Synthesis of the Anomeric Methyl 2-Deoxy-4-thio-D-erythro-pentofuranosides

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4-THIO-β-D-RIBOFURANOSYL-PURINES[1] and -PYRIMIDINES[2] have been found to possess antibiotic and antileukaemic action.[3] In view of this, we have synthesised nucleosides containing the 2-deoxy-4-thio-β-D-ribofuranosyl unit. We report here the preparation of methyl 2-deoxy-4-thio-α- and β-D-*erythro*-pentofuranosides.

The starting material, 3-deoxy-1,2-*O*-isopropylidene-D-*ribo*-hexofuranose[4,5] (V) was prepared in very high yields from 1,2 : 5,6-di-*O*-isopropylidene-3-*O*-tosyl-α-D-glucofuranose (I). The S_N2 displacement of the 3-*O*-tosyloxy-group in (I), with potassium thiolacetate in *NN*-dimethylformamide (DMF) gave 3-*S*-acetyl-1,2 : 5,6-di-*O*-isopropylidene-3-thio-α-D-allofuranose (II) which on selective hydrolysis with 50% aqueous acetic acid gave 3-*S*-acetyl-1,2-*O*-isopropylidene-3-thio-α-D-allofuranose (III). Acetylation of compound (III) furnished 5,6-di-*O*-acetyl-3-*S*-acetyl-1,2-*O*-isopropylidene-3-thio-α-D-allofuranose (IV) which on desulphurization with Raney nickel in refluxing ethanol followed by deacetylation gave compound (V) in an overall yield of 55·6% based on compound (I).

Treatment of compound (V) in dry pyridine at −15° with a solution of benzoyl chloride (1.1 equiv.) in alcohol-free chloroform gave 6-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-D-*ribo*-hexofuranose (VI) (80%), m.p. 135—136°, $[\alpha]_D^{25}$ −4·25° (*c* 0·998, $CHCl_3$). Treatment of (VI) with toluene-*p*-sulphonyl chloride in pyridine–chloroform at 40° for 18 hr. gave an essentially quantitative yield of 6-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulphonyl)-D-*ribo*-hexofuranose (VII), m.p. 121—122°, $[\alpha]_D^{25}$ + 16·06°, (*c* 1·007, $CHCl_3$). A chloroform solution of (VII) with

sodium methoxide in methanol, initially at −15° for 2 hr. and then at 0° for 18 hr., gave 5,6-anhydro-3-deoxy-1,2-*O*-isopropylidene-L-*lyxo*-hexofuranose (VIII) (94%), b.p. 75°/0·5 mm, $[\alpha]_D^{25}$ − 27·6° (*c* 1·1, $CHCl_3$). Ring opening of (VIII) with sodium benzyl oxide in benzyl alcohol at 25° for 18 hr. gave 6-*O*-benzyl-3-deoxy-1,2-*O*-isopropylidene-L-*lyxo*-hexofuranose (IX) (90%), m.p. 39—40°, $[\alpha]_D^{25}$ −2·14° (*c* 1·03, $CHCl_3$). Compound (IX) in pyridine, on addition of toluene-*p*-sulphonyl chloride in chloroform at 40° for 18 hr., gave 6-*O*-benzyl-3-deoxy-1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulphonyl)-L-*lyxo*-hexofuranose (X) (95%), m.p. 59—60°, $[\alpha]_D^{25}$ −17·9° (*c* 1·05, $CHCl_3$). S_N2 displacement of the tosyloxy-group in (X) with potassium thiolacetate (4 equiv.) in dry DMF at 115° for 2 hr. in a current of N_2 gave 5-*S*-acetyl-6-*O*-benzyl-3-deoxy-1,2-*O*-isopropylidene-5-thio-D-*ribo*-hexofuranose (XI) (85·2%) m.p. 48°, $[\alpha]_D^{25}$ −10·08° (*c* 1·13, $CHCl_3$).

Hydrolysis of compound (XI) with 50% aqueous acetic acid at 50° for 24 hr. in nitrogen removed the isopropylidene group selectively to give 5-*S*-acetyl-6-*O*-benzyl-3-deoxy-5-thio-D-*ribo*-hexofuranose (XII) (96%), m.p. 86—88°, $[\alpha]_{25}^{D}$ −50° (*c* 1, $CHCl_3$). Oxidation of (XII) in ethanol with sodium periodate (1·1 mol.) dissolved in an equal volume of water gave a quantitative yield of 4-*S*-acetyl-5-*O*-benzyl-2-deoxy-4-thio-*aldehydo*-D-ribose (XIII) which exhibited i.r. absorptions at 1685 cm.$^{-1}$ (*S*-acetyl) and 1730 cm.$^{-1}$ (aldehyde). Compound (XIII) was immediately treated with 0·25% methanolic hydrogen chloride at 25° for 18 hr. to give a mixture of the anomeric methyl 5-*O*-benzyl-2-deoxy-4-thio-D-*erythro*-pentofuranosides (XIV) and (XV). These anomers were separated readily on a silica gel column with benzene–ethyl acetate 6 : 1 (v/v) as eluant, to give syrupy α-D-isomer (XIV) (26·6%), $[\alpha]_D^{25}$ + 212·5° (*c* 1·04, $CHCl_3$) and syrupy β-D-isomer (XV) (52·8%), $[\alpha]_D^{25}$ − 186·7° (*c* 1·13, $CHCl_3$). The i.r. spectra of the compounds (XIV) and (XV) showed no *S*-acetyl absorption at 1685 cm.$^{-1}$. The stereochemistry of the anomeric centres was temporarily assigned on the basis of Hudson's rules of isorotation[6] which correlate optical rotation and anomeric configuration.

Debenzylation of (XIV) and of (XV) with sodium in liquid ammonia gave syrupy methyl 2-deoxy-4-thio-α-D-*erythro*-pentofuranoside (XVI) $[\alpha]_D^{25}$ + 315° (*c* 1, $CHCl_3$) and methyl 2-deoxy-4-thio-β-D-*erythro*-pentofuranoside (XVII), $[\alpha]_D^{25}$ − 277·6° (*c* 1·03, $CHCl_3$). The n.m.r. spectrum of the α-D-isomer (XVI) in $CDCl_3$ integrated for 12 protons, showed the anomeric proton signal as a quartet (a clear doublet of doublets) centred at τ 4·93 [$J_{(H1,H2a)}$ + $J_{(H1,H2b)}$ 6 Hz], the 2-proton signals as a series of poorly resolved multiplets centred at τ 7·72, and the *O*-methyl proton signals at τ 6·7. The n.m.r. spectrum of the β-D-isomer (XVII) also integrated for 12 protons of which the anomeric proton gave a quartet centred at τ 5·07 [$J_{(H1,H2a)}$ + $J_{(H1,H2b)}$ 7 Hz], the 2-protons gave multiplets centred at τ 7·72, and the *O*-methyl protons resonated at τ 6·74. These findings are in agreement with some of the spectral data provided by Leonard, *et al.*,[7] on the corresponding oxygen analogue.

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[1] E. J. Reist, D. E. Gueffroy, and L. Goodman, *J. Amer. Chem. Soc.*, 1964, **86**, 5668.
[2] B. Urbas and R. L. Whistler, *J. Org. Chem.*, 1966, **31**, 813.
[3] A. Bloch and R. L. Whistler, unpublished work.
[4] M. Černy and J. Pacak, *Coll. Czech. Chem. Comm.*, 1956, **21**, 1003.
[5] E. J. Hedgley, W. G. Overend, and R. A. Rennie, *J. Chem. Soc.*, 1963, 4701.
[6] C. S. Hudson, *J. Amer. Chem. Soc.*, 1909, **31**, 66; C. S. Hudson, *Adv. Carbohydrate Chem.*, 1948, **3**, 1.
[7] N. J. Leonard, F. C. Sciavolino, and V. Nair, *J. Org. Chem.*, 1968, **33**, 3169.