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Note

Synthesis of methyl 3,5-di-*O*-benzoyl-2,6-dideoxy-β-L-*lyxo*-hexofuranoside, a nucleoside precursor

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As part of a search for antitumor agents, and for inhibitors of the enzyme purine nucleoside phosphorylase (PNPase), we have recently reported the synthesis and antitumor activity of a number of purine nucleosides of 6-deoxy-L-talofuranose[1]. Wishing to compare the activity of these nucleosides with those of their 2-deoxy analogs, we searched the literature for a suitable synthesis of 2,6-dideoxy-L-*lyxo*-hexose, but failed to find a convenient one. We therefore undertook the synthesis of a methyl furanoside of this sugar that would be suitable for conversion into the chloride, and thence, into the nucleoside. The results of our work, reported herein, comprise the development of a facile, four-step synthesis of crystalline methyl 3,5-di-*O*-benzoyl-2,6-dideoxy-β-L-*lyxo*-hexofuranoside (**5**), its conversion into the chloride **6**, and conversion of the latter, in two steps, into the isomeric, 7- and 9-substituted-hypoxanthine nucleosides.

The synthesis started with the known methyl 2-deoxy-α-D-*arabino*-hexofuranoside (**1**), obtainable from 2-deoxy-D-*arabino*-hexose[2]. The methyl furanoside was converted in 80% yield into the 6-*p*-toluenesulfonate (**2**) by reaction with one equivalent of *p*-toluenesulfonyl chloride in pyridine at 0°. Reduction of **2** with lithium aluminum hydride yielded the intermediate methyl 2,6-dideoxy-α-D-hexofuranoside (**3**), which was treated with methanesulfonyl chloride and triethylamine to produce the 3,5-dimesylate (**4**). Treatment of **4** with tetrabutylammonium benzoate in refluxing benzene resulted in replacement of both mesylate groups by benzoate, and inversion of the configuration at the two chiral centers (C-3 and C-5), to yield crystalline methyl 3,5-di-*O*-benzoyl-2,6-dideoxy-β-L-*lyxo*-hexofuranoside (**5**) in an overall yield of 47%, based on **1**. This methyl glycoside **5** was readily converted into the corresponding chloride (**6**) by treatment with hydrogen chloride in a mixture of ether and acetic acid. Because the halides of 2-deoxy sugars are extremely labile, no attempt was made to obtain this compound in a crystalline form, and it was directly converted into the hypoxanthine nucleoside.

The syrupy chloride **6** was stirred with 1,9-bis(trimethylsilyl)hypoxanthine in dichloroethane in the presence of tin tetrachloride. From our previous experience

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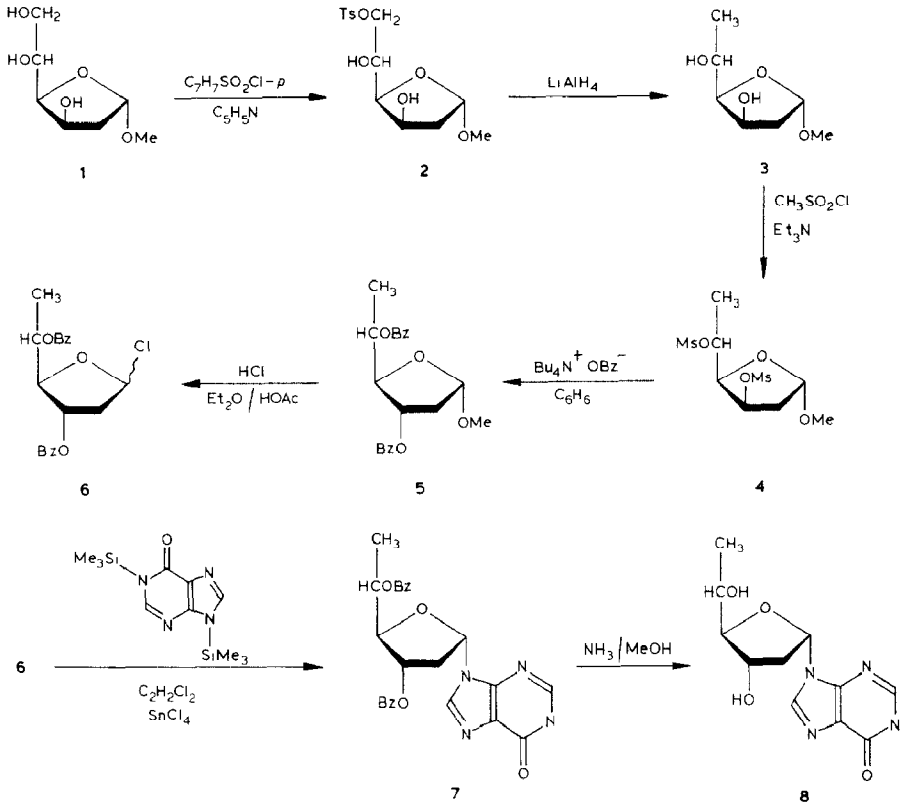

with this method[1,3], we expected to obtain both the 7- and 9-substituted hypoxanthines. Furthermore, as we were dealing here with a 2-deoxy sugar, we presumed that both anomers of each would be formed, rendering the separation quite difficult. When the mixture of benzoylated nucleosides obtained was chromatographed on silica gel, it afforded pure 9-(3,5-di-*O*-benzoyl-2,6-dideoxy-β-L-*lyxo*-hexofuranosyl)hypoxanthine (**7**), and an unresolved mixture of the other isomers. Upon debenzoylation with methanolic ammonia, nucleoside **7** yielded 9-(2,6-dideoxy-β-L-*lyxo*-hexofuranosyl)hypoxanthine (**8**). The β-L configuration of nucleoside **8** was verified by comparing its circular dichroism (c.d.) spectrum with those of the (6-deoxyhexofuranosyl)hypoxanthines previously studied[1,3]. The c.d. spectrum of **8** showed a positive Cotton effect at ~255 nm, characteristic of a C-1′(*S*), that is, β-L, configuration in a 9-substituted hypoxanthine. That the purine was joined at N-9 to the glycosyl group was evident from its u.v. spectrum, which showed the following maxima: 247.7 (pH 2), 248.1 (5), and 253.2 nm (12). These values are typical of *N*-9-substituted hypoxanthine nucleosides, and differ markedly from those of the *N*-7-substituted hypoxanthines, which show absorption at 252, 256, and 263 nm at the same pH values[1,3].

The rest of the blocked nucleoside mixture was deblocked, to yield a mixture

of 7- and 9-substituted-hypoxanthine nucleosides that showed no PNPase inhibition *in vitro,* and no *in vivo* antitumor activity on L1210, and was not studied further.

EXPERIMENTAL

General. — Optical rotations were measured with a Bendix series 1100 automatic polarimeter. Circular dichroism measurements were made by the Michigan Molecular Institute, Midland, Michigan. Microanalyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, Michigan. Ultraviolet spectra were recorded with a Perkin–Elmer Lambda 3 spectrophotometer, and infrared spectra with a Perkin–Elmer 735B spectrophotometer. Nuclear magnetic resonance spectra were recorded with a Varian EM360A 60-MHz spectrometer, using tetramethylsilane as standard.

*Methyl 2-deoxy-6-*O*-p-tolylsulfonyl-α-*D-arabino-*hexofuranoside* (**2**). — A mixture of methyl 2-deoxy-α-D-*arabino*-hexofuranoside[2] (**1**; 3.8 g, 12 mmol) and freshly recrystallized *p*-toluenesulfonyl chloride (4.28 g, 13 mmol) in dry pyridine (30 mL) was stirred for 12 h at 0°. The mixture was poured onto ice plus aqueous sodium hydrogencarbonate solution, extracted with chloroform, and the extract dried, and evaporated, yielding a thick oil which was chromatographed on silica gel. Elution with 1:9 methanol–chloroform afforded the product as a thick oil (5.6 g, 80% yield). Crystallization from ether–hexane at low temperature yielded solid **2**, m.p. 70–73°; ν_{max}^{neat} 3600–3100 (OH), 2930 (C–H), 1600 (ArH), 1450, 1360 (SO_2), 1180 (SO_2), 1100 and 1025 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 2.14 (m, H-2), 2.44 (s, C_6H_4Me), 3.28 (s, OCH_3), 3.40–4.90 (m, H-3,4,5,6, OH), 5.10 (t, H-1), 7.40 (m, ArH), and 7.90 (m, ArH).

Anal. Calc. for $C_{14}H_{20}O_7S$: C, 50.59; H, 6.07. Found: C, 51.02; H, 5.78.

*Methyl 2,6-dideoxy-α-*D-arabino-*hexofuranoside* (**3**). — The monotosylate **2** (5.6 g, 17 mmol) in dry oxolane (50 mL) was stirred with an excess of lithium aluminum hydride for 12 h at room temperature, and then for 2 h under reflux. An excess of ethyl acetate was added, followed by 15% aqueous sodium hydroxide (2.6 mL) and water (10.3 mL). The mixture was filtered, and the filtrate evaporated to a thick oil which was chromatographed on silica gel. Elution with 1:9 methanol–chloroform yielded **3** as an oil (2.1 g, 77%); $\nu_{max}^{CHCl_3}$ 3600–3200 (OH), 2900, 1720, 1360, 1220, 1100, and 1030 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.34 (d, H-6), 2.13 (m, H-2), 3.40 (s, OCH_3), 3.70 (m, H-5), 4.03 (m, H-4, OH), 4.60 (m, H-3), and 5.20 (t, H-1).

*Methyl 2,6-dideoxy-3,5-di-*O*-(methylsulfonyl)-α-*D-arabino-*hexofuranoside* (**4**). — Compound **3** (2.1 g, 13 mmol) in dichloromethane (50 mL) was stirred at 0° with triethylamine (3.9 g, 39 mmol), and methanesulfonyl chloride (3.3 g, 29 mmol) was added dropwise. The mixture was stirred for 20 min, poured into ice plus aqueous sodium carbonate, and extracted with chloroform. The extract was dried, and evaporated, to yield **4** as an oil (4.2 g, 100%); ν_{max}^{neat} 3100–2800 (C–H),

1720, 1340, 1160 (SO_2), 1100, 1040, 960, and 900 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.60 (d, H-6), 2.35 (m, H-2), 3.10 (ds, $MeSO_2$), 3.46 (s, OCH_3), 4.00 (m, H-4,3), and 5.05 (m, H-1,5).

*Methyl 3,5-di-*O*-benzoyl-2,6-dideoxy-β-*L*-lyxo-hexofuranoside* (**5**). — The dimesylate **4** (4.2 g, 13 mmol) in benzene was refluxed with an excess of tetrabutylammonium benzoate for 6 h, and then poured into aqueous sodium hydrogencarbonate and extracted with chloroform. The extract was washed with aqueous sodium chloride, dried, and evaporated, to yield an oil which was chromatographed on silica gel. Elution with 1:1 hexane–ether yielded **5** as a viscous glass (3.7 g, 77%) that crystallized from ether–hexane; m.p. 46–49°; ν_{max}^{neat} 2930 (CH), 1720 (C=O), 1600, 1450 (Ph), 1280 (C–O), 1110, 1070, 1030, and 720 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.43 (d, H-6), 2.32 (m, H-2), 3.46 (s, OCH_3), 4.42 (m, H-4), 5.32 (m, H-1,3,5), 7.52, and 8.06 (m, Ph).

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.17; H, 5.92.

*3,5-Di-*O*-benzoyl-2,6-dideoxy-*L*-lyxo-hexofuranosyl chloride* (**6**). — The methyl glycoside **5** (3.7 g, 0.01 mol) in a mixture of acetic acid (30 mL) and ether (30 mL) was stirred for 0.5 h at 0° as hydrogen chloride was bubbled in. The mixture was then evaporated to dryness, and coevaporated with toluene, to give syrupy glycosyl chloride, **6**, which was used immediately in the next step.

*9-(3,5-Di-*O*-benzoyl-2,6-dideoxy-α,β-*L*-lyxo-hexofuranosyl)hypoxanthine* (**7**). — The crude chloride **6** was stirred for 12 h with 1,9-bis(trimethylsilyl)hypoxanthine (3.08 g, 1 mmol) and tin tetrachloride(3.13 g, 12 mmol) in dichloroethane. Ethanol (70 mL) and triethylamine (10 mL) were added, and the mixture was evaporated to dryness. The resulting syrup was dissolved in chloroform, and the solution washed with aqueous sodium hydrogencarbonate, dried, and evaporated; the crude product was chromatographed on silica gel. Elution with ethyl acetate–acetone yielded isomer **7** as a solid (0.3 g, 6%); ^{1}H-n.m.r. ($CDCl_3$): δ 1.54 (d, H-6), 2.98 (m, H-2), 4.40–4.90 (m, H-4), 5.68 (m, H-3,5), 6.79 (m, H-1), 7.46 (m, Ph), 8.10 (s, purine H), and 8.36 (s, purine H).

Anal. Calc. for $C_{25}H_{22}N_4O_6$: C, 63.29; H, 4.67; N, 11.87. Found: C, 63.20; H, 4.61; N, 11.87.

Elution with acetone yielded an unresolved mixture of nucleoside isomers (1.9 g, 38%).

*9-(2,6-Dideoxy-β-*L*-lyxo-hexofuranosyl)hypoxanthine* (**8**). — A solution of nucleoside **7** (0.3 g, 630 μmol) in ammonia-saturated methanol was kept for several days, evaporated, and the residue dissolved in distilled water. The solution was washed several times with chloroform, and evaporated to dryness, giving a glass that was dissolved in ethanol, and the nucleoside precipitated by addition of ether; yield, 0.12 g (70%); $[\alpha]_D$ +29.2° (H_2O); $\lambda_{max}^{H_2O}$ 247.7 (pH 2), 248.1 (5), and 253.2 nm (12); ν_{max}^{KBr} 3600–2700 (OH, NH), 1680 (C=O), 1580, 1540, 1510, 1400, 1220, and 1090 cm^{-1}; ^{1}H-n.m.r. (Me_2SO-d_6): δ 1.14 (d, H-6), 2.43 (m, H-2), 3.40 (q, H-5), 3.78 (m, H-3), 4.04 (m, H-4), 4.44 (m, OH), 6.44 (m, H-1), 8.23 (s, purine H), 8.54 (s, purine H), and 11.00 (m, NH).

Anal. Calc. for $C_{11}H_{14}N_4O_4 \cdot 0.5\ H_2O$: C, 48.00; H, 5.49; N, 20.35. Found: C, 48.29; H, 5.39; N, 20.42.

Similar treatment of the blocked nucleoside mixture (1.9 g, 4 mmol) with methanolic ammonia yielded a mixture of nucleosides, which was not separated.

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