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BRANCHED-CHAIN *N*-SUGAR NUCLEOSIDES

PART IV. NUCLEOSIDES OF 3-*C*-BRANCHED-CHAIN, 3-*C*-(CYANOMETHYL)- AND 3-*C*-(2-AMINOETHYL)-2,3-DIDEOXY-D-*threo*-PENTOSE

ALEX ROSENTHAL AND COLIN M. RICHARDS
Department of Chemistry, The University of British Columbia,
Vancouver 8, British Columbia (Canada)
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ABSTRACT

2-Deoxy-D-*erythro*-pentose (**1**) was treated with 0.05% methanolic hydrogen chloride, followed by chlorotriphenylmethane in pyridine, to afford methyl 2-deoxy-5-*O*-trityl-α(and *β*)-D-*erythro*-pentofuranoside (**3** and **4**). Oxidation with ruthenium tetraoxide and reaction of the product with diethylphosphonate cyanomethylid, followed by hydrogenation, afforded methyl 3-*C*-(cyanomethyl)-2,3-dideoxy-5-*O*-trityl-α-D-*erythro*(and *threo*)-pentofuranoside (**9** and **10**) and methyl 3-*C*-(cyanomethyl) 2,3-dideoxy-5-*O*-trityl-*β*-D-*threo*-pentofuranoside (**11**). Compounds **10** and **11** were converted into the same *p*-bromobenzoyl derivative, which was directly fused with 2,6-dichloropurine to yield 9-[4-*O*-(*p*-bromobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-*β* (and α)-D-*threo*-pentopyranosyl]-2,6-dichloropurine (**14** and **15**) and 1,5-anhydro-4-*O*-(*p*-bromobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-D-*threo*-pent-1-enitol (**16**). Both **14** and **15** were treated with 25% aqueous dimethylamine solution, to give 2-chloro-9-[3-*C*-(cyanomethyl)-2,3-dideoxy-*β*(and α)-D-*threo*-pentopyranosyl]-6-(*N*,*N*-dimethylamino)purine. Compound **14** was reduced over platinum oxide in acetic anhydride and ethanol to give 9-[3-(2-acetamidoethyl)-2,3-dideoxy-*β*-D-*threo*-pentopyranosyl]-2-chloro-6-(*N*,*N*-dimethylamino)purine (**19**).

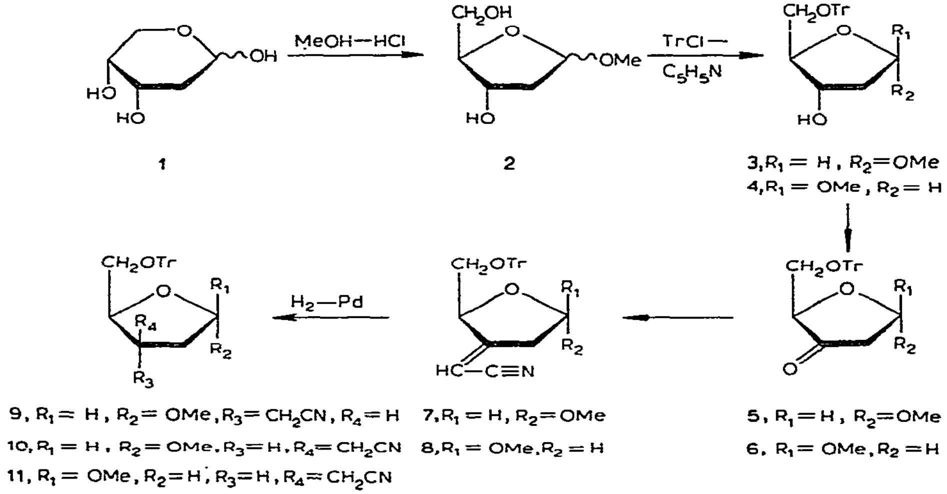
DISCUSSION

In a previous report[1] from this laboratory, the synthesis of *β*-nucleosides of 3-*C*-(cyanomethyl)-, 3-*C*-(*N*,*N*-dimethylcarbamoylmethyl)-, and 3-*C*-(2-aminoethyl)-2,3-dideoxy-D-*ribo*-hexopyranoses was described. The present paper deals with an extension of this research to the synthesis of branched-chain, *N*-sugar *β*- and α-nucleosides of 2,3-dideoxy-D-*threo*-pentopyranoses. The starting material for this synthesis was the readily available 2-deoxy-D-*erythro*-pentose. The rationale for the interest in branched-chain sugar nucleosides has already been presented[1–4].

2-Deoxy-D-*erythro*-pentose (**1**) was treated with 0.05% methanolic hydrogen chloride solution under anhydrous conditions, to afford an anomeric mixture of the methyl 2-deoxy-D-*erythro*-pentofuranosides[5]. Tritylation of the mixture for 5 days at room temperature with trityl chloride in pyridine[6] gave, in 65% overall yield, the α- and β-furanosides **3** and **4**, which could readily be separated by column chromatography on silica gel.

Oxidation of **3** (or **4**) by the "catalytic" ruthenium tetraoxide method[7] resulted in essentially quantitative formation of the crystalline ketose **5** (or **6**), which exhibited a strong infrared (i.r.) band at 1755 cm^{-1}. Application of the modified Wittig reaction[1,8] to methyl 2-deoxy-5-*O*-trityl-α-D-*glycero*-pentofuranosid-3-ulose (**5**) [using the carbanion formed from diethyl (cyanomethyl)phosphonate and sodium hydride in 1,2-dimethoxyethane] afforded crystalline (*Z*)- and (*E*)-methyl 3-*C*-(cyanomethylene)-2,3-dideoxy-5-*O*-trityl-α-D-*glycero*-pentofuranoside (**7**) in 94% yield. The alkenic proton of **7** was observed, in its n.m.r. spectrum, as a multiplet at τ 4.78 superimposed upon the anomeric proton. The i.r. spectrum revealed the presence of the nitrile group, absorbing at 2250 cm^{-1}. Similarly, treatment of **6** under the same conditions gave the β anomer **8** in 94% yield.

Palladium-catalyzed hydrogenation of the α-glycoside **7** in ethanol yielded two new, epimeric, branched-chain glycosides (**9** and **10**), R_F 0.29 (major) and R_F 0.25 (minor) (silica gel; with 4:1 petroleum ether–ethyl ether), which were separated by column chromatography with t.l.c.-grade silica gel (silica gel H) under a pressure of 8 lb.in^{-2} and a ratio of 300:1 of silica gel to compound, or by extensive, preparative t.l.c.



The minor component **10** was assigned the structure methyl 3-*C*-(cyanomethyl)-2,3-dideoxy-5-*O*-trityl-α-D-*threo*-pentofuranoside, partly on the basis of its n.m.r. spectrum, as irradiation of H-5 (τ 6.83) collapsed the H-4 doublet of triplets (τ 5.70) to a doublet, thus revealing $J_{3,4}$ as 6.5 Hz. Furthermore, **10** was transformed by 1% methanolic hydrogen chloride into its pyranosides, namely, methyl 3-*C*-(cyanomethyl)-2,3-dideoxy-α,β-D-*threo*-pentopyranoside (**12**) (α:β = 10:3). Product **12** was converted into the *p*-chloro- and *p*-bromo-benzoates **13a** and **13b**; their n.m.r. spectra clearly showed the H-4 signals, and thus permitted an analysis of values of coupling with H-3 ($J_{3,4}$ 1.05 Hz) and with H-5 (10.5 Hz and 5.5 Hz). These large couplings established the *trans*-diaxial nature of H-3,H-4. Similar information was obtained on analysis of the multiplet assigned to the two C-2 protons.

As compound **10** has the *threo* configuration, it follows that the other hydrogenation product of the unsaturated glycoside **7**, namely **9**, must be of the *erythro* configuration. This conclusion was substantiated by irradiation of H-5 (τ 6.76), which changed the H-4 multiplet (τ 6.09) to a doublet giving $J_{3,4}$ 3.0 Hz.

Hydrogenation of the unsaturated β-glycosides **8** [(*Z*)- and (*E*)-methyl 3-*C*-(cyanomethylene)-2,3-dideoxy-5-*O*-trityl-α-D-*glycero*-pentofuranoside] resulted in only one compound which, it is suggested, is methyl 3-*C*-(cyanomethyl)-2,3-dideoxy-5-*O*-trityl-β-D-*threo*-pentofuranoside (**11**). This assignment was based on the conversion of **11** into the pyranoside **12** and its benzoates (**13a** and **13b**), identical in all respects to those derived from **10**.

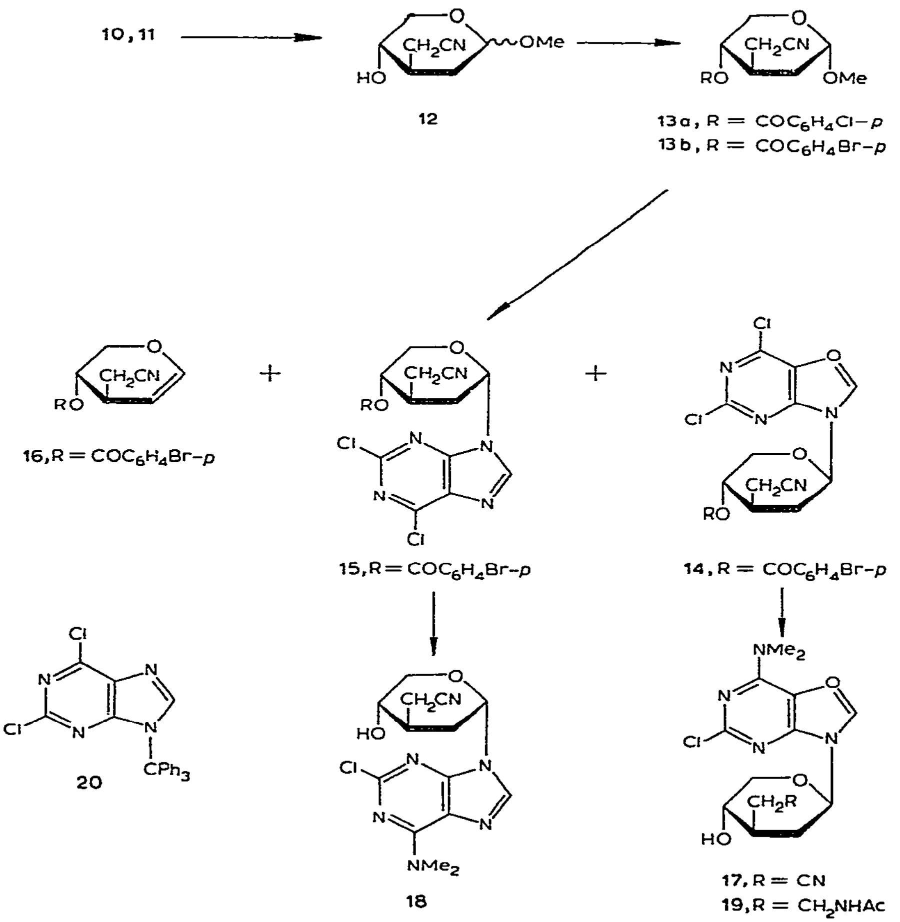
The facts that, on hydrogenation, the α-unsaturated sugar **7** gave compounds having both *threo* and *erythro* configurations, whereas the β anomer **8** was stereospecifically reduced to **11**, are probably attributable to the combined steric influence of the triphenylmethyl ether group on O-5 and the methoxyl group on C-1. In compound **8**, both groups totally hinder hydrogenation from "above" the ring, and hence, it proceeds stereospecifically from "below", whereas, the triphenylmethyl group in **7** hinders hydrogenation from "above" and the methoxyl group hinders hydrogenation from "below" the ring, resulting in occurrence of both processes, affording both **9** and **10**. It appears that orientation of the methoxyl group greatly influences the direction of attack on the double bond, as the *erythro* product preponderated. This type of steric influence has been observed[9] in osmylation of 2,3-double bonds in unsaturated α- and β-glycosides.

A number of unsuccessful attempts to achieve selective hydrolysis of the 5-trityl ether group and to retain the glycosidic substituents were made; these included acid hydrolysis with 33–80% acetic acid[10], hydrogenolysis[11] in the presence of palladium-on-charcoal and palladium-on-calcium carbonate at pressures of 14–60 lb.in.$^{-2}$ and temperatures up to 55°, and reductive cleavage with lithium in liquid ammonia[12]. Treatments with trifluoroacetic acid in chloroform or in boron trifluoride were unsuccessful. The fact that, under most of the foregoing conditions, both the trityl and the methyl glycoside were either not hydrolyzed or simultaneously hydrolyzed, as in all hydrogenations and in 33–50% acetic acid, showed a surprising similarity in acid labilities of the 5-*O*-trityl group and the aglycon. Treatment of **9**, **10**, or **11** with lithium in liquid ammonia selectively removed the trityl group, but, as evidenced by t.l.c., afforded a number of products, due in part to reduction of the nitrile[13].

Direct fusion of the protected α-glycoside **13b** with 2,6-dichloropurine at 155°/30 torr afforded a mixture containing the α- and β-nucleosides (**15** and **14**) and, in addition, a novel, branched-chain, unsaturated hexitol **16**, in 13, 29, and 19% yields, respectively.

Treatment of 9-[4-*O*-*p*-bromobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-β-D-*threo*-pentopyranosyl]-2,6-dichloropurine (**14**) with 25% aqueous dimethylamine in methanol for 6 h afforded, after evaporation and chromatography, 2-chloro-9-[3-*C*-(cyanomethyl)-2,3-dideoxy-β-D-*threo*-pentopyranosyl]-6-(*N*,*N*-dimethylamino)purine (**17**) in 76% yield. Assignment of the β anomeric configuration was based on n.m.r. data, which revealed $J_{1,2a}$ 10.0 Hz and $J_{1,2e}$ 2.5 Hz. In addition, the c.d. spectrum of **17** in ethanol exhibited a negative Cotton-effect[14,15] at 273 nm. Evidence that the cyanomethyl group had not been hydrolyzed to an *N*,*N*-dimethylcarbamoylmethyl group, as has been observed[8], was afforded by the n.m.r. spectrum of **17**, which showed the presence of only one dimethylamino group. Also, the mass spectrum and elemental analyses were consistent with the structure suggested for **17**.

Hydrogenation of the *threo*-cyanomethyl nucleoside **17** in ethanol and acetic anhydride, with platinum oxide as the catalyst at 60 lb.in.$^{-2}$ for 4 h afforded two components, as evidenced by t.l.c. The n.m.r. spectrum of the crude, hydrogenated material indicated that, in addition to forming the acetamido-nucleoside **19**, some



acetylation of the secondary hydroxyl group had occurred. Treatment of this crude, hydrogenated nucleoside with a 25% aqueous solution of dimethylamine for 3 h at room temperature afforded only one nucleoside component; this was isolated by preparative t.l.c. 9-[3-(2-Acetamidoethyl)-2,3-dideoxy-β-D-*threo*-pentopyranosyl]-2-chloro-6-(*N*,*N*-dimethylamino)purine (**19**) exhibited a doublet of doublets at τ 4.26 assigned to the anomeric hydrogen atom ($J_{1',2'a}$ 10 Hz, $J_{1',2'e}$ 3 Hz), a singlet at τ 6.50 integrating for six protons (NMe_2), and a three-proton singlet at τ 8.00 (NAc).

2-Chloro-9-[3-*C*-(cyanomethyl)-2,3-dideoxy-α-D-*threo*-pentopyranosyl]-6-(*N*,*N*-dimethylamino)purine (**18**) was obtained by treatment of the protected nucleoside **15** with 25% aqueous dimethylamine in methanol for 3 h at room temperature, and was purified by preparative t.l.c. Compound **18** exhibited a triplet at τ 4.06 ($J_{1',2'a}$ 4 Hz, $J_{1',2'e}$ 4 Hz) assigned to the anomeric proton, and exhibited in its c.d. spectrum a positive Cotton-effect[14,15] at 272 nm.

Attempted direct fusion of the tritylated β-glycoside **11** with 2,6-dichloropurine at 160° was unsuccessful, and yielded, as the main component, compound **20**, in which the triphenylmethyl group is linked directly to the purine residue.

EXPERIMENTAL

General. — The apparatus and general procedures are described in the preceding paper[1].

*Methyl 2-deoxy-α,β-*D-erythro-*pentofuranoside*[5] (**2**). — To 2-deoxy-D-*erythro*-pentose (**1**, 5.0 g) was added 0.05% methanolic hydrogen chloride solution (175 ml), and the mixture was stirred for 15 min at room temperature. Silver carbonate (10 g) was then added, and the suspension was vigorously stirred for 20 min, passed through charcoal, and the solvent removed under diminished pressure at 40°, to yield **2** as a colorless, mobile syrup; yield 4.96 g (90%).

*Methyl 2-deoxy-5-*O*-trityl-α-*D-erythro-*pentofuranoside* (**3**) *and methyl 2-deoxy-5-*O*-trityl-β-*D-erythro-*pentofuranoside*[6] (**4**). — Chlorotriphenylmethane (19.0 g) in pyridine (200 ml) was added to **2** (9.6 g), and the mixture was stirred for 5 days at room temperature. The solution was then slowly poured into ice–water (1 liter) with stirring, and the resultant gum was washed several times with cold water. Drying was accomplished by azeotroping with ethanol, to afford crude **3** plus **4** (28.5 g). Chromatography on a column (7 × 60 cm) of Silica Gel G (1.3 kg) with 9:1 benzene–ethyl acetate afforded **3** (6.7 g), **4** (6.5 g), and a mixture of **3** and **4** (3.1 g); overall yield 65%.

*Methyl 2-deoxy-5-*O*-trityl-α-*D-glycero-*pentofuranosid-3-ulose* (**5**). — To a mixture of a solution of **3** (2.0 g) in carbon tetrachloride (40 ml), water (6 ml) containing sodium hydrogen carbonate (0.4 g), and ruthenium dioxide (40 mg) was slowly added, with vigorous stirring, a 5% solution of sodium metaperiodate until the characteristic, yellow-green coloration of ruthenium tetraoxide was observed; no more periodate was added until the solution had fully reverted to the (black) ruthenium dioxide stage. This process was repeated until all of the starting material had been used up (16 h), as evidenced by t.l.c. on silica gel with 19:1 benzene–methanol. Unreacted oxidant was decomposed by the addition of 3–4 drops of isopropyl alcohol, the mixture was filtered, and the aqueous layer was extracted with chloroform (4 × 200 ml). The extracts were combined, successively washed with 5% sodium thiosulfate solution (25 ml) and water (25 ml), dried (sodium sulfate), and evaporated, to afford crystalline **5** (1.96 g, 98%). An analytical sample was obtained by recrystallization from ethanol; m.p. 122.2–122.7°; $[\alpha]_D^{24}$ +182.4° (*c* 1.2, chloroform); ν_{max}^{Nujol} 1755 cm^{-1} (C=O); n.m.r. data (in $CDCl_3$): τ 4.52 (d.d, 1, $J_{1,2'}$ 5.2 Hz, $J_{1,2''}$ 1.0 Hz, H-1), 5.94 (t, 1, $J_{4,5'}$ 2.6 Hz, $J_{4,5''}$ 3.4 Hz, H-4), 6.53 (s, 3, OCH_3), 6.58 [ABM multiplet, 2, Δ_{AB} 12 Hz, J_{AB} (observed) 10 Hz, H-5], and 7.37 [mult., 2, Δ_{AB} 34 Hz, J_{AB} (observed) 18 Hz, H-2].

Anal. Calc. for $C_{25}H_{24}O_4$: C, 77.30; H, 6.18. Found: C, 77.33; H, 6.06.

*Methyl 2-deoxy-5-O-trityl-β-*D-glycero-*pentofuranosid-3-ulose* (**6**). — To a mixture of a solution of **4** (2.0 g) in carbon tetrachloride (40 ml), water (6 ml), sodium hydrogen carbonate (0.4 g), and ruthenium dioxide (40 mg) was added a 5% solution of sodium metaperiodate with vigorous stirring, as just described. After 17 h, the reaction was complete. After filtration of the suspension, the aqueous layer was extracted with chloroform (4 × 200 ml); the extracts were combined, successively washed with 5% sodium thiosulfate solution (25 ml) and water (25 ml), dried (sodium sulfate), and evaporated, to afford **6** (1.90 g, 96%) as a mobile syrup that moved as a single spot in t.l.c. An analytical sample was prepared by distillation at 125°/0.1 torr; $[\alpha]_D^{27}$ −26° (*c* 0.5, chloroform); ν_{max}^{film} 1760 cm^{-1} (C=O); n.m.r. data (in $CDCl_3$): τ 4.71 (d.d, 1, $J_{1,2'}$ 5.5 Hz, $J_{1,2''}$ 1.8 Hz, H-1), 5.84 (m, 1, $J_{4,5''}$ 6.5 Hz, $J_{4,5''}$ 32 Hz, $J_{4,2'}$ 1.2 Hz, H-4), 6.72 (s, 3, OCH_3), 6.70 (ABM multiplet, 2, Δ_{AB} 20 Hz, J_{gem} 10 Hz, H-5), and 7.46 (m, 2, H-2).

Anal. Calc. for $C_{25}H_{24}O_4$: C, 77.30; H, 6.18. Found: C, 77.12; H, 6.00.

(Z)- *and* (E)-*Methyl 3-*C*-(cyanomethylene)-2,3-dideoxy-5-*O*-trityl-α-*D-glycero-*pentofuranoside* (**7**). — A solution of **5** (0.96 g) in 1,2-dimethoxyethane (10 ml) was added to a filtered solution of the carbanion from diethyl (cyanomethyl)phosphonate (0.60 g) and sodium hydride (0.08 g) in 1,2-dimethoxyethane (20 ml) under a nitrogen atmosphere, during 1.5 h at 0°, and then stirred for 1 h at room temperature. Water (40 ml) was added, and the aqueous layer was successively extracted with chloroform (2 × 100 ml) and ether (2 × 50 ml); the extracts were combined, dried (sodium sulfate), and evaporated, affording **7** (0.96 g, 94%). Recrystallization of **7** from ethanol yielded an analytical sample; m.p. 165.5–167.0°; $[\alpha]_D^{25}$ +120° (*c* 3.1, chloroform); i.r. (film) 2250 (C≡N), 1660 (C=C, alkenic), and 1600 cm^{-1} (C=C, aromatic); n.m.r. data (in $CDCl_3$): τ 4.78 (m, 2, H-1, H-1′), 5.27 (m, 1, H-4), 6.61 (m, 5, OCH_3, H-5), and 7.07 (m, 2, H-2). Irradiation at τ 5.27 simplified the multiplet at τ 6.66. Irradiation at τ 4.78 produced a doublet at τ 7.07.

Anal. Calc. for $C_{27}H_{25}NO_3$: C, 78.78; H, 6.08; N, 3.40. Found: C, 78.70; H, 5.78; N, 3.70.

(Z)- *and* (E)-*Methyl 3-*C*-(cyanomethylene)-2,3-dideoxy-5-*O*-trityl-β-*D-glycero-*pentofuranoside* (**8**). — A solution of **6** (1.80 g) in 1,2-dimethoxyethane (10 ml) was added under a nitrogen atmosphere to a filtered solution of diethyl (cyanomethyl)-phosphonate (1.2 g) and sodium hydride (0.16 g) in 1,2-dimethoxyethane (30 ml) at 0°. The mixture was stirred for 1 h at room temperature, and the product isolated as described in the previous section, to yield **8** as a syrup (1.78 g, 94%) which was used without further purification.

*Methyl 3-C-(cyanomethyl)-2,3-dideoxy-5-O-trityl-α-*D-erythro-*pentofuranoside* (**9**) *and methyl 3-C-(cyanomethyl)-2,3-dideoxy-5-O-trityl-α-*D-threo-*pentofuranoside* (**10**). — Hydrogenation of **7** (0.95 g) in 9:1 ethanol–benzene, with hydrogen at atmospheric pressure and 10% palladium-on-charcoal (150 mg) as the catalyst, afforded a colorless syrup in quantitative yield; this showed two components, R_F 0.29 (major) and R_F 0.25 (minor), by t.l.c. on silica gel after double development with 4:1 petroleum ether–ethyl ether. Column chromatography of a portion of the material (0.55 g) on t.l.c.-grade silica gel (180 g), packed and eluted with the same solvent system under a pressure of 8 lb.in.$^{-2}$, afforded the two components.

Compound **9** (403 mg, 73%) was purified by distillation at 125°/0.1 torr; $[\alpha]_D^{21}$ +79° (*c* 0.6, dichloromethane); i.r. (film) 2250 cm^{-1} (C≡N); n.m.r. data (in $CDCl_3$): 4.95 (d.d, 1, $J_{1,2'}$ 4.5 Hz, $J_{1,2''}$ 1.0 Hz, H-1), 6.09 (m, 1, $J_{4,5}$ 4.5 Hz, $J_{4,3}$ 3.0 Hz, H-4), 6.67 (s, 3, OCH_3), 6.76 (m, 2, H-5), and 7.4–8.2 (m, 5, H-2, H-3, H-1'). Irradiation at τ 6.76 produced a doublet at τ 6.09.

Anal. Calc. for $C_{27}H_{27}NO_3$: C, 78.45; H, 6.54; N, 3.39. Found: C, 78.81; H, 6.60; N, 3.15.

Compound **10** (55 mg, 10%) was recrystallized from ethanol; m.p. 155–157°; $[\alpha]_D^{25}$ +62° (*c* 2.1, chloroform); i.r. (Nujol) 2250 cm^{-1} (C≡N); n.m.r. data (in $CDCl_3$): τ 4.88 (d.d,. 1, $J_{1,2a}$ 4.5 Hz, $J_{1,2b}$ 2.5 Hz, H-1), 5.70 (doublet of triplets, 1, $J_{4,3}$ 6.5 Hz, $J_{4,5}$ 4.0 Hz, H-4), 6.63 (s, 3, OCH_3), 6.83 (m, 2, H-5), 7.0–7.7 (m, 1, H-3), and 7.4–8.2 (m, 4, H-2, H-3'). Irradiation at τ 6.83 produced a doublet at τ 5.70 (*J* 6.5 Hz).

Anal. Calc. for $C_{27}H_{27}NO_3$: C, 78.45; H, 6.54; N, 3.39. Found: C, 78.15; H, 6.35; N, 3.45.

*Methyl 3-C-(cyanomethyl)-2,3-dideoxy-5-O-trityl-β-*D-threo-*pentofuranoside* (**11**). — Hydrogenation of **8** (1.70 g) in ethanol (60 ml), with 10% palladium-on-carbon (0.20 g) as the catalyst and hydrogen at atmospheric pressure, afforded **11** (1.61 g, 94%) as a clear syrup that crystallized on trituration with ethanol; m.p. 107–108°; $[\alpha]_D^{23}$ −50° (*c* 0.8, chloroform); i.r. (Nujol) 2255 cm^{-1} (C≡N); n.m.r. data (in $CDCl_3$): τ 5.02 (d.d, 1, $J_{1,2'}$ 2.0 Hz, $J_{1,2''}$ 5.0 Hz, H-1), 5.74 (doublet of triplets, 1, $J_{4,3}$ 5.0 Hz, $J_{4,5'}$ 5.0 Hz, $J_{4,5''}$ 7.0 Hz, H-4), 6.71 (s, 3, OCH_3), 6.78 (ABX mult., 1, H-5), and 7.3–8.1 (m, 5, H-2,3,1'). Irradiation at τ 5.74 (X) simplified the AB part (τ 6.78) of the ABX system to give a quartet.

Anal. Calc. for $C_{27}H_{27}NO_3$: C, 78.45; H, 6.56; N, 3.39. Found: C, 78.40; H, 6.56; N, 3.59.

*Methyl 2-C-(cyanomethyl)-2,3-dideoxy-α,β-*D-threo-*pentopyranoside* (**12**). — (*A*) *From* **10**. Compound **10** (123 mg) in 1% methanolic hydrogen chloride solution (6 ml) was stirred overnight at room temperature; then, silver carbonate (1.3 g) was added, and the suspension was stirred for 2 h. Filtration of the mixture and evaporation of the filtrate afforded a quantitative yield of **12** as a mobile syrup. The ratio of α to β was 10:3 (as shown by the n.m.r. spectrum). Compound **12** was purified by preparative t.l.c. on silica gel with 9:1 benzene–methanol; $[\alpha]_D^{22}$ $+45°$ (c 1.2, chloroform); i.r. (film) 2250 cm^{-1} (C≡N); n.m.r. data (in $CDCl_3$): τ 5.20 (d.d, 1, $J_{1,2'}$ 1 Hz, $J_{1,2''}$ 3 Hz, H-1), 5.51 (d.d, $J_{1,2'}$ 7 Hz, $J_{1,2''}$ 2 Hz), 6.2–6.8 (m, 7, OCH_3, H-4, H-5, OH), 7.35–7.45 (m, 2, H-1′), 7.9 (m, 1, H-3), and 7.9–8.5 (part of ABMX multiplet, 2, H-2). Irradiation at τ 5.20 simplified the ABMX system.

Anal. Calc. for $C_8H_{13}NO_3 \cdot 0.5\ CH_3OH$: C, 54.55; H, 8.01; N, 7.48. Found: C, 54.93; H, 7.43; N, 7.54.

(*B*) *From* **11**. Compound **11** (39 mg) in 1% methanolic hydrogen chloride solution (2 ml) was stirred for 7.5 h. Silver carbonate (0.5 g) was then added, and the suspension was stirred for 1 h. Filtration of the suspension and evaporation of the filtrate afforded **12** (15 mg, 93%) after preparative t.l.c. on silica gel with 9:1 benzene–methanol. I.r. and n.m.r. spectroscopy and t.l.c. indicated that this product was identical to that derived from **10**.

*Methyl 4-*O*-(*p*-chlorobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-α-*D-threo*-pentopyranoside* (**13a**). — Compound **12** (11 mg) was converted into its *p*-chlorobenzoate according to the procedure previously described, and the product was purified by preparative t.l.c. on silica gel with 9:1 benzene–ethyl acetate to yield pure **13a** (17 mg, 85%), which was recrystallized from ethanol; m.p. 121.5–122.5°; $[\alpha]_D^{21}$ $-13.4°$ (c 4.0, chloroform); ν_{max}^{KBr} 2250 (C≡N) and 1730 cm^{-1} (C=O); n.m.r. data (in $CDCl_3$): τ 5.07 (doublet of triplets, 1, $J_{4,3}$ 10.5 Hz, $J_{4,5a}$ 10.5 Hz, $J_{4,5e}$ 5.5 Hz, H-4), 5.24 (d.d, 1, $J_{1,2a}$ 3.5 Hz, $J_{1,2e}$ 1.5 Hz, H-1), 6.0–6.5 (m, 2, H-5), 6.62 (s, 3, OCH_3), 7.4 (m, 1, H-3), 7.55 (m, 2, H-1′), 7.87 (8-line mult., J_{gem} 13 Hz, $J_{2e,3}$ 5 Hz, H-2*e*), and 8.28 (6-line mult., $J_{2a,3}$ 12 Hz, H-2*a*). Irradiation at τ 5.07 simplified the multiplet at τ 6.0–6.5 and that at τ 7.4. Irradiation at τ 5.24 simplified the multiplet at τ 7.8–8.4.

Anal. Calc. for $C_{15}H_{16}ClNO_4$: C, 58.15; H, 5.17; N, 4.52. Found: C, 57.86; H, 5.10; N, 4.25.

*Methyl 4-*O*-(*p*-bromobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-α-*D-threo*-pentopyranoside* (**13b**). — Compound **12** (113 mg) was converted into its *p*-bromobenzoate, and the product purified by preparative t.l.c. on four plates (20 × 20 cm) of silica gel with 9:1 benzene–ethyl acetate to afford **13b** (214 mg, 85%), which was recrystallized from methanol; m.p. 149.5–150.0°; $[\alpha]_D^{21}$ $-11°$ (c 1.0, chloroform); ν_{max}^{KBr} 2250 (C≡N) and 1760 cm^{-1} (C=O); n.m.r. data (in $CDCl_3$): τ 5.04 (doublet of triplets, 1, $J_{4,3}$ 10 Hz, $J_{4,5a}$ 10.5 Hz, $J_{4,5e}$ 5.5 Hz, H-4), 5.22 (d.d, 1, $J_{1,2a}$ 3 Hz, $J_{1,2e}$ 1 Hz, H-1), 6.02–6.48 (ABX mult., 2, H-5), 6.61 (s, 3, OCH_3), 7.35 (m, 1, H-3), 7.55 (m, 2, H-1′), and 7.75–8.43 (part of ABMX multiplet, 2, H-2).

Anal. Calc. for $C_{15}H_{16}BrNO_4$: C, 50.89; H, 4.53; N, 3.96. Found: C, 50.91; H, 4.64; N, 3.95.

*9-[4-*O*-(*p*-Bromobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-β-*D-threo*-pentopyranosyl]-2,6-dichloropurine* (**14**), *9-[4-*O*-(*p*-bromobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-α-*D-threo*-pentopyranosyl-2,6-dichloropurine* (**15**), *and 1,5-anhydro-4-*O*-(*p*-bromobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-*D-threo*-pent-1-enitol* (**16**). — Compound **13b**

(98 mg) and 2,6-dichloropurine (113 mg) were intimately mixed and dried overnight under vacuum. The mixture was fused for 1 h at 145°/30 torr and then for 2 h at 145–160°/0.1 torr. The brown glass was dissolved in 3:2 benzene–ethyl acetate (15 ml), the suspension filtered to remove insoluble matter (29 mg), and the filtrate applied to a column (3 × 25 cm) of t.l.c.-grade silica gel (60 g) packed and eluted with 3:2 benzene–ethyl acetate, to afford **16** (17 mg, 19%), **14** (41 mg, 29%), and **15** (19 mg, 13%).

Compound **16** was a syrup that had $[\alpha]_D^{23}$ $-127°$ (*c* 0.8, dichloromethane); i.r. (film) 2300 (C≡N), 1730 (C=O), and 1650 cm^{-1} (C=C); n.m.r. data (in $CDCl_3$): τ 3.50 (d.d, 1, $J_{1,2}$ 6.5 Hz, $J_{1,3}$ 2.0 Hz, H-1), 4.95 (doublet of triplets, 1, $J_{4,3}$ 6 Hz, $J_{4,5a}$ 6.5 Hz, $J_{4,5e}$ 3.2 Hz, H-4), 5.30 (d.d, 1, $J_{2,3}$ 3.0 Hz, H-2), 5.98 (ABX multiplet, 2, H-5), 7.30 (m, 1, H-3), and 7.56 (m, 2, H-1'). Irradiation at τ 3.50 produced a doublet at τ 5.30, and simplified the multiplet at τ 7.30. Irradiation at τ 4.95 simplified the multiplets at τ 5.98 and 7.30.

Anal. Calc. for $C_{14}H_{12}BrNO_3$: C, 52.19; H, 3.76; N, 4.35. Found: C, 52.48; H, 3.72; N, 4.29.

Compound **14** was recrystallized from ethanol; m.p. 222.5–223.5°; $[\alpha]_D^{24}$ $-15°$ (*c* 5, chloroform); n.m.r. data (in $CDCl_3$): τ 1.66 (s, 1, H-8), 2.0–2.6 (d.d, 4, aromatic protons), 4.05 (d.d, 1, $J_{1,2a}$ 10 Hz, $J_{1,2e}$ 2 Hz, H-1), 4.90 (m, 1, H-4), 5.51 (d.d, 1, $J_{5e,4}$ 5 Hz, $J_{5e,5a}$ 12 Hz, H-5'*e*), 6.34 (d.d, 1, $J_{5a,4}$ 10 Hz, H-5*a*), 7.3 (m, 5, H-3', H-2', H-1'').

Anal. Calc. for $C_{19}H_{14}BrCl_2N_5O_3$: C, 44.64; H, 2.76; N, 13.70. Found: C, 44.74; H, 2.69; N, 13.64.

Compound **15** was recrystallized from 1:1 ethyl acetate–ethanol; m.p. 250.5–252°; $[\alpha]_D^{24}$ $-38°$ (*c* 0.06, dichloromethane); n.m.r. data (in $CDCl_3$): τ 1.65 (s, 1, H-6), 1.9–2.7 (d.d, 4, aromatic protons), and 3.92 (t, 1, $J_{1,2a}$ 4 Hz, $J_{1,2e}$ 4 Hz, H-1'). A satisfactory analysis of this compound could not be obtained.

Anal. Calc. for $C_{19}H_{14}BrCl_2N_5O_3$: C, 44.64; H, 2.76; N, 13.70. Found: C, 43.20; H, 2.31; N, 18.47.

*2-Chloro-9-[3-*C*-(cyanomethyl-2,3-dideoxy-β-*D-threo-*pentopyranosyl]-6-*(N,N-*dimethylamino)purine* (**17**). — A suspension of nucleoside **14** (47 mg) in methanol (13 ml) and 25% aqueous dimethylamine (13 ml) was stirred for 6 h at room temperature and then for 12 h at 5°. After evaporation of the mixture, the residue was dissolved in 3:2 benzene–ethyl acetate, and chromatographed on a column (2 × 25 cm) of t.l.c.-grade silica gel (30 g), packed with 3:2 benzene–ethyl acetate and eluted therewith under a pressure of 5 lb.in.$^{-2}$, to afford **17** (25 mg, 76%) as an amorphous material. An analytical sample was obtained by recrystallization from ethanol–pentane; m.p. 188.5–189.5°; $[\alpha]_D$ $+30.7°$ (*c* 0.6, chloroform); i.r. datum: 2260 cm^{-1} (C≡N); λ_{max}^{EtOH} 217 nm (ε_{mM} 8.05), 275 nm (ε_{mM} 7.50); c.d. (*c* 0.005, in ethanol) $[\theta]_{273}$ $-3{,}000$ (trough); n.m.r. data (in $CDCl_3$): τ 2.12 (s, 1, H-6), 4.17 (d.d, 1, $J_{1,2e}$ 2.5 Hz, $J_{1,2a}$ 10.0 Hz, H-1'), 5.80 (d.d, 1, $J_{5e,4}$ 4 Hz, $J_{5e,5a}$ 11 Hz, H-5'*e*), 6.1–6.7 [m, 8, $N(CH_3)_2$, H-4', H-5'*a*], and 7.3–8.1 (m, 5, H-2', H-1'', H-3'). Irradiation at τ 7.98 produced a singlet at τ 4.17.

Anal. Calc. for $C_{14}H_{17}ClN_6O_2$: C, 49.95; H, 5.09; N, 24.96. Found: C, 49.98; H, 5.19; N, 24.67.

*2-Chloro-9-[3-C-(cyanomethyl)-2,3-dideoxy-α-*D-threo-*pentopyranosyl]-6-*(N,N-*dimethylamino)purine* (**18**). — A mixture of crude **15** (6 mg) with a 25% aqueous solution of dimethylamine (1 ml) and methanol (1 ml) was stirred for 3 h at room temperature. The solution was evaporated to dryness, and the unprotected nucleoside purified by preparative t.l.c. on plates (10×20 cm) of silica gel multideveloped with 9:1 benzene–methanol to afford **18** (2.9 mg), which was recrystallized from methanol; m.p. 213.0–214.5°; $[\alpha]_D^{23}$ $+29.4°$ (c 0.3, chloroform); λ_{max}^{EtOH} 217 (ε_{mM} 7.94), 274 (ε_{mM} 7.33); c.d. (c 0.005, ethanol) $[\theta]_{272}$ $+2{,}100$; n.m.r. data (in $CDCl_3$): τ 3.08 (s, 1, H-8), 4.06 (t, 1, $J_{1,2}$ 4 Hz, H-1′), and 6.50 [s, $N(CH_3)_2$].

Anal. Molecular weight by mass measurement, $C_{14}H_{17}{}^{35}ClN_6O_2$ requires: 336.109937. Found: 336.109937. $C_{14}H_{17}{}^{37}ClN_6O_2$ requires: 338.107241. Found: 338.107241.

*9-[3-C-(2-Acetamidoethyl)-2,3-dideoxy-β-*D-threo-*pentopyranosyl]-2-chloro-6-*(N,N-*dimethylamino)purine* (**19**). — A solution of compound **17** (7.0 mg) in ethanol (10 ml) and acetic anhydride (1 ml) was hydrogenated over platinum oxide (15 mg) at 60 lb.in.$^{-2}$ for 4 h. Filtration of the suspension and evaporation of the filtrate afforded a crude syrup (10 mg) that showed (by t.l.c.) the presence of two components, R_F 0.20 and 0.15 in 9:1 chloroform–ethanol. Treatment of the crude material with 25% aqueous dimethylamine (0.5 ml) in methanol (0.5 ml) for 3 h at room temperature converted one of the components (R_F 0.15) into the other (R_F 0.20). The mixture was evaporated to dryness, and purified by preparative t.l.c. on a plate (10×20 cm) of silica gel with 9:1 chloroform–ethanol, to afford **19** (6.3 mg, 79%) as a syrup; $[\alpha]_D^{22}$ $-62°$ (c 0.6, chloroform); λ_{max}^{EtOH} 217 nm (ε_{mM} 9.10), 276 (ε_{mM} 8.60); c.d. (c 0.003, ethanol) $[\theta]_{276}$ $-4{,}450$; n.m.r. data (in $CDCl_3$): τ 2.13 (s, 1, H-8), 4.05 (m, 1, N-H), 4.26 (d.d, 1, $J_{1',2'a}$ 10 Hz, $J_{1',2'e}$ 3 Hz, H-1′), 6.50 [s, 6, NMe_2], and 8.00 (s, 3, NAc). Molecular ions required for $C_{16}H_{23}ClN_6O_3$: 382 and 384. Found by mass spectrometry: 382 and 384.

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