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 sulphur-containing 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*.

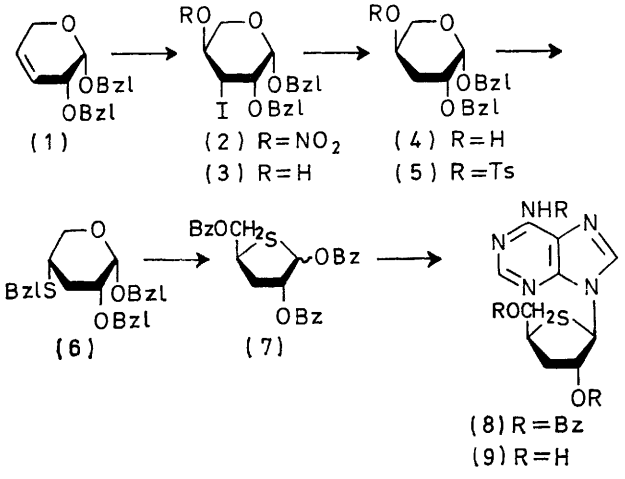
The present synthesis involved hydration of the readily available unsaturated sugar (**1**)[6],† by way of the addition of the pseudohalogen iodine nitrate.[8] Thus, treatment of (**1**) with silver nitrate and iodine in acetonitrile afforded in 90% yield a syrupy mixture in which the iodo-nitrate (**2**) 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° (*c* 1·25)}, and benzyl 2-*O*-benzyl-4-deoxy-4-iodo-α-D-*xylo*-pentopyr-

† Compound (**1**) was originally prepared[6] 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*-(methylsulphonyl)-β-L-arabinopyranoside by treatment with a large excess of sodium iodide in refluxing *NN*-dimethylformamide in the presence of zinc dust (Tipson–Cohen procedure[7]).

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

anoside {10%; m.p. 89—91°, $[\alpha]_D$ + 130° (*c* 1·34)}.§ Further hydrogenation of (**3**) over Raney nickel afforded the key intermediate (**4**) in 55% overall yield from (**1**); $[\alpha]_D$ + 135° (*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 (width[9] *ca.* 8 Hz) was consistent with the axial orientation of the *p*-tolylsulphonyloxy-group, and (**5**) being in the *C*1(L) conformation.

Heating the toluene-*p*-sulphonate (**5**) for 48 h at reflux temperature in methanol containing toluene-α-thiol and sodium methoxide afforded, in almost quantitative yield, the 4-*S*-benzyl glycoside (**6**), b.p. 168—173° at 0·10 Torr, $[\alpha]_D$ +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, $J_{3ax,4}$ 10·5, $J_{3eq,4} = J_{4,5eq}$ = 5·0 Hz) indicated the equatorial orientation for the *S*-benzyl group with compound (**6**) in the *C*1(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 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° (*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-9-chloromercuripurine, in the presence of titanium tetrachloride,[4b,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°, $[\alpha]_D$ −25° (*c* 1·05); τ 3·62 (1H, d, $J_{1,2}$ 2·5 Hz, 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 A_2 portion of an apparent A_2B 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° (*c* 0·09 in MeOH), −34° (*c* 1·09 in Me_2SO); λ_{max} (MeOH) 261 nm (ϵ 14,900); τ [$(CD_3)_2SO$–D_2O] 4·11(d, $J_{1',2'}$ 3·4 Hz, H-1′).¶

Biological evaluation of 4′-thiocordycepin is in progress.

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§ The structures assigned to the latter two compounds were corroborated by their conversions into 3-deoxy-*threo*- and 2-deoxy-*threo*-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-*lyxo*- 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 τ 4·70 as a broad band (width[9] 15 Hz) indicated the diequatorial arrangement of the iodo- and nitrate groups at C-3 and C-4, respectively, with (**2**) being in the 1*C* (L) conformation.

¶ In the n.m.r. spectra of a number of 9-β-D-ribofuranosylpurines in [$^2H_6$]dimethyl sulphoxide, the chemical shift of H-1′ is characteristic (τ4·0—4·2).[11]

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[2] For a review of cordycepin, see ref. 1, pp. 50—76.

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