Syntheses of Derivatives of L-Tolyposamine and L-Forosamine [1]

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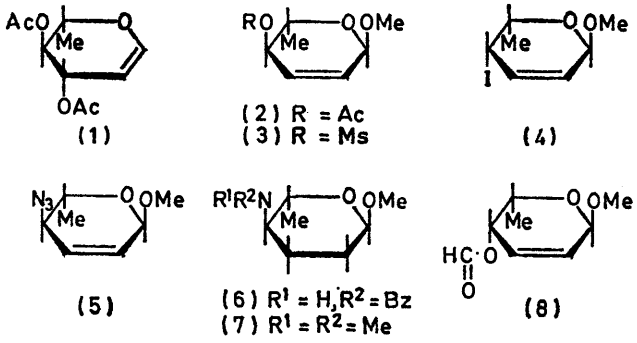
Methyl 4-benzamido-2,3,4,6-tetradeoxy-α-L-*erythro*-hexopyranoside (methyl *N*-benzoyl-α-L-tolyposaminide) (6) and methyl 2,3,4,6-tetradeoxy-4-dimethylamino-α-L-*erythro*-hexopyranoside (methyl α-L-forosaminide) (7) have been synthesized by way of an iodide displacement on the allylic sulphonate, methyl 2,3,6-trideoxy-4-*O*-methylsulphonyl-α-L-*erythro*-hex-2-enopyranoside (3), followed by an azide displacement on the resulting iodide (4).

WE have recently reported [2] the boron trifluoride-catalysed rearrangement of 3,4-di-*O*-acetyl-L-rhamnal (1) in methanol to, *inter alia*, methyl 4-*O*-acetyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (2), and the subsequent conversion of the latter compound into the allylic sulphonate (3). The use of this rearrangement in the synthesis of derivatives of L-amicetose (2,3,6-trideoxy-L-*erythro*-hexose) [3] and L-ossamine (2,3,4,6-tetradeoxy-4-dimethylamino-L-*threo*-hexose) [4] was described. This work has now been extended to provide stereo-



specific syntheses of derivatives of two other rare sugars, namely L-tolyposamine (4-amino-2,3,4,6-tetradeoxy-L-*erythro*-hexose) [5] and L-forosamine (2,3,4,6-tetradeoxy-4-dimethylamino-L-*erythro*-hexose).[6]

Synthesis of the foregoing amino-sugar derivatives was achieved by a double inversion of configuration at C-4 of the allylic sulphonate (3). Treatment of compound (3) with sodium iodide in acetone at room temperature yielded a crystalline iodo-derivative identified as methyl 2,3,4,6-tetradeoxy-4-iodo-α-L-*threo*-hex-2-enopyranoside (4). This assignment was based on the expectation [7] of achieving an S_N2 displacement with the allylic sulphonate (3) and on the assumption that no significant further displacements occurred with the allylic iodo-derivative (4). Subsequent conversion of the latter compound into derivatives of known stereochemistry [*e.g.* (7)] verified the structure assigned. Treatment of the allylic iodide (4) with sodium azide in refluxing aqueous acetone gave the highly volatile azide (5), which was used without extensive purification to minimize losses of material. Methyl 4-benzamido-2,3,4,6-tetradeoxy-α-L-*erythro*-hexopyranoside (methyl *N*-benzyl-α-L-tolyposaminide) (6) was obtained from the azide (5) following hydrogenation over a platinum catalyst and benzoylation of the resulting amine. Although the physical constants of the synthetic derivative showed slight differences (see Experimental section) from those reported [5] for the same derivative prepared from the antibiotic tolypomycin Y, the i.r. spectra of the two materials were indistinguishable.

Hydrogenation of an ethanolic solution of the azide (5) over Raney nickel in the presence of formaldehyde led to reductive *N*-dimethylation of the amine to give methyl 2,3,4,6-tetradeoxy-4-dimethylamino-α-L-*erythro*-hexopyranoside (methyl α-L-forosaminide) (7). The physical constants and n.m.r. spectrum of this compound showed the expected agreement with those of the D-isomer,[8] whose conversion into the free sugar has been described. D-Forosamine is a component of the spiramycin (foromacidin) antibiotics.[6,9]

Attempts to invert the configuration of the allylic sulphonate (3) at C-4 by exchange with acetate or benzoate ions in hot *NN*-dimethylformamide gave complex mixtures of products, but in neither case was the desired ester (an L-rhodinose precursor [10]) isolated. Preparative chromatography of the products from the acetate exchange afforded a low yield of a crystalline compound, suggested by elemental analyses and spectroscopic data to be methyl 2,3,6-trideoxy-4-*O*-formyl-α-L-*threo*-hex-2-enopyranoside (8). The presence of a formate ester group was suggested by the strong i.r. absorption band at $\nu_{max.}$ 1720 cm^{-1} (C=O), and the n.m.r. spectrum exhibited a one-proton singlet at τ 2·35 ascribable to O·CHO; other

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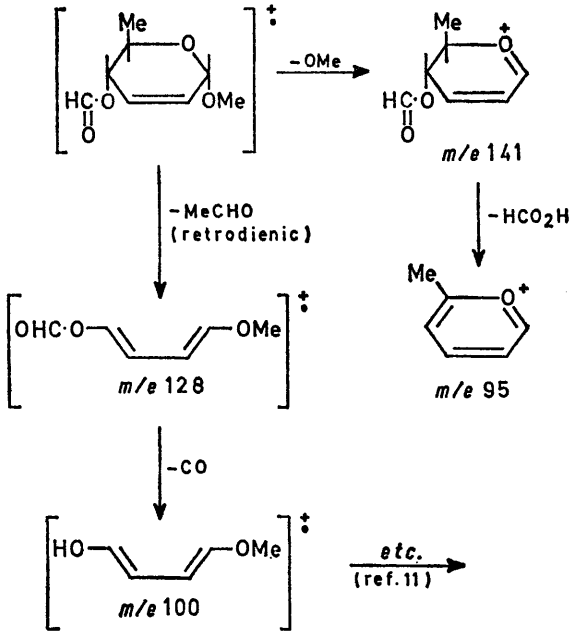
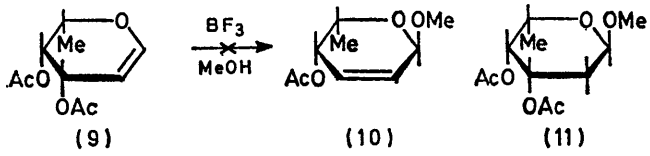
salient signals are recorded in the Experimental section. The mass spectrum of compound (8) was typical [11] of an alkyl hex-2-enopyranoside derivative undergoing fragmentation by loss of the C-1 and C-4 substituents (fragments at *m/e* 141 and 95, see Scheme) and by retrodienic



SCHEME

cleavage (*m/e* 128). The origins of the formate ester (8) produced in the acetate exchange are obscure, but presumably the solvent *NN*-dimethylformamide is involved. In this connection, it is interesting that 6-*O*-formyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulphonyl-β-L-idofuranose is formed [12] on solvolysis of 1,2-*O*-isopropylidene-3,5-di-*O*-*p*-tolylsulphonyl-α-D-glucofuranose in *NN*-dimethylformamide. The yield of the formate ester (8) was more than doubled when the allylic sulphonate (3) was heated with sodium formate in *NN*-dimethylformamide, implying either that displacement involving formate ion was also occurring or, possibly, that formate ion was less effective than acetate or benzoate ions in the competing reactions against the solvent. The configuration at C-4 was assigned on the assumption that displacement of the allylic sulphonate group, by whatever means, occurred by an S_N2 process.[7]

Our failure to achieve displacements on the allylic sulphonate (3) with acetate and benzoate ions led us to examine the boron trifluoride-catalysed rearrangement of 3,4-di-*O*-acetyl-6-deoxy-L-galactal (9) in methanol–dichloromethane (*cf.* ref. 2) as an alternative method for preparing the 4-acetate (10). However, the major product isolated by preparative chromatography was indicated by n.m.r. spectroscopy to be methyl 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranoside (11), whereas little of the desired product (10) was obtained. This



result is in keeping with observations made on related galactal derivatives by Ferrier *et al.*,[13] who have suggested that the rearrangements are probably anchimerically assisted by the 4-acetoxy-group. Such participation is favourable only when the C-3 and C-4 acetoxy-groups have a *trans*-relationship.

EXPERIMENTAL

Kieselgel G (Merck) was used for t.l.c.; spots were detected with vanillin–sulphuric acid.[14] N.m.r. spectra were measured on a Perkin-Elmer R-10 spectrometer and i.r. spectra were usually recorded for either Nujol mulls or liquid films with a Perkin-Elmer Infracord spectrometer. Optical rotations were measured at ambient temperature with a Perkin-Elmer 141 automatic polarimeter. Light petroleum refers to the fraction having b.p. 40—60°. The spectroscopic data obtained for new compounds were compatible with the assigned structures.

Methyl 2,3,4,6-*Tetradeoxy*-4-*iodo*-α-L-threo-*hex*-2-*enopyranoside* (4).—A solution of the allylic sulphonate [2] (3) (5·7 g) in acetone (250 ml) containing sodium iodide (25 g) was set aside at room temperature overnight; t.l.c. then showed that most of the starting material had reacted. The solvent was removed, the residue was extracted with ether (2 × 50 ml), and the extracts were washed with sodium thiosulphate solution and dried. The residue obtained on removal of the solvent was chromatographed on silica gel (elution with light petroleum–ethyl acetate, 8 : 1) to give the *iodide* (4) (1·7 g), m.p. 62·5—63·5° (from aqueous methanol), $[\alpha]_D$ +526° (*c* 0·9 in $CHCl_3$) (Found: C, 32·6; H, 4·2. $C_7H_{11}IO_2$ requires C, 33·1; H, 4·3%), as the second component eluted from the column.

Methyl 4-*Azido*-2,3,4,6-*tetradeoxy*-α-L-erythro-*hex*-2-*enopyranoside* (5).—A solution of the iodide (4) (1·6 g) and sodium azide (0·75 g) in aqueous acetone (50 ml; containing sufficient water to effect dissolution of the azide) was heated under gentle reflux for 3 h; t.l.c. then revealed the formation of a major and several minor products. The solution was dispersed in water and extracted with chloroform (3 × 100 ml), which was washed with sodium thiosulphate solution and dried (Na_2SO_4). Evaporation afforded a slightly impure sample of the *azide* (*ca.* 1·1 g), $\nu_{max.}$ (film) 2100 cm^{-1}, which was used without further purification.

Methyl 4-*Benzamido*-2,3,4,6-*tetradeoxy*-α-L-erythro-*hexopyranoside* (*Methyl* N-*benzoyl*-α-*tolyposaminide*) (6).—The azide (5) (0·51 g) was reduced during 16 h in methanol (30 ml) over Adams catalyst (0·56 g) with a slight overpressure of hydrogen. The catalyst was filtered off and benzoic anhydride (0·5 g) was added to the filtrate, which was set aside for 30 min at room temperature. Water was then added and, after 10 min, the solution was dispersed in

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[12] M. Milković, D. Milković, A. Jokić, V. Andrejević, and E. A. Davidson, *J. Org. Chem.*, 1972, **37**, 2536.
[13] R. J. Ferrier and N. Prasad, *J. Chem. Soc.* (*C*), 1969, 570, 581.
[14] 'Chromatography,' E. Merck AG, Darmstadt, 2nd edn., p. 30.

sodium hydrogen carbonate solution, which was extracted with chloroform (3 × 50 ml). The residue obtained on removal of the solvent was chromatographed on silica gel (elution with light petroleum–ethyl acetate, 4 : 1) and the major component was collected. Recrystallization from ethyl acetate–light petroleum gave *methyl* N-*benzoyl*-α-*tolyposaminide* (6) (0·3 g), m.p. 132—133·5°, $[\alpha]_D$ −150 ± 1° (*c* 1 in EtOH) (Found: C, 67·5; H, 7·45; N, 5·9. $C_{14}H_{19}NO_3$ requires C, 67·5; H, 7·6; N, 5·6%). The i.r. spectrum (KBr disc) of this material was indistinguishable from that of material prepared from natural tolyposamine; the natural derivative is reported [5] to have m.p. 136—140°, $[\alpha]_D$ −139° (*c* 0·5 in EtOH).

Methyl 2,3,4,6-*Tetradeoxy*-4-*dimethylamino*-α-L-erythro-*hexopyranoside* (*Methyl* α-L-*forosaminide*) (7).—Aqueous formaldehyde (*ca.* 40%; 1 ml), sodium acetate (70 mg), and Raney nickel [15] (2 g) were added to a solution of the azide (5) (0·5 g) in ethanol (80 ml), and the mixture was hydrogenated with a slight overpressure of hydrogen for 24 h at room temperature. The catalyst was filtered off and the solvent was removed. The residue was dissolved in aqueous 2% ammonium hydroxide (50 ml), the solution was extracted with dichloromethane (3 × 15 ml), and the combined extracts were dried (Na_2SO_4) and evaporated. The residual oil was distilled to give *methyl* α-L-*forosaminide* (7) (0·12 g), b.p. 95—100° (bath) at *ca.* 15 mmHg, $[\alpha]_D$ −170 ± 2° (*c* 1 in $CHCl_3$), $\nu_{max.}$ (film) 2500 cm^{-1} (NMe) {lit. (D-enantiomer),[8] b.p. 30—35° (bath) at 0·5 mmHg, $[\alpha]_D^{22}$ +174 ± 2° (*c* 1·5 in $CHCl_3$)}. The n.m.r. spectrum was identical with that reported [8] for the D-isomer.

Methyl 2,3,6-*Trideoxy*-4-O-*formyl*-α-L-threo-*hex*-2-*enopyranoside* (8).—A solution of the allylic sulphonate [2] (3) (2·1 g) in *NN*-dimethylformamide (100 ml) containing sodium formate (1·4 g) was heated on a boiling water-bath for 3 h, whereupon t.l.c. showed that most of the starting material had reacted. The solvent was removed under reduced pressure to give a mixture of components, which was separated by chromatography on silica gel (elution with light petroleum–ethyl acetate, 4 : 1). The second component eluted was the 4-*formate* (8) (0·53 g, 32%), m.p. 112·5—113·5° (from ether–light petroleum), $[\alpha]_D$ +267 ± 1° (*c* 1 in $CHCl_3$), $\nu_{max.}$ 1720 cm^{-1} (C=O) (Found: C, 55·8; H, 6·7. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%), τ (CCl_4) 2·35 (1H, s, O·CHO), 4·20—4·30 (2H, m, H-2 and H-3), 5·10—5·40 (2H, m, H-1 and H-4), 5·90 (1H, m, H-5), 6·70 (3H, s, OMe), and 8·78 (3H, d, $J_{5,6}$ 6 Hz, CMe).

When sodium acetate was used in place of sodium formate in the foregoing reaction, the 4-formate (8), m.p. and mixed m.p. 112—113°, was obtained in yields of 10—16%.

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