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Note

Synthesis of 5-(β-D-ribofuranosyl)-1,2,3,4-tetrahydrophthalazine-1,4-diones*

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Since discoveries that several of the naturally occurring *C*-nucleosides[2] have interesting biological properties, considerable effort has been directed toward the synthesis of many structural analogues. One of the principal synthetic methods employed in the *C*-nucleoside area involves "ribose"-derived intermediates in which a side chain of one to three carbon atoms, variously functionalized, is attached through a β linkage to the original anomeric carbon atom. This side chain has then provided the basis for the construction of a multitude of heterocyclic rings[3]. During the course of our research, we have developed a preparative procedure for the versatile *C*-nucleoside precursor 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furan (four carbon atoms), and have utilized it in the synthesis of pyridazine[4] and phthalimide *C*-nucleosides[5]. We now report the synthesis of hitherto unknown phthalazine *C*-nucleosides by cyclization of the phthalic esters, **3** and **6**, which were obtained by aromatization of the Diels–Alder adduct, dimethyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate[5] (**1**). Treatment of **1** with concentrated sulfuric acid in dichloromethane at room temperature afforded the aromatized compound, dimethyl 6-hydroxy-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)phthalate (**2**) in 49% yield, which was purified by column chromatography on silica gel. The presence of ester-group signals at δ 3.75 and 3.87 are characteristic in the ^{1}H-n.m.r. spectrum of **2**. Cyclization of **2** with hydrazine hydrate under a variety of conditions proved unsuccessful. Thus, the *O*-methylation of **2** with diazomethane in ether afforded dimethyl 6-methoxy-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)phthalate (**3**) quantitatively.

Cyclization of **3** with hydrazine hydrate in methanol afforded, after purification by preparative t.l.c., the fully deprotected 8-methoxy-5-(β-D-ribofuranosyl)-1,2,3,4-tetrahydrophthalazine-1,4-dione (**4**) in 51% yield. Compound **4** could be obtained crystalline in high purity, and was readily identifiable by its ^{1}H-n.m.r.

*Part 4 of the series *C*-Nucleosides. For Part 3: see ref. 1.

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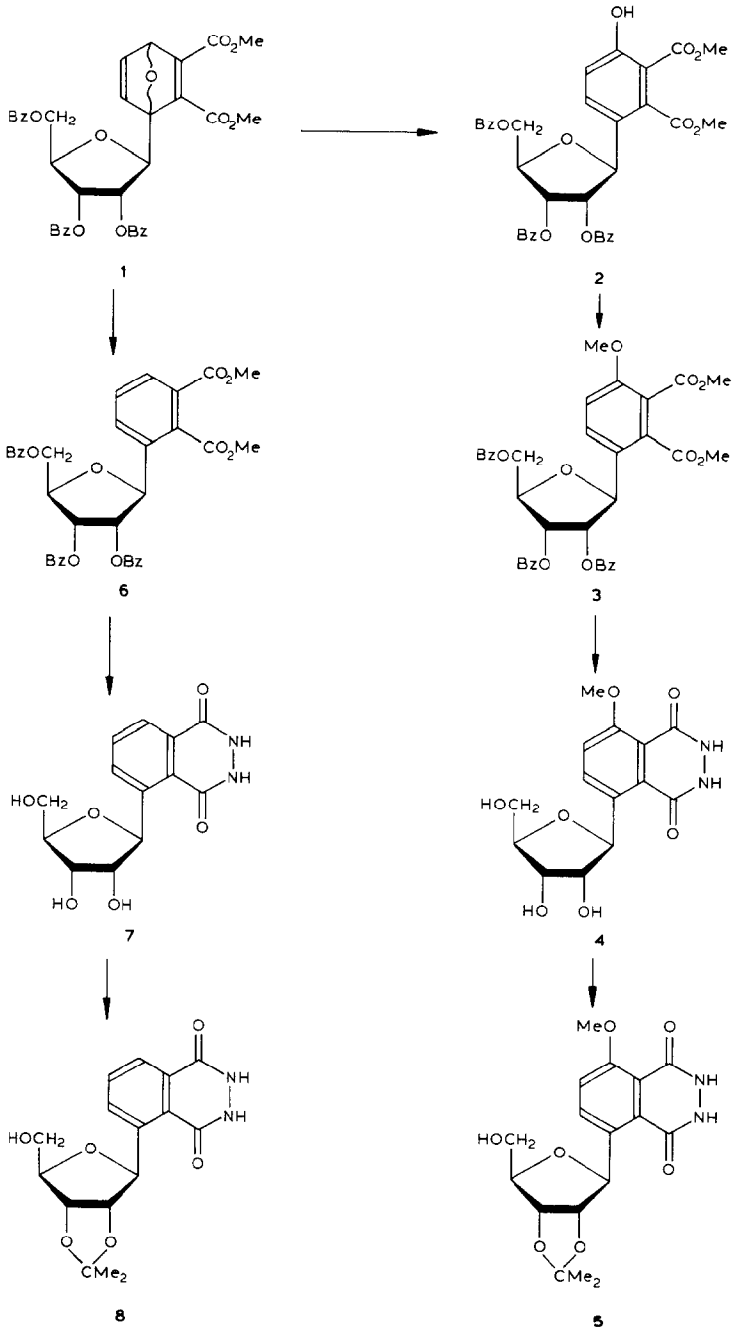
BzOCH2
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spectrum and by elemental analysis. Cyclization of dimethyl 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)phthalate[5] (**6**) by the same procedure just described afforded 5-(β-D-ribofuranosyl)-1,2,3,4-tetrahydrophthalazine-1,4-dione (**7**) in 20% yield. For assignment of the anomeric configurations, of **4** and **7**, the data obtained from the 2′,3′-*O*-isopropylidene derivatives **5** and **8** were used as a basis for the determination. The ^{1}H-n.m.r. chemical-shift differential value ($\Delta\delta$) for the methyl groups in the *O*-isopropylidene derivatives **5** (0.3 p.p.m.) and **8** (0.32 p.p.m.) are indicative of the β stereochemistry, in accordance with Imbach's rules[6].

EXPERIMENTAL

General methods. — Melting points were determined on a Yanagimoto apparatus and are uncorrected. Infrared spectra were recorded with a JASCO IRA-1 spectrometer. ^{1}H-n.m.r. spectra were recorded with a JEOL JNM-PS-100 spectrometer, with tetramethylsilane as the internal standard. Analytical thin-layer chromatography was performed on glass plates coated with a 0.25-mm layer of silica gel GF_{254} (Merck). The compounds were detected with u.v. light (254 nm). Column chromatography was performed on silica gel C-200 (74–149 μm, Wakogel).

*Dimethyl 6-hydroxy-3-(2,3,5-tri-O-*benzoyl-β-D-*ribofuranosyl)phthalate* (**2**). — To a stirred solution of compound[5] **1** (870 mg, 1.3 mmol) in dichloromethane (10 mL) was added 10 drops of concentrated sulfuric acid. The mixture was stirred for 48 h at room temperature. The solvent was removed *in vacuo* below 30° to a syrup that was purified on a silica gel column with purified chloroform as the eluent, to afford 420 mg of **2** (48%) as a colorless syrup; $[\alpha]_D^{20}$ −15.6° (*c* 0.48, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 1730, 1680 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.75, 3.87 (s, 3 H each, CH_3), 4.49–4.98 (m, 3, H-4′, H-5′), 5.23 (d, 1, $J_{1',2'}$ 6 Hz, H-1′), 5.62, 5.82 (t, 1 H each, $J_{1',2'} = J_{2',3'} = J_{3',4'} = 6$ Hz, H-2′, H-3′), 6.97 (d, 1, $J_{4,5}$ 9 Hz, H-5), 7.72 (d, 1, $J_{4,5}$ 9 Hz, H-4), 7.19–8.19 (m, 15, Ar H), and 10.94 (s, 1, OH).

Anal. Calc. for $C_{36}H_{30}O_{12}$: C, 65.62; H, 4.53. Found: C, 66.05; H, 4.62.

*Dimethyl 6-methoxy-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)phthalate* (**3**). — To a solution of **2** (500 mg, 0.8 mmol) in Et_2O–MeOH (10:1, 5.5 mL) was added 13 mL of Et_2O containing diazomethane, and the resulting solution was stored at room temperature for 17 h. After processing, acetic acid was added, and evaporation of the solvent *in vacuo* gave a syrup that was purified on a column of silica gel with 1:2 chloroform–hexane as the eluent, to afford 490 mg of **3** (96%) as a colorless syrup; $[\alpha]_D^{25}$ −17.8° (*c* 1.11, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 1725, 1600, 1580 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 3.67 (s, 3, CH_3), 3.77, 3.81 (s, 3 H each, ester CH_3), 4.27–4.99 (m, 3, H-4′, H-5′), 5.64 (m, 3, H-1′, H-2′, H-3′), 6.82 (d, 1, $J_{4,5}$ 9 Hz, H-5), and 7.10–8.07 (m, 16, Ar H, H-4).

Anal. Calc. for $C_{37}H_{32}O_{12}$: C, 66.24; H, 4.96. Found: C, 66.46; H, 4.82.

8-Methoxy-5-(β-D-ribofuranosyl)-1,2,3,4-tetrahydrophthalazine-1,4-dione (**4**). — A solution of **3** (150 mg, 0.22 mmol) and hydrazine hydrate (0.3 mL) in methanol (7.5 mL) was boiled under reflux for 3 h. After removal of the solvent *in*

vacuo, the residue was crystallized from ethanol to give pure **4**; yield 37 mg (50%); m.p. 225–227°, $[\alpha]_D^{25}$ +37.5° (*c* 0.02, methanol); ν_{max}^{KBr} 3280, 1715 cm^{-1}; ^{1}H-n.m.r. (Me_2SO-d_6): δ 3.48–3.87 (m, 5, H-2′, H-3′, H-4′, H-5′), 3.89 (s, 3, CH_3), 4.77 (m, 5, NH, OH), 5.57 (d, 1, $J_{1',2'}$ 6 Hz, H-1′), 7.37 (d, 1, $J_{6,7}$ 9 Hz, H-7), and 7.93 (d, 1, $J_{6,7}$ 9 Hz, H-6).

Anal. Calc. for $C_{14}H_{16}N_2O_7 \cdot 0.5\ H_2O$: C, 51.22; H, 5.06; N, 8.62. Found: C, 51.14; H, 5.06; N, 8.52.

5-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-8-methoxy-1,2,3,4-tetrahydrophthalazine-1,4-dione (**5**). — Ethyl orthoformate (0.16 mL) was added to a well-stirred suspension of **4** (20 mg, 0.06 mmol) in acetone (1 mL) containing *p*-toluenesulfonic acid monohydrate (9 mg) and the mixture was kept for 16 h at room temperature. The resulting solid was collected by filtration and thoroughly washed with acetone. The filtrates were combined and evaporated to dryness, and the residue was chromatographed on a column of silica gel with 100:7 chloroform–ethanol as the eluent, to afford 12 mg (54%) of **5** as a light-yellow solid, m.p. 222–223°; ^{1}H-n.m.r. ($CDCl_3$): δ 1.34 (s, 3, isopropylidene CH_3), 1.64 (s, 3, isopropylidene CH_3), 2.72 (br s, 1, OH), 3.84–3.98 (m, 2, H-5′), 4.00 (s, 3, CH_3), 4.02–4.28 (m, 3, NH, H-4′), 4.73 (m, 1, H-2′), 4.96 (m, 1, H-3′), 5.30 (d, 1, $J_{1',2'}$ 6 Hz, H-1′), 7.15 (d, 1, $J_{6,7}$ 8 Hz, H-7), and 7.66 (d, 1, $J_{6,7}$ 8 Hz, H-6).

5-(β-D-Ribofuranosyl)-1,2,3,4-tetrahydrophthalazine-1,4-dione (**7**). — The same procedure was used as for the reaction of **3** with hydrazine hydrate.

Compound **7** was isolated in 20% yield; m.p. 215–216°, $[\alpha]_D^{25}$ +44.4 (*c* 0.04, methanol); ν_{max}^{KBr} 3340, 1705 cm^{-1}; ^{1}H-n.m.r. (Me_2SO-d_6): δ 3.10–4.20 (m, 5, H-2′, H-3′, H-4′, H-5′), 4.88 (apparent s, 5, OH, NH), 5.58 (d, 1, $J_{1',2'}$ 6 Hz, H-1′), 7.70 (m, 2, H-6, H-7), 7.97 (m, 1, H-8).

Anal. Calc. for $C_{13}H_{14}N_2O_6 \cdot 1.5\ H_2O$: C, 49.02; H, 4.49; N, 8.73. Found: C, 48.60; H, 5.33; N, 8.72.

5-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-1,2,3,4-tetrahydrophthalazine-1,4-dione (**8**). — The same procedure was used as for the reaction of **4** with acetone. ^{1}H-n.m.r. ($CDCl_3$): δ 1.37 (s, 3, isopropylidene CH_3), 1.68 (s, 3, isopropylidene CH_3), 2.62 (br s, 1, OH), 3.97 (m, 2, H-5′), 4.00–4.29 (m, 3, NH, H-4′), 4.70 (dd, 1, $J_{1',2'}$ 5, $J_{2',3'}$ 6 Hz, H-2′), 4.98 (dd, 1, $J_{2',3'}$ 6, $J_{3',4'}$ 8 Hz, H-3′), 5.41 (d, 1, $J_{1',2'}$ 5 Hz, H-1′), and 7.60–7.88 (m, 3, Ar H).

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