Synthesis of the Anomeric Methyl 4-Thio-D-arabinofuranosides

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CARBOHYDRATE analogues in which the hemiacetal ring oxygen atom has been replaced by sulphur, nitrogen, and carbon are of chemical and biochemical interest because of the potential usefulnes of their derivatives as medicinal agents.

Since certain nucleosides of D-arabinose possess antitumour activity,[1] it is of interest to prepare and evaluate nucleosides containing the analogue 4-thio-D-arabinose. Although a recent report[2] describes the conversion of 9-(4-thio-β-D-xylofuranosyl)adenine to 9-(4-thio-β-D-arabinofuranosyl)adenine, the availability of 4-thio-D-arabinose will make possible the synthesis of a variety of nucleosides of this carbohydrate analogue. We report the synthesis of the anomeric methyl 4-thio-D-arabinofuranosides.

Hydrolysis of 5-*S*-acetyl-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (I)[3] in 50% aqueous acetic acid at 70° gave a good yield of crystalline 5-*S*-acetyl-3,6-di-*O*-benzyl-5-thio-D-glucofuranose (II), m.p. 104—105°, $[\alpha]_D^{25}$ −40° ($CHCl_3$). The presence of the *S*-acetyl group was confirmed by an absorption in the i.r. spectrum at 1685 cm.$^{-1}$ and by a resonance in the n.m.r. spectrum at τ 7·76. The absence of a signal between τ 8·5 and 8·7 confirmed the absence of the isopropylidene group. Compound (II) was characterized further as the 1,2-di-*O*-acetyl derivative, m.p. 85—86°, $[\alpha]_D^{26}$ + 1·2° ($CHCl_3$), the n.m.r. spectrum for which integrated for 30 protons and indicated the presence of the *S*-acetyl group at τ 7·73 and of the *O*-acetyl groups at τ 7·95 and τ 7·98. The presence of these groups was shown also in the i.r. spectrum with absorption maxima at 1740 (*O*-acetyl) and 1685 cm.$^{-1}$ (*S*-acetyl).

Oxidation of (II) in ethanol with 1·1 mol. sodium periodate dissolved in an equal volume of water gave a quantitative yield of 4-*S*-acetyl-2,5-di-*O*-benzyl-4-thio-*aldehydo*-D-arabinose which exhibited absorptions at 1685 cm.$^{-1}$ (*S*-acetyl) and 1730 cm.$^{-1}$ (aldehyde) in the i.r. spectrum. Refluxing this aldehyde in 0·5% methanolic hydrogen chloride gave a mixture of the anomeric methyl 2,5-di-*O*-benzyl-4-thio-D-arabinofuranosides [(III) and (IV)]. These anomers were separated readily on a column of silica gel by use of benzene–ethyl acetate, 10 : 1 (v/v).

The n.m.r. spectrum of methyl 2,5-di-*O*-benzyl-4-thio-α-D-arabinofuranoside (III), m.p. 43—44°, $[\alpha]_D^{25}$ + 112° ($CHCl_3$), integrated for 24 protons, as did the n.m.r. spectrum of methyl 2,5-di-*O*-benzyl-4-thio-β-D-arabinofuranoside (IV), m.p. 74—75°, $[\alpha]_D^{25}$ − 139° ($CHCl_3$). The absence of an absorption between 1680—1700 cm.$^{-1}$ in the i.r., and of a resonance signal between τ 7·6—7·8 in the n.m.r. spectrum, confirmed the absence of the *S*-acetyl group in both (III) and (IV).

Debenzylation of (III) and of (IV) with sodium in liquid ammonia and 1,2-dimethoxyethane gave methyl 4-thio-α-D-arabinofuranoside (V), m.p. 71—72°, $[\alpha]_D^{25}$ + 299° (MeOH), and syrupy methyl 4-thio-β-D-arabinofuranoside (VI), $[\alpha]_D^{25}$ − 156° (MeOH), respectively. The assignment of anomeric

configuration to (V) and (VI) was made by analogy with the known methyl D-arabinofuranosides.[4]

Elemental analyses for all new compounds agreed satisfactorily with the calculated value for the proposed structures.

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