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Synthesis of 2,3,5-Tri-O-benzyl- α - (and β -)-D-ribofuranosylethyne, Potential Intermediates for the Synthesis of C-Nucleosides

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Summary Two methods are described for the synthesis of the anomers of 2,3,5-tri-O-benzyl-D-ribofuranosyelthyne; the β -anomer has been converted into 1,2,3-triazole derivatives by reaction with benzyl azide.

WE have been interested in the preparation of D-ribofuranosyl derivatives of acetylene as potential intermediates for the synthesis of naturally occurring C-nucleoside antibiotics^{1,2} and related compounds³⁻⁶ by 1,3-dipolar additions⁷ and other reactions.

In the first method, the ribofuranose $(1)^8$ was treated with ethynylmagnesium bromide in tetrahydrofuran.⁹ The crude product was shown to be a mixture of epimers (2)and (3) by the n.m.r. spectrum of the derived mixture of diacetates (4) and (5); the isomer ratio, calculated both from the relative intensities of the acetylenic proton signals and from those of the C-methyl groups, was 7:3. That the predominant diol isomer had the D-altro-configuration (2) is shown later. The mixture of diols (2) and (3) was treated with toluene-p-sulphonyl chloride in pyridine and the resulting mixture chromatographed on silica gel. The major product, which crystallised after nine months, was the ribofuranosyl-ethyne (6) \ddagger [51% from (1)], m.p. 63—64°, $[\alpha]_{D}$ + 9.7° (c 4.9 in CHCl₃), together with a small amount of the impure syrupy anomer (7) (8%) and a mixture of disulphonates (8) and (9) (16%). The formation of cyclic, sulphur-free products was to be expected from the work of Rabinsohn and Fletcher;¹⁰ Gero¹¹ has recently described further examples. The assignment of the β -D-ribo-configuration (6) to the major product required some proof, and this was provided by the second method of synthesis now to be described.

The ribofuranosyl chloride $(10)^{12}$ reacted with ethynylmagnesium bromide¹³ in tetrahydrofuran to yield, after chromatography on silica gel, the β -D-*ribo*-compound (6) (8%), $[\alpha]_{\rm D} + 13.0^{\circ}$ (c 2.5 in CHCl₃), whose n.m.r. spectrum was indistinguishable from that of the compound assigned this structure above. The major product was the α -anomer (7)[†] (61%), m.p. 52–53°, $[\alpha]_{\rm D}$ + 79.7° (c 2.2 in CHCl₃). These two products were assigned the D-ribo-configuration



from their mode of formation from the chloride (10), and the anomeric configurations were assigned by Hudson's rule.

[†] This compound gave correct elemental analysis and spectroscopic data.

It was no surprise that the α -anomer (7) was the major product in the reaction from the chloride (10).12 Thus, the two methods of synthesis are complementary, the first giving a reasonable yield of the β -anomer and the second yielding mainly the α -anomer.

In the formation of the β -D-ribo-isomer (6) in the first synthesis it is assumed that monosulphonylation of the D-altro-diol (2) occurs to give the sulphonate (11) which undergoes ring closure by attack of the C-6 hydroxy-group at C-3, with inversion. The diol (2) is therefore the major product from the initial Grignard reaction. The impure α -D-ribo-compound would arise similarly from the D-allodiol (3) to form the sulphonate (12), followed by ring closure. There was evidence (t.l.c.) for the formation of small amounts of other sulphonate-free products. We assume these to be cyclic compounds of the L-lyxo-configuration arising from the monosulphonates (13) and (14).

When the acetylene (6) was hydrogenated (5% Pd-C), β -D-ribofuranosyl ethane (15), † $[\alpha]_{D}$ + 0.9° (c 1.14 in H₂O), was formed in high yield; the derived triacetate (16)[†] had $[\alpha]_{\rm D}$ + 6.2° (c 1.78 in MeOH). Similarly, from the acetylene (7) was formed the crystalline α -D-ribofuranosylethane (17), † m.p. 94–95°, $[\alpha]_{D}$ + 32.7° (c 1.5 in H₂O); triacetate (18),† $[\alpha]_{p}$ + 43.9° (c 0.7 in MeOH). The specific rotations of compounds (16)-(18) agree with the earlier assignments of anomeric configuration to (6) and (7).

The acetylene (6) was heated with benzyl azide^{14,15} to give, in very high yield, a mixture of isomeric triazoles (19)[†] and (20).[†] The isomers were separated by treatment with ethanol, from which one of them crystallised virtually quantitatively (41%), m.p. 125–126°, $[\alpha]_{D} + 13^{\circ}$ (c 1.38 in CHCl₃). The other isomer (49%) was a syrup, $[\alpha]_{\rm D} - 20.5^{\circ}$ (c 1.95 in CHCl₃). Analytical and spectral data (n.m.r. and mass spectrum) left no doubt that the two compounds were isomeric, but no decision could be made between the two structures.

The ribosylacetylenes (6) and (7) should be versatile intermediates for the elaboration of the heterocyclic ring systems present in the C-nucleosides showdomycin,¹ formycin B,² and variants of these structures.

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