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Synthesis of 4'-Thiocordycepin

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Summary 4'-Thiocordycepin [9-(3-deoxy-4-thio- β -D-erythro-pentofuranosyl)adenine], an analogue of the nucleoside antibiotic cordycepin, has been synthesised by a route involving addition of the pseudohalogen iodine nitrate to an unsaturated sugar.

STRUCTURAL changes at C-3 of the D-ribose system of purine nucleosides have resulted in nucleosides with antibiotic and/or antitumour properties.¹ The 3'-deoxyadenine nucleoside antibiotics puromycin and cordycepin (3'deoxyadenosine)² have been excellent tools for studying numerous biochemical reactions. Here we report the synthesis of 4'-thiocordycepin (9). There has been considerable recent interest in the synthesis of carbohydrates containing heteroatoms other than oxygen in the ring, especially nitrogen or sulphur.³ Some of the sulphurcontaining analogues, particularly nucleoside derivatives,⁴ have exhibited interesting biological properties; 4c,4e,5 for example, some 4'-thio-analogues of the nucleoside antibiotic toyocamycin have been recently reported 4e to be effective inhibitors of the growth of leukemia L-1210 cells *in vitro*.

The present synthesis involved hydration of the readily available unsaturated sugar $(1)^{6}$,[†] by way of the addition of the pseudohalogen iodine nitrate.⁸ Thus, treatment of (1) with silver nitrate and iodine in acetonitrile afforded in 90% yield a syrupy mixture in which the iodo-nitrate (2) preponderated. When a solution of the syrup in ethanol and triethylamine containing Raney nickel was subjected to a hydrogen pressure, there was an initial conversion into three compounds, which were isolated by column chromatography,[‡] namely, the unsaturated sugar (1) (11%), the syrupy 3-iodo-glycoside (3) {68%; $[\alpha]_D + 110^\circ$ (c 1·25)}, and benzyl 2-O-benzyl-4-deoxy-4-iodo- α -D-xylo-pentopyr-

[†] Compound (1) was originally prepared⁶ by heating benzyl 2-O-benzyl-β-L-arabinopyranoside 3,4-thionocarbonate in trimethyl phosphite. In the present work, (1) was more conveniently obtained in high yield from benzyl 2-O-benzyl-3,4-bis-O-(methylsul-phonyl)-β-L-arabinopyranoside by treatment with a large excess of sodium iodide in refluxing NN-dimethylformamide in the presence of zinc dust (Tipson-Cohen procedure⁷).

 \pm Column chromatography was performed on silica gel. Optical rotations were measured at $26 \pm 3^{\circ}$ in chloroform, unless otherwise stated. N.m.r. spectra were determined in [²H]chloroform at 60 MHz unless otherwise stated. Satisfactory elemental analyses were obtained for compounds (2), (5), (6), (7), and (9).

anoside $\{10\%; \text{ m.p. } 89-91^\circ, [\alpha]_D + 130^\circ (c \ 1.34)\}$.§ Further hydrogenation of (3) over Raney nickel afforded the key intermediate (4) in 55% overall yield from (1); $[\alpha]_D + 135^\circ$ (c 1.83). The alcohol (4) gave a crystalline toluene-p-sulphonate (5) in 76% yield; m.p. 57–58°, $[\alpha]_D$ + 99° (c 1·33). The observation of the n.m.r. signal for H-4 in compound (5) at τ 5.30 as a narrow band (width⁹ ca. 8 Hz) was consistent with the axial orientation of the p-tolylsulphonyloxy-group, and (5) being in the C1(L)conformation.

Heating the toluene-p-sulphonate (5) for 48 h at reflux temperature in methanol containing toluene-a-thiol and sodium methoxide afforded, in almost quantitative yield, the 4-S-benzyl glycoside (6), b.p. 168-173° at 0.10 Torr, $[\alpha]_{\rm D}$ +62° (c 1.08). The observation of the n.m.r. signal for H-4 at τ 7.31 as a seven-line multiplet ($J_{4,5ax}$ 10.0, $J_{33x,4}$ 10.5, $J_{3eq,4} = J_{4,5eq} = 5.0 \text{ Hz}$ indicated the equatorial orientation for the S-benzyl group with compound (6) in the C1(D) conformation. All of the benzyl groups in (6) were removed with sodium in liquid ammonia, and the resultant free sugar was converted, on treatment with



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benzoyl chloride-pyridine, into a 1:3 mixture of the α - and β -anomers, respectively, of the 4-thio-sugar (7). The α anomer was obtained in crystalline form by trituration of the benzoylation product with methanol containing a small amount of diethyl ether, and had m.p. 140–141°, $[\alpha]_D$ + 249° (c 1.08); τ 3.39 (1H, d, $J_{1,2}$ 4.3 Hz, H-1) and 4.21 (1H, 6-line m, $J_{2,3} = J_{2,3'} = 7.8$ Hz, H-2). The β -anomer was obtained as a homogeneous syrup by column chromatography; $[\alpha]_D - 110^\circ$ (c 1·30); τ 3·58br (1H, s, $J_{1,2}$ ca. 0·5 Hz) and 4.10 (1H, narrow m, J_{2.3} 2.5, J_{2.3}, 3.4 Hz, H-2). The presence of thiofuranoid rings in the crystalline and syrupy tribenzoates was confirmed by the absence of S-benzoyl carbonyl bands in their i.r. spectra.

Each anomer of (7) was separately treated, in 1,2-dichloroethane for 7 h at reflux temperature, with 6-benzamido-9chloromercuripurine, in the presence of titanium tetrachloride, 40,10 to give, after column chromatography, the protected nucleoside (8) as a white, brittle foam (82 and 78%yields from the α - and β -anomers, respectively), m.p. 135°, $[\alpha]_{\rm D} = -25^{\circ} \ (c \ 1.05); \ \tau \ 3.62 \ (1\text{H}, \ \text{d}, \ J_{1.2} \ 2.5 \ \text{Hz}, \ \text{H-1'}), \ 3.97$ (1H, 4-line m, $J_{2',3'} + J_{2',3''} = 7.0$ Hz, H-2'). As regards the assignment of the β -anomeric configuration to (8), it is noteworthy that the H-2' signals in the n.m.r. spectra of (8) and the β -anomer of (7) were observed in each case as a narrow multiplet; moreover, the two H-5' nuclei were observed as the A₂ portion of an apparent A₂B spin system in the spectrum of the α -anomer of (7), and as the AB portion of an ABX system in the spectra of (8) and the β -anomer of (7). The nucleoside (8) was deacylated by treatment with methanolic sodium methoxide for 2 h at reflux temperature to give 4'-thiocordycepin (9) as white needles [75% yield from (8)], m.p. 257-260° (decomp.) (from methanol), $[\alpha]_D - 55^\circ$ (c 0.09 in MeOH), -34° (c 1.09 in Me₂SO); λ_{max} (MeOH) 261 nm (ϵ 14,900); τ [(CD₃)₂SO- D_2O 4·11(d, $J_{1',2'}$ 3·4 Hz, H-1').¶

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§ The structures assigned to the latter two compounds were corroborated by their conversions into 3-deoxy-threo- and 2-deoxythreo-L-pentitol tetra-acetates, respectively, on reductive deiodination with Raney nickel, followed by O-debenzylation with sodium in liquid ammonia, reduction of the resultant free sugars with sodium borohydride, and finally acetylation of the pentitols with acetic anhydride-pyridine. The structures of the two tetra-acetates were established by comparison with authentic samples (g.l.c., mass spectrometry, and polarimetry). The *L-lyzo-* and *D-xylo-*configurations were assigned to the 3-deoxy-3-iodo- and 4-deoxy-4-iodo-compounds, respectively, on the assumption that a usual, *trans*-addition (*cf.* refs. 8*c* and *d*) of iodine nitrate had occurred to the unsaturated sugar (1). Evidence for a *trans*-addition was obtained from the n.m.r. spectrum of the mixture of adducts; the observation of the signal for H-4 of the preponderant adduct (2) at $\tau 4.70$ as a broad band (width 15 Hz) indicated the diequatorial arrangement of the iodo- and nitrate groups at C-3 and C-4, respectively, with (2) being in the 1C (L) conformation.

¶ In the n.m.r. spectra of a number of 9- β -D-ribofuranosylpurines in [²H₆]dimethyl sulphoxide, the chemical shift of H-1' is characteristic ($\tau 4.0 - 4.2$).¹¹

¹ For a comprehensive review of 3'-deoxypurine nucleosides, see R. J. Suhadolnik, 'Nucleoside Antibiotics,' Wiley-Interscience, New York, 1970, pp. 1-95.

² For a review of cordycepin, see ref. 1, pp. 50-76.

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