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Note

# Synthesis and condensation reactions of 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)phthaloyl]-L-arabinitol

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**Abstract**

1-Amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)phthaloyl]-L-arabinitol hydrochloride was prepared from L-arabinose, and its inter- and intra-molecular condensation reactions were studied. In these reactions, a mixture of oligomers (in HMPA: 30%) besides the monomeric compound 2,3,4-tri-*O*-methyl-1-deoxy-1-phthalimido-L-arabinitol (in HMPA: 51%) were obtained. © 1997 Elsevier Science Ltd.

*Keywords:* 1-Amino-1-deoxy-L-arabinitol, protected derivatives; Polycondensation reaction; Oligomers; Intramolecular condensation; Imidation

Synthetic polymers containing carbohydrates are considered, with steadily increased interest, due to their potential as biodegradable and biocompatible material useful for medical applications [1,2]. We have recently described the synthesis [3,4] and hydrolytic degradation [5] of poly(ester amides) derived from L-arabinose or D-xylose and aliphatic acid anhydrides. The separation and characterization of oligomers formed during the polymerization of polyesters, polyethers, polysulfides, polyamides, and several other condensation polymers have been described [6–11]. We now report the synthesis of 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)phthaloyl]-L-arabinitol hydrochloride (**4**) and its inter- and intra-molecular condensation reactions.

The preparation of compound **4** starts from 1-(*tert*-butoxycarbonylamino)-1-deoxy-2,3,4-tri-*O*-methyl-L-arabinitol [3] (**1**), which was condensed with phthalic anhydride in dry pyridine to yield **2** as a syrup, followed by treatment with dicyclohexylcarbodiimide and pentachlorophenol to give the active ester **3**. Removal of the *N*-protecting group with hydrogen chloride in dry ethyl acetate led to the hydrochloride **4**. Attempted polycondensation of this monomer led to a mixture of oligomers **5** (in HMPA: 30%) besides the monomeric compound **6** which turned out to be the main product (in HMPA: 51%) (Scheme 1). Apparently, a competing reaction involving imidation is observed to a significant extent. This

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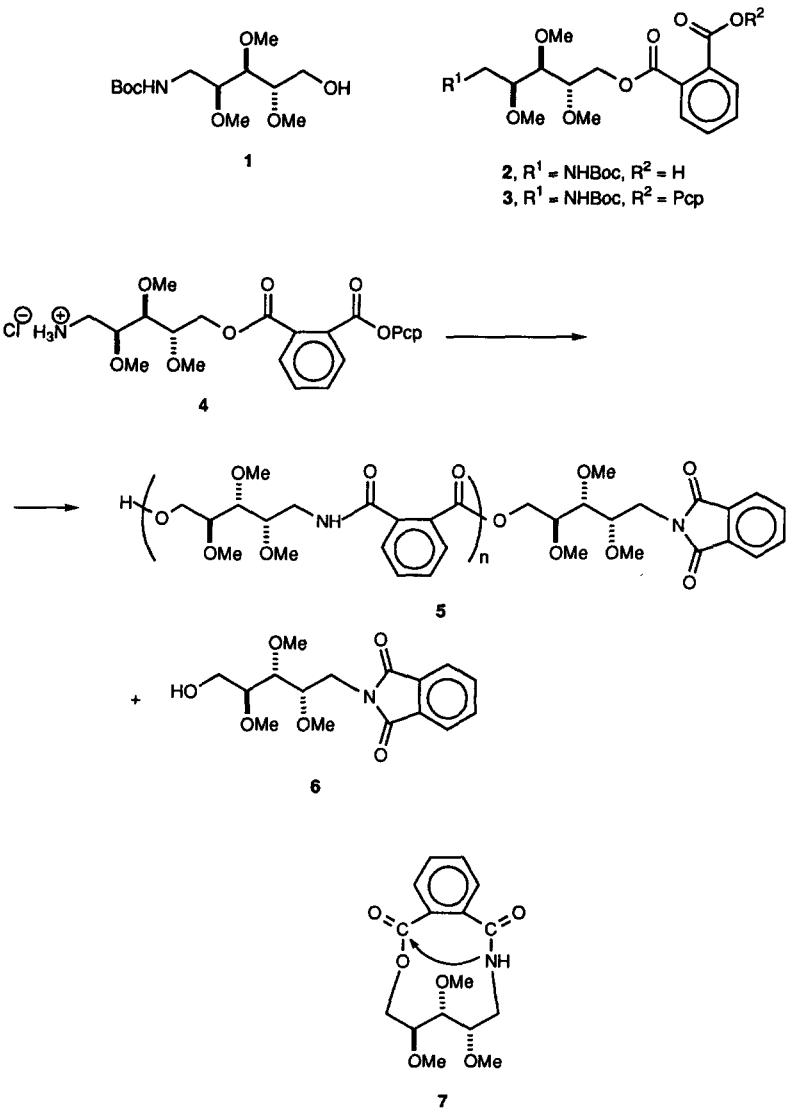
probably takes place due to the special constitution of the phthalic acid part of the molecule which might facilitate the formation of the cyclic monomer **7** (not identified) which undergoes a subsequent intramolecular reaction leading to **6**. This condensation reaction was carried out in different solvents; in all cases the main product was the phthalimide **6** which was isolated in good to high yields.

Both IR and NMR spectroscopical data were in agreement with structure **6**. The IR spectrum contained the characteristic imide absorptions at 1770 and 1712 $cm^{-1}$, the first being of lower intensity. The most significant signal found in the $^{1}H$ NMR spectrum of this compound appeared at 4.54 ppm as a triplet and was assigned to the primary alcohol function because it disappeared when the sample was treated with deuterium oxide. The $^{13}C$ NMR spectrum revealed only one signal at 167.96 ppm, assigned to the carbonyl groups. At higher field, three signals appeared at 123.03, 131.46, and 134.54 ppm as expected for the phenyl ring of the phthalimido group. The presence of a free hydroxy group at C-5 of **6** was confirmed by the fact that this carbon appeared at higher field [12] ($\Delta\delta \sim 5$ ppm) than the same carbon in compounds **4** and **2**. Elemental analysis and mass spectral data confirmed the structure of **6**.

The mixture of oligomers **5** was only obtained when the polymerization reaction took place in hexamethylphosphoramide. The degree of oligomerization in **5** was found to be 2–6. Direct evidence of their nature was obtained from the fast-atom bombardment mass spectrum (FABMS). Thus, in the FAB mass spectrum using nitrobenzene–NaI as matrix, five sig-




Scheme 1.

nals were found at *m/z* 669, 992, 1315, 1638, and 1961 corresponding to the molecular ion as $[M + Na]^+$ of an oligomeric mixture **5** with $n = 1–5$. Gel permeation chromatography (GPC) showed that **5** was of low molecular weight with a low polydispersity.

The presence of a phthalimido end group in the mixture of linear oligomers **5** was based not only on the results of FABMS spectra, but also on the ultraviolet spectrum. Thus, the UV–vis spectrum of **5** in dry acetonitrile showed a shoulder at 297 nm, the same wavelength where **6** showed its maximum absorption. It was also observed that the UV spectrum of **5**, in acetonitrile containing water, changed with time. The initial spectrum showed a maximum of absorption at 273.5 nm and a shoulder at 297 nm. However, after 23 h, only one peak was detected at 297 nm. This could be explained by a gradual hydrolysis of the mixture of linear oligomers **5** in this medium. The hydrolysis–imidation reaction was appreciated more clearly by HPLC. It was observed that the peaks with higher elution times disappeared gradually while the peaks with lower elution times increased in intensity. After 23 h, only one major peak, with low elution time and high intensity, was seen in the chromatogram. However, NMR spectroscopy of a sample hydrolyzed for 23 h revealed that it was not a single compound but a mixture. The NMR study confirmed that, during the hydrolysis of the chains, an imidation reaction was taking place. The $^{13}C$ NMR spectrum of the hydrolyzed sample showed that the intensities of the peaks corresponding to the phthalimido group had increased considerably.

## 1. Experimental

*General methods.*—Optical rotations were measured at $20 \pm 5$ °C with a Bellingham and Standley Inc., P20 polarimeter (5-cm cell). TLC was performed on Silica Gel 60 $F_{254}$ (E. Merck) with detection by UV light or charring with $H_2SO_4$. Compounds containing the NH group were visualized by reaction with ninhydrin. Flash column chromatography was performed using E. Merck Silica Gel 60 (230–400 mesh). FT IR spectra (films or KBr discs) were recorded with a Michelson 100 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker 200 AC-P spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane. Intrinsic viscosity measurements were determined in dichloroacetic acid (DCA) with a Cannon-Ubbelohde 100/L30 semi-microviscometer placed in a water bath at a temperature maintained at $25.0 \pm 0.1$ °C. Elemental analyses were determined in the Microanalysis Laboratories at the Universidad de Sevilla and the Universidad Complutense de Madrid. FABMS analyses were performed on a double-focusing Kratos MS 80RFA mass spectrometer equipped with the standard FAB source. Argon was used as the bombarding gas. Spectra were obtained using nitrobenzene–NaI as a matrix. Ultraviolet spectra were measured on a Perkin–Elmer Lambda 5 spectrophotometer at 25 °C. Gel permeation chromatography (GPC) analyses were carried out in a Waters apparatus fitted with a Waters model 410 RI detector, and a Millenium 2010 computerized data station. Two GPC columns were placed in series, and the analysis was performed in $CHCl_3$ at a flow rate of 1 mL/min. Molecular weight studies were determined relative to polystyrene; calibration was done using twelve polystyrene samples of narrow molecular weight distribution. HPLC analyses were carried out in a Waters apparatus fitted with an ultraviolet detector. The analysis was performed at a flow rate of 1 mL/min using an RP C-18 column and acetonitrile–water (50%) as the mobile phase. Melting points were determined with a Gallenkamp apparatus and are uncorrected.

*1-(*tert*-Butoxycarbonylamino)-1-deoxy-2,3,4-tri-O-methyl - 5 - O - [(pentachlorophenoxy)phthaloyl] - L - arabinitol* (**3**).—A mixture of **1** [3] (5.0 g, 17.03 mmol), phthalic anhydride (3.32 g, 22.4 mmol), and 4-dimethylaminopyridine (0.3 g) in dry pyridine (75 mL) was heated at 40 °C for 24 h. The solvent was evaporated under diminished pressure to give a residue that was extracted with $CH_2Cl_2$ ($3 \times 25$ mL). The extracts were combined, concd to a residue that was dissolved in dry EtOAc (100 mL), and to this soln pentachlorophenol (5.33 g, 20.0 mmol) and dicyclohexylcarbodiimide (4.13 g, 20.0 mmol) were added. After 72 h of stirring, the solid formed was filtered off and washed with EtOAc. The filtrate and washings were combined, concd, and separated by chromatography (2:1 to 1:2 hexane–ether) to give **3** as a syrup (8.8 g, 75%): $[\alpha]_D$ +10° (*c* 1.0, $CHCl_3$); IR (film): $\nu$ 3486–3301 (NH), 1766, 1730, and 1718 $cm^{-1}$ (CO); NMR data ($CDCl_3$): $^1H$ $\delta$ 8.26–8.16 and 7.77–7.60 (2m, 4 H, phthalic), 4.91 (bs, 1 H, NH), 4.81 (dd, 1 H, H-5b), 4.34 (dd, 1 H, $J_{5a,5b}$ 12.1 Hz, H-5a), 3.62 (ddd, 1 H, $J_{4,5a}$ 4.6, $J_{4,5b}$ 2.6 Hz, H-4), 3.56–3.40 (m, 2 H, H-1b, 2), 3.45, 3.40 (2 s, 9 H, 3 $OCH_3$), 3.32 (m, 1 H, $J_{2,3}$ 2.7, $J_{3,4}$ 7.2 Hz, H-3), 3.25 (m, 1 H, $J_{1a,2}$ 7.0, $J_{1a,1b}$ 15.2 Hz, H-1a),

1.44 (s, 9 H, CC*H*3); $^{13}C$ $\delta$ 167.27, 161.84 (CO), 156.0 (CONH), 143.9, 134.81, 133.2, 132.0, 130.4, 128.9, 127.88, 127.36 (aromatic), 80.97 (C-3), 78.74 (C-2), 78.50 (C-4), 79.25 (*C*CH3), 63.66 (C-5), 60.66, 58.79, 57.71 (3 $OCH_3$), 40.67 (C-1), 28.32 (C*C*$H_3$). Anal. Calcd for $C_{27}H_{30}Cl_5NO_9$: C, 47.01; H, 4.38; N, 2.03. Found: C, 47.15; H, 4.45; N, 1.99.

*1-Amino-1-deoxy-2,3,4-tri-O-methyl-5-O-[(pentachlorophenoxy)phthaloyl]-*L*-arabinitol hydrochloride* (**4**).—A soln of **3** (18.0 g, 26.1 mmol) in dry EtOAc (60.0 mL) was added to a cooled 14% HCl soln in EtOAc (100.0 mL). After stirring for 4 h, a stream of nitrogen was bubbled into the soln giving a gel, which was filtered and washed thoroughly with ethyl ether to give **4** as a solid (12.0 g, 85%): mp 101–131 °C; $[\alpha]_D$ +5° (*c* 2.0, $CHCl_3$); IR (KBr): $\nu$ 3305–2516 (broad, $NH_3^+$), 1783 and 1746 $cm^{-1}$ (CO); NMR data ($Me_2SO$-*d*6): $^1H$ $\delta$ 8.35–8.15 and 7.95–7.75 (2m, 4 H, phthalic), 8.23 (bs, 3H, NH), 4.61 (dd, 1 H, H-5b), 4.22 (dd, 1 H, $J_{5a,5b}$ 12.1 Hz, H-5a), 3.70 (m, 1 H, H-2), 3.59 (ddd, 1 H, $J_{4,5a}$ 5.3, $J_{4,5b}$ 2.3 Hz, H-4), 3.49 (dd, 1 H, $J_{2,3}$ 3.4, $J_{3,4}$ 6.3 Hz, H-3), 3.38, 3.36, 3.30 (3 s, 9 H, 3 $OCH_3$), 3.03 (m, 1 H, $J_{1b,2}$ 3.7 Hz, H-1b), 2.88 (m, 1 H, $J_{1a,2}$ 8.5, $J_{1a,1b}$ 13.1 Hz, H-1a); $^{13}C$ $\delta$ 166.61, 161.77 (CO), 143.51, 134.21, 133.9, 131.68, 131.36, 131.10, 130.12, 129.07, 127.29, 126.35 (aromatic), 79.11 (C-3), 77.96 (C-4), 77.49 (C-2), 63.81 (C-5), 59.54, 58.80, 57.23 (3 $OCH_3$), 39.50 (C-1). Anal. Calcd for $C_{22}H_{23}Cl_6NO_7 \cdot \frac{3}{4}HH_2O$: C, 41.31; H, 3.86; N, 2.19. Found: C, 41.21; H, 3.57; N, 2.15.

*Polycondensation reaction.*—To a stirred suspension of **4** (3.4 g, 5.43 mmol) in 3 mL of the chosen solvent [*N*-methyl-2-pyrrolidinone; $Ch_2Cl_2$; hexamethylphosphoramide (HMPA)], ethyldiisopropylamine (EDPA, 2.0 mL) was added. After 10 days at 25 °C, the soln was poured into ethyl ether (1500 mL). Oligomers **5** (0.5 g, 30%) precipitated from the medium only when the reaction was carried out in HMPA. Anal. Calcd for $C_{16}H_{21}NO_6 \cdot \frac{3}{4}H_2O$: C, 57.04; H, 6.73; N, 4.15. Found: C, 57.02; H, 6.77; N, 4.33.

The filtrate obtained from each reaction was concd and the residue subjected to chromatography on a silica gel column (20:1 $CH_2Cl$–MeOH) giving 2,3,4-tri-*O*-methyl-1-deoxy-1-phthalimido-L-arabinitol (**6**) as a solid. Yields: 51% (HMPA), 86% ($CH_2Cl$), and 94% (*N*-methyl-2-pyrrolidinone): mp 96–97 °C; $[\alpha]_D$ −20° (*c* 1.3, $CHCl_3$); IR: $\nu_{max}$ 3460 (broad, OH), 1772, 1712 $cm^{-1}$ (CO); NMR data ($Me_2SO$-$d_6$): $^1H$ $\delta$ 7.85 (m, 4 H, phthalic), 4.54 (t, 1 H, $J_{OH,5a(5b)}$ 5.3 Hz, OH), 3.90–3.10 (m, 7 H, H-1/5), 3.41, 3.28, 3.24 (3s, 9 H, 3 $OCH_3$); $^{13}C$ $\delta$ 167.96 (CO), 134.54, 131.46, 123.03 (phthalic), 80.58, 79.02, 77.56 (C-2/4), 58.39 (C-5), 59.70, 58.51, 56.79 (3 $OCH_3$), 38.22 (C-1). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.54; N, 4.33. Found: C, 59.41; H, 6.55; N, 4.28.

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