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Note

A branched-chain sugar from an aldol condensation of *tert*-butyl 3,4-*O*-isopropylidene-α-L-*erythro*-pentopyranosidulose

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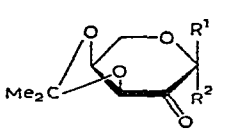
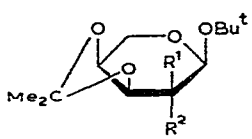
Anomeric pairs of pyranosid-2-ulose derivatives, in which aglycon carbon atoms attached to glycosidic oxygen atoms did not carry hydrogen atoms, were required for photochemical studies[1]. For this purpose, the α anomer of *tert*-butyl 3,4-*O*-isopropylidene-L-*erythro*-pentopyranosidulose (**1**) was synthesised and an attempt was made to anomerise it. This reaction led instead to the formation of a branched-chain sugar derivative, the structure and formation of which are discussed here.

tert-Butyl 3,4-*O*-isopropylidene-α-L-arabinopyranoside (**2**) was oxidised[2] with ruthenium tetraoxide to give the 2-ulose derivative **1**, the structure of which followed from its elemental composition, mass-spectral molecular weight, and absorptions at ν_{max} 1750 cm^{-1} and at λ_{max} 306 nm. The long-wavelength u.v. absorption is typical of a carbonyl group adjacent to the anomeric centre[2]. The n.m.r. spectrum exhibited signals of the required intensities at the correct chemical shifts for *tert*-butyl and isopropylidene groups and for five ring protons. It was shown that compound **2** had been converted into compound **1**, without anomerisation, by reducing it with lithium aluminium hydride. This gave, in high yield, a crystalline *tert*-butyl 3,4-*O*-isopropylidene-pyranoside (**3**) with the *ribo* structure (acid hydrolysis to ribose) and the α-L configuration (optical rotation and a $J_{1,2}$ value of 4.5 Hz, cf. $J_{1,2}$ 7.5 Hz for the arabinoside **2**).

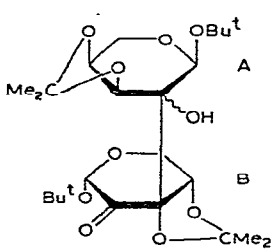


1 R^1 = OBu^t, R^2 = H



2 R^1 = H, R^2 = OH
3 R^1 = OH, R^2 = H

Attempts were made to convert the α-L-glycosidulose **1** into its thermodynamically more-stable β-L anomer by base-catalysed isomerisation of the substituent at C-1 *via* a 1-en-2-olate intermediate. With diethylamine, only decomposition products were detected; this was surprising, since this base successfully transformed methyl 2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose into the β-D-*ribo* isomer by epimerisation of the C-5 methyl group[3]. However, heating the pyranosidulose **1** in dichloromethane with 1,5-diaza[5.4.0]undec-5-ene converted it almost completely into a new, crystalline compound. I.r. spectroscopy showed that it was a hydroxyketone, and the elemental composition, molecular weight, and n.m.r. spectrum indicated that it was a dimeric form of the pyranosidulose of the type **4**, formed by an aldol condensation. In the n.m.r. spectrum (see **4** in Table I), there were nine sharp singlets of various intensities equivalent to one, three, and nine protons. Two singlets arose from two *tert*-butyl groups, four others from two isopropylidene residues, and one (δ 3.35), which was exchangeable with deuterium oxide, from a hydroxyl group. The remaining two singlets at δ 5.10 and 5.44 were assigned, for reasons given below, to the anomeric protons in rings A and B (see **4**), respectively. Also, there were seven multiplets which were amenable to the following first-order analysis. The doublet at δ 4.72 and the three quartets at δ 4.13, 3.82, and 3.44 were found, from their splittings, to arise, respectively, from H-3,4,5,5′ of ring A (structure **4**), and a triplet and a complex two-proton doublet were assigned to H-4 and the protons of the C-5 methylene group in ring B. These results show that there must be tetrasubstitution at C-2 and C-3 in ring A and B, respectively.



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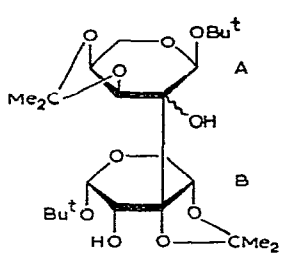

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Reduction of the dimer with lithium aluminium hydride gave, in high yield, a crystalline diol. Its empirical formula and molecular weight indicated that it had structure **5**, which would be expected if the carbonyl group in dimer **4** had been converted into an alcohol function. The n.m.r. spectrum (see **5** in Table I) corroborated this structural assignment; it exhibited six singlets for the *tert*-butyl and isopropylidene groups, and signals for twelve other protons (two more than for compound **4**). There was a striking similarity between the six signals due to the pentosyl protons and the hydroxyl group on ring A in the spectrum of compound **4**, and the pattern and chemical shifts of the three quartets at δ 4.16, 3.89, and 3.43, the doublet at δ 4.56, the singlet at δ 5.03, and the exchangeable singlet at δ 3.30 in the spectrum of the reduced material.

TABLE I

N.M.R. PARAMETERS[a] FOR COMPOUNDS 4 AND 5

H	1_A	3_A	4_A	5_A	$5'_A$	*OH*	1_B	2_B	4_B	5_B	$5'_B$	*OH*	Bu^t	Me_2
4[b]	5.10s	4.72d	4.13q	3.82q	3.44q	3.35s	5.44s		5.39t[d]	——— 4.19d ———			1.28s	1.54s
													1.18s	1.48s
														1.40s
		$J_{3_A,4_A}$ 6.5	$J_{4_A,5_A}$ 6.5	$J_{5_A,5'_A}$ 11.8	$J_{5'_A,4_A}$ 6.0				$J_{4_B,5_B}$ 3.0 $J_{4_B,5'_B}$ 3.0	J 3.0				1.22s
5[c]	5.03s	4.56d	4.16q	3.89q	3.43q	3.30s	5.22d	4.45bd	4.86q	4.30q	3.95q	4.4	1.30s	1.80s
													1.20s	1.60s
														1.50s
		$J_{3_A,4_A}$ 6.5	$J_{4_A,5_A}$ 6.0	$J_{5_A,5'_A}$ 12.0	$J_{5'_A,4_A}$ 6.0		$J_{1_B,2_B}$ 2.0	$J_{2_B,OH}$ 9.5	$J_{4_B,5'_B}$ 2.0	$J_{5_B,5'_B}$ 12.5	$J_{5'_B,4_B}$ 2.5			1.30s

[a]In benzene-d_6; δ in p.p.m., J in Hz. [b]100 MHz. [c]220 MHz. [d]Irradiation at 5.39 perturbs only the signal at 4.19.

These signals could therefore reasonably be assigned to H-4,5,5',3,1, and the hydroxyl on ring A of compound **5**, because this ring is the same in both compounds. The other signals in the n.m.r. spectrum of **5** must have arisen from the protons in the reduced ring B, because their resonance patterns and chemical shifts differed from the resonances in the spectrum of the dimer **4**. The signals could be assigned as shown in Table I. Particularly significant were the new signals for H-2 and HO-2, and the narrowly spaced doublet which was assigned to the anomeric proton.

Ring B in compound **5** probably has the *ribo* configuration since $J_{1,2}$ is 2.0 Hz, indicating a *cis* relationship at C-1 and C-2. This is reasonable since reduction of **1** with lithium aluminium hydride afforded a riboside derivative. The configuration of ring A in compounds **4** and **5** has not been determined, and is not easy to predict since reactions of compound **1** with reagents possessing nucleophilic carbon atoms have not been studied. Such reagents have been added to methyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosid-2-ulose, but the stereochemistry of these reactions is not clear-cut since some reagents gave *ribo* products[4] whilst others gave *arabino* products[5,6]. However, *ribo* products would be more probable from compound **1**, because the substituent at its anomeric centre is *cis* to the substituents at C-3 and C-4.

Branched-chain sugar derivatives related to **4** have been prepared by aldol condensations of a pyrano-4-ulose derivative[7] and a furano-3-ulose derivative[8]. It has also been pointed out that such compounds could serve as precursors for modified sugars[7].

It is noteworthy that compound **1** did not anomerise and that it dimerised through C-3 rather than C-1. This indicates that enolisation occurred at the carbon atom carrying the least number of oxygen atoms, in keeping with the results of Hine *et al.*[9] and some of our results[1].

EXPERIMENTAL

Unless otherwise stated, optical rotations were measured for chloroform solutions with a Bellingham and Stanley polarimeter. Ultraviolet spectra were measured for ethanol solutions with a Perkin–Elmer spectrometer model 402, and infrared spectra for solids dispersed in potassium bromide were measured with an Infracord model 137. Molecular weights were determined with a Mechrolab Inc., Vapour Pressure Osmometer, Model 301A, with solutions in tetrachloroethylene. N.m.r. spectra were usually measured for chloroform solutions with Varian A-60D, Varian HA-100D, or Jeol JMN-MH-100 instruments. Mass spectra were measured with an A.E.I. MS-902 instrument operating at 70 eV. The last measurement and the 200-MHz spectra were carried out by the P.C.M.U. at Harwell.

T.l.c. was performed on silica gel G. A Varian Aerograph model 202 was used for g.l.c. analysis with hydrogen as carrier gas and a thermal-conductivity detector. Paper chromatograms were developed by downard irrigation.

tert-Butyl α-L-arabinopyranoside. — A solution of 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide[10] (80 g) in anhydrous chloroform (500 ml) was added

dropwise during 12 h, in the absence of light, to a vigorously stirred mixture of finely powdered, anhydrous calcium sulphate (80 g), freshly prepared silver carbonate (80 g), and distilled *tert*-butyl alcohol which had been dried with potassium metal. The usual work-up for a Koenigs–Knorr reaction gave a solid (76 g, 96%) which, after one crystallisation from ethyl ether–light petroleum (b.p. 60–80°), yielded *tert*-butyl 2,3,4-tri-*O*-acetyl-α-L-arabinoside as needles, m.p. 111–112°. N.m.r. data: δ 1.24 (s, Bu^t); 2.00, 2.05, and 2.13 (3 s, 3 Ac); 5.0–5.4 (m, H-1,2,3); 4.59 (q, $J_{4,3}$ 6.0 Hz); 4.01 (q, $J_{5,4}$ 2.5 Hz); 3.61 (q, $J_{5',4}$ 1.5, $J_{5',5}$ 13.0 Hz). The triacetate (65 g) was deacetylated by the Zemplén method to give, after work-up, the title compound as a syrup which solidified (40 g, 95%), $[\alpha]_D^{20}$ +11.0° (*c* 1.4, water), ν_{max} 3300 cm^{-1} (OH).

Anal. Calc. for $C_9H_{18}O_5$: C, 52.4; H, 8.8. Found: C, 52.0; H, 8.7.

tert-*Butyl 3,4-O-isopropylidene-α-L-arabinopyranoside* (**2**). — A solution of *tert*-butyl α-L-arabinoside (10 g) in acetone (100 ml) was stirred vigorously with phosphorus pentaoxide (5 g) for 15 min, according to the method of Honeyman[11]; t.l.c. then showed that the reaction was complete. The coloured solution was decanted, neutralised by stirring with potassium carbonate for 1 h, and then evaporated to give a solid (10.5 g, 87%). Recrystallisation from ethyl ether–light petroleum (b.p. 60–80°) gave the title compound (7.5 g), m.p. 94–95°, $[\alpha]_D^{20}$ +49° (*c* 0.8), ν_{max} 3400 cm^{-1} (OH). N.m.r. data: δ 1.28 (s, Bu^t), 1.38 and 1.53 (2 s, Me_2C), 4.37 (d, $J_{1,2}$ 7.5 Hz), 4.2–3.4 (m, H-2,3,4,5,5'), 3.18 (s, exchangeable with D_2O, OH). Mass-spectral data: *m/e* 246 (0.5%) [M^+], 231 (1.0) [M^+-15(Me)], 189 (26) [M^+-57(Bu^t)], 131 (53) [$M^+-57-58(Me_2C)$, m* at 90.8 arises for this fragmentation], 173 (23) [M^+-73(Bu^{t}O)].

Anal. Calc. for $C_{12}H_{22}O_5$: C, 58.5; H, 9.0. Found: C, 58.3; H, 9.1.

tert-*Butyl 3,4-O-isopropylidene* α-L-erythro-*pentopyranosidulose* (**1**). — Compound **2** (26.4 g) was oxidised during 30 min with ruthenium tetraoxide in carbon tetrachloride, in the usual way, to give the pyranosidulose derivative **1** (13.2 g, 52%). Recrystallisation from light petroleum (b.p. 60–80°) gave needles, m.p. 123–124° (sealed tube), $[\alpha]_D$ +4.5° (*c* 1.2), ν_{max} 1750 cm^{-1} (C=O), λ_{max} 306 (ε 20). Mass-spectral data: *m/e* 229 (M^+-15). N.m.r. data (100 MHz): δ 1.30 (s, Bu^t), 1.49 and 1.39 (2 s, Me_2C), 5.05 (d, $J_{1,3}$ 0.7 Hz), 4.57 (q, $J_{3,4}$ 7.5 Hz), 4.77 (sex, $J_{4,5}$ 6.0, $J_{4,5'}$ 6.0 Hz), 4.00 (d, *J* 6.0 Hz, H-5,5').

Anal. Calc. for $C_{12}H_{20}O_5$: C, 59.0; H, 8.3. Found: C, 58.7; H, 8.2.

Reduction of the pyranosidulose **1**. — A solution of **1** (0.11 g) in anhydrous ethyl ether (20 ml) was heated under reflux with lithium aluminium hydride (0.3 g) for 18 h. Water was then cautiously added, the ethereal solution was filtered, and the residual aluminium salts were extracted several times with ether and methanol. G.l.c. analysis of the combined solutions, on a column (10 ft × 0.25 in.) of SE52 (20%) at 145°, showed that all the pyranosidulose **1** (*T* 16.0 min) had been reduced to a product (*T* 19.0 min) which was easily distinguished from *tert*-butyl 3,4-*O*-isopropylidene-α-L-arabinoside (**2**) (*T* 22 min). Recrystallisation of the crude product from light petroleum (b.p. 60–80°) gave *tert*-butyl 3,4-*O*-isopropylidene-α-L-ribopyranoside (**3**) (0.1 g, 87%), m.p. 124–125°, $[\alpha]_D^{20}$ −120° (*c* 1.1), ν_{max} 3600 cm^{-1} (OH). N.m.r. data

(C_6D_6): δ 1.10 (s, Bu^t), 1.26 and 1.52 (2 s, Me_2C), 4.90 (d, $J_{1,2}$ 4.5 Hz), 2.56 (d, J 12.0 Hz, OH), 3.3–4.4 (m, H-2 to 5'). Mass-spectral data: *m/e* values and peak intensities were identical to those found for compound **2**.

Anal. Calc. for $C_{12}H_{22}O_5$: C, 58.5; H, 9.0. Found: C, 58.3; H, 8.9.

The reduction product (0.01 g) was hydrolysed in 2M hydrochloric acid (0.5 ml) at 100° for 2 h. Examination of the neutralised hydrolysate by paper chromatography revealed only ribose.

Attempted isomerisation of pyranosidulose **1** *with base.* — (*a*) *Triethylamine.* A solution of **1** (70 mg) in ethanol (2 ml) containing triethylamine (30 μl) was heated under reflux for 30 min. T.l.c. then showed only unchanged **1**, and decomposition products on the base line.

(*b*) *1,5-Diazabicyclo[5.4.0]undec-5-ene.* Pyranosidulose **1** (2.4 g) in dichloromethane (140 ml) was heated under reflux with the title reagent (3.2 ml) and water (1.6 ml) for 1 h. The solution was dried with anhydrous sodium sulphate and evaporated to give a gum, which contained (t.l.c.; benzene–ethyl acetate, 3:2) **1** (R_F 0.28) and a product having R_F 0.48. These compounds were separated on a column (2.5 × 25 cm) of silica gel, affording impure **1** (0.4 g) and a dimeric product **4** (1.7 g, 70%). Recrystallisation of the latter product from light petroleum (b.p. 60–80°) gave the dimer **4**, m.p. 155–156°, ν_{max} 3450 (OH) and 1750 cm^{-1} (C=O), λ_{max} 303 nm ($\varepsilon \sim 10$). Mol. wt.: found, 484; calc., 488. For n.m.r. data, see Table I.

Anal. Calc. for $C_{24}H_{40}O_{10}$: C, 59.0; H, 8.3. Found: C, 59.1; H, 8.3.

Reduction of the dimer **4**. — The dimer **4** (0.9 g) in ethyl ether (150 ml) was heated under reflux with lithium aluminium hydride (0.5 g). The usual work-up afforded a waxy solid (0.3 g) which, after recrystallisation from light petroleum (b.p. 60–80°), gave the diol **5** (0.51 g), m.p. 159–161°, ν_{max} 3500 cm^{-1} (OH). Mol. wt.: found, 425; calc., 490. For n.m.r. data, see Table I.

Anal. Calc. for $C_{24}H_{42}O_{10}$: C, 58.8; H, 8.6. Found: C, 58.9; H, 8.1.

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REFERENCES

1 P. M. COLLINS AND B. R. WHITTON, *J. Chem. Soc. Perkin I*, (1973) 1470, and earlier papers.
2 P. J. BEYNON, P. M. COLLINS, P. T. DOGANGES, AND W. G. OVEREND, *J. Chem. Soc., C*, (1966) 1131.
3 P. M. COLLINS AND P. GUPTA, *J. Chem. Soc., C*, (1971) 1965; C. L. STEVENS AND K. K. BALASUBRAMANIAN, *Carbohyd. Res.*, 21 (1972) 166.
4 W. G. OVEREND AND N. R. WILLIAMS, *J. Chem. Soc.*, (1965) 3446; A. A. FEAST, W. G. OVEREND, AND N. R. WILLIAMS, *J. Chem. Soc., C*, (1966) 303; A. M. SEPULCHRE, A. GATEAU-OLESKER, G. LUKACS, G. VASS, W. VOELTER, AND S. D. GERO, *Tetrahedron Lett.*, (1972) 3945; H. PAULSEN, V. SINNWELL, AND P. STADLER, *Angew. Chem. Int. Ed. Engl.*, 11 (1972) 149.
5 J. S. BURTON, W. G. OVEREND, AND N. R. WILLIAMS, *Chem. Ind. (London)*, (1961) 175; *J. Chem. Soc.*, (1965) 3433.

6 S. W. GUNNER, R. D. KING, W. G. OVEREND, AND N. R. WILLIAMS, *J. Chem. Soc., C*, (1970) 1954, R. D. KING, W. G. OVEREND, J. WELLS, AND N. R. WILLIAMS, *Chem. Commun.*, (1967) 726.
7 D. HORTON AND E. K. JUST, *Carbohyd. Res.*, 9 (1969) 129.
8 J. M. J. TRONCHET AND J. TRONCHET, *Helv. Chim. Acta*, 53 (1970) 1174.
9 J. HINE, L. G. MAHONE, AND C. L. LIOTTE, *J. Amer. Chem. Soc.*, 89 (1967) 5911.
10 C. S. HUDSON AND J. M. JOHNSON, *J. Amer. Chem. Soc.*, 37 (1915) 2748.
11 J. HONEYMAN, *J. Chem. Soc.*, (1946) 990.