New Approach to Aminoglycoside Antibiotics

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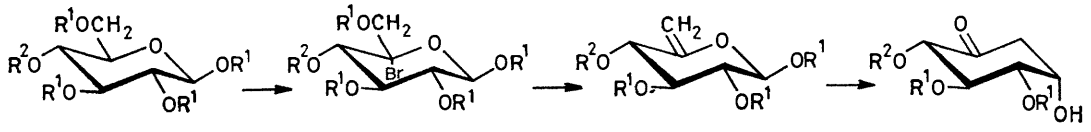
Summary Photobromination of peracylated hexopyranoses and treatment of the resultant 5-bromo-derivatives with zinc and acetic acid afforded 6-deoxy-5-enose esters which, with mercury(II) salts in aqueous media, gave 2-deoxyinosose triesters, applied to β-D-maltose octa-acetate, these procedures afforded an α-glucosylated inosose derivative which on further α-glycosylation gave a 'pseudotrisaccharide' related to those upon which aminoglycoside antibiotics are based

WE have recently reported that penta-*O*-acyl-β-D-glucopyranoses (**1**) and (**2**), on treatment with bromine radicals generated photochemically from bromine or *N*-bromosuccinimide, undergo substitution at C-5,[1,2] and that the products (**3**) and (**4**), with zinc and acetic acid, afford mainly the corresponding 6-deoxyhex-5-enopyranose esters (**5**) and (**6**), respectively [3] In addition, we have shown that such alkenes are converted into 2-deoxyinosose triesters when heated in aqueous media in the presence of mercury(II) salts [4] By a combination of these processes the inososes (**7**) and (**8**) have now been produced as shown, and in 45 and 50% yield, from penta-*O*-acetyl- and -*O*-benzoyl-β-D-glucopyranose, respectively The acetate (**7**) has m p 142—144 °C, $[\alpha]_D$ −5 5° ($CHCl_3$), and the benzoate (**8**) m p 196—197 °C, $[\alpha]_D$ −4° ($CHCl_3$), and both give ^1H n m r spectra consistent with the assigned structures In particular, the methylene group resonances are observable near δ 2·7 and 2·9, H-1 signals are at δ 4·35 and 4·6, respectively, and the configurations at all the chiral centres are readily determined from the ring proton splitting patterns The stereochemistry at the new chiral centres (C-1, carbohydrate numbering) is the same as was found for the original rearrangement product [4]



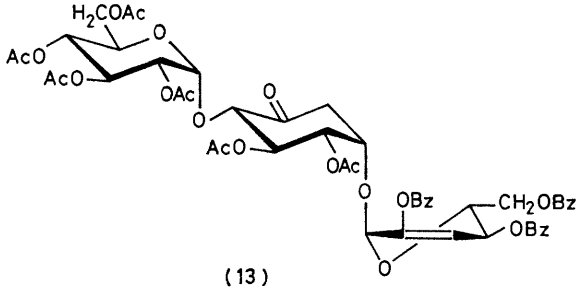
	R^1	R^2		R^1	R^2		R^1	R^2		R^1	R^2
(**1**)	Ac	Ac	(**3**)	Ac	Ac	(**5**)	Ac	Ac	(**7**)	Ac	Ac
(**2**)	Bz	Bz	(**4**)	Bz	Bz	(**6**)	Bz	Bz	(**8**)	Bz	Bz
(**9**)	Ac	Ac_4G	(**10**)	Ac	Ac_4G	(**11**)	Ac	Ac_4G	(**12**)	Ac	Ac_4G

Ac_4G = tetra-*O*-acetyl-α-D-glucopyranosyl

Whereas glycopyranosyl esters react with bromine radicals at C-5, methyl tetra-*O*-benzoyl-β-D-glucopyranoside afforded 48% of a 2-bromoaldono-1,5-lactone ester,[5] suggesting that initial radical abstraction occurred in this case at the anomeric centre. It was also observed that α-anomers of both glycopyranosides[6] and glycopyranosyl esters[2] react less readily than do the corresponding β-compounds, conceivably because, with the α-glycosides, the equatorial anomeric hydrogen atoms are less readily abstracted[7] and, with the glycosyl esters, the axial acyloxy groups at C-1 inhibit approach by bromine radicals to the *syn*-axial hydrogen atoms at C-5. It was therefore rationalised that octa-*O*-acetyl-β-D-maltose (**9**), on photobromination, could give the 5-bromide (**10**), and when it was treated in boiling carbon tetrachloride in the presence of *N*-bromosuccinimide and under a 275 W tungsten filament, reflector heat lamp for 2 h, a chromatographically more mobile product was obtained, as anticipated, together with several less mobile compounds. Treatment of the unfractionated mixture with zinc and acetic acid, followed by chromatography on a column of silica gel, gave the known alkene (**11**) in 12% yield after recrystallisation from methanol. Recrystallised further from ether—light petroleum, it had m.p. 132—134 °C [α] + 60° ($CHCl_3$), ν_{max} 1665 cm^{-1} (C=C str). It has previously been prepared[8] by an 8-step procedure, and in about 6% yield, from compound (**9**) [m.p. 128—131·5 °C, [α] +64° ($CHCl_3$)].

When the alkene (**11**) was treated in refluxing aqueous acetone with a trace of added acetic acid, in the presence of mercury(II) acetate, the expected rearrangement[4] occurred to give the glycosylinosose (**12**) as a syrup, $[\alpha]_D$ +77° ($CHCl_3$). The ^1H n.m.r. spectrum of this product showed the 2-proton resonance at δ 2·7 expected for the carbocyclic product as well as other consistent spectral features.

This product possesses basic structural features of many 'pseudodisaccharides' of the aminoglycoside antibiotic group;[9] in particular, the interunit linkage has the required α-configuration. Furthermore, it has one free hydroxy-group rendering it subject to specific further glycosylation; and when treated with 1,5-anhydro-2,3,4,6-tetra-*O*-benzoyl-D-*arabino*-hex-1-enitol in cooled dichloroethane in the presence of boron trifluoride–ether,[10] it gave the crystalline α,α-linked 'pseudotrisaccharide' (**13**) [m.p. 94—97 °C, [α] +110° ($CHCl_3$)] in 68% yield after chromatographic purification. This product had a ^1H n.m.r. spectrum with the appropriate acetyl and benzoyl resonances, the signal for the methylene group of the inosose moiety (δ 2·6), and a broadened singlet at δ 6·00 which is characteristic of that expected for H-3 of the unsaturated unit.[10]



(13)

Compound (**13**) contains the di-*O*-α-D-hexopyranosylcyclohexane structure common to many antibiotic substances, although the relationship of the glycosyl units is 1,4 rather than the normal 1,3.[9] The glycosylation procedure involving the unsaturated sugar derivative has been used before to prepare α-linked unsaturated 'pseudodisaccharides' from which biologically active unprotected compounds containing deoxy- and aminodeoxy-groups have been prepared,[11] and, in parallel work, diglycosylation of a 2,5-dideoxystreptamine derivative with tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol gave a 'pseudotrisaccharide' derivative containing two double bonds from which unprotected antibiotics were obtained.[12]

The New Zealand Ministry of Foreign Affairs is thanked for the award of a Bilateral Aid Programme Postgraduate Scholarship (to P.P.).

(*Received, 4th July* 1980; *Com.* 725.)

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