 R = H; R′ = Bz

7 R = Bz; R′ = H



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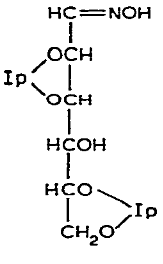
RESULTS AND DISCUSSION

The nitrile **2** was prepared by conversion of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose[10] (**8**) into the 2,3:5,6-di-*O*-isopropylidene-D-mannose oxime (**9**), and treatment of the latter compound with benzoyl chloride. I.r. spectral analysis of **9** showed no absorption peak for an oxime group, and its acyclic structure was suggested by the n.m.r. spectrum, which was characteristic of acyclic *syn* and *anti* oxime isomers, respectively[11-13]. The suggested, acyclic structure of the nitrile **2** is in agreement with the i.r. spectrum; no absorption that would indicate the presence of the isomeric cyclic structure **10** was observed.



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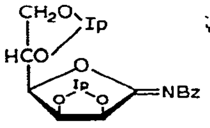

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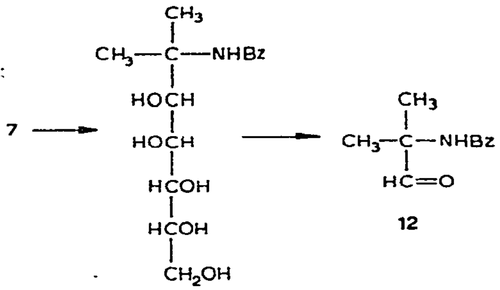
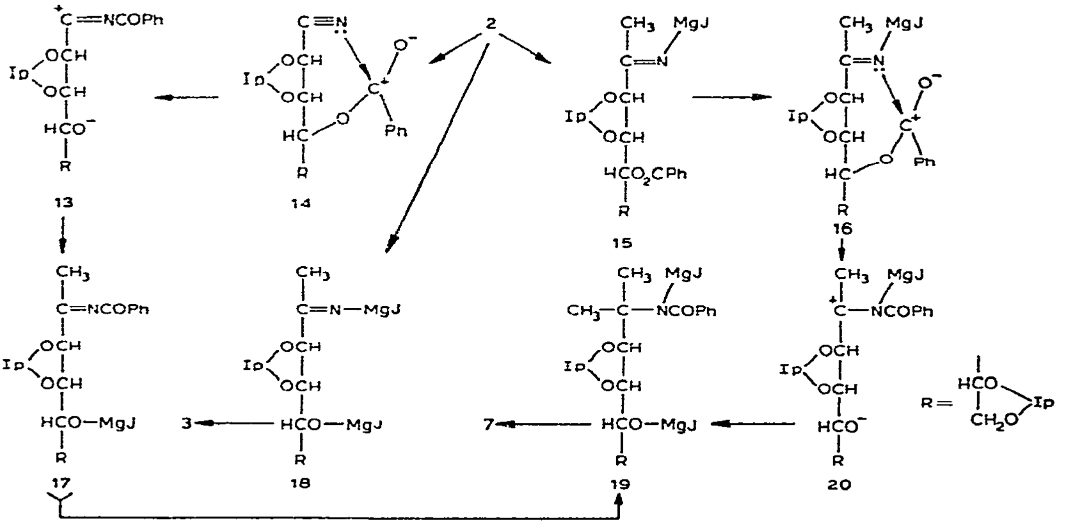


11

12

Reaction of methylmagnesium iodide with **2** (in 8:1 molar proportions) gave a nitrogen-containing crystalline compound. The n.m.r. spectrum suggested either structure **6** or **7**, and the i.r. spectrum indicated a free-hydroxyl group rather than an ester. The compound was recovered unchanged after alkaline treatment, and mild acid hydrolysis gave two moles of acetone, isolated as the 2,4-dinitrophenylhydrazone, and a crystalline compound. The n.m.r. spectrum of this compound and the result of the periodate oxidation indicated that it was 1-benzamido-1-deoxy-1,1-*C*-dimethyl-D-mannitol (**11**). This was confirmed by the isolation, from the oxidation products, of crystalline 2-benzamido-2-methylpropanal (**12**), characterized by the oxime.

The isolation of **11** and **12** as reaction products, indicated the structure of 1-benzamido-1-deoxy-2,3:5,6-di-*O*-isopropylidene-1,1-*C*-dimethyl-D-mannitol (**7**) for the condensation product of **2**. Although no chromatographic or spectral evidence of **10** was observed, its presence in small amounts in admixture with **2** cannot be excluded. If **10** was not present at the start of the reaction, the high yield of **7** (25%) would require that an O→N benzoyl migration occurred under the reaction conditions. This might have occurred by two routes (Scheme 1). In the sequence **2**→**14**→**13** →**17**→**19**→**7**, the O→N benzoyl migration occurs in **2** prior to the Grignard reaction, and it is analogous to the intramolecular O→N acyl migration that was suggested for the Wohl degradation of *O*-acylated aldononitriles[14,15]. In the sequence **2**→ **15**→**16**→**20**→**19**→**7**, the migration occurs after the nitrile **2** has reacted. Both routes show seven-membered ring intermediates, and they suggest that the benzamido group of **17**, which is more acidic than the group =N–MgJ of **16**, reacted with the Grignard reagent whereas the latter group did not. A second crystalline compound isolated from the Grignard reaction products gave a crystalline 2,5-dichlorophenylhydrazone **4**, and acid hydrolysis produced two moles of acetone, isolated as the 2,4-dinitrophenylhydrazone. On the basis of the n.m.r. and the i.r. spectra, structure **3**



SCHEME 1

was assigned to this second compound rather than the tautomeric furanose structure. Acid hydrolysis produced 1-deoxy-D-*manno*-heptulose (**1**). The product, presumably consisting of an equilibrium mixture of the acyclic, furanose, and pyranose forms, was chromatographically indistinguishable from **1** synthesized by a different route[9], and it gave positive Selivanoff (ketose) and haloform reactions. Compound **1** was characterized by its n.m.r. spectrum and by formation of the 2,5-dichlorophenylhydrazone and penta-*O*-benzoyl derivative.

EXPERIMENTAL

Solutions in organic solvents were dried with sodium sulfate. Evaporation of solvents was carried out *in vacuo* in a Rotavapor (Buchi). Unless otherwise stated, petroleum ether (60–80°) was used for crystallization. Thin-layer chromatography was performed on Kieselgel D-5 silica for t.l.c. (Camag, Muttenz, Switzerland) on 2.5 × 7.5 cm microscope slides with 1:1 ethyl acetate–cyclohexane (solvent A), or 40:10:12 butyl alcohol–ethanol–water (solvent B). The compounds were detected by spraying with 5% sulfuric acid in ethanol and heating. R_F values were determined on plates (10 × 20 cm). Descending paper chromatography was performed on Whatman paper No. 1 or 3MM with solvent B and spraying with orcinol–trichloroacetic acid[16]. Melting points were determined with a Buchi melting point apparatus (Tottoli) and are not corrected. Optical rotations were determined in 1-dm polarimeter tubes with a Perkin–Elmer Model 141 polarimeter. I.r. absorption spectra of **2** and **9** were recorded with a Beckman spectrophotometer Model IR7 and other spectra with a Perkin–Elmer spectrophotometer Model 337. N.m.r. spectra were measured in dimethyl sulfoxide-d_6, chloroform-d, and acetone-d_6 with tetramethylsilane (τ 10.0) as internal standard, or in deuterium oxide with tetramethylsilane as external standard, with a Varian T-60 n.m.r. spectrometer or with a HA-100 spectrometer. Microanalyses were performed by the Microanalysis Laboratory of the Weizmann Institute of Science, Rehovot, Israel.

2,3:5,6-Di-O-isopropylidene-D-mannose oxime (**9**). — A freshly made, still warm, solution of sodium ethoxide (3.45 g sodium, 0.15 mole) in ethanol (120 ml) was added to a warm solution of hydroxylamine hydrochloride (10.4 g, 0.15 mole) in water (6 ml). The solution was cooled, filtered, and added to a solution of 2,3:5,6-di-*O*-isopropylidene-D-mannose[17] (27.4 g, 0.1 mole) in ethanol (250 ml). The solution was heated at reflux for 1 h, concentrated to about one third of its volume, and filtered. The product crystallized on cooling, m.p. 140° (21.9 g, 80%) and was recrystallized from ethanol, m.p. 142°; $[\alpha]_D^{28}$ $-176.6°$ (c 2.0, chloroform); n.m.r. data [Varian T-60; 1:1 chloroform-d-dimethylsulfoxide-d_6]: τ -0.99 (singlet, exchangeable with D, *anti*-isom., =N–OH), -0.82 (singlet, exchangeable with D, *syn*-isom., =N–OH), 2.45 (doublet, $J_{1,2}$ 8 Hz, *syn*-isom., C-1), 3.03 (doublet, $J_{1,2}$ 4 Hz, *anti*-isom., C-1); n.m.r. data [Varian HA-100, acetone-d_6]: τ 7.24 changed to 7.34 on dilution (singlet, 1-proton exchangeable with D, C-4-OH); t.l.c.: R_F 0.32 (solvent A).

Anal. Calc. for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.51; H, 7.66; N, 5.19.

4-O-Benzoyl-2,3:5,6-di-O-isopropylidene-D-mannononitrile (**2**). — Benzoyl chloride (74 ml, 0.6 mole) was added in three portions, within 15 min, to a solution of **9** (55.0 g, 0.2 mole) in pyridine (250 ml). The solution was heated for 3 min at reflux and allowed to cool to room temperature. After 3 h, ice was added, and an hour later the solution was poured into ice–water (2.5 kg). The oily precipitate crystallized overnight. The product was dissolved in chloroform, and the solution was washed with 0.5M sulfuric acid, water, 8% sodium hydrogen carbonate solution, again with water, and dried. The solution was evaporated, and the residue crystallized from benzene, m.p. 140–144° (23.6 g). A second crop was obtained from the filtrate (9.5 g, total yield 45.9%). Two crystallizations from the same solvent raised the m.p. to 148°; $[\alpha]_D^{28}$ +21.2° (*c* 2.0, chloroform); i.r. data: $\nu_{max}^{CHCl_3}$ 1160 (C↔O–C=O), 1270 (C–O↔C=O), 1730 cm^{-1} (C_6H_5C=O); t.l.c.: R_F 0.57 (solvent A).

Anal. Calc. for $C_{19}H_{23}NO_6$: C, 63.14; H, 6.42; N, 3.88. Found: C, 62.97; H, 6.66; N, 3.99.

1-Benzamido-1-deoxy-2,3:5,6-di-O-isopropylidene-1,1-C-dimethyl-D-mannitol (**7**). — A solution of **2** (36.1 g, 0.1 mole) in a mixture of ether (320 ml) and benzene (125 ml) was added dropwise to a stirred, gently refluxing ether solution (320 ml) of methylmagnesium iodide prepared from methyl iodide (49.6 ml, 113.6 g, 0.8 mole) and magnesium turnings (19.2 g, 0.8 mole). The reaction mixture was heated for 1 h at reflux, cooled, and treated with a saturated ammonium chloride solution (500 ml). The phases were separated, and the aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined organic phases were extracted with ice-cooled M hydrochloric acid (4 x 80 ml), and this aqueous acid extract was treated separately for the isolation of **3** (see later). The organic phase was washed with water, dried, and evaporated. The residue was crystallized from benzene–petroleum ether to give needles (9.97 g, 25.4%), m.p. 165–168°; recrystallization from ethanol–water raised the m.p. to 173–174°; $[\alpha]_D^{28}$ −2.8° (*c* 1.96, chloroform); i.r. data: $\nu_{max}^{CHCl_3}$ 1650 (NHCO), 3350 (NH), 3520 cm^{-1} (OH); n.m.r. data (Varian HA-100, chloroform-*d*): τ 2.07 and 2.67 (multiplets, 5 aromatic protons), 5.55, 6.0 (multiplets, carbon-chain protons), 7.06 (doublet, $J_{4,OH}$ 9 Hz, 1 proton, exchangeable with deuterium, OH), 8.28, 8.37, 8.43, 8.59, 8.66, and 8.71 (singlets, 6 Me); t.l.c.: R_F 0.45 (solvent A).

Anal. Calc. for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 64.37; H, 8.00; N, 3.40.

A 2M sodium hydroxide solution (2.0 ml) was added to a solution of **7** (200 mg) in ethanol (10 ml) and water (1 ml). No hydrolysis was detected by t.l.c. (solvent A), after heating the solution for 3 h at reflux. The solution was concentrated and extracted with chloroform to give crystals (153 mg), m.p. and mixed m.p. 173–174°.

Sulfuric acid (1.25mM, 30 ml) was added to a solution of **7** (300 mg, 0.763 mmole) in acetic acid (5 ml). A stream of nitrogen was passed for 1 h through the solution, which was heated on a steam bath, and then into a cooled trap containing a saturated solution of 2,4-dinitrophenylhydrazine in 2M hydrochloric acid (150 ml). The acetone 2,4-dinitrophenylhydrazone was filtered off, washed, and dried (329.0 mg, 90.5%), m.p. 125°; lit.: m.p. 128° (Ref. 18), 126° (Ref. 19).

*1-Benzamido-1-deoxy-1,1-*C*-dimethyl-*D*-mannitol* (**11**). — A solution of compound **8** (1.0 g) in ethanol (50 ml) and 0.125M sulfuric acid (25 ml) was heated for 40 min at reflux. The cooled solution was neutralized with barium carbonate, the suspension filtered, and the salts washed with 2:1 ethanol–water (75 ml). The combined filtrates were evaporated, and the resulting syrup was crystallized from chloroform–petroleum ether, m.p. 120–135° (660 mg, 82.8%). Recrystallization from the same solvent raised the m.p. to 142–143°; $[\alpha]_D^{28}$ −17.8° (*c* 1.0, methanol); i.r data: ν_{max}^{Nujol} 1650 (CONH), 3200 (NH), and 3370 cm^{-1} (OH); n.m.r. data (dimethyl sulfoxide-d_6): τ 1.75, 3.08 (two multiplets, 5 aromatic protons), 8.40, and 8.53 (singlets, 2-Me); t.l.c.: R_F 0.62 (solvent B).

Anal. Calc. for $C_{15}H_{23}NO_6$: C, 57.49; H, 7.40; N, 4.47. Found: C, 57.44; H, 7.24; N, 4.62.

Compound **11** (6–24 mg) was oxidized with 10mM sodium periodate in the presence of sodium hydrogen carbonate (5–12 mg) at room temperature. Determination of the oxidant consumed with arsenite[20] indicated that the oxidation was terminated in 10 min and that 3.88–4.16 equiv. of oxidant were consumed per mole of **11**.

2-Benzamido-2-methylpropanal (**12**). — To a stirred, cooled solution of **11** (930 mg, 3 mmoles) in water (40 ml) and M sodium hydrogen carbonate solution (60 ml) was added dropwise 0.3M periodic acid (60 ml). Crystals formed at the start of oxidation. The mixture was stirred for 30 min after the addition of the oxidant, and then the crystals were filtered off (430 mg, 76%), m.p. 162–163°. Recrystallization from benzene–petroleum ether did not change the m.p.; i.r. data: ν_{max}^{Nujol} 1630 (CONH), 1740 (CHO), and 3250 cm^{-1} (NH); n.m.r. data (chloroform-*d*): τ 0.28 (singlet, 1 proton, CHO), 1.80, 2.66 (multiplets, 5 aromatic protons), 2.82 (broad singlet, 1 proton, NH), and 8.67 (singlet, 6 protons, 2 Me); t.l.c.: R_F 0.33 (solvent A).

Anal. Calc. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.97; H, 6.83; N, 7.51.

2-Benzamido-2-methylpropanal oxime. — A solution of **12** (95 mg, 0.5 mmole) in ethanol (3 ml) was added to a solution of hydroxylamine hydrochloride (70 mg, 1 mmole) in water (1 ml). The solution was neutralized with 2M sodium hydroxide, heated at reflux for 30 min, evaporated to dryness, and the residue extracted with boiling benzene (2 × 10 ml). Petroleum ether was added to the extract, and needles formed on cooling (94 mg, 92%) m.p. 130°; n.m.r. data (chloroform-*d*): τ 0.76 (singlet, 1 proton, N–OH), 1.82, 2.54 (multiplets, 5 aromatic protons), 2.18 (singlet, CH=N), and 8.33 (singlet, 2 Me); t.l.c.: R_F 0.37 (solvent A).

Anal. Calc. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.04; H, 6.78; N, 13.37.

*1-Deoxy-3,4:6,7-di-*O*-isopropylidene-*keto-D-manno*-heptulose imine hemihydrate* (**3**). — The aqueous, acid solution obtained in the preparation of **7** (once extracted with dichloromethane) was cooled and poured into a 16% sodium hydroxide solution (100 ml) cooled in an ice–salt mixture. The cold, alkaline solution was extracted with dichloromethane (3 × 250 ml). The extract was washed with water, dried, and evaporated to give a syrup (14.0 g, 51.3%) which crystallized on addition of water (0.3 ml). The product was recrystallized from cyclohexane as the hemihydrate, m.p. 71–72°; $[\alpha]_D^{28}$ −34.6° (*c* 2.1, chloroform); i.r. data: ν_{max}^{Nujol} 1660 (C=N), 3380 (NH), 3460, and 3500 cm^{-1} (OH); n.m.r. data (chloroform-*d*): τ 5.18, 5.65, 5.95, 6.38 (multiplets, 6 protons, C-3–7 carbon-chain protons), 7.77 (singlet, 2 protons exchangeable with D, C-4-OH, water), 8.33, 8.38, 8.42, 8.48, and 8.53 (singlets, 5 Me); t.l.c.: R_F 0.14 (solvent A), 0.52 (solvent B).

Anal. Calc. for $C_{13}H_{23}NO_5 \cdot 0.5\,H_2O$: C, 55.35; H, 8.56; N, 4.97. Found: C, 55.22; H, 8.48; N, 4.86.

Crude syrupy **3** (281.9 mg, 1.033 mmole), dried by azeotropic distillation of benzene, was hydrolyzed in 125mM sulfuric acid (50 ml) and the acetone trapped as described for the hydrolysis of **7**. The acetone 2,4-dinitrophenylhydrazone (448.7 mg, 91.2%) had m.p. 125–126°.

*1-Deoxy-3,4:6,7-di-*O*-isopropylidene-*keto-D-manno*-heptulose 2,5-dichlorophenylhydrazone* (**4**). — A solution of 2,5-dichlorophenylhydrazine (1.59 g, 9 mmoles) in ethanol (10 ml), acetic acid (0.52 ml, 9 mmoles), and water (2 ml) was added to a solution of **3** (2.3 g, 8.0 mmoles) in ethanol (12 ml). The mixture was kept for 1 h at room temperature and then extracted with chloroform (150 ml). The chloroform extract was washed (M hydrochloric acid, water, and M sodium hydrogen carbonate solution), dried, and evaporated. The residue was crystallized from petroleum ether (2.7 g, 78%), m.p. 128–129°. Two recrystallizations from benzene–petroleum ether raised the m.p. to 142–144°; $[\alpha]_D^{28}$ +56.0° (*c* 1.03 chloroform); t.l.c.: R_F 0.58 (solvent A).

Anal. Calc. for $C_{19}H_{26}Cl_2N_2O_5$: C, 52.66; H, 6.06; N, 6.46. Found: C, 52.69; H, 5.95; N, 6.33.

*1-Deoxy-*D-manno*-heptulose* (**1**). — Dowex 50-WX12 (H$^+$, 4.0 g, air dried) was added to a solution of **3** (4.0 g, 14.6 mmoles) in water (40 ml). The suspension was stirred overnight at room temperature. After a further addition of resin (2.0 g), stirring was continued for an additional 24 h to complete the hydrolysis. The aqueous solution was decanted and, after addition of water (60 ml), the resin was stirred for 1 h. The combined aqueous solutions were evaporated, and the residue was dried by addition and evaporation of ethanol and then of benzene. The syrupy residue (2.5 g, 85%) consisted of **1** and two byproducts. A portion of it (800 mg) in ethanol was chromatographed on 3 sheets of Whatman paper 3MM (46 × 57 cm) in solvent B. Compound **1**, detected by spraying a side band of the paper, was extracted from the paper sheets with boiling water (3 × 200 ml). The residue (520 mg, 65%), obtained on evaporation of the solvent, was crystallized from ethanol–petroleum ether (63–69°, Ref. 1), m.p. 109–111°; recrystallization from the same solvent raised the m.p. to 110–112°; $[\alpha]_D^{25}$ +27.1° (*c* 1.97, water, after 30 min); n.m.r. datum (deuterium oxide): τ 8.50 (singlet, Me); t.l.c.: R_F 0.40 (solvent B); lit.[1]: m.p. 90–91°; $[\alpha]_D^{25}$ +24.2°. Our product is presumably a mixture of the acyclic α and β furanose, and α and β pyranose forms of **1**, different from that reported earlier[1].

Anal. Calc. for $C_7H_{14}O_6$: C, 43.29; H, 7.27. Found: C, 43.01; H, 7.10.

*Penta-O-benzoyl-1-deoxy-*D-manno*-heptulose.* — Crude **1** was chromatographed as just described. The syrup obtained on evaporation of the solvent (82 mg, 0.43 mmole) was dissolved in pyridine (1.5 ml). The solution was cooled in an ice-bath and benzoyl chloride (0.5 ml) was added. The solution was kept overnight at room temperature. The product, isolated in the usual manner, crystallized as the monohydrate from methanol–water; m.p. 178°, raised by recrystallization to 180–181°; $[\alpha]_D^{28}$ $-88.0°$ (c 0.5, chloroform); n.m.r. datum (chloroform-d): τ 8.39 (singlet, Me); t.l.c.: R_F 0.52 (solvent A).

Anal. Calc. for $C_{42}H_{34}O_{11}\cdot H_2O$: C, 68.84; H, 4.95. Found: C, 68.77; H, 4.92.

*1-Deoxy-*D*-mannoheptulose 2,5-dichlorophenylhydrazone.* — A solution of 2,5-dichlorophenylhydrazine (354 mg, 2 mmoles) in ethanol (3 ml), acetic acid (0.12 ml), and water (0.5 ml) was added to a solution of crude **1** (388 mg, 2 mmoles) in ethanol (2 ml), and the mixture was kept for 1 h at room temperature. The hydrazone was extracted with chloroform, and the extract was washed, dried, and evaporated. The residue was crystallized from methanol, m.p. 175–176°; $[\alpha]_D^{23}$ $-6.0°$ (c 0.78, methanol); t.l.c.: R_F 0.65 (solvent B).

Anal. Calc. for $C_{13}H_{18}Cl_2N_2O_5$: C, 44.20; H, 5.13; N, 7.93. Found: C, 44.32; H, 5.18; N, 7.95.

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