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Note

Synthesis of *p*-aminophenyl β-D-allopyranoside and 1-thio-β-D-allopyranoside as analogs of glycosidase substrates*

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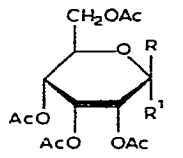
As part of a program on the synthesis of aryl glycosides of uncommon aldohexoses for glycosidase-specificity studies, we have previously described the synthesis of *p*-nitrophenyl and *p*-aminophenyl glycosides of α-D-talopyranose and 1-thio-α-D-talopyranose[1], and of 1-thio-α- and -β-D-idopyranose[2]. We report here the synthesis of analogous derivatives (**5–8**) of β-D-allopyranose and 1-thio-β-D-allopyranose. These derivatives are also of interest as the presence of three aryl β-D-allopyranosides, namely, rubropilosin, dihydrorubropilosin, and pilorubrosin, has recently been observed in the leaves of a higher plant (*Protea rubropilosa*)[3]. Specifically, the three derivatives are 2-hydroxy-4-(hydroxymethyl)phenyl glycosides of 6-*O*-cinnamoyl-, 6-*O*-(3-phenylpropanoyl)-, and 6-*O*-benzoyl-β-D-allopyranose, respectively.

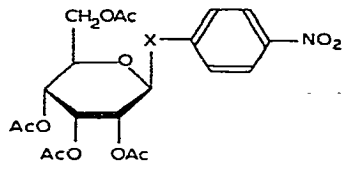
RESULTS AND DISCUSSION

The reaction of tetra-*O*-acetyl-D-allopyranosyl bromide (**2**) with *p*-nitrophenol in aqueous acetone in the presence of sodium hydroxide, according to conditions employed for the preparation of aryl β-D-glucosides[4] and β-D-galactosides[5], resulted in considerable hydrolysis of **2**. The product from the reaction, after re-acetylation with pyridine and acetic anhydride, showed in t.l.c. in solvent *A* the presence of β-D-allopyranose tetraacetate (**1**) as the predominant component and a small amount of the desired *p*-nitrophenyl β-D-allopyranoside tetraacetate (**3**). Latham *et al.*[6] have reported low yields (9 and 24%, respectively) of glycosides from the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with 2,4-dinitrophenol and *p*-nitrophenol under similar conditions. In view of the low yield of **3** encountered under these conditions, the Purves[7–9] procedure for the synthesis of aryl 1-thioglycosides, which employs chloroform–methanol as the medium for reaction of the glycosyl halide with thiophenols in the presence of potassium hydroxide, was applied to the condensation of **2** with *p*-nitrophenol. Three products were formed under these

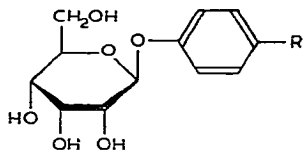
*Part III of the series: Aryl Glycosides of Uncommon Aldohexoses.



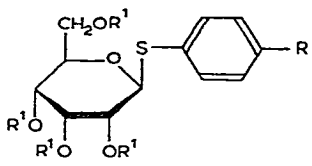
1 R = OAc, R^1 = H
2 R = H, R^1 = Br



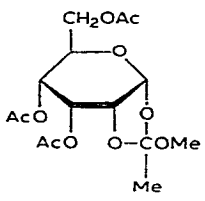
3 X = O
4 X = S



5 R = NO_2
6 R = NH_2



7 R = NO_2, R^1 = H
8 R = NH_2, R^1 = H
9 R = NHAc, R^1 = Ac



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conditions, of which 3 (R_F 0.47 in solvent *B*) was present, once again, as a minor component. The R_F values (solvent *B*) of the other two components were 0.34 and 0.41. The crystalline *p*-nitrophenyl tetra-*O*-acetyl-β-D-allopyranoside (**3**) was isolated in ~5% yield after chromatography on silica gel.

The component having R_F 0.34 was characterized as 3,4,6-tri-*O*-acetyl-D-allopyranose 1,2-(*exo*-methyl orthoacetate) (**10**) on the basis of elemental analyses, and i.r.- and 100-MHz-n.m.r. spectral data. The n.m.r. spectrum (100 MHz) of **10** showed the presence of one *exo*-methoxyl[10–12] (τ 6.68), one *endo*-*C*-methyl[11–13] (τ 8.23), and 3 acetoxyl groups [τ 7.88 (3 H) and 7.90 (6 H)]. Signals for sugar-ring protons were not assigned, except for the doublet ($J_{1,2}$ 5.8 Hz) at lowest field (τ 4.22, H-1).

The component having R_F 0.41 was not characterized, but it is possible that it is the *endo*-methyl isomer of **10**.

The reaction[7–9] of **2** with *p*-nitrobenzenethiol in chloroform–methanol in the presence of potassium hydroxide afforded, after chromatography on silica gel, 22.1% of *p*-nitrophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-allopyranoside (**4**).

The *p*-nitrophenyl β-D-allosides (**3** and **4**) were deacetylated[14] with catalytic amounts of sodium methoxide in methanol. The resulting *p*-nitrophenyl β-allosides **5** and **7** were hydrogenated under pressure (50 lb. in.$^{-2}$) over palladium-on-barium sulfate catalyst. The *p*-aminophenyl β-D-allopyranoside (**6**) was obtained crystalline, whereas the 1-thio analog (**8**) was obtained as a chromatographically homogeneous syrup. Acetylation of **8** with acetic anhydride in pyridine gave a product that showed, in solvent *C*, a predominant spot for **9**, together with traces of 3 other contaminants.

The β configuration of **3** and **4** was established from 250-MHz n.m.r. spectral data (Table I). These data also show that both **3** and **4** exist in the $^4C_1$(D) conformation in chloroform solution.

TABLE I

CHEMICAL SHIFTS (τ VALUES) AND COUPLING CONSTANTS (Hz) FROM 250-MHz N.M.R. SPECTRA[a,d] OF *p*-NITROPHENYL 2,3,4,6-TETRA-*O*-ACETYL-β-D-ALLOPYRANOSIDE (**3**) AND 1-THIO-β-D-ALLOPYRANOSIDE (**4**)

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*2 H-6*	*Acetoxyl*
3	4.53 (d) $J_{1,2}$ 8.2	4.80 (q) $J_{2,3}$ 3.0	4.23 (t) $J_{3,4}$ 3.0	4.93 (q) $J_{4,5}$ 9.4	5.64–5.72[b]		7.82 (C-3)[c], 7.92, 7.95, 7.97
4	4.82 (d) $J_{1,2}$ 10.3	4.99 (q) $J_{2,3}$ 2.9	4.30 (t) $J_{3,4}$ 2.9	5.03 (q) $J_{4,5}$ 10.3	5.65–5.94[b]		7.81 (C-3)[c], 7.89, 7.94, 7.98

[a]Abbreviations: d = doublet, q = quartet, t = triplet. [b]Unresolved multiplet. [c]Axial acetoxyl protons (see ref. 15). [d]In chloroform-*d* solution, using tetramethylsilane as the internal reference.

EXPERIMENTAL

General methods. — These are as described in ref. 1. The solvents employed for t.l.c. were (*A*) 3:1 petroleum ether (low-boiling)–acetone, (*B*) 5:2 benzene–ethyl acetate, (*C*) 10:0.4 chloroform–methanol, and (*D*) 3:1:0.2 ethyl acetate–acetic acid–water. The 100-MHz ^{1}H-n.m.r. spectrum was recorded on a Varian XL-100 n.m.r. spectrometer equipped with a Nicolet NIC-80 data system.

p-*Nitrophenyl 2,3,4,6-tetra*-O-*acetyl*-β-D-*allopyranoside* (**3**). — β-D-Allopyranose pentaacetate[16] (**1**, 2.03 g) was dissolved in 30–32% hydrogen bromide in acetic acid (8 ml), and the solution was kept for 2 h at room temperature. The solvent was evaporated off under diminished pressure, traces of hydrogen bromide and acetic acid being removed by distillation of toluene from the residue. The residual yellow, syrupy bromide **2** was dissolved in chloroform (10 ml), and the resulting solution was mixed with a solution of *p*-nitrophenol (0.900 g) in 0.5M methanolic potassium hydroxide (14 ml). The mixture was stirred for 18 h at room temperature, and filtered to remove a small amount of insoluble solid. The filtrate was evaporated, and the residue was acetylated overnight with pyridine (10 ml) and acetic anhydride (10 ml). The mixture was evaporated, and the residual syrup was dissolved in benzene (35 ml). The benzene solution was washed successively with cold, M sodium hydroxide

and water, dried over magnesium sulfate, and evaporated to a syrup (0.875 g) that showed the presence of 3 major components on t.l.c. in solvent *B*; R_F 0.34, 0.41, and 0.47. The slowest-moving (R_F 0.34) component was characterized as the orthoester **10** (see later). Compound **3** (R_F 0.47) was isolated by chromatography on silica gel with 5:1 benzene–ethyl acetate as the eluant; yield, 0.120 g (4.9% from **1**); m.p. 143–145°, $[\alpha]_D$ −34.5° (*c* 0.21, chloroform); R_F (solvent *B*) 0.47; ν_{max}^{KBr} 1750 (C=O), 1612, 1592, and 1497 (aromatic), 1510 and 1345 (NO_2), 1230 (broad, acetate C–O–C), 868, 859, 822, 758, 740, 719, 690, and 680 cm^{-1}; n.m.r.: see Table I.

Anal. Calc. for $C_{20}H_{23}NO_{12}$: C, 51.18; H, 4.94; N, 2.98. Found: C, 51.39; H, 5.04; N, 2.86.

The component having R_F 0.41 was not characterized.

3,4,6-Tri-O-acetyl-D-allopyranose 1,2-(exo-methyl orthoacetate) (**10**). — The bromide **2**, prepared from **1** (1.01 g) as already described, was dissolved in chloroform (7.5 ml), and added to a solution of *p*-nitrophenol (0.543 g) in 0.5M methanolic sodium hydroxide (7.4 ml). After 20 h at room temperature, the mixture was evaporated to dryness, and the residue was partitioned between chloroform (30 ml) and water (15 ml). The organic layer was washed successively with cold water (3 × 15 ml), cold M sodium hydroxide (4 × 15 ml), and water (5 × 15 ml), dried over sodium sulfate, and evaporated. The residue was crystallized from ethanol to afford 0.233 g (24.9%) of the ortho ester **10**, m.p. 184–185°, $[\alpha]_D$ +39.4° (*c* 0.30, chloroform); R_F (solvent *B*) 0.34; ν_{max}^{KBr} 1745 and 1733 (C=O), 1392 and 1370 (C–CH_3), 1250, 1232, and 1220 cm^{-1} (C–O–C); no aromatic absorption; n.m.r. data (100 MHz): τ 4.22 (d, $J_{1,2}$ 5.8 Hz, H-1), 6.68 (*exo*-methoxyl), 7.88 (acetyl, 3 H), 7.90 (acetyl, 6 H), and 8.23 (*endo*-CMe).

Anal. Calc. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; OCH_3, 8.56. Found: C, 49.73; H, 5.90; OCH_3, 8.82.

p-*Nitrophenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-allopyranoside* (**4**). — A solution of the syrupy bromide **2**, prepared from β-D-allose pentaacetate[16] (**1**, 2.00 g) by treatment with 32% hydrogen bromide in acetic acid, in chloroform (10 ml) was added to a solution *p*-nitrobenzenethiol (0.640 g) in 0.5M methanolic potassium hydroxide (9.3 ml). The mixture was stirred overnight under nitrogen, and the precipitated solid was filtered off and washed with 1:1 chloroform–methanol. The combined filtrates were evaporated to dryness, and pyridine was evaporated twice from the residue to remove traces of methanol. The residual syrup was acetylated conventionally for 20 h with pyridine (10 ml) and acetic anhydride (10 ml). The solvents were removed by distillation of toluene from the residue, and the residual syrup containing **4** was chromatographed on a column (2.5 cm diameter) of silica gel (75 g) packed in benzene. The column was washed with benzene to remove degradation products of *p*-nitrobenzenethiol before elution of **4** with 5:1 benzene–ethyl acetate. Fractions were monitored by t.l.c., in solvent *B*, and those containing **4** were pooled and evaporated to give a yellow foam (0.550 g, 22.1%) that was chromatographically homogenous (R_F 0.54). Crystallization of the foam from methanol afforded 0.258 g of **4**, m.p. 129–130.5°. Evaporation of the filtrates gave a yellow syrup whose chromatographic mobility was identical with that of crystalline **4**. The analytical sample, recrystallized

from methanol, had m.p. 129–130.5°, $[\alpha]_D$ −4.68° (*c* 0.34, chloroform); R_F (solvent *B*) 0.54; ν_{max}^{KBr} 1750 (C=O), 1595, 1578, and 1478 (aromatic), 1510 and 1340 (NO_2), 1255, 1230, and 1210 (acetate C–O–C), 853, 845 (shoulder), and 745 cm^{-1}; n.m.r.: see Table I.

Anal. Calc. for $C_{20}H_{23}NO_{11}S$: C, 49.48; H, 4.78; N, 2.89. Found: C, 50.51; H, 5.20; N, 2.80.

p-*Nitrophenyl-β-*D-*allopyranoside* (**5**). — To a suspension of compound **3** (0.294 g) in dry methanol (2 ml) was added[14] 0.5M sodium methoxide in methanol (25 μl). After 3 h at room temperature, the solution was neutralized with methanol-washed Dowex-50 (H^+) resin and evaporated. The crystalline residue was triturated with anhydrous ether and filtered to give 0.179 g (95.0%) of **5** as colorless crystals, m.p. 122–125°, $[\alpha]_D$ −102.6° (*c* 0.24, methanol); R_F (solvent *D*) 0.65; ν_{max}^{KBr} 3520, 3390, and 3300 (OH), 1608, 1596, and 1493 (shoulder) (aromatic), 1505 and 1345 (NO_2), 875, 869 (shoulder), 855, 760, and 725 cm^{-1}.

Anal. Calc. for $C_{12}H_{15}NO_8$: C, 47.84; H, 5.02; N, 4.65. Found: C, 48.01; H, 5.09; N, 4.60.

p-*Nitrophenyl 1-thio-β-*D-*allopyranoside* (**7**). — The *p*-nitrophenyl 1-thio-β-D-allopyranoside tetraacetate (**4**, 0.201 g) was deacetylated[14] as already described for **5** to give 0.107 g (81.7%) of light-yellow crystals of **7**, m.p. 147–150°, $[\alpha]_D$ −105.6° (*c* 0.22, methanol); R_F (solvent *D*) 0.68; ν_{max}^{KBr} 3570, 3490, and 3300 (OH), 1595, 1580, and 1480 (aromatic), 1510 and 1340 (NO_2), 858, 850, (shoulder), and 750 cm^{-1}.

Anal. Calc. for $C_{12}H_{15}NO_7S$: C, 45.42; H, 4.76; N, 4.41. Found: C, 45.52; H, 4.83; N, 4.39.

p-*Aminophenyl β-*D-*allopyranoside* (**6**). — Compound **5** (0.125 g) was dissolved in methanol (45 ml), and the solution was hydrogenated for 14 h over 5% palladium-on-barium sulfate catalyst (0.100 g) at an initial pressure of 50 $lb.in.^{-2}$. The catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness. The residue was crystallized from 2-propanol containing a small amount of methanol to give light-tan crystals (0.083 g, 73.6%) of **6**, m.p. 137–139° $[\alpha]_D$ −68.0° (*c* 0.23, methanol); R_F (solvent *D*) 0.11; ν_{max}^{KBr} 3500–3300 (broad, OH), 1620 (NH_2), 1512 (aromatic), 837, 820, 785, and 715 cm^{-1}.

Anal. Calc. for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.16. Found: C, 53.29; H, 6.46; N, 5.03.

p-*Acetamidophenyl 2,3,4,6-tetra-*O-*acetyl-1-thio-β-*D-*allopyranoside* (**9**). — Compound **7** (0.150 g) was hydrogenated as already described for **6**, to give **8** as a yellow syrup that could not be crystallized; yield 0.158 g (116%); R_F (solvent *D*) 0.42 (major), 0.33 (trace).

Acetylation of **8** with pyridine (3 ml) and acetic anhydride (1 ml) at room temperature, followed by evaporation of solvents with use of toluene, gave 0.235 g of **9** (100% from **7**) as a yellow foam that could not be crystallized; R_F (solvent *C*) 0.61 (predominant), and 0.20, 023, and 0.99 (>trace).

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