Carbohydrate Research, 38 (1974) C9–C11

Preliminary communication

Studies on 4-*C*-(hydroxymethyl)pentofuranoses. Synthesis of 9-[4-*C*-(hydroxymethyl)-α-L-*threo*-pentofuranosyl]adenine

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(Received August 19th, 1974; accepted, in revised form, September 24th, 1974)

All branched-chain furanose nucleosides[1] prepared thus far appear to be branched through C-2′, C-3′, or C-5′. The only 4′-*C*-substituted nucleoside derivative reported is nucleocidin (4′-fluoro-5′-*O*-sulfamoyladenosine)[2,3]. The novelty of this naturally occurring antibiotic prompted these syntheses of 4-*C*-hydroxymethylated pentofuranose derivatives and the conversion of one of them into 9-[4-*C*-(hydroxymethyl)-α-L-*threo*-pentofuranosyl]-adenine, the first example of a 4′-*C*-branched-chain carbohydrate nucleoside.

4-*C*-(Hydroxymethyl)-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose (3) was first synthesized by Schaffer[4] as an intermediate in the synthesis of L-apiose; the mixture of oxidation products[5] derived by periodate cleavage of 1,2-*O*-isopropylidene-α-D-glucofuranose (1), when condensed with formaldehyde under strongly basic conditions, gave 3. We prepared 3 by treating 1 with sodium periodate in aqueous solution and adding ethanol to precipitate inorganic material. The organic product was condensed with formaldehyde in aqueous sodium hydroxide solutions; a major product was formed (t.l.c.) within 2–3 h. The mixture was neutralized (acidic ion-exchange resin) after 16–20 h and the major component, isolated by column chromatography, crystallized from chloroform to give 50–60% of pure 3, m.p. 98–100°**; p.m.r. δ 5.87 (1H, d, H-1, $J_{1,2}$ 5 Hz), 5.27 (1H, d, 3-OH, J 5 Hz), 4.7–4.0 (4H), 3.6–3.3 (4H, CH_2), and 1.43 and 1.23 (two s, CMe_2). Addition of D_2O caused exchange of the OH protons and revealed signals of H-2 (δ 4.58, pair of d, $J_{2,3}$ 1.8 Hz), H-3 (4.17, d), and the methylene protons (4-proton s at δ 3.53).

Treatment of pure, crystalline 1,2-*O*-isopropylidene-α-D-allofuranose[6] (4) with periodate followed by condensation with 2.5 equiv. of formaldehyde in the presence of 2 equiv. of sodium hydroxide for 22 h yielded (t.l.c.) two closely migrating major components. The faster-migrating component was isolated pure by chromatography over silica gel and unexpectedly found to be compound 3. The second product, further purified by fractional crystallization from ethyl acetate–benzene, was 4-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (6), m.p. 114–115°; p.m.r. δ 5.65 (1H, d, H-1,

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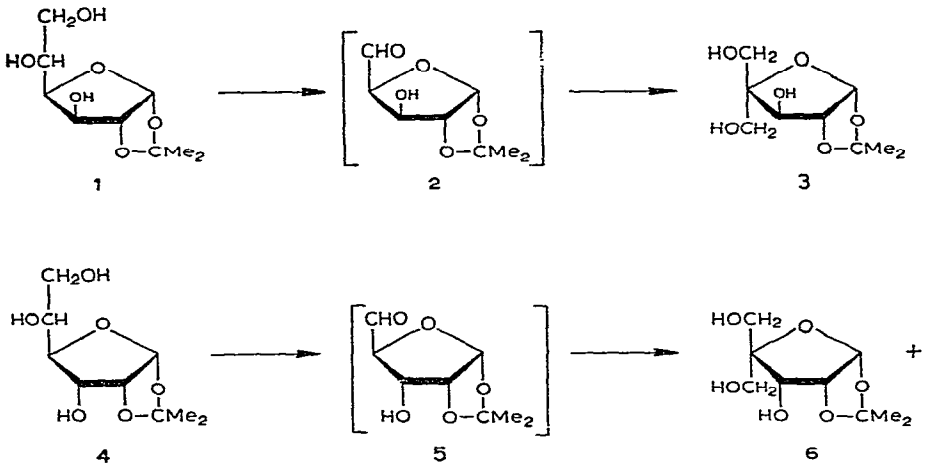
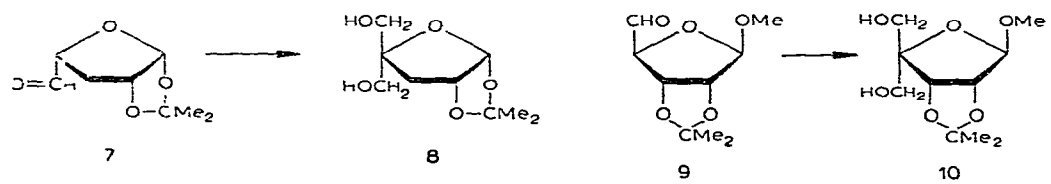
**Satisfactory C, H, and N analyses were obtained for all crystalline compounds reported. P.m.r. spectra were recorded in Me_2SO-d_6 with a Varian T-60A spectrometer.



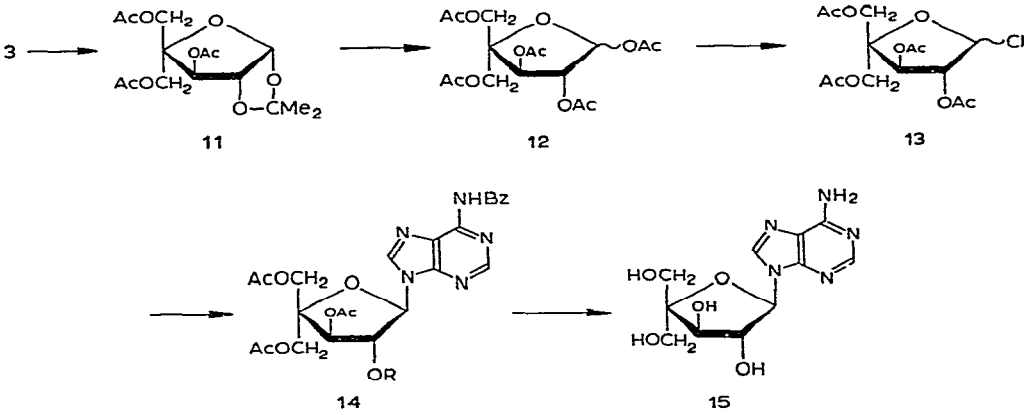
$J_{1,2}$ 3.5 Hz) and 4.92 (3-OH, d, J 5.5 Hz). Addition of D_2O exchanged this doublet and H-2 resonated as a quartet (δ 4.55, $J_{2,3}$ 1.8 Hz). The ratio of **3** to **6**, obtained in a combined yield of 80% based on **4**, was approximately 2:1. This epimerization of the 3-hydroxyl group was not observed during the formation of compound **3**, and reasons for it are not readily apparent. That the aldol–Cannizzaro sequence[4] during the conversion **2** → **3** did not require the presence of a free 3-hydroxyl group was demonstrated by the following experiments.

Treatment of the syrupy aldehyde **7**, obtained by periodate cleavage of 1,2-*O*-isopropylidene-3-deoxy-α-D-*xylo*-hexofuranose[7], with formaldehyde–base gave **8**, m.p. 91–93°, in 70% yield. The structure of **8** was clearly evident from p.m.r. spectroscopy, which showed the methylene resonances as a pair of sharp doublets (δ 3.42 and 3.32). On addition of D_2O, these doublets collapsed to singlets. Likewise, treatment of methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdofuranoside[8] (**9**) under the standard condensation conditions gave the anticipated 4-*C*-(hydroxymethyl) derivative **10**, m.p. 94–96.5°, although in somewhat lower yield.



The hydroxymethyl derivative **3** was converted into the syrupy triacetate **11**, acetolysis of which gave an approximately equal mixture of the anomeric pentaacetates **12**. This mixture was converted into the glycosyl chlorides **13** by treatment with titanium tetrachloride in refluxing chloroform and then condensed with 6-benzamidopurine by the mercuric cyanide–nitromethane procedure[9]. The syrupy nucleosidic product **14** was isolated by chromatography in 43% yield (based on **12**). The assignment of a 1′,2′-*trans* configuration for nucleoside **14** was made on the basis of Baker's *trans* rule[10] and by the

observation that the chemical shifts for the acetate protons[11] of **14** occur downfield from δ 2.04 in chloroform-*d* solution. Deacylation of **14** by aqueous ammonia gave crystalline 9-[4-*C*-(hydroxymethyl)-α-L-*threo*-pentofuranosyl]adenine (**15**), m.p. 251–253.5°; p.m.r. δ 5.83 (*J* 7.0 Hz, H-1′) in Me_2SO-d_6–D_2O.



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