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Note

Aspects of formation of anhydronucleosides

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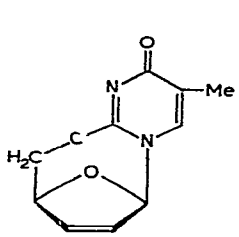
Synthesis of an anhydronucleoside (**1**), has been attempted, but without success[1]. The need for compounds of this type as models for circular-dichroism measure-



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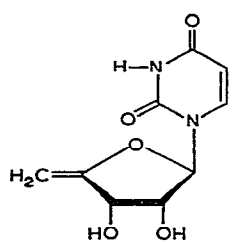

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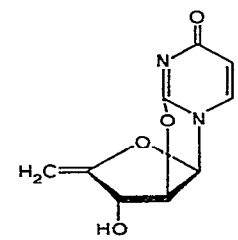

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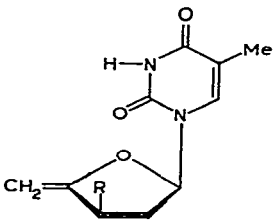
ments[2–4] prompted further study of the synthesis of anhydronucleosides having unsaturation in the sugar moiety. The ease with which anhydronucleosides form generally follows the rule[5] 2,2′>2,3′>2,5′. This order provided a rationale for synthesis of the anhydronucleoside **4** in which the 2′-position is involved in the anhydro bridge.

Treatment of 1-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil[6] (**3**) with diphenyl carbonate according to the vigorous conditions of Hampton and Nichol[7], followed by preparative t.l.c. on silica gel, gave the crystalline anhydronucleoside, 2,2′-anhydro-1-(5-deoxy-β-D-*threo*-pent-4-enofuranosyl)uracil (**4**) in 24% yield. The presence of an anhydro bridge in **4** was established by its u.v. spectrum [λ_{max}^{MeOH} 224 (ε 11,430), 247 nm (9,050), λ_{max}^{MeOH} 213 (10,000), 238 (8,850)], which compares closely with that of 2,2′-anhydrouridine[8] [λ_{max}^{EtOH} 224 (10,600), 248 (8,680), λ_{min}^{EtOH} 210 (7,130), 237 (7,560)]. P.m.r. spectroscopy showed that a 5′-methylene group and a hydroxyl group were present (see experimental section), but the u.v. and p.m.r. data do not exclude the possibility of a 2,3′-anhydronucleoside structure. Recent investigations of the mechanism of the diphenyl carbonate reaction[8] reinforce the arguments for structure **4**.

In an attempt to synthesise an unsaturated 2,3′-anhydronucleoside, 1-(2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)thymine[6] (**5**) was first converted into an



5 R = OH, D-*glycero*-epimer
6 R = I

iodinated nucleoside by treatment with methyltriphenoxyphosphonium iodide[9]. The crystalline product had the analytical and spectral data required for structure **6** or its D-*glycero* epimer. The p.m.r. spectrum (in methyl sulfoxide-d_6) of compound **6** showed the H-5′ signal as a 2-proton singlet at δ 4.10 and the H-1′ signal as an *evenly* spaced, one-proton multiplet (width 13.5 Hz) of four peaks (having equal heights) centered at δ 6.60. The parent compound **5** showed an AB doublet at δ 4.19 and δ 4.31 (J_{AB} = 1 Hz) for the C-5′ protons and a pseudo-triplet signal (width 13 Hz) centered at δ 6.47 for H-1′. Empirical p.m.r. rules[10] derived by Verheyden and Moffat for the assignment of configuration of halogenated nucleosides suggest the assignment of the L-*glycero* configuration to **6**.

Treatment of **6** with silver acetate and triethylamine in refluxing acetonitrile[11] for 1.25 h gave a major component (t.l.c.) migrating faster than **5** but slower than **6** and it was isolated as a syrup by preparative t.l.c. Its u.v. spectrum did not resemble that of an anhydronucleoside. Treatment of this material with ammonium hydroxide in methanol gave (t.l.c.) two products. The faster-moving, major product was separated by crystallization and was shown to be identical with **5**. The other component, which was also somewhat unstable, was not isolated pure. Its p.m.r. spectrum did indicate that it was an unsaturated thymine nucleoside and that it was probably the L-*glycero* epimer of **5**.

Reaction of **6** with silver nitrate and triethylamine in dry acetonitrile at room temperature gave a complex mixture of products.

This report and the previous one[1] support the established order for ease of formation of anhydronucleosides[5] (2,2′>2,3′>2,5′) in that, of the unsaturated nucleosides studied, only a 2,2′-anhydronucleoside was formed readily.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover capillary apparatus and are uncorrected. P.m.r. spectra were measured in methyl sulfoxide-d_6 with an internal standard of tetramethylsilane, on Varian A-60 n.m.r. spectrometer. First-order J values are given. U.v. spectra were determined with a Cary 14 spectrophotometer. I.r. spectra were determined with a Beckmann IR-5 spectrophotometer. Detection of components on SilicAR 7GF (Mallinckrodt) was by u.v. light. Silica gel was chromatographic grade (J. T. Baker Chemical Co). Solvent proportions were by volume. Evaporations were performed under diminished pressure at 35°.

*2,2′-Anhydro-1-(5-deoxy-β-*D-threo-*pent-4-enofuranosyl)uracil* (**4**). — A mixture

of 1-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil[6] (1.0 g), diphenyl carbonate (1.14 g) and sodium hydrogen carbonate (20 mg) in *N*,*N*-dimethylformamide (2 ml) was heated for 20 min at 145–150°. After the initial effervescence had largely ceased the red solution was poured with magnetic stirring into ether (100 ml). The solid precipitated was dissolved in aqueous methanol. The solution was applied to the short edge of a plate (400 × 200 × 2 mm) of SilicAR 7GF and the plate was developed twice with 9:1 ethyl acetate–methanol. The slowest moving, major band was excised. The product was extracted with methanol and crystallized from ethanol to give **4**; yield 0.22 g (24%), m.p. 193–194° dec. Decolorization and recrystallization gave pure **4**, m.p. 194–195° dec; $[\alpha]_D^{26}$ +34.9° (*c* 1 methanol), λ_{max}^{KBr} 1600–1680 cm^{-1} (broad carbonyl absorption of heterocycle), λ_{max}^{MeOH} 224 (ε 11,430), 247 nm (9,050), λ_{min}^{MeOH} 213 (10,000), 238 (8,850), p.m.r. data: δ 4.47, 4.60 (doublets, J_{AB} 2 Hz, C-5′ protons), 4.73 (doublet, $J_{3',OH}$ 5 Hz, H-3′), 5.32 (doublet, $J_{1',2'}$ 5 Hz, H-2′), 5.96(doublet $J_{5,6}$ 7 Hz, H-5), 6.20 (doublet, 3′-OH), 6.63 (doublet, H-1′) 8.00 (doublet, H-6).

Anal. Calc. for $C_9H_8N_2O_4$: C, 51.92; H, 3.87; N, 13.46. Found: C, 51.99; H, 3.81; N, 13.89.

*1-(2,3,5-Trideoxy-3-iodo-β-*L-glycero-*pent-4-enofuranosyl)thymine* (**6**). — A sealed mixture of 1-(2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)thymine[6] (**5**, 5.0 g) and methyltriphenoxyphosphonium iodide (11.0 g) in dry *N*,*N*-dimethylformamide (80 ml) was swirled until solution occurred, and the solution was kept for 2 h at room temperature. The solution was evaporated in vacuo to a syrup and the residue was dissolved in chloroform. The solution was washed consecutively with sodium thiosulfate solution and water. The dried ($MgSO_4$) solution was evaporated, and trituration of the resultant crystalline solid with ethyl acetate–ether gave 3.0 g (42%) of cream-colored crystals, m.p. 124–125° dec. Recrystallization from methanol gave pure **6**, m.p. 125–126° dec, λ_{max}^{KBr} 1650, 1690 cm^{-1} (C=O of thymine); λ_{max}^{MeOH} 263 nm (14000); p.m.r. spectrum δ 1.78 (singlet, 5-CH_3), 4.10 (singlet C-5′ protons) 5.30 (multiplet H-3′), 6.60 (quartet width 13.5 Hz, "*J*" 4.5, 9.0 Hz, H-1′) 7.20 (doublet $J_{6,5-CH_3}$ 1 Hz, H-6), 11.28 p.p.m. (singlet, 3-NH).

Anal. Calc. for $C_{10}H_{11}N_2O_3I$: C, 35.95; H, 3.32; N, 8.38. Found: C, 36.01; H, 3.36; N, 8.49.

Reaction of **6** *with silver acetate.* — Compound **6** (0.87 g), silver acetate (1.50 g) and triethylamine (0.5 ml) in dry "nanograde" (Mallinckrodt) acetonitrile (50 ml) were heated for 1.25 h under reflux with stirring. The hot solution was filtered through Celite and the filter was washed with warm, dry acetonitrile. The filtrate was concentrated and treated with gaseous hydrogen sulfide. The resultant mixture was filtered through Celite and then the filtrate was concentrated and applied to the short edge of a plate (400 × 200 × 2 mm) of SilicAR 7GF. The plate was developed twice with 4:1 chloroform–ethyl acetate. The main zone was excised and the product was extracted with methanol. The solution was evaporated to a syrup and applied to another plate of SilicAR 7GF and the processes were repeated. The final methanol extract was evaporated to a syrup and this syrup was extracted with chloroform. Removal of solvent gave a foam (0.24 g, 35%), λ_{max}^{EtOH} 265 nm (ε10,150).

A portion (0.22 g) of the syrup was dissolved in methanol (5 ml) containing concentrated ammonium hydroxide solution (5 ml), and the solution was kept for 1 h at room temperature. Evaporation of the solution gave partially crystalline material. Recrystallization from ethanol gave white crystals (40 mg, 21%) of crude **5**, m.p. 189–190°. Recrystallization from methanol–ethanol gave almost pure **5** (m.p. 205–206°) having an i.r. spectrum identical with that of authentic **5**. The mother liquor was examined by t.l.c. with ethyl acetate as developer and found to be a mixture of two components, an unknown, slower-moving component, and **5**. The mother liquor was evaporated and applied to the edge of a plate (400 × 200 × 2 mm) of SilicAR 7GF. The plate was developed twice with ethyl acetate and the major, slower-moving zone was excised and extracted with methanol. The extract was evaporated to a syrup, which was purified by t.l.c. once more. The p.m.r. spectrum of the purified, uncrystallized syrup showed δ1.73 (singlet 5-CH_3), 2.38–3.10 (multiplet, H-2′ and solvent), 3.92 (doublet "*J*" 5 Hz, C-5′ protons), 4.80–5.18 (multiplet H-3′ and HO-3′), 6.44 (quartet width 13.5 Hz, "*J*" 9.0, 4.5 H-1′) 7.10 (singlet H-6) 11.10 (singlet, 3-NH).

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