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2-DEOXY SUGARS

PART XVII. PYRIMIDINE NUCLEOSIDES DERIVED FROM 2-DEOXY-β-D-*lyxo*-HEXOPYRANOSE*

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ABSTRACT

A new, crystalline *O*-acylglycosyl halide of 2-deoxy-D-*lyxo*-hexose has been prepared by the following sequence of reactions: methyl 2-deoxy-α-D-*lyxo*-hexopyranoside→methyl 2-deoxy-6-*O*-trityl-α-D-*lyxo*-hexopyranoside→methyl 3,4-*O*-carbonyl-2-deoxy-6-*O*-trityl-α-D-*lyxo*-hexoside→methyl 3,4-*O*-carbonyl-2-deoxy-α-D-*lyxo*-hexopyranoside→methyl 3,4-*O*-carbonyl-2-deoxy-6-*O*-*p*-nitrobenzoyl-α-D-*lyxo*-hexoside→3,4-*O*-carbonyl-2-deoxy-6-*O*-*p*-nitrobenzoyl-α-D-*lyxo*-hexosyl bromide. The new halide was treated with 2,4-dimethoxypyrimidine by the Hilbert–Johnson procedure to afford 1-(3,4-*O*-carbonyl-2-deoxy-6-*O*-*p*-nitrobenzoyl-β-D-*lyxo*-hexosyl)-4-methoxy-2(1*H*)-pyrimidinone, which underwent ammonolysis to yield 1-(2-deoxy-β-D-*lyxo*-hexopyranosyl)cytosine. Demethylation of the pyrimidinone, followed by deacylation, gave the corresponding uracil nucleoside. 1-(2-Deoxy-β-D-*lyxo*-hexopyranosyl)thymine, the C-4′ epimer of 1-(2-deoxy-β-D-*arabino*-hexopyranosyl)thymine (a powerful and specific inhibitor of a pyrimidine phosphorylase obtained from Ehrlich ascites tumor cells) was prepared in a manner similar to that for the uracil nucleoside.

INTRODUCTION

1-(2-Deoxy-β-D-*arabino*-hexopyranosyl)thymine ["2-deoxy-D-glucosylthymine"][1] is a powerful and specific inhibitor of a non-specific pyrimidine nucleoside phosphorylase obtained from Ehrlich ascites cells[2]. It also enhances incorporation of 2′-deoxy-5-iodouridine into the 2′-deoxy-D-ribonucleic acid (DNA) of cat tissues *in vivo*, by inhibition of a "uridine-deoxyuridine" phosphorylase present therein[3]. In terms of the carbohydrate component of the synthetic nucleoside, the structural requirements for inhibition of the enzyme(s) appear to be highly specific. Although "2-deoxy-D-glucosylthymine" is a powerful inhibitor, the corresponding β-D-glucopyranosyl nucleoside is without effect[2a]. Also ineffective as an inhibitor is 1-(2-deoxy-β-D-*ribo*-hexopyranosyl)thymine ["2-deoxy-D-allosylthymine"][2b,4], the structure of which differs from that of "2-deoxy-D-glucosylthymine" only with respect to a reversal

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of configuration at C-3 of the carbohydrate component. On the basis of the latter situation, it is logical to predict that 1-(2-deoxy-β-D-*xylo*-hexopyranosyl)thymine (having, therefore, the same configuration at C-3 of the sugar residue) would likewise be ineffective; consequently, this nucleoside has been eliminated as a candidate for phosphorylase inhibition studies. However, the effect brought about by a reversal of configuration at C-4 of the carbohydrate fragment of "2-deoxy-D-glucosylthymine" has not yet been determined, and it is for this reason that we undertook the preparation of a thymine nucleoside that contains a 2-deoxy-β-D-*lyxo*-hexopyranose (C-4 epimer of 2-deoxy-β-D-*arabino*-hexopyranose) residue. In addition to describing the thymine nucleoside, we now report the preparation of two additional 2-deoxy-β-D-*lyxo*-hexopyranosyl ("2-deoxy-β-D-galactopyranosyl") pyrimidine nucleosides; each of the three was synthesized *via* a uniquely constituted, crystalline *O*-acyl-2-deoxyglycosyl halide, the preparation of which has been accomplished in six steps, starting with the commercially available "2-deoxy-D-galactose".

DISCUSSION AND RESULTS

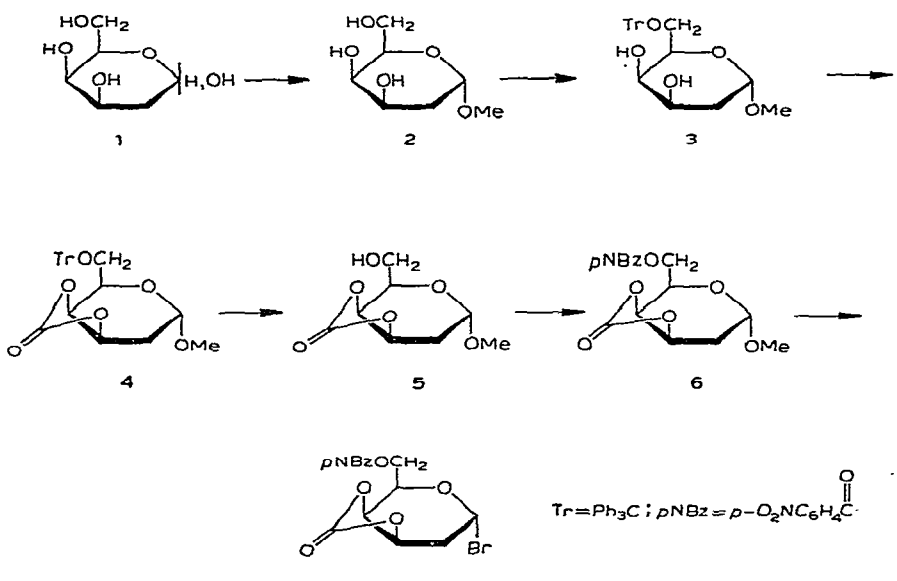
We have shown[5] that *p*-nitrobenzoic esters of 2-deoxy sugars yield stable, *crystalline* *O*-acyl-2-deoxyglycosyl halides; these may be prepared by the simple expedient of stirring the *p*-nitrobenzoic ester in dichloromethane presaturated with anhydrous hydrogen halide. The *p*-nitrobenzoyloxy group at C-1 is rapidly replaced by halogen, and, because of its very low solubility in dichloromethane, the liberated *p*-nitrobenzoic acid separates in almost quantitative yield. Filtration of the suspension and evaporation of the filtrate affords the desired halide as a solid residue which may readily be obtained in crystalline form.

By this method, we were successful in preparing crystalline halides of acylated digitoxose (2,6-dideoxy-D-*ribo*-hexose)[5], 2-deoxy-D-*arabino*-hexose[6], and 2-deoxy-D-*ribo*-hexose[7], each of which was employed successfully in a modified Koenigs–Knorr synthesis of cardiac glycosides[6–8] containing the respective sugar residues. The utility of the three halides was further demonstrated in the synthesis of some 2-deoxy-aldohexopyranosyl nucleosides[9]; for the pyrimidine nucleosides thus obtained, the Hilbert–Johnson procedure[10] was the method of choice, because basic conditions, which tend to eliminate the elements of hydrogen halide from the *p*-nitrobenzoylated glycosyl halide, are avoided[1]. Also, the three halides are of sufficient reactivity to condense readily at room temperature with either 2,4-diethoxy- or 2,4-dimethoxy-pyrimidines, and, in each case studied, the reaction was highly stereoselective, affording the β-D anomers. Although it is unlikely that at least small proportions of the other anomers were not formed, these were not observed under the conditions by which the reaction products were processed. In one instance, involving the condensation of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*arabino*-hexosyl bromide with 2,4-diethoxypyrimidine[11], removal of unreacted pyrimidine by extraction left a crystalline residue that was almost pure β-D nucleoside (protected), not requiring further purification.

Because of the aforementioned success in the preparation of such pyrimidine

nucleosides, it appeared desirable to perform, in an analogous manner, the synthesis of some pyrimidine nucleosides containing "2-deoxy-D-galactose" residues. 2-Deoxy-D-*lyxo*-hexose ("2-deoxy-D-galactose", **1**) was readily converted into an anomerically pure tetrakis-*p*-nitrobenzoic ester, which underwent reaction with hydrogen bromide in dichloromethane to afford crystalline 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*lyxo*-hexosyl bromide that reacted readily with methanol in the presence of silver carbonate to give, by inversion, methyl 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-β-D-*lyxo*-hexoside[9]. In sharp contrast, the new halide failed to condense with 2,4-diethoxypyrimidine, even on heating the mixture at 75°, and in no experiment could even trace amounts of material identifiable as protected nucleoside be recovered from the reaction mixture. We have explained this failure[9] on the grounds that the approach of the dialkoxypyrimidine to C-1 of the halide is hindered by the axially oriented *p*-nitrobenzoyloxy group on C-4, and that the same group in the corresponding halides prepared from digitoxose, "2-deoxy-D-glucose", and "2-deoxy-D-allose" is an equatorial substituent; consequently, with the latter, C-1 is unhindered, and the condensations proceed in the normal way.

Because of the failure with 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*lyxo*-hexosyl bromide in the Hilbert–Johnson synthesis[10], we strove to prepare an acylated glycosyl halide of 2-deoxy-D-*lyxo*-hexopyranose in which the substituent at C-4 would have

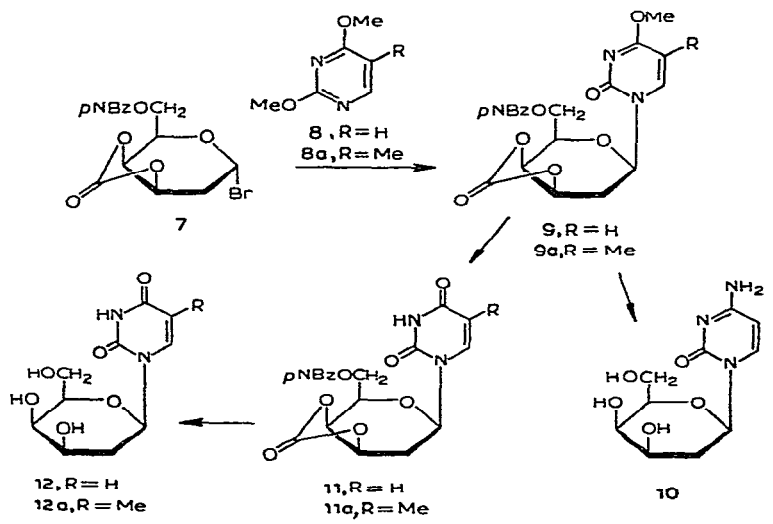


the smallest possible bulk, thus overcoming the steric resistance displayed by the *p*-nitrobenzoylated bromide. 2-Deoxy-D-*lyxo*-hexose (**1**) was converted into the known methyl 2-deoxy-α-D-*lyxo*-hexopyranoside[12] (**2**) in improved yield[13], and unimolar tritylation of **2** afforded, in good yield, the 6-trityl ether (**3**), accompanied by a small proportion (about 5%) of another product, the composition of which agreed with that of a ditrityl ether of **2**. The second trityl group is, most probably, located on

O-3 (equatorial), tritylation on O-4 being precluded because of the axial orientation of the hydroxyl group at this position. Furthermore, it is unlikely that a second trityl group would enter at O-4, because of the proximity of the 4- and 6-positions, which would cause severe crowding.

Treatment of **3** with carbonyl chloride gave the expected methyl 3,4-*O*-carbonyl-6-*O*-trityl-α-D-*lyxo*-hexoside (**4**) as a crystalline product. Quantitative detritylation of **4** in glacial acetic acid with one molar equivalent of hydrogen bromide[14] was almost instantaneous, resulting in **5** as a syrupy product, which was, nevertheless, homogeneous on thin-layer chromatograms. Compound **5** reacted with *p*-nitrobenzoyl chloride in pyridine to yield the 6-*p*-nitrobenzoate (**6**). In the conversion of **6** into 3,4-*O*-carbonyl-6-*O*-*p*-nitrobenzoyl-α-D-*lyxo*-hexosyl bromide (**7**), the concentration of hydrogen bromide is critical. With dichloromethane presaturated with hydrogen bromide[5], only ~60% conversion of **6** into **7** was observed (t.l.c.) after 24 hours. When a 1:1 solution of 30% hydrogen bromide–acetic acid and dichloromethane was employed, for example, gross decomposition of the product occurred. However, when the conversion was performed in dichloromethane under conditions in which both the concentration and the time of reaction were carefully regulated, excellent yields of crystalline **7** were obtained. Provided that the new halide was recrystallized, it proved to be extremely stable, and could be stored under anhydrous conditions for relatively long periods of time.

From past experience in this Laboratory, it has been shown that, when the Hilbert–Johnson synthesis[10] is conducted on a large scale, the yield of protected nucleoside becomes very low. It is, therefore, more efficient to scale down the synthesis and to repeat the reaction on the same basis as many times as is necessary to consume the total amount of halide to be employed. Accordingly, several small-scale reactions between **7** and 2,4-dimethoxypyrimidine (**8**) were performed, in which the two compounds reacted readily at room temperature (the reaction being judged complete in



30 min) to afford the acylated pyrimidinone* (**9**) in yields of 55–60%. Ammonolysis of **9** was readily effected in methanol presaturated with ammonia, to yield 1-(2-deoxy-β-D-*lyxo*-hexopyranosyl)cytosine (**10**). Demethylation of **9** afforded the acylated uracil nucleoside (**11**), which, on deacylation in methanol with methoxide ion, gave 1-(2-deoxy-β-D-*lyxo*-hexopyranosyl)uracil (**12**). Because 2,4-dimethoxy-5-methylpyrimidine (**8a**) is a solid at room temperature, it was necessary to heat a mixture of **7** and **8a** to effect intimate mixing; as with **8**, the reaction was complete in about 30 min, giving comparable yields of the pyrimidinone* (**9a**). Demethylation of **9a**, followed by removal of the protecting groups of the acylated intermediate (**11a**), afforded 1-(2-deoxy-β-D-*lyxo*-hexopyranosyl)thymine (**12a**).

The β-D configuration for the thymine nucleoside (**12a**) has been assigned on the basis of its n.m.r. spectrum, which showed, for the anomeric proton, a quadruplet (two doublets) centered at τ 4.4 ($J_{a,a}$ 9 and $J_{a,e}$ 3.5 Hz). An analysis of the n.m.r. spectrum of the cytosine nucleoside (**10**) was somewhat complicated, owing to the fact that one of the doublets of the quartet (centered at τ 4.38) for the anomeric proton was obscured by the peak for the C-5 proton of the pyrimidine ring (τ 4.25). However, a careful examination of the peaks and the integration curve indicated that the doublet was obscured by one-half of the doublet for the C-5 proton, giving $J_{a,a}$ ~9 and $J_{a,e}$ ~3.5 Hz, indicative of a β-D-nucleoside. This fact, taken together with the rotational data, compared with those for both the protected and unsubstituted thymine nucleosides (**9a** and **12a**), confirm the β-D configuration for **10**, from which, that of the uracil nucleoside (**12**) must follow.

Tests with "uridine–deoxyuridine" phosphorylase disclosed that the thymine nucleoside (**12a**) was completely inactive as an inhibitor**, and these results are in agreement with the structure–activity relationships for the enzyme, as set forth by Etzold *et al.*[15].

EXPERIMENTAL

All melting points were determined with a Kofler hot-stage, optical rotations were measured with a Rudolph Model 80 polarimeter, i.r. spectra were recorded with a Perkin–Elmer Model 457 spectrophotometer, and n.m.r. spectra were recorded on a Varian Model A-60 spectrometer, with methyl sulfoxide-d_6 as the solvent.

T.l.c. was performed on 250-μm, silica gel (Camag DF-5) plates, and the following solvents were employed: *A*, 1:1 ethyl acetate–cyclohexane; *B*, 1:4 ethyl acetate–cyclohexane; *C*, 1:4 cyclohexane–ethyl acetate; *D*, 1:1:8 butyl alcohol–2,2,4-trimethylpentane–ethyl acetate, and *E*, upper layer of 3:5:6:10 2,2,4-trimethylpentane–water–ethyl alcohol–ethyl acetate. The spots were visibilized either with u.v. light, or by spraying with 80% aqueous sulfuric acid and charring at 110° for 5 min.

*As disclosed by t.l.c., the crude reaction product was contaminated with about 5% of what was probably the anomer.

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Methyl 2-deoxy-6-O-trityl-α-D-lyxo-hexopyranoside (**3**). — To a solution of 10 g (56.5 mmoles) of methyl 2-deoxy-α-D-*lyxo*-hexopyranoside[13] (**2**) (m.p. 115.5–117°) in 220 ml of anhydrous pyridine was added 19.7 g (70.5 mmoles) of freshly prepared chlorotriphenylmethane. The mixture was stirred under exclusion of moisture until it became homogeneous, and it was then kept in the dark for 4 days, during which time the reaction was monitored periodically by t.l.c. (solvents *A* and *B*). The mixture was slowly poured, with vigorous stirring, into 1.9 l of ice–water, and the amorphous precipitate that separated was filtered off, and washed thoroughly with water. The solid was dissolved in 1 liter of dichloromethane, and the solution was washed with two 300-ml portions of water and dried with sodium sulfate. The solvent was evaporated off at 35° under diminished pressure, and the residual pyridine was removed by co-evaporation with three 100-ml portions of toluene. The residue was dissolved in the minimal volume of dichloromethane, and pentane was added, in small portions, until a gel-like precipitate had formed; on standing, the gel became crystalline, and pentane was added until its total volume was 1.5 times that of the dichloromethane solution. The resulting crystals were collected by filtration and dissolved in hot ethyl acetate, followed by the addition of a small volume of cyclohexane and sufficient pentane to double the volume of the solution, giving 14.9 g of pure **3**, m.p. 111–112°. By carefully processing the mother liquors, there was obtained an additional 4.01 g of product, m.p. 109.5–111.5°, bringing the total yield to 80%.

An analytical sample was prepared by chromatographing 1.25 g of **3** on a column (4 × 50 cm) of 250 g of Silica Gel (E. Merck AG, Darmstadt; 0.05–0.2 mm); elution was performed with 1:8 cyclohexane–ethyl acetate, 6-ml fractions being collected from the time of appearance of triphenylmethanol. The chromatography was monitored continuously by t.l.c. with solvent *C* (R_F of **3**, 0.44), and, from fractions 30–55, 1.05 g of chromatographically homogeneous product was obtained; $[\alpha]_D^{23}$ +53° (*c* 1.00, dichloromethane).

Anal. Calc. for $C_{26}H_{28}O_5$: C, 74.26; H, 6.71. Found: C, 74.11; H, 6.81.

Methyl 2-deoxy-3,6-di-O-trityl-α-D-lyxo-hexopyranoside. — The liquors remaining from the preceding experiment were combined and evaporated to dryness, leaving a residue which was digested with 160 ml of boiling 1:15 tetrahydrofuran–ethyl alcohol. The solid was filtered off, to give 3 g (8%) of the ditrityl derivative, m.p. 232–235°. An analytical sample was prepared by dissolving the material in the minimal volume of warm tetrahydrofuran, followed by the addition of ethyl alcohol, to afford pure product, m.p. 235–237°, $[\alpha]_D^{23}$ +46.1° (*c* 1.0, chloroform), $\nu_{max}^{CHCl_3}$ 3590 cm^{-1} (CHOH); t.l.c. with solvent *B*, R_F 0.36.

Anal. Calc. for $C_{45}H_{42}O_5$: C, 81.54; H, 6.38. Found: C, 81.78; H, 6.84.

Methyl 3,4-O-carbonyl-2-deoxy-6-O-trityl-α-D-lyxo-hexoside (**4**). — To a solution of 18.9 g (45 mmoles) of **3** in 300 ml of dry pyridine in a 500-ml flask (fitted with a dropping funnel) and precooled to −18° (ice–salt bath), was added dropwise, during 1 h (vigorous magnetic stirring), 75 ml of a 19% (w/w) solution of carbonyl chloride in toluene. The mixture was stirred for 2 h at −18°, and was then poured into a stirred suspension of 25 g of freshly prepared barium carbonate in 2 l of ice–water,

stirring being maintained until the ice had melted. The liquid was decanted from the oily residue that collected on the bottom of the beaker, and was extracted with three 800-ml portions of dichloromethane. The residue in the beaker was extracted with three 200-ml portions of dichloromethane, and all extracts were combined, thoroughly washed with water, dried (sodium sulfate), and filtered through a bed of Celite 545; the filtrate was evaporated under diminished pressure at 35°. Residual pyridine was removed by co-evaporation with three 50-ml portions of toluene, the resulting syrup was dissolved in ether–tetrahydrofuran, and the solution was treated with Darco G-60 decolorizing carbon. The suspension was filtered on a bed of Celite 545, the filtrate was evaporated to dryness under diminished pressure at 35°, and the syrup was dissolved in 100 ml of ether. Crystallization was effected by the portionwise addition of small volumes of pentane during 3 days (with refrigeration), yielding 16.85 g (83.5%) of product (**4**), m.p. 132–134.5°, sufficiently pure for the following conversion.

An analytical sample was prepared by chromatographing 600 mg of the product on a column (4 × 50 cm) of 220 g of Silica Gel (E. Merck AG, Darmstadt; 0.05–0.2 mm). Elution was performed with solvent *A*, and the effluent was monitored continuously by t.l.c. (solvents *A* and *C*). Collection (6-ml fractions) was begun with the first appearance of product in the eluate, and the pure compound (**4**) was collected in fractions 1–25. Evaporation of the solvent and recrystallization of the residue from ether–pentane gave 480 mg of **4**, m.p.* 135–136°, $[\alpha]_D^{23}$ −25.0° (*c* 1.05, dichloromethane).

Anal. Calc. for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.44; H, 5.94.

*Methyl 3,4-O-carbonyl-2-deoxy-α-*D*-lyxo-hexopyranoside* (**5**). — To a solution of 12.35 g (27.7 mmoles) of **4** (m.p. 132–134°) in 50 ml of glacial acetic acid precooled to 0°, was added, with vigorous stirring, 5.0 ml (28 mmoles) of a freshly prepared, 35% (w/w) solution of hydrogen bromide in glacial acetic acid. The mixture was filtered after 10 sec, and the crystalline bromotriphenylmethane was washed with 10 ml of acetic acid. The filtrate was poured, with stirring, into a solution of 8 g of sodium hydrogen carbonate in 600 ml of water, and solid sodium hydrogen carbonate was added, in small portions with stirring, until the solution had pH 5. The mixture was filtered through a bed of Celite 545, the Celite was washed with 100 ml of water, and the filtrate was extracted with twelve 500-ml portions of 1:3 ethyl alcohol–chloroform. The extracts were combined and dried (sodium sulfate), the solvent was evaporated off under diminished pressure at 35°, and the residue was co-evaporated with three 100-ml portions of toluene and then with three 100-ml portions of absolute ethyl alcohol. The syrupy product (**5**) weighed 5.08 g (90%), and was virtually homogeneous by t.l.c. (solvents *C* and *D*).

It was further purified by chromatographing 500 mg on a column (4 × 55 cm) of 200 g of silicic acid (Mallinckrodt), elution being conducted (collection of 5-ml fractions) with solvent *D*. From fractions 150–280, there was obtained 450 mg of

*On occasion, the compound melts at 95–105°, crystallizes again at 105–110°, and remelts at 135–136°.

pure **5** (t.l.c., solvent *D*), which resisted all efforts to crystallize it; $[\alpha]_D^{23}$ +54.6° (*c* 1.03, chloroform), $\nu_{max}^{CHCl_3}$ 3630 (CH_2OH) and 1815 cm^{-1} (C=O).

*Methyl 3,4-O-carbonyl-2-deoxy-6-O-p-nitrobenzoyl-α-*D-lyxo-*hexoside* (**6**). — To a solution of 5.1 g (25 mmoles) of **5** in 120 ml of dry pyridine, precooled to 0°, was added 5.76 g (31.2 mmoles) of *p*-nitrobenzoyl chloride, and the mixture was stirred for 30 min at 0° and then at room temperature to effect complete dissolution. After being kept in a refrigerator for 24 h, the mixture was slowly poured, with stirring, into 500 ml of 5% aqueous sodium hydrogen carbonate, and the resulting suspension was stirred for 15 min and then diluted with ice-water. After the ice had melted, the solid that formed was collected by filtration, washed well with water, and then dried in a vacuum desiccator (phosphorus pentaoxide). The crude product was dissolved in 120 ml of dichloromethane, the solution was treated with Darco G-60 decolorizing carbon, and the suspension was filtered through a bed of Celite 545, followed by washing with a small volume of dichloromethane. The filtrate was concentrated to about 120 ml and, on portionwise addition of about 200 ml of pentane, there was obtained 6.9 g (78.5%) of product (**6**), melting at 150–151.5° and homogeneous by t.l.c. (R_F 0.50) with solvent *C*. An analytical sample was prepared by recrystallization from dichloromethane–pentane; m.p. 151.5–152.5°, $[\alpha]_D^{23}$ +26.5° (*c* 1.09, dichloromethane).

Anal. Calc. for $C_{15}H_{15}NO_9$: C, 50.99; H, 4.28; N, 3.96. Found: C, 51.19; H, 4.24; N, 3.86.

*3,4-O-Carbonyl-2-deoxy-6-O-p-nitrobenzoyl-α-*D-lyxo-*hexosyl bromide* (**7**). — To a solution of 2.0 g (5.7 mmoles) of **6** in 20 ml of dry dichloromethane was added 2.5 ml of a freshly prepared, 36% (w/w) solution of hydrogen bromide in glacial acetic acid. Separation of crystalline product (**7**) was observed in ~45 min and, after 1 h, examination of the reaction mixture by t.l.c. (solvent *C*) showed complete disappearance of the starting compound (**6**) (R_F 0.51) and presence of the bromide (R_F 0.40) as the sole carbohydrate component. Dry ether (30 ml) was added, followed by 30 ml of dry pentane after 15 min. After the mixture had been kept for an additional 20 min, the separated halide (**7**) was collected by filtration and washed with five 10-ml portions of dry ether; it had m.p. 120–122° and was of sufficient purity for the nucleoside syntheses that follow*. Recrystallization was effected by dissolving it in 75 ml of warm dichloromethane and adding 30 ml of dry ether. After 15 min, 50 ml of pentane was added, to afford 1.72 g (75.4%) of **7**, m.p. 120–122°, $[\alpha]_D^{23}$ +64.5° (*c* 0.53, dichloromethane). (In small-scale preparations, with 75–150 mg of **6**, the yield of **7** was 90–94%.)

*1-(3,4-O-Carbonyl-2-deoxy-6-O-p-nitrobenzoyl-β-*D-lyxo-*hexosyl)-4-methoxy-2(1H)-pyrimidinone* (**9**). — The bromide (**7**) (750 mg, 1.85 mmoles) was divided into three equal portions, and each was added, with mixing, to 1 g of 2,4-dimethoxypirimidine[16] (**8**), in a small, stoppered test-tube. The bromide dissolved rapidly, and the pale-yellow solution solidified completely within 20–30 min. The mixtures were transferred

*The product must, however, be scrupulously free from hydrogen bromide.

to a 125-ml Erlenmeyer flask by rinsing with ether, additional ether was added to bring the volume to 100 ml, and the mixture was stirred to effect complete dissolution of unreacted **8**. The resulting, amorphous precipitate was collected by filtration, washed with ether, and recrystallized twice from a small volume of dichloromethane–ether–pentane; yield of **9**, 460 mg (55%), m.p. 222–225°, $[\alpha]_D^{23}$ +106.8° (*c* 1.01, dichloromethane); homogeneous by t.l.c. [R_F 0.29 (solvent *D*) and R_F 0.68 (solvent *E*)]. An analytical sample, m.p., 223–225.5°, was obtained by an additional recrystallization from dichloromethane–ether.

Anal. Calc. for $C_{19}H_{17}N_3O_{10}$: C, 51.01; H, 3.83; N, 9.39. Found: C, 50.89; H, 3.82; N, 9.23.

*1-(2-Deoxy-β-*D-lyxo-*hexopyranosyl)cytosine* (**10**). — A solution of 300 mg (670 μmoles) of **9** in 25 ml of anhydrous methanol presaturated with ammonia was heated in a pressure flask for 12 h at 85–90°. The solvent was removed under diminished pressure at 30°, the residue was partitioned between 15 ml of water and 15 ml of chloroform, and the chloroform layer was discarded. The aqueous layer was extracted (to remove the *p*-nitrobenzamide) with two 15-ml portions of chloroform and three 15-ml portions of ether, and stirred with a small amount of decolorizing carbon, and the suspension was filtered through a bed of Celite 545, followed by washing with a small volume of 1:1 ethyl alcohol–water. The filtrate was evaporated to dryness under diminished pressure, and the residue was dissolved in 1 ml of water, followed by addition of 4 ml of absolute ethyl alcohol; crystallization was completed by the portionwise addition of 20 ml of ether during 1 day; yield of **10**, 153 mg (89%), m.p. 246–250° (dec.), $[\alpha]_D^{23}$ +55.6° (*c* 0.55, water); homogeneous by t.l.c. (R_F 0.04, solvent *E*). Two additional recrystallizations from water (1.5 ml)–ethyl alcohol (5 ml)–ether (20 ml) gave analytically pure **10**, m.p. 251–253°.

Anal. Calc. for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.33. Found: C, 46.51; H, 5.91; N, 16.18.

*1-(3,4-*O*-Carbonyl-2-deoxy-6-*O*-*p*-nitrobenzoyl-β-*D*-lyxo-hexosyl)uracil* (**11**). — To a solution of 279 mg (624 μmoles) of **9** in 15 ml of dichloromethane was added 5.2 ml of a 39% (w/w) solution of hydrogen chloride in absolute ethyl alcohol, the demethylation being complete in 2 h, as disclosed by t.l.c. with solvent *D*. The solution was concentrated to a small volume by evaporation *in vacuo* at <20°, diluted with dichloromethane, and reconcentrated by evaporation. This procedure was repeated several times and the solution was then evaporated to dryness, leaving a residue which was suspended in 10 ml of dichloromethane and dissolved by addition of methanol. The solution was treated with decolorizing carbon, the suspension was filtered through a bed of Celite 545, and the crude product (**11**) was precipitated from the filtrate by addition of ether. After being filtered off, the solid was suspended in dichloromethane (10 ml) and dissolved by addition of methanol (1 ml); portionwise addition of ether gave 152 mg (57%) of **11**, m.p. 234–235.5° (dec.), $[\alpha]_D^{23}$ +80.9° (*c* 0.503, 1:9 methanol–dichloromethane).

Anal. Calc. for $C_{18}H_{15}N_3O_{10}$: C, 49.89; H, 3.49; N, 9.70. Found: C, 49.79; H, 3.47; N, 9.69.

*1-(2-Deoxy-β-*D*-lyxo-hexopyranosyl)uracil* (**12**). — To a stirred suspension of 142 mg (330 μmoles) of compound **11** in 15 ml of dry methanol was added 200 μl of M methanolic sodium methoxide. After 2 h, the mixture was stirred for 10 min with 1 g of Dowex-50W X8 (H^+) ion-exchange resin, and filtered, and the resin was washed with methanol. The filtrate was evaporated to dryness under diminished pressure at 30°, the residue was partitioned between 15 ml of water and 15 ml of ether, and the ether layer was discarded. The aqueous layer was washed with three 15-ml portions of ether, and stirred with a small amount of decolorizing carbon, and the suspension was filtered through a bed of Celite 545. The filtrate was evaporated to dryness, and the residue was co-evaporated with absolute ethyl alcohol to afford 50 mg (59%) of crude, hygroscopic nucleoside (**12**), which was chromatographically homogeneous by t.l.c. (R_F 0.16) with solvent *E*. The compound was dried by co-evaporating it three times with absolute ethyl alcohol; it was then dissolved in 2 ml of absolute alcohol, and ether was added to incipient turbidity, affording crystalline **12**, m.p. 217.5–220°, $[\alpha]_D^{23}$ +15.1° (*c* 0.10, water); similar recrystallization gave an analytically pure sample.

Anal. Calc. for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.73; H, 5.41; N, 11.09.

*1-(3,4-*O*-Carbonyl-2-deoxy-6-*O*-p-nitrobenzoyl-β-*D*-lyxo-hexosyl)-4-methoxy-5-methyl-2(1*H*)-pyrimidinone* (**9a**). — The bromide (**7**) (850 mg, 2.11 mmoles) was divided into three equal portions, and each was added, with mixing, to 850 mg of premelted 2,4-dimethoxy-5-methylpyrimidine[16] (**8a**) in a small flask, which was then evacuated for 4 min at 60°. The vacuum was disconnected, each flask was stoppered and kept for 30 min at 60°, and the resulting solid (from each of the experiments) was transferred to a 125-ml Erlenmeyer flask with the aid of ether. Sufficient ether was added to bring the total volume to 100 ml, the suspension was stirred until complete dissolution of unreacted **8a** was effected, and the remaining solid was filtered off and washed with ether. Two recrystallizations from dichloromethane–ether–pentane gave 575 mg (59%) of chromatographically pure (t.l.c., solvent *E*) **9a**, m.p. 213–216°, $[\alpha]_D^{23}$ +101.4° (*c* 1.38, dichloromethane). An additional recrystallization from dichloromethane–ether afforded an analytical sample, m.p. 215–218°.

Anal. Calc. for $C_{20}H_{19}N_3O_{10}$: C, 52.06; H, 4.15; N, 9.11. Found: C, 52.00; H, 4.01; N, 8.91.

*1-(3,4-*O*-Carbonyl-2-deoxy-6-*O*-p-nitrobenzoyl-β-*D*-lyxo-hexosyl)thymine* (**11a**). — To a solution of 500 mg (1.08 mmoles) of the pyrimidinone **9a** in 12 ml of dry dichloromethane was added 5 ml of a 39% (w/w) solution of hydrogen chloride in ethyl alcohol, and the mixture was stirred for 6 h at room temperature. The product (250 mg) that separated (fraction *A*)* was collected by filtration, and the filtrate was evaporated to dryness at 40° under diminished pressure. The resulting residue was dissolved in 10 ml of 1:9 methanol–dichloromethane, and sufficient ether was added

*This fraction is sufficiently pure (m.p. 255–260°) for conversion into the unsubstituted nucleoside **12a**.

to precipitate virtually all of the product (140 mg) in the solution; this was combined with fraction *A*, and dissolved (with heating) in 75 ml of 1:4 methanol–dichloromethane. The volume of the solution was diminished to about one-third by boiling, yielding 338 mg (70%) of **11a**, m.p. 260–265°, $[\alpha]_D^{23}$ +86.2° (*c* 0.21, 1:4 methanol–dichloromethane).

Anal. Calc. for $C_{19}H_{17}N_3O_{10}$: C, 51.01; H, 3.83; N, 9.39. Found: C, 51.65; H, 3.67; N. 9.20.

*1-(2-Deoxy-β-*D*-lyxo-hexopyranosyl)thymine* (**12a**). — A suspension of 336 mg (750 μmoles) of compound **11a** in 40 ml of 30 mM methanolic sodium methoxide was stirred for 4 h at room temperature. To the resulting solution was added 2 g of Dowex-50W X8 (H^+) ion-exchange resin (100–200 mesh), the suspension was stirred for 10 min and filtered, and the filtrate was evaporated to dryness at 45° under diminished pressure. The residue was rinsed into a separatory funnel with 15 ml of water, and the solution was extracted with 4 × 15 ml of ether, treated with a little Darco G-60 decolorizing carbon, and the suspension filtered. The filtrate was evaporated to dryness at 50° under diminished pressure, leaving a crystalline residue which was dissolved in 1 ml of water; 10 ml of absolute ethyl alcohol and sufficient ether to produce turbidity were then added. The solution was kept overnight in a refrigerator, and the crystals that formed were collected by filtration, to give 173 mg (82%) of pure **12a**, m.p. 252–254°, $[\alpha]_D^{23}$ +38.7° (*c* 0.95, water).

Anal. Calc. for $C_{11}H_{16}N_2O_6$: C, 48.53; H, 5.92; N, 10.29. Found: C, 48.34; H, 5.97; N, 10.12.

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