The Synthesis of D-Daunosamine *N*-Benzoate

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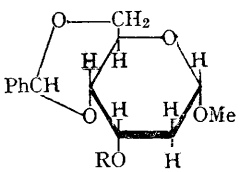
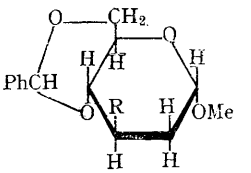
DAUNOSAMINE, the carbohydrate component of the anti-tumour antibiotic daunomycin, has been shown to be 3-amino-2,3,6-trideoxy-L-*lyxo*-hexose (see XI for the D-enantiomer) on the basis of chemical degradation, n.m.r., and optical rotation data.[1] This communication reports the synthesis of derivatives of the D-enantiomorph, which unequivocally supports the structure and stereochemistry previously assigned to daunosamine.

Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (I) was readily prepared by reduction of the corresponding epoxide with lithium aluminium hydride[2] and was converted into its methanesulphonate ester (II). This ester underwent a facile replacement reaction with sodium azide in boiling *NN*-dimethylformamide to give, with inversion of configuration at C-3, the 3-azido-*arabino*-hexopyranoside (III) in 74% yield.[3]

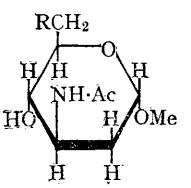
Catalytic reduction of the azide afforded the 3-amino-derivative, which was best isolated as its highly crystalline *N*-acetyl derivative (IV).[3,4] Attempted removal of the 4,6-*O*-benzylidene residue with hot aqueous acetic acid evidently caused partial hydrolysis of the glycosidic group, but methanolysis at room temperature effected removal of the blocking group without disruption of the glycosidic group to give (V). Selective esterification of (V) with toluene-*p*-sulphonyl chloride in pyridine gave the 6-sulphonate (VI) in 93% yield. The 4-hydroxyl group was quite unreactive towards this acid chloride, so that even when an excess of this reagent was used, good yields of (VI) were still obtained. This is in



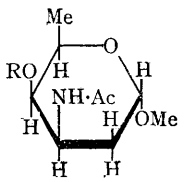
(I) R = H
(II) R = SO_2·Me



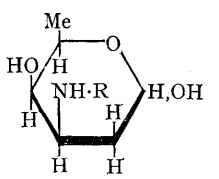
(III) R = N_3
(IV) R = NH·Ac



(V) R = OH
(VI) R = OSO_2·C_6H_4·Me
(VII) R = I
(VIII) R = H



(IX) R = H
(X) R = Ac



(XI) R = H

(XII) R = CO·Ph

[1] F. Arcamone, G. Cassinelli, P. Orezzi, G. Franceschi, and R. Mondelli, *J. Amer. Chem. Soc.*, 1964, **86**, 5335.
[2] D. A. Prins, *J. Amer. Chem. Soc.*, 1948, **70**, 3955.
[3] R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, in the press.
[4] D. H. Buss, L. Hough, and A. C. Richardson, *J. Chem. Soc.*, 1965, 2736.

accord with our results on the selective benzoylation of methyl α-pyranosides in which the 4-hydroxyl is, in all cases studied, the least reactive.[5] Reaction of the 6-sulphonate (VI) with sodium iodide in boiling acetone gave the 6-iodo-derivative (VII) catalytic hydrogenation of which yielded methyl 3-acetamido-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (VIII).

The next stage in the synthesis was the stereochemical inversion of the 4-hydroxyl group to give the required D-*lyxo*-stereochemistry. This was achieved by virtue of the vicinal *trans*-acetamido-group by the method described originally in the carbohydrate field by Baker and Schaub.[6] The 4-hydroxyglycoside (VIII) was converted into the methanesulphonate ester which, without isolation, was heated under reflux in aqueous sodium acetate solution. The latter treatment resulted in elimination of the methanesulphonyloxy-group by the neighbouring *trans*-acetamido-group, followed by hydrolysis of the intermediary oxazolinium cation so formed, to give methyl 3-acetamido-2,3,6-trideoxy-α-D-*lyxo*-hexopyranoside (IX). This compound gave an *O*-acetate (X) with m.p. 182—183° and $[\alpha]_D$ + 192° ($CHCl_3$). The infrared spectrum of this compound was almost identical with that of the diacetyl derivative of methyl α-daunosaminide for which m.p. 176—178°, $[\alpha]_D$ — 130° ($CHCl_3$) have been reported. It is possible that the naturally derived derivative may contain some of the β-anomer, thus accounting for the differences in physical properties. Alkaline hydrolysis of (IX) gave the free amine which afforded an *N*-benzoyl derivative on treatment with benzoic anhydride in ethanol. This benzamidoglycoside was very easily hydrolysed with dilute acetic acid to give 3-benzamido-2,3,6-trideoxy-D-*lyxo*-hexose (XII), m.p. 150·5—151·5°, $[\alpha]_D$ + 110·5° (EtOH), which was enantiomorphous (i.r. spectrum) with daunosamine *N*-benzoate,[1] for which m.p. 154—156° and $[\alpha]_D$ — 107·5° (EtOH) have been reported.

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[5] A. C. Richardson and J. M. Williams, *Chem. Comm.*, 1965, 104, and unpublished results.
[6] B. R. Baker and R. E. Schaub, *J. Org. Chem.*, 1954, **19**, 646.