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SYNTHESIS OF SOME DERIVATIVES OF 3-*C*-METHYL-D-PSICOSE, 3-*C*-METHYL-D-FRUCTOSE, AND 6-DEOXY-3-*C*-METHYL-D-PSICOSE*

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ABSTRACT

The synthesis of di-*O*-isopropylidene derivatives of 3-*C*-methyl-D-psicose (**3**) and 3-*C*-methyl-D-fructose by the reaction of 1,2 4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose (**2**) with methylmagnesium iodide and methyllithium is described The reaction of **2** with diazomethane and reduction of the resulting epoxides gave the same branched-chain sugars Isomerisation of **3** and its transformation into the 6-deoxy-5-iodo derivative **9**, followed by catalytic hydrogenation and hydrolysis of the isopropylidene groups, gave 6-deoxy-3-*C*-methyl-D-psicose

INTRODUCTION

Branched-chain sugars have been found as components of substances having physiological activity, mainly antibiotics[1] There have been several reports on the structural elucidation and synthesis of *C*-methyl-, *C*-hydroxymethyl-, and *C*-formylpentoses[2], and deoxy-*C*-methylhexoses[3], but few about branched-chain hexuloses the synthesis of 1-deoxy-3-*C*-methyl-D-psicose has been reported[4]

Branched-chain sugars are usually synthesised by the reaction of an aldulose or diulose derivative with a Grignard reagent, organolithium compound, diazomethane, or dimethylsulfoxonium methylide[5] We have been interested in the synthesis of 1-deoxy-3-*C*-methylhexuloses, in connection with studies of the Knoevenagel reaction[6] between α-alkyl-β-keto acids and aldehydo sugars

RESULTS AND DISCUSSION

Oxidation of 1,2 4,5-di-*O*-isopropylidene-β-D-fructopyranose[7] (**1**) to give 1,2.4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose (**2**) has been achieved by using methyl sulfoxide–acetic anhydride[8 9] or ruthenium tetraoxide[10] We have effected the conversion **1**→**2** (85%) by using methyl sulfoxide–phosphorus

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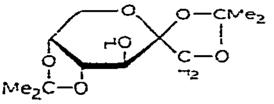
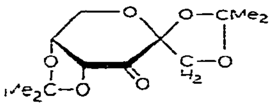
*Branched-chain Sugars Part I

pentaoxide in *N,N*-dimethylformamide, which avoids the formation of the 3-*O*-methylthiomethyl derivative



1



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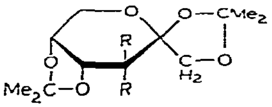
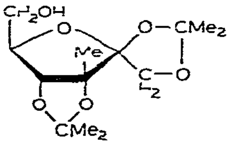


3 R = OH R = Me
4 R = Me R = OH
5 R = –O– R = –CH$_2$–
6 R = –CH$_2$– R = –O–



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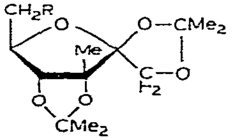
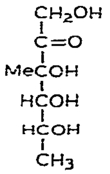


8 R = OTs
9 R = I
10 R = H



$$\begin{array}{c} CH_2OH \\ | \\ C{=}O \\ | \\ MeCOH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ CH_3 \end{array}$$

11

The reaction of **2** with methylmagnesium iodide in anhydrous ether followed by column chromatography gave 1,2 4,5-di-*O*-isopropylidene-3-*C*-methyl-β-D-psicopyranose (**3**, 50%), and 1,2 4 5-di-*O*-isopropylidene-3-*C*-methyl-β-D-fructopyranose (**4** 30%) The configurations of these compounds at C-3 were established by ^{1}H-n m r spectroscopy The signals for MeC-3 in **3** and **4** occurred as singlets at δ 1 21 and 1 30, respectively consistent[11] with equatorial and axial orientation The reaction of **2** with methyl-lithium gave only **3** (80%), whereas, with diazomethane, **2** gave a mixture of 3 3'-anhydro-3-*C*-hydroxymethyl-1,2 4,5-di-*O*-isopropylidene-β-D-psicopyranose (**5**, 34 5%) and 3,3'-anhydro-3-*C*-hydroxymethyl-1,2 4,5-di-*O*-isopropylidene-β-D-fructopyranose (**6**, 40%), which were isolated by column chromatography Compounds **5** and **6** were identified by reduction with lithium aluminium hydride, which gave **3** and **4**, respectively These results accord with those[2 12 13] for the reaction of methyl 3,4-*O*-isopropylidene-β-D- or -L-*erythro*-pentopyranosid-2-ulose with methylmagnesium iodide, methyl-lithium, and diazomethane The stereoselectivity of the reaction of **2** with methyl-lithium reflects steric approach control, the equatorial side of **2** being the less-hindered for formation of the four-centre transition-state[16] On the other hand, the lower stereoselectivity of the reaction of **2** with methylmagnesium iodide could be due to an interaction of the magnesium with the glycosidic oxygen[17] The results of the reaction of **2** with diazomethane are in agreement with those previously reported[13 17], in which an axial addition product is preferentially obtained

Treatment of **3** with 5% sulfuric acid in acetone effected isomerisation into 1,2 3,4-di-*O*-isopropylidene-3-*C*-methyl-β-D-psicofuranose (**7**), the structure of which was established on the basis of analytical and spectroscopic data The signals of the methyl groups of the dioxolane rings appeared as a singlet at δ 1 43, as did that of MeC-3 at δ 1 54 in the ^{1}H-n m r spectrum of **7** The marked differences in ^{1}H-n m r spectra of **3** and **7** reflect the change in ring size from pyranoid to furanoid The

β-D configuration of **7** was reflected by its $[M]_D$ value (—120 5°), and by the low value of $J_{4,5}$ (~1 4 Hz) which accords with those reported[14,15] for the spiroacetals of pentulo- and hexulo-furanoses Attempted isomerisation of **2** was unsuccessful Conventional tosylation of **7** gave the crystalline 6-tosylate **8** (80%), which was converted quantitatively into the syrupy 6-deoxy-6-iodo derivative **9** by treatment with sodium iodide in acetone at 110° Catalytic hydrogenation of **9** in the presence of Raney nickel gave a high yield of 6-deoxy-1,2 3,4-di-*O*-isopropylidene-3-*C*-methyl-β-D-psicofuranose (**10**) Reduction of **8** with lithium aluminium hydride in ether gave **10** together with **7** The structure of **10** was confirmed by ^{1}H-n m r spectroscopy The doublet at δ 1 24 was characteristic of a MeCH group and indicated that **10** was a derivative of 6-deoxy-D-psicose and not of 1-deoxy-D-psicose This conclusion was confirmed by double-resonance experiments Acid hydrolysis of the isopropylidene groups in **10** gave syrupy 6-deoxy-3-*C*-methyl-D-psicose (**11**, 80%)

EXPERIMENTAL

General methods — Melting points were determined with a Reichter hot-plate microscope, and are uncorrected Solutions in organic solvents were dried over Na_2SO_4 before concentration under diminished pressure ^{1}H-N m r spectra (internal Me_4Si, 60 MHz) were recorded with a Perkin–Elmer R20 spectrometer see Table I I r spectra (Table II) were recorded with a Perkin–Elmer Infracord spectrometer A Perkin-Elmer Model 141 polarimeter and 1-dm tubes were used for measurement of optical rotations G l c was performed on a Carlo Erba Model Fractovap-G gas chromatograph equipped with a flame-ionisation detector and a glass column (2 m × 1 75 mm i d) packed with 3% of SE-30 on Chromosorb G (AW-DMCS 100–120 mesh) kept at 160° The N_2 flow-rate was 30 ml/min, the injection-port temperature 250°, and the zone-detector temperature 200° T l c was performed on Silica Gel G (Merck) with detection by charring with sulfuric acid Column chromatography was performed on silica gel (Merck 7734, 0 05–0 2 mm) Columns were packed in the conventional manner Paper chromatography (p c) was performed by the descending technique on Whatman No 1 paper with 1-butanol–ethanol–water (28 7 13) and detection with silver nitrate[19]

*Reactions of 1,2 4,5-di-O-isopropylidene-β-*D*-erythro-hexo-2,3-diulo-2,6-pyranose* (**2**) — (*a*) *With methylmagnesium iodide* To a stirred solution of methylmagnesium iodide (11 g, 66 mmol) in anhydrous ether (50 ml) was added gradually a solution of[8] **2** (7 g, 27 mmol) in anhydrous ether (100 ml), and the mixture was heated under reflux After 2 5 h, t l c (3 2 ether–hexane) showed that **2** had disappeared, and two spots (R_F 0 53 and 0 42) were observed The reaction mixture was cooled, and the excess of methylmagnesium iodide destroyed with 10% aqueous ammonium chloride The organic layer was separated and the aqueous layer was extracted with ether Concentration of the combined ethereal extracts gave a crystalline residue (7 g), which was eluted from a column of silica gel with ether–hexane (1 2→1 1) Concentration of the fractions that contained the compound of R_F 0 53 and recrystallisation

TABLE I

N M R SPECTRAL DATA (60 MHz, $CDCl_3$) FOR COMPOUNDS 3–10

Compound	Chemical shifts[a] (δ) (J in Hz)												
	H-1 ($J_{1,1'}$)	H-1'	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H 6 ($J_{6,6'}$)	H-6' ($J_{5,6'}$)	MeC-3	MeC 5 ($J_{5,Me}$)	Me_2C	HO-3	HO-6	H-3''[b] ($J_{3'',3''}$)	H 3''[b]
3	3 90d (9 0)	4 28d	4 00–4 15		4 12		1 22s		1 36s, 1 40s 1 48s, 1 58s	2 60s			
4	3 85d (9 0)	4 18d	3 85–4 40		4 22		1 30s		1 31s, 1 41s 1 50s, 1 60s	2 50s			
5	3 90d (9 0)	4 15d	3 91d (7 5)	4 28dt	3 70				1 25s[c] 1 40s, 1 45s			2 58d (6 0)	3 10d
6	3 87d (9 0)	4 14d	4 40d	4 40dt	4 00				1 35s, 1 40s 1 50[c]			2 78d (5 30)	2 88d
7	4 05d (10 0)	4 28d	4 56d (1 5)	4 20m	3 65–3 80m		1,54s		1 45s[d]		3 00s		
8[e]	3 95d (10 0)	4 41d	4,05–4 20		4 10		1 40s		1 40s[d]				
9	3 98d (10 1)	4 21d	4 45d (1 5)	4 20m[f]	3 28m[g]		1 50s		1 38s, 1 40s[c]				
10	3 98d (10 0)	4 20d	4 20d (1 5)	4 20m			1 45s	1 24d (7 5)	1 40s[d]				

[a] Signal multiplicities d, doublet, m, multiplet, dt, double triplet, s, singlet [b] Oxirane ring protons at C 3 [c] Signal of two methyl groups [d] Signal of four methyl groups [e] The aromatic protons of the OTs group appeared at δ 7 35 and 7 82 [f] Part X of an ABX system [g] Part AB of an ABX system

TABLE II

I R SPECTRAL DATA FOR COMPOUNDS 3–10

Compound	*Phase*[a]	*ν (cm^{-1})*			
		OH	*C-H*[b c]	*-O-C-O-*[d]	*C—CH$_2$* *O*
3	S	3500	1380	1150	
				1040	
				858	
4	S	3460	1380	1150	
				1040	
				858	
5	S		1380	1150	1250
				1040	915
				848	810
6	S		1380	1150	1250
				1040	908
				855	813
7	S	3500	1380	1150	
				1045	
				860	
8	S		1380	1150	
				1050	
				865	
9	L		1380	1160	
				1040	
				860	
10	L		1380	1150	
				1040	
				865	

[a]Key L, liquid, S, KBr pellet [b]*Gem*-dimethyl [c]Doublet [d]1,3-Dioxolane ring

of the residue from hexane gave 1,2 4 5-di-*O*-isopropylidene-3-*C*-methyl-β-D-psicopyranose (3, 3 75 g, 50%), m p 94–96°, $[\alpha]_D^{25}$ −130° (*c* 1 17, chloroform) Spectral data are given in Tables I and II

Anal Calc for $C_{13}H_{22}O_6$ C, 56 93, H 8 03 Found C, 56 84, H, 8 48

Concentration of the fractions that contained the compound of R_F 0 42 and crystallisation of the residue from hexane gave 1,2 4,5-di-*O*-isopropylidene-3-*C*-methyl-β-D-fructopyranose (4, 2 21 g, 30%), m p 84–86°, $[\alpha]_D^{25}$ −95° (*c* 1 05, chloroform) Spectral data are given in Tables I and II

Anal Found C, 56 92, H, 7 83

(*b*) *With methyl-lithium* To a stirred suspension of small pieces of lithium (0 38 g) in anhydrous ether (5 ml) were added a few drops of methyl iodide When reaction commenced, a solution of methyl iodide (3 5 g) in anhydrous ether (15 ml) was added slowly to maintain gentle boiling

The solution was then stirred and heated under reflux for 2 h After cooling, a solution of **2** (0 7 g 2mmol) in ether (5 ml) was added slowly with stirring and the solution was stirred and heated under reflux for further 3 h T l c then showed that **2** had disappeared and that only **3** was present Water was added with stirring until two layers were obtained The aqueous phase was separated, and extracted with ether (5 × 20 ml), and the combined ether solutions were washed with water (2 × 10 ml) and concentrated Recrystallisation of the residue from hexane gave **3** (0 6 g, 81%)

(*c*) *With diazomethane* To a solution of **2** (5 6 g, 21 mmol) in methanol (70 ml) at 0° was added, portionwise, 2 8% ethereal diazomethane (70 ml) until the mixture remained yellow The solution was stored overnight at room temperature T l c (3 2, ether–hexane) then revealed two spots, R_F 0 47 and 0 38 Evaporation of the solvent gave a residue (6 g) a portion (1 g) of which was subjected to chromatography on a column of silica gel to give, first, $3,3^1$-anhydro-3-*C*-hydroxymethyl-1,2 4,5-di-*O*-isopropylidene-β-D-fructopyranose (**6**, 0 463 g 47%), m p 90–92°, $[\alpha]_D^{25}$ −111° (*c* 1 32, chloroform) Spectral data are given in Tables I and II

Anal Calc for $C_{13}H_{20}O_6$ C, 57 35, H, 7 35 Found C, 57 35 H, 7 49

Eluted second was $3,3^1$-anhydro-3-*C*-hydroxymethyl-1,2 4 5-di-*O*-isopropylidene-β-D-psicopyranose (**5**, 0 35 g, 34 4%) m p 142 5–143 5°, $[\alpha]_D^{25}$ −88 5° (*c* 1 4, chloroform) Spectral data are given in Tables I and II

Anal Found C, 57 50 H, 7 23

Lithium aluminium hydride (1 5 g) was added in portions with stirring to anhydrous ether (70 ml) A solution of the mixture of **5** and **6** (6 g) in ether (70 ml) was added and the mixture was heated under reflux for 8 h T l c then showed that **5** and **6** had disappeared and that **3** and **4** were present The excess of hydride was decomposed by dropwise addition of aqueous ammonium chloride The ethereal layer was separated and the aqueous phase was extracted with ether (3 × 20 ml) The combined extracts were concentrated to give a mixture of **3** and **4** which was fractionated by chromatography into **3** (2 07 g, 32 5%) and **4** (2 50 g, 39 3%)

1 2 3,4-Di-O-isopropylidene-3-C-methyl-β-D-psicofuranose (**7**) — A solution of **3** (3 5 g, 12 8 mmol) in a 5% solution of sulfuric acid in acetone (70 ml) was stored at room temperature for 15 min G l c then revealed that **3** (*T* 112 s) had disappeared and a product had been formed (*T* 88 s) The mixture was neutralised with powdered anhydrous potassium carbonate, filtered, and concentrated A solution of the semicrystalline residue in dichloromethane (50 ml) was washed with water and concentrated and the residue was recrystallised from hexane, to give **7** (3 3 g, 94%), m p 69–70° $[\alpha]_D^{25}$ −44° (*c* 1 06, chloroform) Spectral data are given in Tables I and II

Anal Calc for $C_{13}H_{22}O_6$ C, 56 93 H, 8 03 Found C, 56 84, H, 8 13

1,2 3,4-Di-O-isopropylidene-3-C-methyl-6-O-tosyl-β-D-psicofuranose (**8**) — Conventional treatment of **7** (3 3 g, 12 mmol) with pyridine (20 ml) and tosyl chloride (3 5 g, 18 4 mmol) gave **8** (4 1 g, 80%), m p 81–83° (from ether–hexane), $[\alpha]_D^{25}$ −27° (*c* 1 03, chloroform) Spectral data are given in Tables I and II

Anal Calc for $C_{20}H_{28}O_8S$ C, 56 07, H, 6 54 Found C, 56 20, H, 6 54

6-Deoxy-6-iodo-1,2 3,4-di-O-isopropylidene-3-C-methyl-β-D-psicofuranose (**9**)

— A solution of **8** (4 g, 9 5 mmol) and sodium iodide (3 g, 20 mmol) in acetone (50 ml) was heated for 6 h at 110° in a sealed tube T l c (1 2 ether–hexane) then showed one spot (R_F 0 70) (*cf* 0 40 for **8**) The mixture was filtered and concentrated A solution of the semicrystalline residue in ether was washed sequentially with water, 20% aqueous sodium thiosulfate, and water, and concentrated and the residue was subjected to column chromatography to give **10** as a syrup (3 5 g), $[\alpha]_D^{25}$ −48° (*c* 1 42, chloroform) Spectral data are given in Tables I and II

Anal Calc for $C_{13}H_{21}IO_5$ C, 40 62 H 5 47 Found C, 40 65 H 5 68

1-Deoxy-1,2 3,4-di-O-isopropylidene-3-C-methyl-β-D-psicofuranose (**10**) — A solution of **9** (3 g, 8 mmol) in ethanol (50 ml) and triethylamine (1 5 ml) was hydrogenated at normal pressure in the presence of Raney nickel (5 g) The hydrogen uptake was complete in ~1 h T l c (1 2 ether–hexane) then showed only one spot (R_F 0 57) (*cf* 0 70 for **9**) The mixture was filtered and concentrated and the microcrystalline residue was partitioned between ether and water The ether layer was washed twice with water and concentrated, and the oily residue was subjected as chromatography, to give **10** as a colourless syrup (2 g) $[\alpha]_D^{25}$ −80° (*c* 1 81 chloroform) Spectral data are given in Tables I and II

Anal Calc for $C_{13}H_{22}O_5$ C 60 47, H 8 53 Found C, 60 37 H, 8 71

To a suspension of lithium aluminium hydride (500 mg) in anhydrous ether (25 ml) was added a solution of **8** (1 g, 2 mmol) in ether (25 ml), and the mixture was heated under reflux for 20 h T l c then showed that **8** had disappeared and that **10** and **7** were present Treatment of the reaction mixture in the usual manner, followed by column chromatography, gave **10** (0 25 g, 42%)

6-Deoxy-3-C-methyl-D-psicose (**11**) — A mixture of **10** (1 45 g, 5 6 mmol) and 20% aqueous trifluoroacetic acid (25 ml) was stirred at room temperature After 8 h, t l c showed that **10** had disappeared The solution was concentrated and water was repeatedly evaporated from the residue to remove trifluoroacetic acid A solution of the residue in water was treated with active charcoal filtered, and concentrated and the colourless, syrupy residue was subjected to chromatography on a column of microcrystalline cellulose (Merck), using 90% ethanol The syrupy product (**11** 1 g, 80%) was homogeneous by p c (R_I 0 66) and had $[\alpha]_D^{25}$ −27° (*c* 1 46, water) No mutarotation was observed

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