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Note

The synthesis of *p*-nitrophenyl 5-*O*-α-L-arabinofuranosyl-α-L-arabinofuranoside

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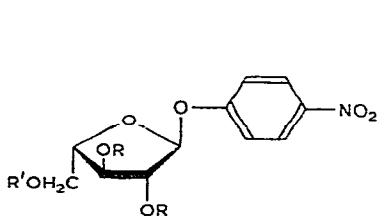
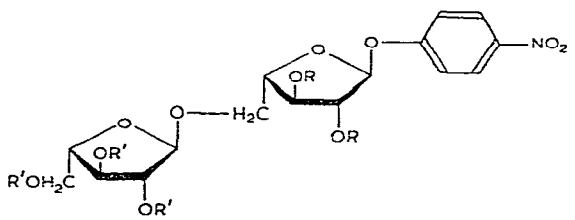
The high activity of *p*-[bis(2-chloroethyl)amino]phenol as an inhibitor of the growth of tumour cells is reduced by glycosidation of the hydroxyl group[1]. These glycosides are cleaved in tissue, especially tumour tissue, by the appropriate enzyme, with a dependence on the pH value[2]. Preliminary results have shown that the detoxication of the foregoing phenolic compound by glycosidation with disaccharides is much higher than with monosaccharides[3]. In view of the suitability of the enzyme α-L-arabinofuranosidase for this approach, we have undertaken a synthesis of a derivative containing the α-L-arabinofuranosyl-α-L-arabinofuranoside moiety. We now report the synthesis of the precursor **6**.

Treatment of *p*-nitrophenyl α-L-arabinofuranoside[4] (**1**) with triphenylmethyl bromide gave *p*-nitrophenyl 5-*O*-trityl-α-L-arabinofuranoside (**2**). Acetylation of **2** followed by hydrolysis with dilute acetic acid afforded a good yield of *p*-nitrophenyl 2,3-di-*O*-acetyl-α-L-arabinofuranoside (**4**). Compound **4** condensed with the anomeric 2,3,5-tri-*O*-benzoyl-L-arabinofuranosyl bromides[5] or chlorides[6] in anhydrous benzene in the presence of silver oxide, iodine, and a drying agent, to give crystalline *p*-nitrophenyl 2,3-di-*O*-acetyl-5-*O*-(2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl)-α-L-arabinofuranoside (**5**). The mass-spectral data for **5** are shown in Table I.



1 R = R' = H
2 R = H, R' = Tr
3 R = Ac, R' = Tr
4 R = Ac, R' = H



5 R = Ac, R' = Bz
6 R = R' = H

TABLE I

MASS-SPECTRAL DATA FOR **5**

Mass (m/e)		*Formula*	*Relative intensity*	*Fragment*
Found	*Calc.*			
799		$C_{41}H_{37}NO_{16}$	0.013	M^+
798		$C_{41}H_{36}NO_{16}$	0.019	$(M-1)^+$
782		$C_{41}H_{36}NO_{15}$	0.022	$(M-OH)^+$
769.2131	769.2133	$C_{41}H_{37}O_{15}$	0.016	$(M-NO)^+$
661.1913	661.1932	$C_{35}H_{32}O_{13}$	0.85	(M − Aglycon)$^+$
445.1275	445.1287	$C_{26}H_{21}O_7$	27.7	(Tri-*O*-benzoylarabinose)$^+$
338.0878	338.0876	$C_{15}H_{16}NO_8$	1.0	(M − Tri-*O*-benzoylarabinose)$^+$
139.0269	139.0269	$C_6H_5NO_3$	5.4	(Aglycon)$^+$
105		C_7H_5O	100.0	$C_6H_5CO^+$

O-Deacylation of **5** with sodium methoxide yielded a mixture of *p*-nitrophenyl 5-*O*-α-L-arabinofuranosyl-α-L-arabinofuranoside (**6**) and **1** which was fractionated by column chromatography. Hydrolysis of **6** with α-L-arabinosidase gave *p*-nitrophenol and L-arabinose. The transformation of the nitro group in **6** into the bis(2-chloroethyl)amino group is now being investigated.

EXPERIMENTAL

General. — Melting points were determined on a Kofler microscope hot-stage and are uncorrected. Optical rotations were determined on a Zeiss Kreispolarimeter, using a 1-dm microcell.

N.m.r. spectra were recorded for solutions in methyl sulphoxide (internal Me_4Si) at 25°, using a KRH 100 AW instrument (AWF Berlin-Adlershof). Mass spectra were determined with an A.E.I. MS-902 instrument.

T.l.c. was performed on Silica Gel F-254 (Merck), and column chromatography on Silica Gel H (Merck).

p-*Nitrophenyl 5-O-trityl-α-L-arabinofuranoside* (**2**). — To a solution of *p*-nitrophenyl -α-L-arabinofuranoside (**1**, 5 g) in dry pyridine (150 ml), finely powdered trityl bromide (20 g) was added, and the mixture was stirred at room temperature overnight. The resulting suspension was filtered, and concentrated at 50° (bath). T.l.c. (ethyl acetate–chloroform, 1:1) of the syrupy residue revealed one product together with starting materials. Elution of the mixture from a column (5 × 55 cm) of silica gel (450 g) with ethyl acetate–chloroform (1:1) yielded **2** (5.1 g, 54%), m.p. 149–151° (from di-isopropyl ether), $[\alpha]_D^{20}$ −101° (*c* 1.4, methanol).

Anal. Calc. for $C_{30}H_{27}NO_7$: C, 70.15; H, 5.30; N, 2.73. Found: C, 70.01; H, 5.45; N, 2.65.

p-*Nitrophenyl 2,3-di-O-acetyl-5-O-trityl-α-L-arabinofuranoside* (**3**). — To a solution of **2** (2.5 g) in dry pyridine (10 ml), acetic anhydride (5 g) was added. The mixture was stored overnight at room temperature, then diluted with chloroform

(100 ml), washed three times with water, dried (Na_2SO_4), and concentrated. Crystallization of the syrupy residue (2.8 g, 96%) from methanol gave **3**, m.p. 151–152°, $[\alpha]_D^{20}$ −102° (*c* 1.45, chloroform).

Anal. Calc. for $C_{34}H_{31}NO_9$: C, 68.33; H, 5.23; N, 2.35. Found: C, 68.30; H, 5.20; N, 2.24.

p-*Nitrophenyl 2,3-di-*O*-acetyl-α-*L*-arabinofuranoside* (**4**). — A mixture of **3** (2.5 g) and 80% acetic acid (20 ml) was heated to reflux for 10 min, then cooled, filtered from triphenylmethanol, and concentrated to dryness *in vacuo* at 40°. The pale-yellow oil was eluted from a column (3 × 50 cm) of silica gel (200 g) with ethyl acetate–chloroform (1:1). The major product crystallized from di-isopropyl ether to give long needles of **4** (1.1 g, 74%), m.p. 77–79°, $[\alpha]_D^{20}$ −142° (*c* 1.2, chloroform). N.m.r. data: τ 4.72 (H-1), 4.95 (t, HO-5, disappeared on equilibration with D_2O). Mass spectrum: *m/e* 324 (1.56%) $(M-CH_2OH)^+$, 217 (100%) $(M-NO_2C_6H_4OH)^+$, 139 (25%) $(NO_2C_6H_4OH)^+$.

Anal. Calc. for $C_{15}H_{17}NO_9$: C, 50.70; H, 4.82; N, 3.95. Found: C, 50.76; H, 4.85; N, 3.85.

p-*Nitrophenyl 2,3-di-*O*-acetyl-5-*O*-(2,3,5-tri-*O*-benzoyl-α-*L*-arabinofuranosyl)-α-*L*-arabinofuranoside* (**5**). — To a solution of **4** (0.75 g) in anhydrous benzene (15 ml), freshly prepared silver oxide (1.4 g) and molecular sieve 4A (2 g) were added. The mixture was shaken at room temperature for 15 min, and then iodine (0.24 g) and a solution of 2,3,5-tri-*O*-benzoyl-αβ-L-arabinofuranosyl bromide (1.1 g) in benzene (10 ml) were added. The mixture was stirred at room temperature in the dark for 24 h, then filtered, and concentrated *in vacuo*. T.l.c. (chloroform) of the syrupy residue indicated one product in addition to starting materials. Elution of the mixture from a column (5 × 63 cm) of silica gel (400 g) with chloroform gave **5** as colourless plates (0.5 g, 30%), m.p. 60–65°, $[\alpha]_D^{20}$ −62° (*c* 1.2, chloroform). For mass-spectral data, see Table I.

Anal. Calc. for $C_{41}H_{37}NO_{16}$: C, 61.57; H, 4.66; N, 1.75. Found: C, 61.55; H, 4.70; N, 1.90.

p-*Nitrophenyl* 5-O-α-*L*-*arabinofuranosyl*-α-*L*-*arabinofuranoside* (**6**). — To a solution of **5** (0.8 g) in dry dichloromethane (60 ml) and dry methanol (100 ml), sodium methoxide (from 9 mg of sodium and 3 ml of methanol) was added. After 3 h at room temperature, the starting material was not detectable (t.l.c.; chloroform–methanol, 94:6). Dowex 50W X8 (H^+) resin (1.5 g) was added, and the solution was filtered and concentrated. The resulting oil (0.5 g) was eluted from a column of silica gel (200 g) with ethyl acetate–chloroform (1:1) to yield oily **6** (0.1 g, 25%), $[\alpha]_D^{20}$ −163° (*c* 1.2, methanol), and **1** (0.15 g), m.p. 151–155°.

Anal. Calc. for $C_{16}H_{21}NO_{11}$: C, 47.64; H, 5.25; N, 3.48. Found: C, 47.55; H, 5.18; N, 3.41.

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