Note

Nucleosides from sugars having a terminal cyclopropyl group. 9-[4-*C*-Cyclopropyl-α(and β)-D-*xylo*-tetrofuranosyl]adenine*†

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In an earlier paper[2] we reported the synthesis of 4-*C*-cyclopropyl-α (and β)-D-*xylo*-tetrofuranose (**1**) and their conversion into the corresponding triacetates **2**. Synthesis from **2** of the corresponding adenine nucleosides, 9-(4-*C*-cyclopropyl-α-D-*xylo*-tetrofuranosyl)adenine (**4**) and the β-D anomer (**3**), is now described.

Condensation of the mixed, anomeric acetates **2** with 6-benzamido-9-(chloromercuri)purine in the presence of titanium tetrachloride[3] gave a mixture of protected nucleosides in 62% yield. The ratio of α-D and β-D anomers was approximately 3:7, as indicated by n.m.r. spectroscopy (see Experimental section). Removal of *O*-acetyl and *N*-benzoyl groups by sodium methoxide gave a mixture of free nucleosides that was readily resolved by column chromatography on silica gel. The first component to be eluted, obtained crystalline in 23% overall yield from **2**, was identified by its physical properties as 9-(4-*C*-cyclopropyl-β-D-*xylo*-tetrofuranosyl)adenine (**3**). The second component was also obtained crystalline and was identified as the α-D anomer (**4**); it was obtained in 8% overall yield from **2** as a hydrate that became anhydrous on drying.

Both nucleosides gave acceptable elemental analyses and showed maximal u.v. absorption near 260 nm in neutral and in acid solution, indicating[4] that the adenine moiety is substituted in each case at N-9 and not at N-3 or N-7. Both products showed a peak at *m/e* 277 in their mass spectra for the molecular ion, together with fragmentation products at *m/e* 164, 136, and 135 (see Experimental section for details) characteristic[5] of adenine nucleosides, and the two compounds showed signals for the cyclopropyl group at high field in their n.m.r. spectra.

Assignment of anomeric configurations to the two products was based on n.m.r. spectral (see Table I) and optical rotatory data. The n.m.r. spectrum of the major product in pyridine-d_5 shows the H-1 signal at τ 3.57 as an essential singlet ($J_{1,2}$ <1 Hz), whereas the minor product shows the H-1 signal at lower field (τ 2.93) as a doublet ($J_{1,2}$ 3.5 Hz); these data are consistent[6] with the major product being the

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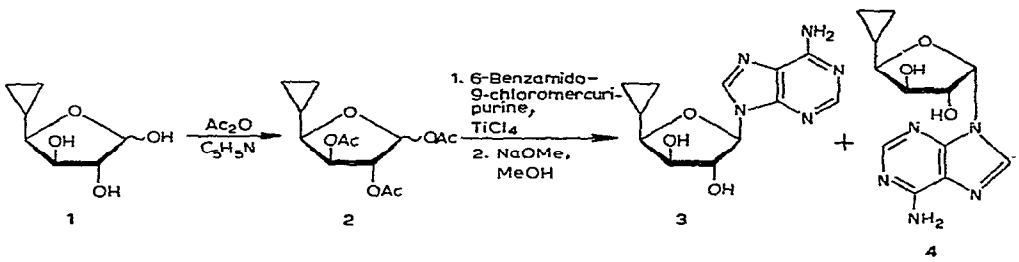
β-D anomer (3) and the minor product being the α-D anomer (4). The specific rotation of the α-D anomer 4 is positive ($[\alpha]_D^{25}$ +12.5° in ethanol) and increases with decreasing wavelength, whereas that of the β-D anomer 3 is negative ($[\alpha]_D^{25}$ −44° in ethanol) and decreases with decreasing wavelength.



The coupling reaction of 2 to give nucleosides presumably proceeds by way of the acetylated glycosyl chloride. The successful outcome of the reaction indicates that the cyclopropyl group withstands the conditions required for formation of the glycosyl chloride, at least when the chloride is coupled *in situ* to a nitrogenous, heterocyclic base.

Deoxygenation of adenine nucleosides at C-5′ has been shown[7] to stabilize the adenine moiety towards *in vivo* deamination. Biological evaluation of these cyclopropyl nucleosides is in progress.

EXPERIMENTAL

Solutions were evaporated below 50° under diminished pressure. Melting points were determined with a Thomas–Hoover "Unimelt" apparatus and are uncorrected. I.r. spectra were measured with a Perkin–Elmer Model 137 i.r. spectrophotometer. U.v. spectra were measured with a Cary Model 14 u.v. spectrophotometer. Optical rotations were measured in 1-dm tubes with a Perkin–Elmer Model 141 polarimeter. Mass spectra were measured with an A.E.I. MS-9 double-focusing, high resolution spectrometer with an accelerating potential of 8 kV, an ionizing potential of 70 eV, and a source temperature of 250°. N.m.r. spectra were measured at 100 MHz with a Varian HA-100 n.m.r. spectrometer. Chemical shifts are given on the τ scale, with tetramethylsilane (τ = 10.00) as the internal standard. Spectra were analyzed on a first-order basis. Microanalyses were performed by W. N. Rond. X-ray powder diffraction data give interplanar spacings, Å, for CuKα radiation. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest). The camera diameter was 114.59 mm. T.l.c. was performed with 250-μm layers of Silica Gel G containing a fluorescent indicator (E. Merck, Darmstadt, Germany) activated at 110°, and indication was effected with u.v. light and sulfuric acid. Column chromatography was performed with Silica Gel 7734 (70–325 mesh ASTM, E. Merck).

Preparation of 4-C-cyclopropyl-α,β-D-xylo-tetrofuranose (**1**). — A suspension of 4-*C*-cyclopropyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranose[2] (10.0 g, 50 mmoles) and Amberlite IR-120 (H^+) ion-exchange resin (20 g) in water (100 ml) was stirred for 3 h at 45°. The suspension was filtered and the filtrate evaporated to give a crystalline mass; yield 8.01 g (100%) that was homogeneous by t.l.c. (50:40:49:5 butyl alcohol–ethanol–water–ammonia) and could be used directly in the following step. Recrystallization from acetone–toluene gave pure **1**; yield 7.6 g, m.p. 109–110°, $[\alpha]_D^{20}$ +16 ±0.5° (*c* 1.2, water) [lit.[2] m.p. 109–110°, $[\alpha]_D^{20}$ +16° (water)].

Preparation of 1,2,3-tri-O-acetyl-4-C-cyclopropyl-α and β-D-xylo-tetrofuranose (**2**). — A solution of **1** (6.0 g, 37.5 mmoles) in pyridine (150 ml) was concentrated to 100 ml and acetic anhydride (5 ml) was added. After 12 h at room temperature the solution was poured into 400 ml of ice–water and the resulting suspension was stirred for 0.5 h. The mixture was extracted with dichloromethane (2 × 100 ml) and the extract was washed with water (3 × 100 ml), dried (magnesium sulfate), and evaporated to give **2** as a crystalline mass; yield 10.0 g (94%) that was homogeneous by t.l.c. (R_F 0.85 in 9:1 benzene–methanol). The product, which was used directly without further purification, gave an n.m.r. spectrum in chloroform-*d* identical with that of the syrupy product previously described[2].

6-Benzamido-9-(2,3-di-O-acetyl-4-C-cyclopropyl-α and β-D-xylo-tetrofuranosyl)-purine. — A stirred mixture of **2** (10.2 g, 35.7 mmoles), 6-benzamido-9-(chloromercuri)-purine (21.0 g, 44 mmoles), Celite (20 g), and 1,2-dichloroethane (1 liter) was refluxed and the solvent (150 ml) was distilled from the mixture. The mixture was cooled to ~40° and titanium tetrachloride (8.5 g, 4.9 ml, 44 mmoles) in dry 1,2-dichloroethane (20 ml) was then added dropwise, with stirring, and the mixture was subsequently heated for 24 h at reflux. Saturated aqueous sodium hydrogen carbonate (800 ml) was then added with rapid stirring to the cooled mixture and after 2 h the mixture was filtered through Celite. The filter was washed with 800 ml of hot chloroform and the organic layer was separated and evaporated almost to dryness. Chloroform (150 ml) was added and the solution was washed with two 100-ml portions of 30% aqueous potassium iodide and 100 ml of water. The dried (magnesium sulfate) solution was evaporated to give a yellow syrup that was homogeneous by t.l.c.; yield 10.1 g (62.5%); R_F 0.6 (9:1 benzene–methanol). The 100-MHz n.m.r. spectrum of the mixture in chloroform-*d* showed a doublet of 0.3 proton at τ 3.28 ($J_{1,2}$ 4.5 Hz) assigned to H-1 of the α-D anomer, and a narrower doublet of 0.7 proton at τ 3.73 ($J_{1,2}$ 2.5 Hz) assigned to H-1 of the β-D anomer.

9-(4-C-Cyclopropyl-β-D-xylo-tetrofuranosyl)adenine (**3**) *and 9-(4-C-cyclopropyl-α-D-xylo-tetrofuranosyl)adenine* (**4**). — The foregoing mixture of protected nucleosides (10.1 g, 22.5 mmoles) was dissolved in anhydrous methanol (100 ml) and 100 ml of 0.22M methanolic sodium methoxide was added. The solution was refluxed for 16 h and was then neutralized with Amberlite IR-120 (H^+) ion-exchange resin. The mixture was filtered, evaporated, and the resultant, dark syrup was treated with 200 ml of hot water to dissolve the nucleosides. The cooled solution was extracted with dichloromethane (50 ml) and the aqueous phase was heated to boiling with 0.5 g of activated

charcoal. Filtration of the mixture and evaporation of the filtrate gave a pale-yellow syrup that was chromatographed on a column of silica gel (500 g) with 6:1 chloroform–methanol as eluent. The first product to be eluted was the β-D nucleoside (**3**), obtained crystalline upon trituration with dichloromethane. Recrystallization from water gave **3** as white needles that were dried for 24 h at 80° and 0.1 torr; yield 2.30 g (8.3 mmoles, 23% from **2**), m.p. 125–129°, $[\alpha]_D^{25}$ −43.7 ±0.5°, $[\alpha]_{578}^{25}$ −45.5°, $[\alpha]_{546}^{25}$ −52.3°, $[\alpha]_{436}^{25}$ −94.6°, $[\alpha]_{365}^{25}$ −165° (*c* 1.4, ethanol); R_F 0.50 (4:1 chloroform–ethanol); λ_{max}^{EtOH} 260 nm (ε 1.52×10^4) unchanged on acidification to pH ~1; λ_{max}^{KBr} 2.98, 3.15 (OH, NH), 3.45 (CH), 6.53 μm (NH_2); n.m.r. data, see Table I; mass-spectral data (relative intensities and assignments in parentheses): *m/e* 277 (3, M^+), 248 (2), 218 (10), 207 (3), 206 (11), 194 (5), 190 (2), 189 (2), 188 (5), 179 (4), 178 (41, $HOCH_2CH_2$-base$^+$), 177 (2), 164 (30, HO^+=CH-base), 148 (8), 136 (80, H_2-base$^+$), 135 (100, H-base$^+$), 119 (6), 108 (28), 83 (10), 81 (8), 71 (9), 67 (7), 66 (7), 55 (20), 54 (7), 43 (8), 41 (15, cyclopropyl$^+$); X-ray powder diffraction data: 13.50 s (3), 9.60 w, 6.85 m, 6.37 vs (1), 5.92 vs (2), 5.41 s, 4.86 s, 4.18 m, 3.54 s.

Anal. Calc. for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 51.67; H, 5.51; N, 25.02.

TABLE I

CHEMICAL SHIFT AND FIRST-ORDER COUPLING DATA[a] FOR 9-(4-*C*-CYCLOPROPYL-β-D-*xylo*-TETROFURANOSYL)ADENINE (**3**) AND ITS α-D ANOMER (**4**)

Compound	*Solvent*	*Chemical shifts*[b], τ (*first-order couplings, Hz, in parentheses*)							
		H-1 ($J_{1,2}$)	*H-2* ($J_{2,3}$)	*H-3* ($J_{3,4}$)	*H-4* ($J_{4,5}$)	*H-5*	*H-6,6'*	*H-2*[c]	*H-8*[c]
3	D_2O[d]	3.77 d (1.8)	5.10 t (1.0)	5.43 q (3.7)	6.12 q (10.2)	8.41 m	8.70–9.58	1.40 s	1.62 s
	C_5D_5N[e]	3.57 s (<1)	5.10 s (<1)	5.40 d (3.0)	6.19 q (9.5)	8.36 m	9.1–9.6	1.29 s	1.55 s
4	D_2O[d]	3.23 d (4.5)	5.12 q (2)	5.25 m (4)	5.83 q (10)	8.30——9.65		1.49 s	1.62 s
	C_5D_5N[e]	2.93 d (3.5)	5.03 q (1.6)	5.23 q (2.8)	5.89 q (9.0)	8.38 m	9.0–9.5	1.43 s	1.54 s

[a]From 100-MHz spectra. [b]Shifts and couplings refer, unless otherwise stated, to protons on the sugar residue. [c]Of the adenine moiety; not specifically differentiated. [d]External tetramethylsilane as standard. [e]Containing a small proportion of deuterium oxide.

Further elution of the column gave the α-D anomer **4** as a crystalline solid, which was crystallized from water and dried for 24 h at 100° and 0.1 torr (loss of water of crystallization) to give the pure, anhydrous nucleoside **4**; yield 0.83 g (3.0 mmoles, 8% from **2**), m.p. 205–205.5°, $[\alpha]_D^{25}$ +12.5 ±1°, $[\alpha]_{578}^{25}$ +13.2°, $[\alpha]_{546}^{25}$ +15.6°, $[\alpha]_{436}^{25}$ +34.9°, $[\alpha]_{365}^{25}$ +80.8° (*c* 1.0, ethanol); R_F 0.31 (4:1 chloroform–methanol); λ_{max}^{EtOH} 259 nm (ε 1.45×10^4) unchanged on acidification to pH ~1; λ_{max}^{KBr} 2.92, 3.00, 3.10 (OH, NH), 3.42 (CH), 6.52 μm (NH_2); n.m.r. data see Table I; mass-spectral data

(relative intensities and assignments in parentheses): *m/e* 277 (0.7, $M^{\ddagger}$), 260 (0.5, $M^{\ddagger}-\cdot OH$), 248 (0.5), 242 (2), 218 (2), 194 (5), 190 (3), 189 (1), 188 (4), 178 (40, $HOCH_2CH_2$-base$^+$), 164 (28, HO^+=CH-base), 148 (5), 136 (48, H_2-base$^+$), 135 (100, H-base‡), 108 (23), 83 (8), 55 (15), 43 (6), 41 (12, cyclopropyl$^+$); X-ray powder diffraction data: 15.82 m, 11.47 vs (1), 9.38 m, 8.26 s (2), 6.60 vw, 6.01 m, 5.64 m, 5.44 m, 4.89 s (3), 4.71 w, 4.52 w, 4.35 w, 3.57 s, 3.37 m, 3.28 s.

Anal. Calc. for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 51.65; H, 5.69; N, 24.98.

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