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Note

Synthesis of methyl 2-deoxy-4,5:6,7-di-*O*-isopropylidene-D-*arabino*-hept-3-ulosonate and its use in the preparation of D-*arabino*-tetrahydroxybutylpyrimidine derivatives

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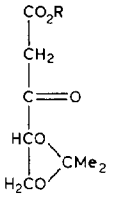
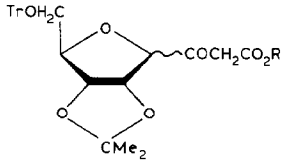
In a previous paper[1], we reported a new and direct synthesis of methyl and ethyl 2-deoxy-4,5-*O*-isopropylidene-D-*glycero*- pent-3-ulosonate (**1**) by the reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde with methyl or ethyl diazoacetate. The structurally related compounds **2**[2] and **3**[3] have also been described. The β-ketoesters **1–3** are useful synthons and we have described[4] the reaction of **1** with *S*-methylthiourea, thiourea, and guanidine to give 6-(1,2-*O*-isopropylidene-D-*glycero*-dihydroxyethyl)pyrimidine derivatives that are structurally closely related to *C*-nucleosides. Similar reactions have been described[2,3] for **2** and **3**. We now report



1



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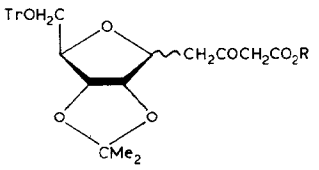

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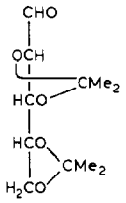

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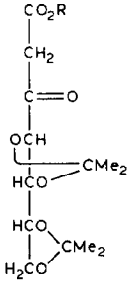

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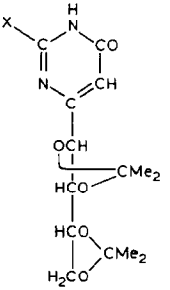
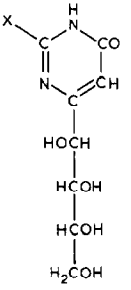


7 X = SMe
8 X = SH
9 X = NH_2



10
11
12

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similar reactions starting from 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose[5] (**4**).

The reaction of **4** with methyl diazoacetate (**5**) in dry ether catalysed by boron trifluoride etherate gave methyl 2-deoxy-4,5:6,7-di-*O*-isopropylidene-D-*arabino*-hept-3-ulosonate (**6**). Isomerisation at C-4 in **6** promoted by the 3-keto group was not detected (t.l.c., ^{1}H-n.m.r. spectroscopy); the C-4 epimer of **6** would have the bulky groups at C-4 and C-5 in **6** in *cis* relationship, and the higher stability of the *trans* arrangement in structurally related 1,3-dioxolane derivatives has been reported[6].

The reaction of **6** with *S*-methylthiourea, thiourea, and guanidine gave 6-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-2-methylthiouracil (**7**), 6-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-2-thiouracil (**8**), and 6-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)isocytosine (**9**), respectively.

Treatment of **7–9** at room temperature with saturated methanolic hydrogen chloride gave the corresponding 6-(D-*arabino*-tetrahydroxybutyl)pyrimidine derivatives **10–12**. No epimerisation was detected in these reactions.

EXPERIMENTAL

General. — Melting points are uncorrected. T.l.c. was performed on silica gel GF_{254} (Merck) with hexane–ethyl acetate mixtures: *A*, 1:1; *B*, 1:2; or *C*, 4:1; and detection by charring with sulphuric acid or by u.v. absorption. Column chromatography was performed on silica gel 60 (0.063–0.200 mm) (Merck). I.r. spectra (KBr disc or film) were recorded with a Beckman Aculab IV spectrometer and u.v. spectra, for solutions in methanol or water, with a Beckman DB-GT spectrometer. ^{1}H-N.m.r. spectra (CCl_4, $CDCl_3$, D_2O, or Me_2SO-d_6; internal Me_4Si or DSS) were recorded with a Perkin–Elmer R-24B or Varian XL-200 spectrometer, and mass spectra with a Hewlett-Packard 5930 A spectrometer. Optical rotations were measured with a Perkin–Elmer 141 polarimeter.

*Methyl 2-deoxy-4,5:6,7-di-*O*-isopropylidene-*D-arabino-*hept-3-ulosonate* (**6**). — To a stirred mixture of 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose[5] (**4**; 10 g, 43 mmol), methyl diazoacetate (**5**; 4.7 g, 47 mmol), and dry ether (5 mL) at −50° was added, dropwise, ethereal 3% BF_3 etherate (5 mL). The mixture was then allowed to attain room temperature, stirred until it was aldehyde-free (t.l.c.), neutralised with sodium hydrogencarbonate, filtered, and concentrated. The residue was distilled at 113–115°/0.25 mmHg to give a mixture (7.8 g) of two products (mainly **6**), which was subjected to column chromatography (solvent *A*) to give **6** (7.5 g, 57%) as a colourless liquid, $[\alpha]_D^{20}$ +3° (*c* 0.7, ethanol), R_F 0.8 (solvent *A*); λ_{max} 240 nm (ε 2,170); ν_{max}^{film} 3800–3200, 2920, 2860, 1740, 1710, 1640, 1625, 1450, 1425, 1370, 1360, 1310, 1225, 1200, 1140, 1060, and 830 cm^{-1}. ^{1}H-N.m.r. data (60 MHz, CCl_4): δ 11.95 (bs, 1 H), 5.20 (s, 1 H), and 3.65 (s, 3 H) corresponding to the enolic form, and 4.40–3.80 (m, 5 H), 3.60 (s, 3 H), 3.50 (s, 2 H), and 1.40–1.20

(4 s, 12 H). Mass spectrum: *m/z* 302 ($M^{\ddagger}$), 287 ($M^+ - Me$), 271 ($M^+ - OMe$), 243 ($M^+ - COOMe$), 229 ($M^+ - CH_2COOMe$), 201, 186, 143, and 43 (100%).

Anal. Calc. for $C_{14}H_{22}O_7$: C, 55.26; H, 7.33. Found: C, 55.77; H, 7.01.

*6-(1,2:3,4-Di-*O*-isopropylidene-*D*-arabino-tetritol-1-yl)-2-methylthiouracil* (**7**). — A mixture of *S*-methylthiourea hydrogen iodide (2.8 g, 12.8 mmol) in water (5 mL) and potassium carbonate (4.75 g, 34 mmol) in water (5 mL) was stirred in the presence of **6** (2 g, 6.6 mmol) and methanol (2 mL) for 6 days at room temperature. The mixture was then neutralised with 50% hydrochloric acid, and the product was recrystallised from ethanol–water to afford **7** (1.55 g, 69%), m.p. 156–158° (dec.), $[\alpha]_D^{20}$ −109° (*c* 0.8, methanol), R_F 0.6 (solvent *B*); $\lambda_{max}^{pH\,1}$ 280 (ε 8,900) and 240 nm (ε 9,400), $\lambda_{max}^{pH\,7}$ 280 (ε 3,300) and 255 nm (ε 10,300), $\lambda_{max}^{pH\,11}$ 280 (ε 6,500) and 240 nm (ε 10,200); ν_{max} 3310, 3210, 3110, 2980, 2625, 2880, 1670, 1650, 1570, 1540, 1450, 1310, 1270, 1230, 1200, 1160, 1145, 1085, 1065, 1050, and 840 cm^{-1}. The ^{1}H-n.m.r. data are given in Table I. Mass spectrum: *m/z* 344 ($M^+ + 2$), 343 ($M^+ + 1$), 342 ($M^{\ddagger}$), 327 ($M^+ - Me$), 285, 284, 270, 227, 59, and 43 (100%).

Anal. Calc. for $C_{15}H_{22}N_2O_5S$: C, 52.63; H, 6.47; N, 8.18. Found: C, 52.51; H, 6.56; N, 7.92.

*6-(1,2:3,4-Di-*O*-isopropylidene-*D*-arabino-tetritol-1-yl)-2-thiouracil* (**8**). — A mixture of thiourea (8.02 g, 105 mmol) and sodium methoxide (1.6 g, 52.8 mmol) in methanol (50 mL) was heated at 70° for 1 h, and **6** (4 g, 13.2 mmol) was then added. The solution was stirred for 2 days at room temperature, neutralised with M hydrochloric acid, and extracted with hot chloroform (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated, and the syrupy residue was subjected to column chromatography (solvent *C*), to afford **8** (1.3 g, 30%), m.p. 164–165° (from ethyl acetate–hexane), $[\alpha]_D^{20}$ −104° (*c* 0.8, ethanol), R_F 0.57 (sol-

TABLE I

200-MHz ^{1}H-N.M.R. DATA FOR SOLUTIONS OF **7–9** IN $CDCl_3$

Atom	*Chemical shift (δ)*		
	7	**8**	**9**
H-5	6.41 (d, *J* 1.0 Hz)	6.16 (d, *J* 1.2 Hz)	6.00 (d, *J* 1.0 Hz)
H-1′	4.60 (dd, *J* 7.0 and 1.0 Hz)	4.64 (dd, *J* 7.2 and 1.2 Hz)	4.54 (dd, *J* 7.0 and 1.0 Hz)
H-2′	4.29 (dd, *J* 7.0 and 5.7 Hz)	3.87 (dd, *J* 8.8 and 7.2 Hz)	4.20–4.00
H-3′	4.38 (ddd, *J* 5.7, 5.7, and 5.7 Hz)	4.13 (ddd, *J* 8.8, 6.0, and 5.4 Hz)	4.34 (ddd, *J* 6.0, 6.0, and 6.0 Hz)
H-4′	4.10 (dd, *J* 5.7 and 7.6 Hz)	4.31 (dd, *J* 8.6 and 6.0 Hz)	4.20–4.00
H-4″	4.03 (dd, *J* 5.7 and 7.6 Hz)	3.98 (dd, *J* 8.6 and 5.4 Hz)	4.20–4.00
Me_2C	1.50–1.35 (3 s)	1.62 (s), 1.49 (s), 1.47 (s), and 1.41 (s)	1.47 (s), 1.45 (s), 1.40 (s), and 1.36 (s)
MeS	2.58 (s)		
NH		9.60 (bs)	
NH		10.30 (bs)	
NH_2			6.80–6.30 (bs)

vent *B*); $\lambda_{max}^{pH\,1}$ 295 (ε 9,200) and 285 nm (ε 10,400), $\lambda_{max}^{pH\,7}$ 315 (ε 12,900) and 255 nm (ε 13,500), $\lambda_{max}^{pH\,11}$ 310 (ε 12,600) and 255 nm (ε 13,100); ν_{max} 3220, 3160, 3120, 3040, 2980, 2925, 2860, 2600, 1705, 1660, 1550, 1450, 1420, 1385, 1375, 1250, 1185, 1160, 1090, 1060, and 845 cm^{-1}. The ^{1}H-n.m.r. data are given in Table I. Mass spectrum: *m/z* 330 ($M^+ + 2$), 329 ($M^+ + 1$), 328 (M^+), 313, 270, 255, 227, 213, 212, 59, and 43 (100%).

Anal. Calc. for $C_{14}H_{20}N_2O_5S$: C, 51.21; H, 6.13; N, 8.52. Found: C, 51.22; H, 6.09; N, 8.54.

*6-(1,2:3,4-Di-O-isopropylidene-*D-arabino-*tetritol-1-yl)isocytosine* (**9**). — A mixture of **6** (1.0 g, 3.2 mmol) and guanidine carbonate (0.29 g, 1.65 mmol) in ethanol (3 mL) was kept at 65–70° for 12 h, neutralised with M hydrochloric acid, and concentrated to dryness. The residue was extracted with chloroform (5 × 10 mL), the combined extracts were dried (Na_2SO_4) and concentrated, and the syrupy residue was subjected to column chromatography (solvent *B*), to afford **9** (0.25 g, 36%), m.p. 174–176°, $[\alpha]_D^{20}$ +13.5° (*c* 0.8, methanol), R_F 0.21 (ethyl acetate); $\lambda_{max}^{pH\,1}$ 263 (ε 7,400) and 220 nm (ε 10,600), $\lambda_{max}^{pH\,7}$ 280 (ε 7,400) and 235 nm (ε 10,200), $\lambda_{max}^{pH\,11}$ 280 (ε 7,600) and 225 nm (ε 10,300); ν_{max} 3480, 3340, 3200, 3080, 2980, 2920, 2880, 1675, 1625, 1540, 1470, 1430, 1380, 1355, 1220, 1150, 1090, 1060, and 840 cm^{-1}. The ^{1}H-n.m.r. data are given in Table I. Mass spectrum: *m/z* 312 ($M^+ + 1$), 296, 254, 253, 238, 210, 196, and 43 (100%).

Anal. Calc. for $C_{14}H_{21}N_3O_5$: C, 54.01; H, 6.79; N, 13.49. Found: C, 53.71; H, 6.83; N, 13.36.

*2-Methylthio-6-(*D-arabino-*tetrahydroxybutyl)uracil* (**10**). — A solution of **7** (0.5 g, 1.46 mmol) in methanol (12 mL) was treated for 3 h at room temperature with saturated methanolic hydrogen chloride (5 mL). The solvents were evaporated and the residue was washed with hot ether, to afford **10** (0.378 g, 99%), m.p. 210° (dec.) (from methanol–water), $[\alpha]_D^{20}$ −44° (*c* 1, water); $\lambda_{max}^{pH\,1}$ 282 (ε 8,200) and 240 nm (ε 9,200), $\lambda_{max}^{pH\,7}$ 282 (ε 9,200) and 236 nm (ε 10,800), $\lambda_{max}^{pH\,11}$ 276 (ε 6,400) and 245 nm (ε 9,200); ν_{max} 3700–3000, 2940, 2920, 1670, 1640, 1580, 1560, 1475, 1460, 1430, 1410, 1265, 1190, 1090, 1065, 1040, and 840 cm^{-1}. ^{1}H-N.m.r. data (60 MHz, D_2O): δ 6.2 (s, 1 H), 5.0–3.5 (m, 9 H), and 3.5 (s, 3 H).

Anal. Calc. for $C_9H_{14}N_2O_5S$: C, 41.21; H, 5.38; N, 10.68. Found: C, 40.90; H, 5.28; N, 10.61.

*6-(*D-arabino-*Tetrahydroxybutyl)-2-thiouracil hydrate* (**11**). — Compound **8** was treated as described above for **7**, to give **11** (91%), m.p. 192° (dec.), $[\alpha]_D^{20}$ −21° (*c* 1, water); $\lambda_{max}^{pH\,1}$ 270 (ε 34,400) and 210 nm (ε 45,000), $\lambda_{max}^{pH\,7}$ 305 (ε 19,000) and 255 nm (ε 20,800), $\lambda_{max}^{pH\,11}$ 310 (ε 18,000) and 260 nm (ε 20,800); ν_{max} 3600–3010, 2940, 2920, 2860, 2540, 1680, 1600, 1555, 1545, 1440, 1430, 1410, 1240, 1175, 1080, 1045, and 860 cm^{-1}. ^{1}H-N.m.r. data (60 MHz, Me_2SO): δ 5.69 (s, 1 H), and 4.70–3.30 (m, 9 H).

Anal. Calc. for $C_8H_{12}N_2O_5S \cdot H_2O$: C, 36.09; H, 5.29; N, 10.51. Found: C, 36.42; H, 4.78; N, 10.20.

*6-(*D-arabino-*Tetrahydroxybutyl)isocytosine hydrochloride* (**12**). — Com-

pound **9** was treated as described above for **7**, to give **12** (99.6%), m.p. 206° (dec.), $[\alpha]_D^{20}$ −32° (*c* 1, water); $\lambda_{max}^{pH\,1}$ 260 (ε 6,150) and 216 nm (ε 5,660), $\lambda_{max}^{pH\,7}$ 277 (ε 5,120) and 255 nm (ε 6,790), $\lambda_{max}^{pH\,11}$ 270 (ε 5,760) and 220 nm (ε 6,850); ν_{max} 3700–3000, 2960, 2920, 2600, 1705–1670, 1540, 1520, 1470, 1460, 1380, 1250, 1200, 1090, 1060, 1040, 950, 930, and 840 cm^{-1}. ^{1}H-N.m.r. data (60 MHz, D_2O): δ 5.60 (s, 1 H) and 5.00–3.50 (m, 12 H).

Anal. Calc. for $C_8H_{13}N_3O_5 \cdot HCl$: C, 35.89; H, 5.27; N, 15.69. Found: C, 35.85; H, 5.23; N, 15.23.

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