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SYNTHESIS AND SPECTRA OF SOME OCTA-*O*-BENZOYLALDOBIONONITRILES

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ABSTRACT

2,3,5,6,2′,3′,4′,6′-Octa-*O*-benzoyl-cellobiononitrile, -lactobiononitrile, -maltobiononitrile, and 2,3,4,5,2′,3′,4′,6′-octa-*O*-benzoyl-melibiononitrile were prepared by benzoylation and dehydration of the corresponding disaccharide oximes, and their ^{1}H- and ^{13}C-n.m.r., and e.i.m.s. spectra are described.

INTRODUCTION

The synthesis of aldobiononitriles has been so far limited to the acetylated derivatives, and several octa-*O*-acetylaldobiononitriles are known[1–7]. We describe herein the synthesis of some octa-*O*-benzoylaldobiononitriles having (1→4)- and (1→6)-glycosidic linkages.

RESULTS AND DISCUSSION

2,3,5,6,2′,3′,4′6′-Octa-*O*-benzoyl-cellobiononitrile (**1**) was prepared, in 78% yield from cellobiose oxime, by benzoylation with benzoyl chloride–pyridine. 2,3,5,6,2′,3′,4′,6′-Octa-*O*-benzoyllactobiononitrile (**2**) (87%), -octa-*O*-benzoylmaltobiononitrile (**3**) (72%), and 2,3,4,5,2′,3′,4′,6′-octa-*O*-benzoylmelibiononitrile (**4**) (87%) were prepared in a similar way. Control of the reaction temperature (90°) was even more important than in the case of analogous monosaccharide derivatives[8].

Analysis of the ^{1}H-n.m.r. spectra. — The ^{1}H-n.m.r. spectra of **1**, **2**, and **3** were measured at 400 MHz, and of **4** at 270 MHz, and allowed first-order analysis. The assignments were ascertained, in all cases, by double-resonance experiments (see Table I and Table II). The spectrum of **3** in $CDCl_3$ solution allowed assignment of all 13 H atoms of the carbohydrate chain. Comparison with the spectrum of the same compound in C_6D_6 solution showed a general downfield shift of the signals. The signal of the most deshielded proton in $CDCl_3$ solution, H-3′, disappeared for a C_6D_6 solution, and we suppose that it appeared with the signals of the aromatic

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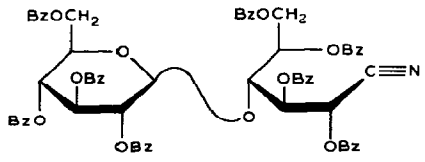

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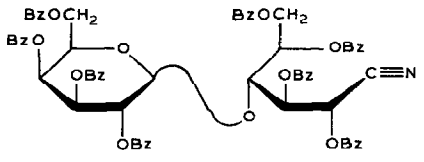

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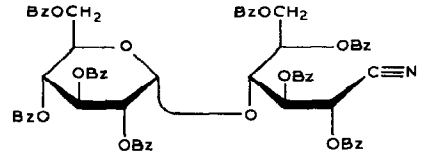

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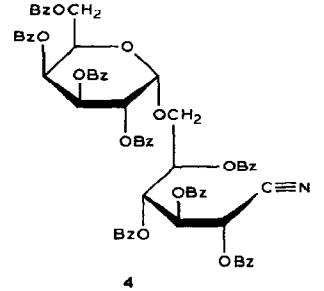

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TABLE I

^{1}H-N.M.R. CHEMICAL SHIFTS (δ) AND MULTIPLICITIES OF COMPOUNDS **1–4**

Atom	**1**[a]	**2**[b]	**3**[b]	**3**[a]	**4**[c]
H-2	6.31 d	[d]	6.48 d	6.16 d	6.02 d
H-3	6.07 dd	6.56 dd	6.43 dd	6.10 dd	6.26 dd
H-4	4.91 dd	5.23 dd	5.05 t	4.90 t	[d]
H-5	5.48 ddd	6.01 ddd	6.21 ddd	5.98 ddd	5.96 dt
H-6a	4.68 dd	4.86 dd	4.97 dd	4.98 dd	4.04 dd
H-6b	4.42 dd	4.77 dd	4.91 dd	4.90 dd	3.63 dd
H-1′	5.27 d	5.18 d	5.83 d	5.78 d	5.46 d
H-2′	5.79 dd	6.50 dd	5.74 dd	5.55 dd	6.17 dd
H-3′	5.93 t	5.85 dd	[d]	6.27 t	6.49 dd
H-4′	5.85 t	6.27 dd	6.08 t	5.74 t	6.28
H-5′	4.24 dt	4.00 ddd	5.07 ddd	4.75 ddd	4.38 ddd
H-6′a	4.87 dd	5.13 dd	4.71 dd	4.36 dd	4.61 dd
H-6′b	4.70 dd	4.65 dd	4.52 dd	4.17 dd	4.18 dd
H-arom.	7.1–8.1	6.7–8.4	6.7–8.4	7.1–8.1	6.7–8.4

[a]Measured at 400 MHz for a solution in $CDCl_3$ with Me_4Si as internal standard. [b]Measured at 400 MHz for a solution in C_6D_6 with Me_4Si as internal standard. [c]Measured at 270 MHz for a solution in C_6D_6 with Me_4Si as internal standard. [d]Possible assignment superposed with the signals for aromatic protons.

protons. A similar situation was obtained for H-3′ in the spectrum of a C_6D_6 solution of 1,2,6,2′,3′,4′,6′-hepta-*O*-benzoyl-β-maltose[9]. In the aldobiononitriles having a β-D-(1→4) linkage (**1** and **2**), H-2 is the most deshielded proton. In the spectrum of **1** in $CDCl_3$ solution, the signals of all the protons appeared well separated from those of the aromatic signals, but in the spectrum of **2** in C_6D_6 solution, the signal

TABLE II

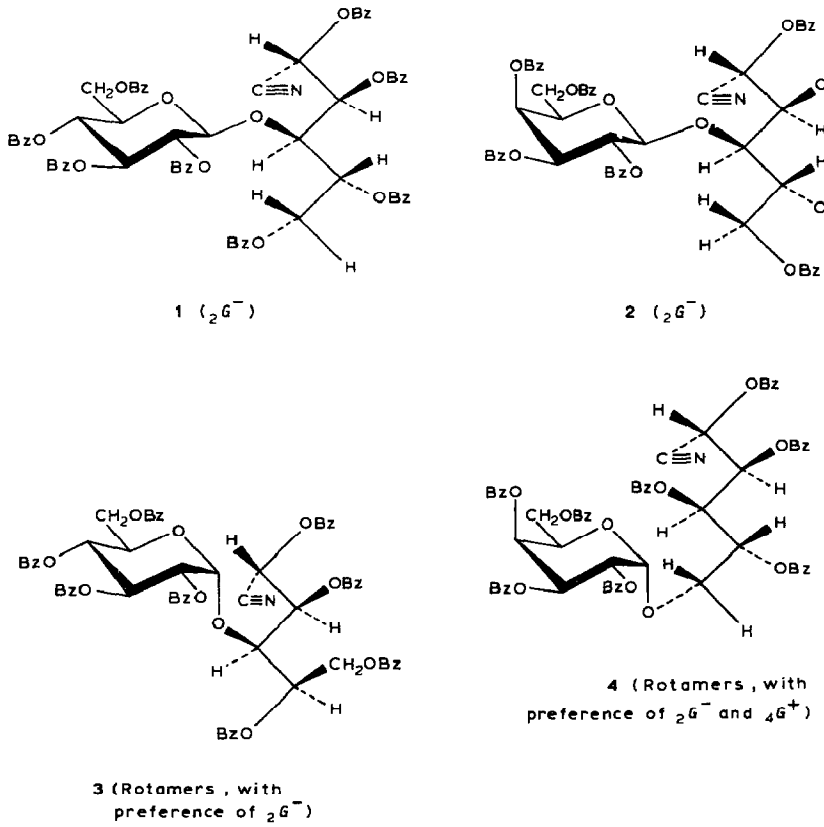
VICINAL PROTON–PROTON COUPLING CONSTANTS (Hz) OF COMPOUNDS **1–4**

Coupling constant	**1**[a]	**2**[b]	**3**[b]	**3**[a]	**4**[b]
$J_{2,3}$	9.5	9.3	7.4	6.8	6.4
$J_{3,4}$	1.6	1.6	3.9	4.2	2.4
$J_{4,5}$	8.0	7.2	4.1	4.2	8.0
$J_{5,6a}$	3.0	3.2	4.2	4.2	3.3
$J_{5,6b}$	4.6	6.0	6.7	6.8	2.5
$J_{6a,6b}$	12.4	12.2	12.2	12.3	11.4
$J_{1',2'}$	7.9	7.9	3.6	3.7	3.5
$J_{2',3'}$	9.6	10.4	10.2	10.1	10.8
$J_{3',4'}$	9.6	3.4	9.8	9.9	3.4
$J_{4',5'}$	9.8	1.0	10.0	9.9	1.2
$J_{5',6'a}$	3.0	6.0	3.0	2.8	6.7
$J_{5',6'b}$	3.6	7.0	4.4	4.3	6.4
$J_{6'a,6'b}$	12.6	11.6	12.4	12.4	11.2

[a]Measured for a $CDCl_3$ solution. [b]Measured for a C_6D_6 solution.

of H-2 was not visible and we supposed that it was shifted to the signals of the aromatic protons. The spectrum of **4** in C_6D_6 solution did not show the signal for H-4 and we suppose that it was shifted to the aromatic part of the spectrum. The signal for H-4 in 2,3,4,5,6-penta-*O*-benzoyl-D-glucononitrile in $CDCl_3$ solution showed that this was the most deshielded proton[10] (δ 6.64), and this observation can be extended to **4**, which has an α-D-(1→6) linkage.

The conformations of **1–4** may be deduced from the ^{1}H-n.m.r. data. The cyclic part is present in the $^4C_1$(D) conformation in **1** and **3**, and shows a slight deformation for **2** and **4** which have the axial benzoyloxy-4′ group. The acyclic part showed a deviation from the planar, extended, zig-zag conformation. The deviation may be explained as a rotamer or as the average between some of the conformations. In **1** ($J_{2,3}$ 9.5 Hz) and **2** ($J_{2,3}$ 9.3 Hz), H-2 and H-3 are in the *anti*-periplanar relationship, which corresponds to a C-2→C-3 rotation[11] ($_2G^-$). In these compounds, the bulky glycosyl group having the β-D-linkage at C-4 is predominant and only one rotamer is present (see Scheme 1). In 2,3,4,5,6-penta-*O*-benzoyl-D-glucononitrile, the $J_{2,3}$ 6.6 Hz value corresponds to an average between two rotamers, with an important contribution of $_2G^-$. We observed the same average for **4** ($J_{2,3}$ 6.4 Hz) which has the α-D-(1→6) linkage. In **3**, the α-D-(1→4) linkage ($J_{2,3}$ 7.4 Hz for a C_6D_6 and 6.8 Hz for a $CDCl_3$ solution) gave rise to the preponderance of the $_2G^-$ rotamer, but a $_4G^+$ rotation was also present ($J_{4,5}$ 4.1 Hz), which is attributed to the bulky α-D-glycosidic substituent at C-4. In both possible rotamers at C-4→C-5, a 1,3-parallel interaction appeared between the two benzoyloxy groups (at C-3 and C-5) or with a benzoyloxy group and C-6. We supposed that the last interaction was the less hindered and we report the rotation as $_4G^+$.



Scheme 1. Preferred conformations in solution.

Assignments of the ^{13}C-n.m.r. spectra. — The assignments of the ^{13}C-n.m.r. spectra were performed by a comparison with model compounds. This is only valid if the compounds have the same conformation and configuration, as reported for benzoylated cyclic monosaccharide and disaccharide derivatives[12–14], and benzoylated acyclic derivatives[15,16]. The compounds used for the assignments of the ^{13}C-n.m.r. signals of octa-*O*-benzoyl-cellobiononitrile (**1**) were 2,3,4,5,6-penta-*O*-benzoyl-D-gluconononitrile[16] and 1,2,3,4,6-penta-*O*-benzoyl-β-D-glucopyranose[12]. The different proportions of the rotamers at the C-2→C-3 linkage in compound **1** and in the reference compound gave important changes in the ^{13}C-n.m.r. chemical shifts for C-2 (Δ 1.96 p.p.m.) and C-3 (Δ 0.86 p.p.m.). On the other hand, the different substituent at C-4, the β-D-glycosyl group in **1** and the benzoyl group in the reference compound, gave rise to a strong difference for C-4 of 8.45 p.p.m., as expected for these types of change[13]. This is also reflected by similar modifications on the neighboring carbon atoms[17]. The cyclic part allowed a good correlation with 1,2,3,4,6-penta-*O*-benzoyl-β-D-glucopyranose. Considering the change in the

TABLE III

^{13}C-N.M.R. CHEMICAL SHIFTS (δ) FOR COMPOUNDS **1–4**

Atom	**1**[a]	**1**[b]	**2**[b]	**3**[c]	**4**[d]
C≡N	114.70	115.79	115.60	114.70	114.11
C-2	61.70	62.63	62.25	61.84	59.70
C-3	69.18	69.97	69.86	70.98	67.19
C-4	76.77	76.34	75.60	76.24	68.31
C-5	69.60	70.52	70.27	72.13	68.31
C-6	61.99	62.67	62.92	61.90	66.56
C-1′	101.32	101.95	101.84	99.19	97.20
C-2′	72.04	72.76	70.75	71.93	67.85
C-3′	73.19	73.73	72.37	70.85	68.94
C-4′	69.02	69.55	68.65	69.95	68.94
C-5′	72.92	73.43	72.03	70.05	69.73
C-6′	62.09	62.77	61.95	62.99	62.28
C-arom.	128.21-133.83		←126.52–133.73→		127.25–133.88
C=O	164.07–166.13		←164.20–166.05→		163.90–165.75

[a]Measured at 100.63 MHz for a solution in $CDCl_3$ with Me_4Si as internal standard. [b]Measured at 15.08 MHz for a solution in C_6D_6 with Me_4Si as internal standard. [c]Measured at 100.63 MHz for a solution in C_6D_6 with Me_4Si as internal standard. [d]Measured at 20.15 MHz for a solution in $CDCl_3$ with Me_4Si as internal standard.

substituent at C-1′, the acyclic part instead of the benzoyl group, we observed main shifts for the signals of C-1′ (Δ 8.54 p.p.m.) and of the vicinal C-2′.

Our assignments for the ^{13}C-n.m.r. signals (Table III) of **1** were compared with those reported by Szilágyi[18] for octa-*O*-acetylcellobiononitrile by a two-dimensional technique, taking into consideration the difference in the acyl group. For the assignments of the signals of **2–4**, a similar analysis was applied, which used as reference compounds 1,2,3,4,6-penta-*O*-benzoyl-α-D-glucopyranose[12], 1,2,3,4,6-penta-*O*-benzoyl-α-D-galactopyranose[12], 2,3,4,5,6-penta-*O*-benzoyl-D-gluconononitrile[16], and methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-β-D-galactopyranoside[19]. That not all the spectra were measured for solutions in the same solvent had to be considered. The assignments of the signals for **3** were performed with the consideration that the acyclic part shows two rotameric changes, at C-2→C-3 and C-4→C-5, and this does not allow a direct comparison.

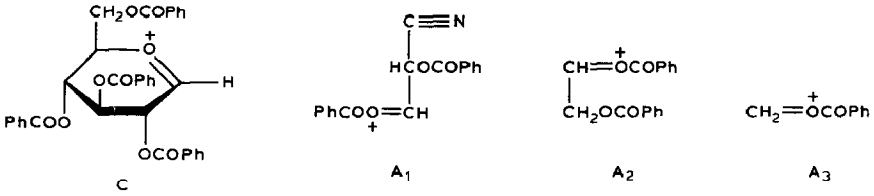
The data in Table III indicate that the correlation of the signals of **1** and **2** in C_6D_6 solution shows a good agreement for the acyclic part, with the highest difference for C-4 (Δ 0.74 p.p.m.). Both compounds have the same conformation and configuration in this part of the molecule. In the cyclic part, several differences were observed, which are due to the configurational inversion at C-4′. The same analyses for **1** and **3** showed the expected change in the cyclic part due to the anomeric inversion from β- to α-D (ΔC-1′ 2.76, ΔC-3′ 2.88, and ΔC-5 3.38 p.p.m.), as we reported for other benzoylated derivatives[12,13]. For the acyclic part, this comparison was not useful as a different conformation is present in solution.

TABLE IV

MAJOR FRAGMENTATION RESULTING FROM ELECTRON-IMPACT IONIZATION OF COMPOUNDS **1–4**[a]

m/z	**1** *Int. (%)*	**2** *Int. (%)*	**3** *Int. (%)*	**4** *Int. (%)*	*Assignments*[b]
579		1.4		0.4	C^+
331	1.0	4.0	1.7	0.7	$(PhCO)_3O^+$
294[c]	0.4	1.3	0.9		A_1^+
269[c]	0.6	1.3	1.4		A_2^+
231	0.5	2.1	0.7	0.5	$M^+ - 4\,PhCO_2H - 2\,(PhCO)_2O$ or $C^+ - (PhCO)_2O - PhCO_2H$
227	0.4	1.3	0.6	0.4	$(PhCO)_2\dot{O}H$
135[b]	0.4	0.3	0.6		A_3^+
122	61.8	83.4	54.1	65.9	$PhCO_2H^+$
107	1.3	2.7	1.7	1.0	$C^+ - H_2 - (PhCO)_2O - 2\,PhCO_2H$
106	19.1	56.5	21.7	15.9	$C_6H_6CO^+$
105	100	100	100	100	$C_6H_5CO^+$
78	7.7	15.3	9.9	7.4	$C_6H_6^+$
77	76.8	95.8	89.1	77.4	$C_6H_5^+$
51	64.5	33.4	18.2	22.1	$C_4H_3^+$

[a]Intensity, expressed as percent of the base peak. Assignments are assumed. [b]See Scheme 2. [c]Characteristic fragments for (1→4) linkage.



Scheme 2.

The comparison of the spectrum of **2** (having the 4-*O*-β-D-galactopyranosyl group) with that of **4** (having the 6-*O*-α-D-galactopyranosyl group) showed the expected high differences in the acyclic part (ΔC-1′ 4.64, ΔC-3′ 3.43, and ΔC-5′ 2.30 p.p.m.) due to the change at the anomeric carbon. In the acyclic part, the glycosidic linkage is present at C-4 in **2** and at C-6 in **4**, which results in important differences for the signals of these carbon atoms. The comparison between the spectra of **4** and 2,3,4,5,6-penta-*O*-benzoyl-D-glucononitrile, which have the same conformation, showed good agreement, except for the signal of C-6 (Δ 4.14 p.p.m.) which has a different substituent.

Mass spectra. — The mass spectra of the octa-*O*-benzoylaldobiononitriles having the (1→4)-glycosidic linkage showed the general fragmentation pattern with opening of the glycosidic linkage. The fragmentation pattern of the cyclic part is similar to that of perbenzoylated monosaccharides[20], with successive losses of

benzoic acid and benzoic anhydride, and that of the acyclic part is similar to that of acyclic perbenzoylated derivatives[21]. The fragments produced by fission of the carbon atom vicinal to the glycosidic linkage are important. The molecular ion was not observed and the base peak was *m/z* 105. The principal fragments and their assignments are given in Table IV. The fragments of *m/z* 294, 269, and 135 are characteristic of the acyclic part of (1→4)-linked disaccharide derivatives and are absent in the (1→6)-linked compound.

In conclusion, the characteristic ^{1}H- and ^{13}C-n.m.r., and mass spectra allow extension of the results presented herein to other benzoylated disaccharide nitriles, and even to some benzoylated oligosaccharide derivatives.

EXPERIMENTAL

General methods. — Melting points are uncorrected. The optical rotations were determined at 20° with a Perkin–Elmer 141 Polarimeter. T.l.c. was performed, on plates coated with Silica gel G (Merck, Darmstadt), with 9:1 benzene–ethyl acetate as the eluent and I_2 vapor for detection. The ^{1}H-n.m.r. spectra were recorded with Bruker WM 400 and WH 270 instruments for solutions in $CDCl_3$ or C_6D_6, with Me_4Si as internal standard. First-order coupling constants were measured from the expanded spectra (1 cm = 2 Hz) and assignments ascertained by double-resonance experiments. The ^{13}C-n.m.r. spectra were recorded with the same instruments and with a Bruker 80 instrument equipped with wide-band proton-decoupling, and Me_4Si as the internal standard. The mass spectra were recorded with a Varian Mat CH7-A mass spectrometer, operated at 70 eV in the e.i. mode and coupled to a Varian Data System 166, by the insertion technique (100–230°). The peak intensities are expressed as a percentage of total ionization.

2,3,5,6,2',3',4',6'-Octa-O-*benzoylcellobiononitrile* (**1**). — Cellobiose (20 g) was dissolved in warm water (40 mL) and a methanolic solution of hydroxylamine, (prepared from 10 g of hydroxylamine hydrochloride) was slowly added at 65°. After 2 h at 65°, the mixture was evaporated, and the residual syrup dissolved in methanol and evaporated several times, and finally dried in a vacuum desiccator. Cellobiose oxime was obtained as a syrup (19.8 g, 95%). It was suspended in anhydrous pyridine (180 mL) and benzoyl chloride (180 mL) was added portionswise, keeping the temperature between 80–90° during the addition. After 24 h at room temperature, the mixture was poured into ice–water and the syrup obtained was washed until it gave a pulverized solid. Compound **1** was purified three times by precipitation from a 2-propanol solution with water, and obtained as an amorphous solid (54 g, 78%), m.p. 98–100°, $[\alpha]_D^{20}$ +31° (*c* 1, chloroform), t.l.c. R_F 0.60.

Anal. Calc. for $C_{68}H_{53}NO_{18}$: C, 69.68; H, 4.53; N, 1.20. Found: C, 69.50; H, 4.74; N, 1.47.

2,3,5,6,2',3',4',6'-Octa-O-*benzoyllactobiononitrile* (**2**). — The same procedure described for compound **1** was applied to lactose and gave compound **2** as an amorphous solid (59.7 g, 87%), m.p. 98–100°, $[\alpha]_D^{20}$ +56° (*c* 1, chloroform), t.l.c. R_F 0.61.

Anal. Calc. for $C_{68}H_{53}NO_{18}$: C, 69.68; H, 4.53; N, 1.20. Found: C, 69.82; H, 4.70; N, 1.10.

2,3,5,6,2',3',4',6'-Octa-O-*benzoylmaltobiononitrile* (**3**). — The same procedure described for compound **1** was applied to maltose and gave compound **3** as an amorphous solid (49.24 g, 72%), m.p. 90–92°, $[\alpha]_D^{20}$ +97.7° (*c* 1, chloroform), t.l.c. R_F 0.55.

Anal. Calc. for $C_{68}H_{53}NO_{18}$: C, 69.68; H, 4.53; N, 1.20. Found: C, 69.50; H, 4.53; N, 1.13.

2,3,4,5,2',3',4',6'-Octa-O-*benzoylmelibiononitrile* (**4**). — Benzoylation of melibiose oxime[7,22] (8.5 g) by the same procedure described for compound **1** gave compound **4** as an amorphous solid (24.2 g, 86.8%), m.p. 96–97°, $[\alpha]_D^{20}$ +91.3° (*c* 0.6, chloroform), t.l.c. R_F 0.58.

Anal. Calc. for $C_{68}H_{53}NO_{18}$: C, 69.68; H, 4.53; N, 1.20. Found: C, 69.63; H, 4.73; N, 1.25.

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