Carbohydrate Research, 85 (1980) 130–135
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

A crystalline furanose derivative of ascarylose. Synthesis of 2,5-di-*O*-benzoyl-3,6-dideoxy-α-L-*arabino*-hexofuranose

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(Received November 15th, 1979; accepted for publication in revised form, January 1st, 1980)

Ascarylose has been identified as a constituent of the eggs of a tapeworm (*Parascaris equorum*)[1] and of a lipopolysaccharide from *Pasteurella pseudotuberculosis*[2], but the anomeric configuration and ring structure were not established. The synthesis of derivatives of the dideoxy sugar should be useful for the identification of the sugar in natural products and for the synthesis of artificial antigens.

Recently, we reported[3] a convenient synthesis of ascarylose in four steps from L-rhamnono-1,5-lactone. When the benzoylation reaction was applied to L-rhamnono-1,4-lactone, double elimination was observed (unpublished results), as reported for other aldono-1,4-lactones[4,5]. Thus, the simple route of β-elimination–catalytic hydrogenation did not yield a derivative of ascarylono-1,4-lactone useful for the synthesis of a furanoid derivative.

When 2,4-di-*O*-benzoyl-3,6-dideoxy-L-*arabino*-hexono-1,5-lactone (**1**) was debenzoylated with sodium methoxide and then boiled in 1,4-dioxane, the more-stable 1,4-lactone was obtained as a syrup. This product was rebenzoylated to give a crystalline compound having a lower mobility than **1**, which was characterized as 2,5-di-*O*-benzoyl-3,6-dideoxy-L-*arabino*-hexono-1,4-lactone (**2**) on the basis of spectroscopic data. Its i.r. spectrum showed absorption at 1800 cm^{-1} characteristic of a 1,4-lactone, and the ^1H-n.m.r. data (Table I) were in accord with the structure. While we cannot differentiate the methylene protons in compound **1** because of their similar environment, their signals appear as two well-separated multiplets for compound **2**. On the other hand, H-4 in the 1,5-lactone resonates at lower field than H-5, and the contrary is true for the 1,4-isomer. Reduction of **2** with lithium aluminium hydride afforded ascarylitol, and treatment of debenzoylated **2** with phenylhydrazine gave 3,6-dideoxy-L-*arabino*-hexonic acid phenylhydrazide[3], indistinguishable from the product obtained from compound **1**. These facts indicate that no configurational

*Research Member of the Consejo Nacional de Investigaciones Científicas y Técnicas.

0008-6215/80/0000–0000/$ 02.25,

TABLE I

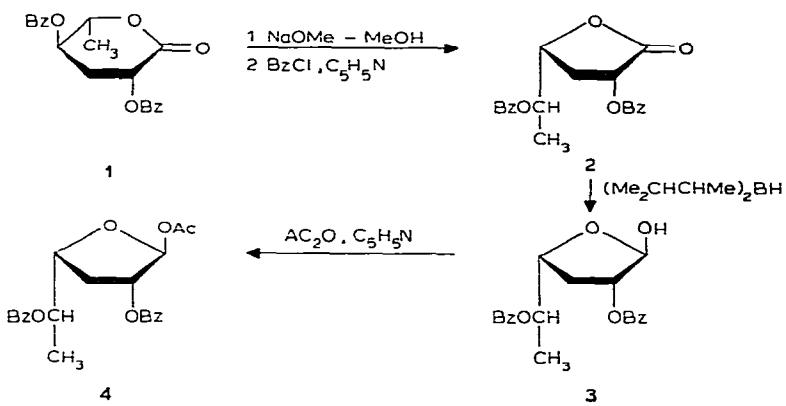
CHEMICAL SHIFTS AND COUPLING CONSTANTS OF COMPOUNDS **1–5**

Compound	*H-1* ($J_{1,2}$)	*H-2* ($J_{2,3}$)	*H-3* ($J_{2,3'}$)	*H-3'* ($J_{3',4}$)	($J_{3,3'}$)	*H-4* ($J_{3,4}$)	*H-5* ($J_{4,5}$)	*H-6* ($J_{5,6}$)	*OBz*
1		5.85(t) (9.0)	2.6(m) (9.0)	2.6(m)		5.25(m)	4.8(m)	1.5(d) (6.0)	7.2–8.2(m)
2		5.68(q) (8.4)	2.96(m) (10.2)	2.34(m) (10.0)	(12.5)	4.63(m) (6.5)	5.37(m) (5.0)	1.49(d) (6.4)	7.3–8.2(m)
3	5.57(d) (<0.5)	5.25(q) (6.7)	2.72(m) (1.8)	2.05(m) (6.2)	(14.2)	4.46(m) (7.0)	5.32(m) (6.5)	1.42(d) (6.5)	7.2–8.2(m)
4	6.37(d) (<0.5)	5.38(q) (6.8)	2.72(m) (2.2)	2.18(m) (5.8)	(14.4)	4.40(m) (7.9)	5.30(m) (6.0)	1.46(d) (6.2)	7.1–8.0(m)
5	5.3(d) (1.5)	5.05(m)	2.6–2.1(m)			4.2(m)	3.7(m)	1.25(d) (6.0)	7.2–8.2(m)

change has taken place. Formation of compound **2** was also observed when a solution of **1** in chloroform was kept at room temperature.

Reduction[6] of **2** with disiamylborane afforded crystalline 2,5-di-*O*-benzoyl-3,6-dideoxy-α-L-*arabino*-hexofuranose (**3**) in 72% yield. In its i.r. spectrum, compound **3** showed absorption at 3300 cm^{-1}, corresponding to the anomeric hydroxyl group. No absorption attributable to the lactone carbonyl group was observed. The ^1H-n.m.r. data of **3** are shown in Table I. The hydroxyl resonance appeared as a broad singlet at δ 3.46, which disappeared on deuteration. The anomeric proton gave a narrow doublet ($J_{1,2}$ <0.5 Hz) at δ 5.57. The small value of the coupling constant suggested the α-anomeric configuration[7]. For 2,4-di-*O*-benzoyl-3,6-dideoxy-L-*arabino*-hexopyranose (**5**), the anomeric proton appeared[3] at δ 5.3. Our results agree with the observation of Angyal and Pickles[8] that the anomeric signal for a furanose derivative appears at a lower field than that for the corresponding pyranose.

Compound **3** was acetylated with acetic anhydride–pyridine[9] for 20 h at 0° to afford crystalline 1-*O*-acetyl-2,5-di-*O*-benzoyl-3,6-dideoxy-α-L-*arabino*-hexofuranose (**4**) in 86% yield. No hydroxyl absorption was observed in its i.r. spectrum.



The ^{1}H-n.m.r. spectrum (Table I) showed $J_{1,2}$ <0.5 Hz, indicating no change in the anomeric configuration. The acetyl group gave a 3-proton singlet at δ 2.10 superposed on the H-3′ signal. The ring structure of **4** was confirmed by its mass spectrum. The ion at *m/e* 249 ($M^+ - 149$, 74% of the base peak) corresponds to cleavage between C-4 and C-5, characteristic of furanose structures[10]. The sequence *m/e* 249→127→85→68 may be explained by subsequent loss of benzoic acid (122 m.u.), ketene (42 m.u.), and of hydroxyl (17 m.u.). The elimination of the acetoxyl group at C-1 gave the ion at *m/e* 339 ($M^+ - 59$, 20%). The loss of two molecules of benzoic acid from the molecule-ion accounts for the cation at *m/e* 154 (33%), which undergoes subsequent elimination of ketene (*m/e* 112, 14%).

Conformational studies of 2,5-di-*O*-benzoyl-3,6-dideoxy-α-L-*arabino*-hexofuranose (**3**), 1-*O*-acetyl-2,5-di-*O*-benzoyl-3,6-dideoxy-α-L-*arabino*-hexofuranose (**4**), and 2,5-di-*O*-benzoyl-3,6-dideoxy-L-*arabino*-hexono-1,4-lactone (**2**) were made on the basis of their ^{1}H-n.m.r. spectra (Table I). The dihedral angles between H-2, H-3, H-3′, and H-4 were estimated by the DAERM method (dihedral angle estimation by the ratio method)[11], which has been used for conformational studies of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-hexofuranoses[12] and for the 2-deoxy-β-D-*erythro*-pentofuranosyl portion of nucleosides[13].

Considering compound **4** first, eight solutions are obtained (Table II). The chemical shifts of H-3 and H-3′ (Table I) were not assigned *a priori*, but result as a consequence of the resolution of the system by DAERM. Cases *ii*, *iv*, *vi*, and *viii* may be rejected, because of the large values of the Karplus constants calculated. The solution *i*/*v* appears as the most probable, as it is compatible with a conformational equilibrium between $E_0 \rightleftharpoons {}^1T_0$, in which the bulky C-4 group is *quasi*-equatorial and eclipsing interactions between the furanose-ring substituents are minimized. Furthermore, the orientation of H-1 and H-2 is in accord with the small value of its $J_{1,2}$ coupling constant (<0.5 Hz), which indicates a dihedral angle of ~90°. Stevens and Fletcher[14] found a preference for the $^0T_1$ conformation in benzoylated derivatives of

TABLE II

DAERM ANALYSIS[a] OF COUPLINGS IN COMPOUND **4**

Protons coupled	*Case*	J_1[b]	J_2	θ_1[b]	$\theta - 2$	k_1	k_2
H-2; H-3; H-3′	*i*	6.8	2.0	2	122	7.09	8.12
	ii	6.8	2.0	53	71	19.55	21.51
	iii	2.0	6.8	53	177	9.70	7.10
	iv	2.0	6.8	70	54	19.49	20.49
H-4; H-3; H-3′	*v*	7.9	5.8	17	141	8.94	10.07
	vi	7.9	5.8	59	65	30.83	34.04
	vii	5.8	7.9	33	157	8.64	9.65
	viii	5.8	7.9	63	61	29.50	34.80

[a] $w = 124$; $k_1/k_2 = 0.9$, typical values for furanoid systems[13]. [b] J_1 *cis*-coupling; θ_1, the corresponding angle.

α-D-arabinofuranose. Hall *et al.*[12] have determined a conformational equilibrium $E_o \rightleftharpoons {}^1T_o \rightleftharpoons {}^1E$ for 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranose, which has the same relative configuration between C-2 and C-4 as compound **4**.

When a similar analysis was applied to 2,4-di-*O*-benzoyl-3,6-dideoxy-α-L-*arabino*-hexofuranose (**3**), the results also indicated an $E_o \rightleftharpoons {}^1T_o$ equilibrium.

Taking into account that considerable variations in the values of k_1/k_2 (between 0.7 and 1.0) or w (between 110 and 130°) have little effect in conformational assignments[11,12], we have applied DAERM to establish the favored conformation of the dideoxy lactone **2**. The solution of the system for this compound indicated a conformation in which C-3 lies below the plane determined by C-2, C-1, and O-4, whereas C-4 lies slightly above it, minimizing the interactions between the substituents.

As far as we know, compounds **3** and **4** are the first crystalline furanose derivatives reported for ascarylose, and they are potentially useful for the synthesis of glycosides and artificial antigens.

EXPERIMENTAL

General methods. — Evaporations were conducted under diminished pressure at a bath temperature below 60°. Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were recorded with a Perkin–Elmer 141 polarimeter and i.r. spectra with a Perkin–Elmer Model 421 spectrophotometer. ^{1}H-N.m.r. spectra were determined with a Varian XL-100-15 spectrometer and solutions in chloroform-*d*, with tetramethylsilane as the internal reference; the apparent coupling-constants (in Hz) reported are the directly observed line-spacings. Assignments were substantiated by double-irradiation experiments. Mass spectra were obtained with a Varian MAT CH 7 spectrometer coupled to a Varian MAT data-system 166. G.l.c. was performed with a Hewlett–Packard 5830 A gas chromatograph equipped with glass columns (180 × 0.2 cm) packed with: (*a*) 3% SE-30 on Chrom-W/AW-DMCS 80–100, with nitrogen at a flow rate of 23 mL/min; T_i 270°, T_d 300°, and T_c 240°; or (*b*) 3% ECNSS-M on Gas-Chrom Q with nitrogen at a flow rate of 31 mL/min; T_i 250°, T_d 250°, and T_c 170°. T.l.c. was performed on Silica Gel G (Merck) with 19:1 benzene–ethyl acetate, and detection was affected with iodine vapor. L-Rhamnono-1,5-lactone was obtained by oxidation of L-rhamnose with bromine as already described[15].

*2,5-Di-*O*-benzoyl-3,6-dideoxy*-L-arabino-*hexono-1,4-lactone* (**2**). — 2,4-Di-*O*-benzoyl-3,6-dideoxy-L-*arabino*-hexono-1,5-lactone (**1**) was debenzoylated with sodium methoxide in methanol as previously reported[3], and the syrup was boiled in 1,4-dioxane for 2 h. After removal of the solvent, the lactone (0.25 g) was dissolved in anhydrous pyridine (1.3 mL), and benzoyl chloride (1.1 mL) added with stirring. The mixture was shaken for 90 min at room temperature and poured into ice–water (20 mL). After 2 h, the product was extracted with dichloromethane and handled as already described[3]. The syrup (0.63 g) was purified by dry-column chromatography on silica gel (3 × 20 cm) with benzene containing increasing concentrations of ethyl

acetate as eluent. Elution was monitored by t.l.c. and, after evaporation of the solvent, the product crystallized upon addition of ethanol; yield 0.46 g (77%); m.p. 83–84°, $[\alpha]_D^{20}$ −9.3° (*c* 0.5, chloroform); R_F 0.32; ν_{max}^{film} 1800 (1,4-lactone C=O); 1720 (benzoate C=O), and 1600 cm^{-1} (aromatic C=C). G.l.c. (column *a*) showed only one peak, having *T* 5.54 relative to hexa-*O*-acetylmannitol. For ^{1}H-n.m.r. data, see Table I.

Anal. Calc. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.92; H, 5.26.

Compound **2** was debenzoylated with sodium methoxide in methanol to give a syrup which, on treatment with an equal amount of phenylhydrazine, gave 3,6-dideoxy-L-*arabino*-hexonic acid phenylhydrazide[3]; m.p. and mixed m.p. 170–172°, $[\alpha]_D^{20}$ +51° (*c* 0.5, water).

Reduction of compound **2** with an excess of lithium aluminium hydride in ether at room temperature gave ascarylitol, identified by g.l.c. of the acetate (column *b*, *T* 1.38 relative to tetra-*O*-acetylerythritol) by comparison with an authentic sample.

On being kept in concentrated chloroform solution, compound **1** is partially converted into 2,5-di-*O*-benzoyl-3,6-dideoxy-L-*arabino*-hexono-1,4-lactone (**2**), as shown by t.l.c. (R_F 0.38 and 0.32, respectively) and g.l.c. (column *a*, *T* 1.36 and 1, respectively, relative to compound **2**; T_i 280°, T_d 280°, and T_c 260°, nitrogen flow-rate 30 mL/min).

2,5-Di-O-benzoyl-3,6-dideoxy-α-L-arabino-hexofuranose (**3**). — A solution of 2,5-di-*O*-benzoyl-3,6-dideoxy-L-*arabino*-hexono-1,4-lactone (**2**; 230 mg, 0.65 mmol) was reduced with disiamylborane as previously described[3,6]. The mixture showed by t.l.c. a main spot (R_F 0.20), together with some starting material (R_F 0.32). The principal product was purified by dry-column chromatography. It separated as a chromatographically homogeneous, colorless syrup that slowly crystallized from ethanol–water; yield 166 mg (72%). Upon recrystallization from the same solvent, it had m.p. 76–78°, $[\alpha]_D^{20}$ +48.3° (*c* 0.5, chloroform); ν_{max}^{Nujol} 3300 (OH) and 1700 cm^{-1} (benzoyl C=O). ^{1}H-N.m.r. data are shown in Table I.

Anal. Calc. for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.59; H, 5.88.

Debenzoylation of **3** with sodium methoxide in methanol for 0.5 h at 0° gave a product indistinguishable from ascarylose (paper chromatography).

1-O-Acetyl-2,5-di-O-benzoyl-3,6-dideoxy-α-L-arabino-hexofuranose (**4**). — Compound **3** (50 mg) was acetylated according to Wolfrom and Wood[9] to give 1-*O*-acetyl-2,5-di-*O*-benzoyl-3,6-dideoxy-α-L-*arabino*-hexofuranose (**4**), which crystallized spontaneously and was recrystallized from ethanol; yield 48 mg (86%), m.p. 100–102°, $[\alpha]_D^{20}$ +10.0° (*c* 0.5, chloroform); ν_{max}^{Nujol} 1740 (acetate C=O) and 1720 cm^{-1} (benzoate C=O); *m/e* 339 (20%), 276 (4%), 249 (74%), 207 (8%), 154 (33%), 127 (22%), 122 (8%), 112 (14%), 105 (100%), 85 (14%), 83 (11%), 81 (7%), 77 (72%), 68 (13%), 51 (12%), and 43 (91%). ^{1}H-N.m.r. data are shown in Table I.

Anal. Calc. for $C_{22}H_{22}O_7$: C, 66.33; H, 5.57. Found: C, 66.07; H, 5.66.

ACKNOWLEDGMENTS

We are indebted to the Consejo Nacional de Investigaciones Científicas y Técnicas (Buenos Aires) for financial support, and to UMYMFOR (CONICET-FCEN, Buenos Aires) for the microanalyses and spectra.

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