Carbohydrate Research, 32 (1974) 53–65

BRANCHED-CHAIN *N*-SUGAR NUCLEOSIDES

PART III. α- AND β-NUCLEOSIDES OF BRANCHED-CHAIN 3-*C*-(CYANOMETHYL)-, 3-*C*-(2-AMINOETHYL)-, AND 3-*C*-(*N*,*N*-DIMETHYLCARBAMOYLMETHYL)-2,3-DIDEOXY-D-*ribo*-HEXOPYRANOSES

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(Received June 28th, 1973; accepted August 27th, 1973)

ABSTRACT

Condensation of diethyl (cyanomethyl)phosphonate with methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**1**) by a Wittig reaction afforded, after chromatographic separation, (*E*)- and (*Z*)-methyl 4,6-*O*-benzylidene-3-*C*-(cyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**2** and **3**) in 69 and 7% yields, respectively. Stereospecific, catalytic reduction of **2** or **3** yielded methyl 4,6-*O*-benzylidene-3-*C*-(cyanomethyl)-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**4**). Compound **2** was selectively debenzylidenated with Dowex 50W X-8 to produce **5**. Under the same conditions, saturated compound **4** underwent debenzylidenation and anomerization to afford the α,β-mixture **7**. The latter product was (*p*-chlorobenzoyl)-ated, and the mixture then separated to yield pure α anomer **8** and impure compound **9**. Fusion of the α anomer **8** with 2,6-dichloropurine afforded, after chromatography, 2,6-dichloro-9-[4,6-di-*O*-(*p*-chlorobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-α-D-*ribo*-hexopyranosyl]purine (**11**) and the β anomer **12** in 37 and 24% yields, respectively. Treatment of the α anomer **11** with aqueous methanolic dimethylamine yielded 2-chloro-9-[2,3-dideoxy-3-*C*-(*N*,*N*-dimethylaminocarbamoylmethyl)-α-D-*ribo*-hexopyranosyl]-6-(*N*,*N*-dimethylamino)purine (**14**) in 54% yield. Similar treatment of the β anomer **12** gave the corresponding, unprotected nucleoside **16**, which still possessed the cyanomethyl group. The unprotected, branched-chain cyano-nucleoside **15** was converted into the corresponding amino sugar nucleoside, namely, 9-[3-*C*-(2-acetamidoethyl)-2,3-dideoxy-α-D-*ribo*-hexopyranosyl]-2,6-di-(*N*,*N*-dimethylamino)purine (**17**).

DISCUSSION

In previous reports from this laboratory[1,2], we have described the synthesis of β-nucleosides of branched-chain, cyanomethyl, aminoethyl, and *N*,*N*-dimethylcarbamoylmethyl derivatives of sugars having the *allo* and *ribo* configurations. These compounds were synthesized in connection with a research program on a study of analogs of the nucleoside antibiotic puromycin[3]. The rationale for this synthesis has been presented previously[1]. In view of the great importance of the 2-deoxy sugars

and their nucleoside derivatives, it seemed important to extend our investigations to the synthesis of *N*-nucleosides having branched-chain 2-deoxyglycosyl groups. This, and the following paper[4], deal with the synthesis of both β- and α-nucleosides of 3-*C*-(branched-chain)-2-deoxy-hexoses and -pentoses.

Condensation of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose[5] (**1**) with the carbanion formed from diethyl (cyanomethyl)phosphonate and sodium hydride in 1,2-dimethoxyethane according to a previously described procedure[1] afforded, after chromatographic separation, two branched-chain, unsaturated glycosides (**2** and **3**) in 69 and 7% yields, respectively. Both glycosides showed the presence of an α,β-unsaturated nitrile function by their infrared (i.r.) spectrum, and were assumed to be the expected *E* and *Z* isomers about the double bond. The stereochemical assignment of structure to compounds **2** and **3** was based primarily upon their nuclear magnetic resonance (n.m.r.) spectra. As the nitrile group is known to have a deshielding effect upon the proton with which it is in cisoid relationship[6], compound **2** must be (*E*)-methyl 4,6-*O*-benzylidene-3-*C*-(cyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside, and compound **3** must be the (*Z*)-isomer (H-2*e* signals occur at τ 6.93 and 7.40, respectively). This conclusion is corroborated by the effect of the nitrile group on H-4 (signals occur at τ 5.91 and 5.72, respectively). The protons on C-2 were assigned to be axial or equatorial[7] based on the fact that H-2*e*–H-1*e* possessed a smaller coupling constant (0.5 Hz) than H-2*a*–H-1*e* of **2** (4.0 Hz). This assignment was confirmed by irradiation at τ 5.13 (H-1), whereby the signal at τ 6.93 was changed into a doublet.

Hydrogenation of the α,β-unsaturated nitrile **2** or **3** in the presence of 5% palladium-on-charcoal at atmospheric pressure afforded a single, crystalline, cyano sugar (**4**). Although benzylidene protecting-groups have been known to be hydrogenolyzed[5] under catalytic conditions, no indication of their removal was observed in the present study. I.r. spectroscopy and thin-layer chromatography (t.l.c.) revealed that the nitrile group was not reduced under these conditions, and n.m.r. spectroscopy indicated the presence of a new methylene group, observed as an ABM multiplet centered at τ 7.12.

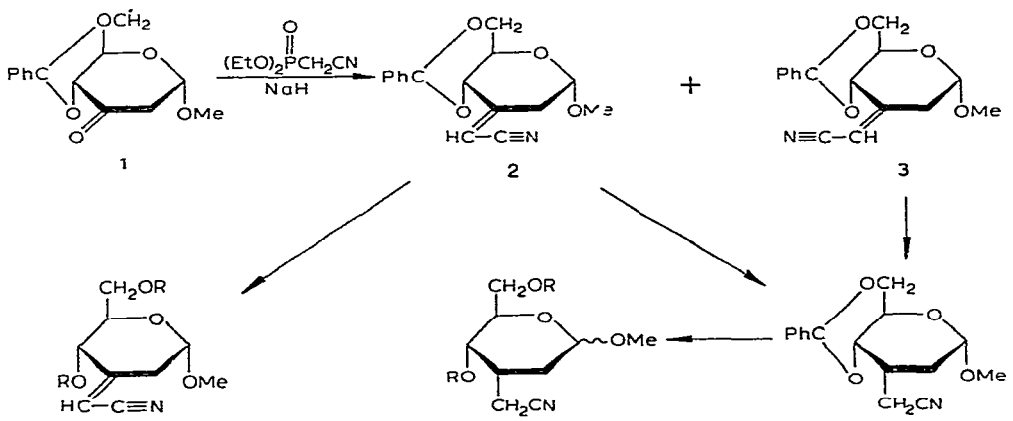
The configuration of C-3 of the cyanomethyl, branched-chain sugar **4** was assigned from its n.m.r. spectrum. Based on the fact that coupling constants between H-3 and H-2*e*, and between H-3 and H-2*a*, were observed to be 2 and 4 Hz, respectively, it was concluded that H-3 must be in the equatorial orientation, and hence, compound **4** must be methyl 4,6-*O*-benzylidene-3-*C*-(cyanomethyl)-2,3-dideoxy-α-D-*ribo*-hexopyranoside. This result is in accord with the accepted mechanism of hydrogenation, in which the catalyst approaches the alkenic double bond from the less-hindered side of the molecule.

When treated with Dowex 50W X-8 (H^+) in anhydrous methanol, the α,β-unsaturated nitrile **2** readily underwent loss of the 4,6-*O*-benzylidene group within 2.25 h at reflux temperature, to afford a single, crystalline product (**5**). N.m.r. spectroscopy revealed that anomerization had not occurred (as the coupling constants between the anomeric proton and H-2*a* and H-2*e* were 4 and 2 Hz, respectively),

and that the unsaturated nitrile was still present (shown by i.r. maxima at 2260 and 1645 cm^{-1}). In addition, the i.r. spectrum revealed the presence of hydroxyl groups (a band at 3400 cm^{-1}). Thus, based on this evidence, coupled with the results of elemental analysis, it was concluded that the benzylidene group of **2** could readily be removed without anomerization of the glycoside or alteration of the unsaturated, nitrile group. This stability of the unsaturated glycoside **2** is in marked contrast to the instability of the saturated glycoside **4**, which underwent anomerization under the same conditions.

The unsaturated glycoside **5** was characterized as its *p*-chlorobenzoate (**6**) which, again, exhibited data consistent with the presence of an α,β-unsaturated, nitrile group. In addition, the protons on C-4 and C-6 were now observed at considerably lower field, due to the deshielding effect of the *p*-chlorobenzoyl groups.

Various methods have allegedly proved successful in removal of benzylidene groups. Although hydrogenation over palladium-on-carbon has been used successfully in the debenzylidenation of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-(methoxycarbonylmethyl)-α-D-*ribo*-hexopyranoside[5] and methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-(nitromethyl)-α-D-*ribo*-hexopyranoside[8], the same procedure was not successful when applied to the unsaturated, cyanomethyl sugar **4**. As cyanomethyl groups may readily be reduced when compounds containing them are hydrogenated at elevated pressures in the presence of platinum oxide[1,2], the reaction had to be conducted at atmospheric pressure. Although it was desired to convert the cyanomethyl group ultimately into a 2-aminoethyl group, the latter reduction had to be avoided, as it has been observed[9] that *N*-acetyl groups may participate therein, to form nitrogen heterocycles in nucleoside synthesis. Therefore, in the light of the favorable results afforded by the acid hydrolysis of the α,β-unsaturated nitrile **2** with Dowex 50W X-8 (H^+) resin, methyl 4,6-*O*-benzylidene-3-*C*-(cyanomethyl)-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**4**) was treated with this Dowex resin in anhydrous methanol. When the

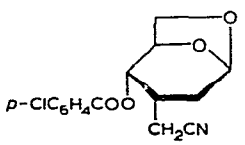


reaction mixture was stirred at room temperature, two products were formed (as shown by n.m.r. spectroscopy) having similar R_F values in t.l.c.; these compounds presumably result from anomerization during the debenzylidenation. These two compounds were separable as their *p*-chlorobenzoyl derivatives. N.m.r. spectrometry revealed a narrow triplet for the anomeric proton of the supposed α anomer **8**, and a doublet of doublets for the β anomer **9**. In addition, a small proportion of the 1,5-anhydro compound **10** was isolated on (*p*-chlorobenzoyl)ation.

When the cyanomethyl sugar **4** was refluxed with Dowex resin for a short time, a complex mixture of products resulted, as evidenced by t.l.c.; compound **7** constituted only a small proportion of the mixture.

A possible explanation of the higher rate of anomerization of **4** than of **2** during the debenzylidenation might involve the configuration of the branched chain. Bishop and Cooper[10] have extensively examined the relative rates of anomerization and furanoside–pyranoside interconversions, and successfully correlated these results with steric interactions based on established 1,3- and 1,2-interactions[11–14]. Thus, on these grounds, it would be expected that **4** would anomerize to relieve the 1,3-interaction between the α-methoxyl group and the cyanomethyl group, whereas, in the unblocking of **2**, there is no comparable steric interaction.

If the pyranoside anomerization proceeds through a skew conformer, as postulated by Bishop and Cooper[10] and Capon[15], it might be envisaged that subsequent attack of the primary hydroxyl group at C-6 upon the positive center would result in the formation of 1,6-anhydro-3-*C*-(cyanomethyl)-2,3-dideoxy-α-D-*ribo*-hexopyranose, a compound isolated in 8% yield as its *p*-chlorobenzoyl derivative (**10**). That compound **10** was present in the $^1C_4$ conformation was shown by the



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observed coupling constants of H-4. The large, *trans*-diaxial coupling previously present between H-4 and H-5 of **4** was no longer observed in the n.m.r. spectrum of **10**, and a value of 0.5 Hz was found, indicating the diequatorial nature of these two protons. Similarly, $J_{3,4}$ of **10** was ~1–2 Hz, confirming this conformational assignment.

The protected α-glycoside **8** was fused directly with 2,6-dichloropurine for 2 h at 155° to afford, after column chromatography on silica gel, an α,β-mixture of nucleosides **11** and **12** in 37 and 24% yields, respectively, and a novel, unsaturated, branched-chain sugar **13**. Although 1,2-glycals are common products[16] of such fusion reactions, it is not clear whether nucleoside synthesis by direct fusion proceeds *via* the intermediacy of glycals or whether glycal formation is a competing reaction.

Nucleosides have been synthesized by acid-catalyzed fusion of 1,2-glycals with purines[17].

The first protected nucleoside to be eluted from the column was assigned the structure 2,6-dichloro-9-[4,6-di-*O*-(*p*-chlorobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-α-D-*ribo*-hexopyranosyl]purine (**11**). The anomeric proton in the n.m.r. spectrum of **11** was observed as a doublet of doublets having coupling constants of 10 and 3 Hz. The coupling constants $J_{4',5'}$ and $J_{3',4'}$ were readily determined to be 1 and 3 Hz, respectively. From these data, it must be concluded that the glycosyl group exists in the $^1C_4$ conformation, and that **11** is indeed an α-nucleoside. This assignment was later corroborated by the circular dichroism spectrum of the unprotected nucleoside.

It is probable that the driving force for the conformational inversion is the considerable 1,3-interaction that the purine base and the C-3′ substituent would experience were the sugar residue in the $^4C_1$ conformation. The interaction between the purine and the cyanomethyl group must, then, be greater than that experienced by the C-5 and C-6 substituents in their 1,3-interaction with the hydrogen atoms on the ring.

From its n.m.r. spectrum, the second protected nucleoside was presumably the β-nucleoside **12**; this conclusion was corroborated by the c.d. spectrum of the unprotected nucleoside **16**. The anomeric proton of **12** was observed as a triplet at τ 3.70, with coupling constants to H-2′*e* and H-2′*a* of 5–6 Hz each. These values are somewhat surprising in that, if H-1′ is axially attached, as expected for the β-nucleoside, the *trans*-diaxial value $J_{1',2a'}$ should be ~8–10 Hz, whereas the axial–equatorial value $J_{1',2e'}$ should be ~3–5 Hz. Similarly, the $J_{4',5'}$ coupling-constant was observed to be 6 Hz, again considerably smaller than the 8–10 Hz expected for the *trans*-diaxial arrangement. These facts might indicate an equilibrium between two chair conformers, or a deformation of the conformation of the sugar residue towards a more planar shape, thus lessening the H-4′–H-5′ and H-1′–H-2′*a* dihedral angles. The driving force for such a deformation is not readily apparent, but it might be associated with the dipolar interaction of the purine base with the ring-oxygen atom. It is to be emphasized that a conformational assignment based on a first-order analysis is suspect when H-2′*a* and H-2′*e* signals are close together.

The *p*-chlorobenzoate **9** was not used, because it could not be obtained in pure, crystalline form.

Treatment of the protected α-nucleoside **11** with 25% aqueous dimethylamine and methanol [1,18] afforded, after column chromatography on silica gel, the unprotected, crystalline nucleoside **14** in 54% yield. This nucleoside exhibits a strong carbonyl absorption in its i.r. spectrum (at 1640 cm^{-1}), but does not show a cyano band. Its n.m.r. spectrum clearly showed that deacylation was complete, and that compound **14** has four methyl groups (two from the substitution of the presumed 6-chloro atom by NMe_2, and two from the replacement of the cyano group by the *N*,*N*-dimethylcarbamoylmethyl group[1]). This evidence, coupled with the fact that the molecular ions of compound **14** were, on mass spectrometry, observed at *m/e* 412 and *m/e* 414, strongly supported the hypothesis that compound **14** is 2-chloro-9-

[2,3-dideoxy-3-*C*-(*N*,*N*-dimethylaminocarbamoylmethyl)-α-D-*ribo*-hexopyranosyl]-6-(*N*,*N*-dimethylamino)purine. The u.v. absorption datum of **14** (λ_{max} 276 nm) substantiates the site of glycosylation as being at[19] N-9. A positive Cotton-effect exhibited by **14** indicated that the nucleoside had the α anomeric configuration[20,21]. In the n.m.r. spectrum of **14**, the anomeric proton was observed as a doublet of doublets at τ 3.97, having coupling constants of 10 and 4 Hz with the C-2′ protons. Thus, it would appear that the glycosyl group of the α-nucleoside **14** exists in the $^1C_4$ conformation.

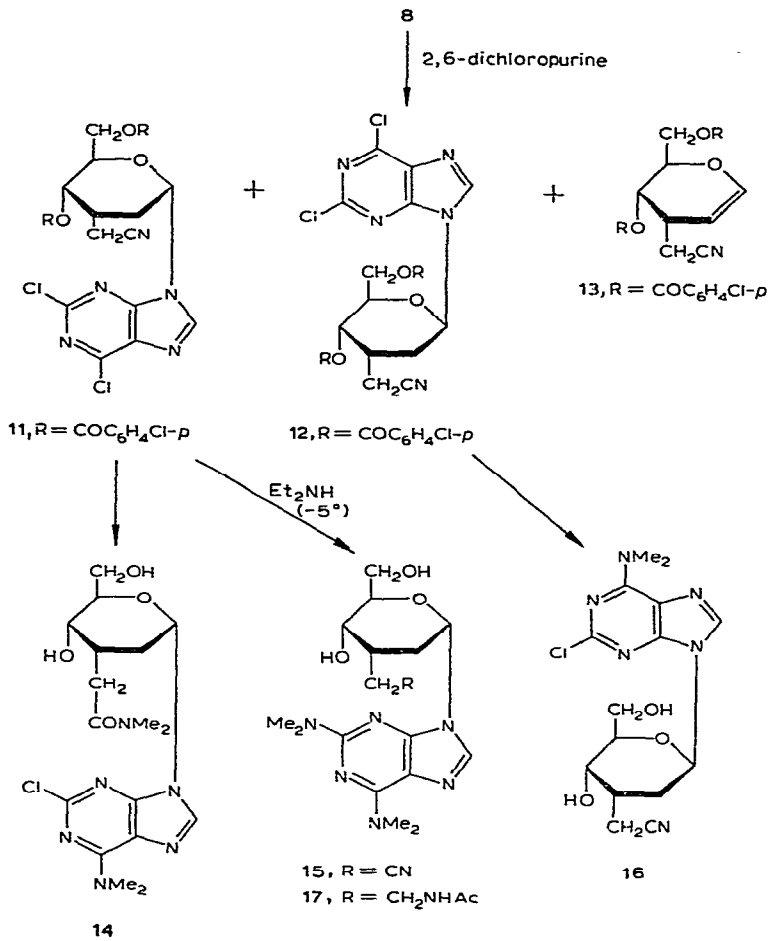
When the fully protected α-nucleoside **11** was treated with anhydrous dimethylamine for several days at −5°, the cyanomethyl nucleoside **15** was isolated in 63% yield. N.m.r. and mass spectrometry indicated that both of the chlorine atoms on the purine had been replaced by *N*,*N*-dimethylamino groups, and that the ester groups had been removed, to afford 9-[3-*C*-(cyanomethyl)-2,3-dideoxy-α-D-*ribo*-hexopyranosyl]-2,6-di-(*N*,*N*-dimethylamino)purine (**15**). Once again, the n.m.r. spectrum indicated that the sugar residue was present in the $^1C_4$ conformation; this was shown by the coupling constants (10 and 3 Hz) for the anomeric proton with the protons on C-2.

Treatment of the protected β-nucleoside **12** with 25% aqueous dimethylamine and methanol effected replacement of the 6-Cl atom by the NMe_2 group (as for the α-nucleoside **11**), but left unaltered the cyano group (in marked contrast to the α-nucleoside, in which conversion into a carbamoyl group has already been noted), to afford the unprotected β-nucleoside **16** in 36% yield. This result strongly indicated that ammonolysis of the cyano group in **11** must be unusually facile. Anchimeric assistance by hydroxyl and ester groups has been suggested in the rapid hydrolysis of some aldose cyanohydrins[22] and other nitrile-containing sugars[23].

The n.m.r. spectrum of the unprotected β-nucleoside **16** could not, alone, be used in deducing the anomeric or conformational assignments; H-1′ of **16** appeared as a doublet of doublets at τ 3.60 with coupling constants of 7 and 4 Hz. Thus, it might appear that the glycosyl group of the β anomer is present in a slightly deformed $^4C_1$ conformation. A negative Cotton-effect for nucleoside **16** indicated that it possesses the β-anomeric configuration[20,21].

Catalytic reduction of the unprotected cyanomethyl, branched-chain α-nucleoside **15** with hydrogen under 4 atm pressure, over 5% rhodium-on-alumina in ethanol presaturated with ammonia, followed by acetylation with acetic anhydride in pyridine, gave the fully acetylated nucleoside of the amino sugar. The latter compound was immediately *O*-deacetylated with 25% aqueous dimethylamine in methanol, to afford, after chromatographic purification, 9-[3-*C*-(2-acetamidoethyl)-2,3-dideoxy-α-D-*ribo*-hexopyranosyl]-2,6-di-(*N*,*N*-dimethylamino)purine (**17**) in 39% yield.

The n.m.r. spectrum of **17** clearly showed the presence of the C-8 proton on the purine residue, and a broad signal at τ 3.80 was assigned to the N-H proton of the acetamido group. A pair of doublets was observed for the anomeric proton, at τ 4.18, with coupling constants of 1 1 and 3 Hz with the protons on C-2, thereby confirming that the glycosyl group of **17** maintained the $^1C_4$ conformation. Sharp singlets were



observed at τ 6.58 and 6.87, corresponding to the dimethylamino groups, and a singlet at τ 8.05 corresponding to the *N*-acetyl group.

Compound **17** exhibited in its c.d. spectrum a positive Cotton-effect at 290 nm. Mass spectrometry afforded the molecular ion *m/e* 421, and revealed the base peak of the spectrum to be *m/e* 206 due to $[B+H]^+$, ($C_9H_{14}N_6$).

EXPERIMENTAL

General methods. — N.m.r. spectra were recorded with a Varian T-60, HA-100, or XL-100 spectrometer; absorptions are given in τ units, with tetramethylsilane (τ 10) as the internal standard. The following abbreviations are used in describing n.m.r. spectra: d, doublet; d.t., doublet of triplets; q, quartet; s, singlet; t, triplet, etc. Mass spectra were recorded with an A. E. I. MS 9 spectrometer. Optical rotations were measured at room temperature with a Perkin–Elmer model 141 automatic

polarimeter. I.r. spectra were recorded with a Perkin–Elmer model 137 spectrometer, and o.r.d. and c.d. measurements were made with a JASCO J-20 Automatic Recording Spectro-Polarimeter or a JASCO ORD/UV-5 spectropolarimeter. U.v. spectra were recorded with a Unicam SP 800 spectrometer. Elemental analyses were made by Mr. P. Borda, Department of Chemistry, University of British Columbia. Melting points were determined on a Leitz Microscope heating-stage model 250, and are corrected.

(E)- *and* (Z)-*Methyl 4,6-O-benzylidene-3-C-(cyanomethylene)-2,3-dideoxy-α-*D-erythro-*hexopyranoside*, (**2**) *and* (**3**), *from methyl 4,6-O-benzylidene-2-deoxy-α-*D-erythro-*hexopyranosid-3-ulose* (**1**). — To a filtered solution of the carbanion of diethyl (cyanomethyl)phosphonate (1.5 g) and sodium hydride (0.21 g) in 1,2-dimethoxyethane (20 ml) at 0° was added a solution of ketose **1** (1.82 g) in 1,2-dimethoxyethane (80 ml) during 1 h, and the mixture was stirred for 15 h at 25°. Water (80 ml) was added, the mixture was successively extracted with diethyl ether (3 × 80 ml) and chloroform (1 × 80 ml), and the extracts were combined, dried (calcium sulfate), and evaporated under diminished pressure to afford the crude product as a yellow syrup (2.34 g).

A portion (1.03 g) of the product was chromatographed on t.l.c.-grade silica gel (150 g, with 9:1 benzene–ethyl acetate) to yield **2** (0.57 g, 69%) and **3** (0.062 g, 7%), having R_F 0.70 and 0.40, respectively.

Compound **2** was recrystallized from ethanol; m.p. 140–141°; $[\alpha]_D^{21}$ +259° (*c* 4.2, chloroform); i.r. (Nujol) 2250 (C≡N) and 1650 cm^{-1} (C=C); n.m.r. data ($CDCl_3$): τ 4.39 (s, 1, H-7), 4.50 (t, 1, $J_{1',4}$ 2 Hz, $J_{1',2a}$ 2 Hz, H-1'), 5.13 (d.d., 1, $J_{1,2a}$ 4 Hz, $J_{1,2e}$ 0.5 Hz, H-1), 5.85 (m, 1, H-4), 5.7–6.6 (m, 3, H-4,5,6), 6.68 (s, OMe), 6.93 (d.d., 1, J_{gem} 15 Hz, H-2*e*), and 7.43 (16-line multiplet, $J_{2a,1'}$ 2 Hz, $J_{2a,4}$ 1 Hz, H-2*a*). Irradiation at τ 4.50 simplified the multiplet at τ 5.85, and simplified the multiplet at τ 7.43 to an 8-line multiplet. Irradiation at τ 5.13 produced a doublet at τ 6.93 and an 8-line multiplet at τ 7.43. Irradiation at τ 5.85 produced a doublet at τ 4.50 and an 8-line multiplet at τ 7.43.

Anal. Calc. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.97; N, 4.88. Found: C, 66.64; H, 5.80; N, 4.63.

Compound **3** was recrystallized from ethanol; m.p. 156.0– 156.5°; $[\alpha]_D^{26}$ +34.5° (*c* 1, chloroform); i.r. (Nujol) 2250 (C≡N) and 1650 cm^{-1} (C=C); n.m.r. data ($CDCl_3$): τ 4.30 (s, 1, H-7), 4.70 (d.t., 1, $J_{1',2a}$ 2 He, $J_{1',2e}$ 1.0 Hz, H-1'), 5.16 (d.d., 1, H-1, $J_{1,2a}$ 3.5 Hz, $J_{1,2e}$ 1.5 Hz, H-1), 5.6–6.6 (m, 4, H-4,5,6), 6.66 (s, 3, OMe), 7.32 (16-line multiplet, 1, J_{gem} 15 Hz, $J_{2a,4}$ 1 Hz, H-2*a*), and 7.50 (multiplet, 1, H-2*e*). Irradiation at τ 4.70 collapsed the multiplet at 7.32 to an 8-line system, and the multiplet at τ 7.50 to a 4-line system. Irradiation at τ 5.16 collapsed H-2*a* (τ 7.32) to an 8-line system, and simplified H-2*e* (τ 7.50).

Anal. Calc. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.97; N, 4.88. Found: C, 66.76; H, 5.83; N, 4.96.

(E)-*Methyl 3-C-(cyanomethylene)-2,3-dideoxy-α-*D-erythro-*hexopyranoside* (**5**). — A solution of unsaturated sugar **2** (0.31 g) in methanol (25 ml) was boiled under

reflux with Dowex 50W X-8 (H^+) (1.2 g, prewashed with methanol), for 2.25 h, or until, as evidenced by t.l.c. (silica gel; 4:1 benzene–ethyl acetate), no starting material remained. Removal of the resin by filtration, followed by evaporation of the filtrate, yielded a syrup which was treated with charcoal and water, and the suspension filtered. After evaporation of the water, the residue was azeotroped with ethanol and benzene under diminished pressure. The clear syrup (0.20 g, 100%) crystallized on trituration with ethanol. An analytical sample was obtained by recrystallization from ethanol–petroleum ether (b.p. 30–60°) and sublimed at 110°/0.1 torr; m.p. 164.0–164.5°; $[\alpha]_D^{23}$ +316° (*c* 0.14, chloroform); i.r. (Nujol) 3400 (OH), 2260 (C≡N), and 1645 cm^{-1} (C=C); n.m.r. data (in Me_2SO-d_6): τ 4.28 (d, 1, $J_{4,5}$ 7 Hz, H-4), 4.34 (m, 1, H-1′), 5.09 (d.d., 1, $J_{1,2a}$ 2 Hz, H-1), 6.74 (s, 3, OMe), and 7.31 (m, 2, J_{gem} 14 Hz, H-2*a*, H-2*e*).

Anal. Calc. for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.40; H, 6.72; N, 6.87.

(E)-*Methyl 4,6-di*-O-(p-*chlorobenzoyl*)-*3*-C-(*cyanomethylene*)-*2,3-dideoxy*-α-D-erythro-*hexopyranoside* (**6**). — To a solution of the unprotected sugar **5** (0.187 g) in pyridine (10 ml) was added *p*-chlorobenzoyl chloride (0.75 ml). The solution was stirred for 24 h at 25°, and then ice–water (200 ml) was added. The resultant solution was extracted with dichloromethane (4 × 100 ml), and the extracts were combined, successively washed with saturated sodium hydrogen carbonate solution (50 ml) and water (2 × 50 ml), dried (calcium sulfate), and evaporated to afford a solid which was recrystallized three times from chloroform (to remove most of the *p*-chlorobenzoic anhydride). Column chromatography on t.l.c.-grade silica gel (150 g; with 9:1 benzene–ethyl acetate) under a pressure of 3 lb.in.$^{-2}$ yielded **6** (0.385 g, 83%) which crystallized on trituration with ethanol. Recrystallization of **6** from ethanol afforded an analytical sample; m.p. 140.5–141.5°; $[\alpha]_D^{24}$ +165° (*c* 1, chloroform); i.r. (Nujol) 2240 (C≡N) and 1740–1730 cm^{-1} (C=O); n.m.r. data (in $CDCl_3$): τ 4.15 (d.d., 1, $J_{4,5}$ 10 Hz, $J_{4,1'}$ 2 Hz, H-4), 4.58 (t, 1, $J_{1',2e}$ 2 Hz, H-1′), 4.94 (d.d., 1, $J_{1,2a}$ 4 Hz, $J_{1,2e}$ 0.5 Hz, H-1), 5.43 (m, 2, H-6), 5.72 (m, 1, H-5), 6.55 (s, 3, OMe), 6.75 (m, 1, J_{gem} 14 Hz, H-2*e*), and 7.26 (m, 1, H-2*a*).

Anal. Calc. for $C_{23}H_{19}Cl_2NO_6$: C, 57.98; H, 4.02; N, 2.93. Found: C, 57.66; H, 3.85; N, 2.69.

Methyl 4,6-O-*benzylidene-3*-C-(*cyanomethyl*)-*2,3-dideoxy*-α-D-ribo-*hexopyranoside* (**4**). — To a suspension of 5% palladium-on-carbon (0.50 g) in ethanol (50 ml) was added **2** (0.85 g), and the mixture was stirred at room temperature with hydrogen under one atmosphere pressure until uptake of hydrogen ceased. Filtration of the mixture and evaporation of the filtrate afforded a colorless syrup which was chromatographed on t.l.c.-grade silica gel (200 g; with 9:1 benzene–ethyl acetate) under a pressure of 3 lb.in.$^{-2}$ to yield **4** (0.57 g, 67%). Compound **4** was recrystallized from ethanol; m.p. 84–86°; $[\alpha]_D^{21}$ +126° (*c* 1.4, chloroform); i.r. (Nujol) 2250 cm^{-1} (C≡N); n.m.r. data (in $CDCl_3$): τ 4.40 (s, 1, H-7), 5.30 (d.d., 1, $J_{1,2a}$ 4 Hz, $J_{1,2e}$ 2 Hz, H-1), 5.72 (d.d., 1, $J_{4,5}$ 8 Hz, $J_{4,3}$ 6 Hz, H-4), 4.1–4.4 (m, 3, H-5,6), 6.66 (s, 3, OMe), 7.12 (8-line multiplet, 2, J_{gem} 16 Hz, $J_{1'a,3}$ 10 Hz, $J_{1'b,3}$ 4 Hz, H-1′), 7.45 (m, 1, H-3),

7.78 (m, 1, J_{gem} 15 Hz, $J_{2e,1}$ 2 Hz, $J_{2e,3}$ 2 Hz, H-2*e*), and 8.02 (m, 1, $J_{2a,1}$ 4 Hz, $J_{2a,3}$ 4 Hz, H-2).

Anal. Calc. for $C_{16}H_{19}NO_4$: C, 66.24; H, 6.62; N, 4.48. Found: C, 66.20; H, 6.56; N, 4.64.

*Methyl 3-*C-(*cyanomethyl*)-*2,3-dideoxy-α,β-*D-ribo-*hexopyranoside* (**7**), *methyl 4,6-di-*O-(p-*chlorobenzoyl*)-*3-*C-(*cyanomethyl*)-*2,3-dideoxy-α-*(*and β*)-D-ribo-*hexopyranoside* (**8** and **9**), *and 1,6-anhydro-4,6-di-*O-(*p-chlorobenzoyl*)-*3-*C-(*cyanomethyl*)-*2,3-dideoxy-α-*D-ribo-*hexopyranose* (**10**). — A solution of compound **4** (0.57 g) in methanol (50 ml) was stirred with Dowex 50W X-8 (H^+) (2.2 g) (prewashed with methanol) until all of the **4** had been used up. Filtration of the suspension and evaporation of the filtrate afforded a clear syrup which, after treatment with charcoal in water, filtration, and removal of the water under diminished pressure, afforded **7** (0.374 g, 100%) as a clear syrup; $[\alpha]_D^{23}$ +42.5° (*c* 1, chloroform); i.r. (film) 3400 (OH) and 2250 cm^{-1} (C≡N); n.m.r. data (in $CDCl_3$): τ 4.97 (m, 1, H-1), 6.25 (m, 4, H-4,5,6), 6.65, 6.75 (2s, 3, OMe), and 7.0–8.4 (m, 7, H-2, H-1′, H-3, OH; two protons exchange; with D_2O).

Anal. Calc. for $C_9H_{15}NO_4 \cdot 0.5\ CH_3OH$: C, 52.50; H, 7.86; N, 6.45. Found: C, 52.49; H, 7.00; N, 6.62.

The α,β-glycoside **7** (0.310 g) in pyridine (20 ml) was (*p*-chlorobenzoyl)ated as for compound **5**. The product (1.20 g) was recrystallized three times from chloroform (to remove *p*-chlorobenzoic anhydride). Column chromatography of the benzoate on t.l.c.-grade silica gel (200 g; with 9:1 toluene–ethyl acetate) afforded the α anomer **8** (0.33 g, 44%), the β anomer **9** (0.29 g, 38%), and **10** (0.05 g, 8%). Compound **8** crystallized on trituration with ethanol, and was recrystallized from ethanol–hexane to yield an analytical sample, m.p. 129.5–130.5°; $[\alpha]_D^{23}$ +118.5° (*c* 1, chloroform); i.r. (Nujol) 2260 (C≡N) and 1730 cm^{-1} (C=O); n.m.r. data (in $CDCl_3$): τ 4.77 (d.d., 1, $J_{4,3}$ 5 Hz, $J_{4,5}$ 10 Hz, H-4), 5.30 (t, 1, $J_{1,2a}$ 3 Hz, $J_{1,2e}$ 3 Hz, H-1), 5.61 (m, 2, H-6), 5.90 (m, 1, H-5), 6.71 (s, 3, OMe), 7.1–7.3 (m, 3, H-1′, H-3), and 7.9 (m, 2, H-2). Irradiation at τ 7.92 produced a singlet at τ 5.30. Irradiation at τ 7.30 produced a doublet at τ 4.77 (*J* 9.5 Hz), and irradiation at τ 4.77 produced a triplet at τ 5.90.

Anal Calc. for $C_{23}H_{21}Cl_2NO_6$: C, 57.73; H, 4.42; N, 2.93. Found: C, 57.67; H, 4.44; N, 2.72.

Compound **9** could not be induced to crystallize; it had $[\alpha]_D^{23}$ −27.6° (*c* 1, chloroform); i.r. (film) 2250 (C≡N) and 1740 cm^{-1} (C=O); n.m.r. data (in $CDCl_3$): τ 4.57 (d.t., 1, $J_{5,4}$ 8 Hz, $J_{5,6'}$ 3 Hz, $J_{5,6''}$ 6 Hz, H-5), 4.94 (d.d, 1, $J_{1,2'}$ 5 Hz, $J_{1,2''}$ 0.5 Hz, H-1), 5.16 (d.d, 1, J_{gem} 12 Hz, H-1′), 5.48 (d.d, 1, $J_{3,4}$ 6 Hz, H-4), and 6.64 (s, 3, OMe).

An analytical sample of **10** was obtained by recrystallization from ethanol followed by sublimation at 130°/0.1 torr; m.p. 148.5–149.0°; $[\alpha]_D^{25}$ −189° (*c* 1, chloroform); n.m.r. data (in $CDCl_3$): τ 4.33 (s, 1, H-4), 4.93 (t, 1, $J_{1,2e}$ 3 Hz, $J_{1,2a}$ 3 Hz, H-1), 5.20 (d.d, 1, $J_{5,6'}$ 4 Hz, $J_{5,6''}$ 2Hz, H-5), 6.10 (m, 2, H-6), and 7.2–8.4 (m, 5, H-3, H-1′, H-2).

Anal. Calc. for $C_{15}H_{14}ClNO_4$: C, 58.57; H, 4.59; N, 4.55. Found: C, 59.29; H, 4.43; N, 4.34.

*2,6-Dichloro-9-[4,6-di-*O*-(*p*-chlorobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-α-*D*-ribo-hexopyranosyl]purine* (**11**), *2,6-dichloro-9-[4,6-di-*O*-(*p*-chlorobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-β-*D*-ribo-hexopyranosyl]purine* (**12**), *and 1,5-anhydro-4,6-di-*O*-(*p*-chlorobenzoyl)-3-*C*-(cyanomethyl)-2,3-dideoxy-*D*-ribo-hex-1-enitol* (**13**). — A mixture of finely powdered 2,6-dichloropurine (300 mg) and **8** (480 mg) was dried by distilling toluene (10 ml) from it, and then evaporated to dryness. The mixture was fused for 1.5 h at 155°/30 torr and then for 0.5 h at 155°/0.1 torr. Dissolution of the light-brown glass in warm, *1:1* ethanol–ethyl acetate, filtration, and evaporation of the filtrate afforded a syrup which was chromatographed on a column of t.l.c.-grade silica gel (170 g; with 3:2 benzene–ethyl acetate) under a pressure of 8 lb.in.$^{-2}$ to yield **13** (153 mg, 34%), **11** (239 mg, 37%), and **12** (159 mg, 24%).

Compound **13** was a syrup; $[\alpha]_D^{23}$ +175° (*c* 2, chloroform); i.r. (film) 2280 (C≡), 1720 (C=O), and 1600 cm^{-1} (C=C); n.m.r. data (in $CDCl_3$): τ 3.46 (d.d, 1, $J_{1,2}$ 6 Hz, $J_{1,3}$ 2 Hz, H-1), 4.27 (d.t, 1, $J_{5,6'}$ 6 Hz, $J_{5,6''}$ 2 Hz, $J_{5,4}$ 6 Hz, H-5), 5.15 (d.d, 1, $J_{2,3}$ 4 Hz, H-2), 5.4–5.6 (m, 3, H-6, H-4), 6.92 (m, 1, H-3), and 7.50 (m, 2, H-1′).

Anal. Calc. for $C_{22}H_{17}Cl_2NO_5$: C, 59.23; H, 3.84; N, 3.14. Found: C, 60.50; H, 3.98; N, 2.86.

Compound **12** was recrystallized from ethanol; m.p. 184–185°; $[\alpha]_D^{23}$ +33.4° (*c* 1.6, chloroform); n.m.r. data (in $CDCl_3$): τ 1.78 (s, 1, H-8), 3.70 (t, 1, $J_{1',2'}$ 6 Hz, H-1′), 4.50 (d.t, 1, $J_{5',4'}$ 6 Hz, $J_{5',6'}$ 6 Hz, H-5′), 5.37 (m, 3, H-6′, H-4′), and 6.8–7.4 (m, 5, H-2′, H-3′, H-3″).

Anal. Calc. for $C_{27}H_{19}Cl_4N_5O_5$: C, 51.05; H, 3.00; N, 11.02. Found: C, 50.71; H, 2.84; N, 10.83.

Compound **11** was recrystallized from ethanol; m.p. 230–231° (sinters at 197–199°); $[\alpha]_D^{27}$ −54.5° (*c* 0.7, chloroform); n.m.r. data (in $CDCl_3$): τ 1.70 (s, 1, H-8), 3.64 (d.d, 1, $J_{1',2a'}$ 10 Hz, $J_{1',2e'}$ 3 Hz, H-1′), 4.62 (m, 1, H-4′), 4.87 (d.d, 1, $J_{6',5'}$ 9 Hz, $J_{6',6''}$ 12 Hz, H-6′), 5.34 (m, 1, H-5′), 5.59 (d.d, 1, $J_{6'',5'}$ 4 Hz, H-6″), and 6.8–7.7 (m, 5, H-2′,3′,3″).

Anal. Calc. for $C_{27}H_{19}Cl_4N_5O_5$: C, 51.05; H, 3.00; N, 11.02. Found: C, 50.87; H, 3.07; N, 10.91.

*2-Chloro-9-[2,3-dideoxy-3-*C*-(*N*,*N*-dimethylaminocarbamoylmethyl)-α-*D*-ribo-hexopyranosyl]-6-(*N*,*N*-dimethylamino)purine* (**14**). — Compound **11** (230 mg), methanol (20 ml), and 25% aqueous dimethylamine (20 ml) were stirred for 5 h at room temperature (until all of the nucleoside had dissolved). The mixture was evaporated to dryness, and azeotroped under diminished pressure with toluene (20 ml) and methanol (20 ml). Chromatography on a column of t.l.c.-grade silica gel (45 g; with 9:1 chloroform–ethanol) afforded an unidentified component (43 mg) and **14** (80 mg, 54%). An analytical sample of **14** was obtained by recrystallization from ethanol; m.p. 189.5–190.0°; $[\alpha]_D^{23}$ +8.2° (*c* 0.6, chloroform); i.r. (Nujol) 3300 (OH) and 1640 cm^{-1} (C=O); λ_{max} 217 nm (ε_{mM} 16.45), 276 nm (ε_{mM} 15.00); c.d. (*c* 0.004,

ethanol) $[\theta]_{276}$ +2,030; n.m.r. data (in $CDCl_3$): τ 2.10 (s, 1, H-8), 3.96 (d.d, $J_{1',2a'}$ 10 Hz, $J_{1',2b'}$ 4 Hz, H-1'), 6.48 (broad s, 6, NMe_2-carbamoyl), 6.96, and 7.04 (2s, 6, NMe_2-purine).

Anal. Calc. for $C_{17}H_{25}ClN_6O_4$: C, 49.45; H, 6.10; N, 20.35. Found: C, 49.65; H, 6.17; N, 20.08. Molecular weight by mass spectrometry 412, 414. $C_{17}H_{25}ClN_6O_4$ requires 412, 414.

*2-Chloro-9-[3-C-(cyanomethyl)-2 3· dideoxy-β-*D-ribo-*hexopyranosyl)-6-(N,N-dimethylamino)purine* (**16**). — A suspension of crude **12** (130 mg) in methanol (10 ml) and 25% aqueous dimethylamine (10 ml) was stirred for 4 h at room temperature, evaporated to dryness, and applied to a column of t.l.c.-grade silica gel (45 g; packed, and eluted, with 9:1 chloroform–ethanol), to afford **16** (30 mg, 36%) as a foam that crystallized on addition of a small volume of ethanol. An analytical sample was obtained by recrystallization from ethanol; m.p. 187.0–188.5°; $[\alpha]_D^{23}$ +33.4° (*c* 1.6, chloroform); λ_{max}^{EtOH} 217 nm (ε_{mM} 9.40), 276 nm (ε_{mM} 8.35); c.d. (*c* 0.003, ethanol) $[\theta]_{275}$ −3,000; n.m.r. data (in $CDCl_3$): τ 1.51 (s, 1, H-8), 3.60 (d.d, 1, $J_{1',2a'}$ 7.5 Hz, $J_{1',2e'}$ 4 Hz, H-1'), and 6.46 (br, s, NMe_2).

Anal. Calc. for $C_{15}H_{19}ClN_6O_3$: C, 49.11; H, 5.23; N, 22.79. Found: C, 49.13; H, 5.10; N, 22.45.

*9-[3-C-(Cyanomethyl)-2,3-dideoxy-α-*D-ribo-*hexopyranosyl]-2,6-di-(N,N-dimethylamino)purine* (**15**). — A solution of the protected nucleoside **11** (112 mg) in anhydrous dimethylamine (15 ml) was kept for 20 days at −5°, and the dimethylamine was removed by gentle warming, to afford the crude, unprotected nucleoside **15** as a syrup. Chromatography of the product on a column of t.l.c.-grade silica gel (40 g; with 93:7 dichloromethane–ethanol) afforded **15** (40 mg, 63%) as crystals. An analytical sample was obtained by recrystallization from methanol: m.p. 220–221°; $[\alpha]_D^{23}$ +46.1° (*c* 0.3, chloroform); λ_{max}^{EtOH} 244 nm (ε_{mM} 6.40), 264 nm (sh, ε_{mM} 3.16), 292 nm (ε_{mM} 3.10); c.d. (*c* 0.003, ethanol) $[\theta]_{292}$ +1,070; n.m.r. data (in Me_2SO-d_6): τ 2.08 (s, 1, H-8), 4.10 (d.d, 1, $J_{1',2e'}$ 3 Hz, $J_{1',2a'}$ 10 Hz, H-1'), 6.62 (s, 6, NMe_2), and 6.90 (s, 6, NMe_2).

Anal. Calc. for $C_{15}H_{25}N_7O_3$: C, 54.39; H, 6.72; N, 26.12. Found: C, 54.40; H, 6.59; N, 26.51.

*9-[3-C-(2-Acetamidoethyl)-2,3-dideoxy-α-*D-ribo-*hexopyranosyl]-3,6-di-(N,N-dimethylamino)purine* (**17**). — Hydrogenation of **15** (15 mg) in ethanol (25 ml) presaturated with ammonia at 0°, with 5% rhodium-on-alumina (15 mg) as the catalyst, for 24 h at 60 lb.in.$^{-2}$, afforded, after filtration and evaporation, a clear syrup which was immediately acetylated with pyridine (0.5 ml) and acetic anhydride (0.5 ml) for 12 h at room temperature. The mixture was evaporated to dryness, and treated with 25% aqueous dimethylamine (2.5 ml) in methanol (2.5 ml) for 3 h; the solution was evaporated to dryness, the residue dissolved in 1:1 chloroform–methanol, and the product purified by preparative t.l.c. (silica gel; with 9:1 dichloromethane–ethanol), to afford **17** (6.5 mg, 39%) as a clear syrup that could not be induced to crystallize; $[\alpha]_D^{23}$ +34.6° (*c* 0.7, chloroform); λ_{max}^{EtOH} 244 nm (ε_{mM} 7.70), 263 nm (ε_{mM} 3.75 sh), 292 nm (ε_{mM} 3.60); c.d. (*c* 0.005, ethanol), $[\theta]_{293}$ +750; n.m.r. data (in $CDCl_3$):

τ 2.38 (s, 1, H-8), 3.80 (m, 1, N-H), 4.18 (d.d, 1, $J_{1',2a'}$ 11 Hz, $J_{1',2e'}$ 3 Hz, H-1'), 6.58, 6.87 (2×s, 12, 2×NMe_2), and 8.05 (s, 3, NAc).

Molecular weight, calc. for $C_{19}H_{31}N_7O_4$: 421. Found (by mass spectrometry): 421.

ACKNOWLEDGMENT

This work was supported by the National Research Council of Canada.

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