Synthesis of Amino-sugar Disaccharides

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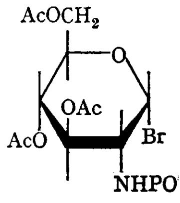
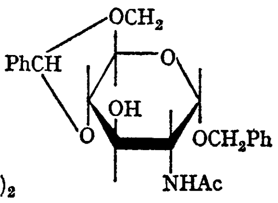
THE Koenigs–Knorr synthesis of 1→3- and 1→4-linked amino-sugar disaccharides with a 2-amino-2-deoxyhexose as the non-reducing moeity is a hitherto unsolved problem. Particularly these linkages, however, are of special interest as they are the most widely distributed in naturally occurring amino-sugar polysaccharides. Halogeno-amino-sugars with a range of *N*-blocking groups (*e.g.*, *N*-acetyl,[1] *N*-benzoyl,[1] *N*-benzyloxycarbonyl,[1] *N*-dinitrophenyl[2]) have been used to prepare 1→6-linked disaccharides[2] and other simpler glucosaminides. These, however, have proved unsuitable for the preparation of 1→3- or 1→4-linked disaccharides, in which side-reactions, such as neighbouring-group effects of the *N*-blocking group, become important.

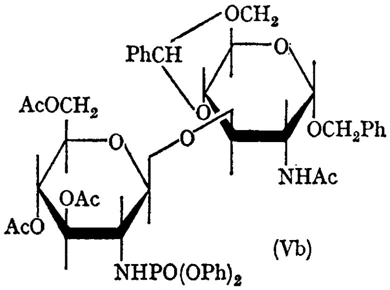
We have found that the diphenoxyphosphinyl group, $-PO(OPh)_2$, which has already been successfully used in glucosaminide synthesis,[1] is very well suited to the synthesis of amino-sugar disaccharides. It showed no observable neighbouring-group reaction and, after trans-esterification to the dibenzyloxyphosphinyl group, $-PO(OCH_2Ph)_2$, could be hydrogenolysed under mild conditions. The yields from the condensations of the halogeno-amino-sugar are good and the reaction is applicable to all 2-amino-2-deoxysugars. The synthesis of 2-acetamido-3-*O*-(2-acetamido-2-deoxy-β-D-glucosyl)-2-deoxy-α-D-glucose (I) and 2-acetamido-4-*O*-(2-acetamido-2-deoxy-α-D-glucosyl)-2-deoxy-α-D-glucose (II) are here described as examples of the general applicability of the method.



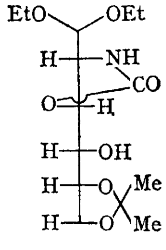
(III)



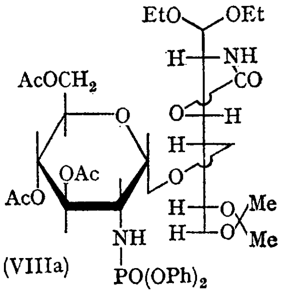
(IV)



(Vb)



(VII)



(VIIIa)

(III) + (IV) → (Vb) → (I)

(III) + (VII) → (VIIIa) → (II)

For the synthesis of (I), the bromide (III) was allowed to react with the partially blocked glucosamine derivative (IV), in benzene containing mercuric cyanide, to give an anomeric disaccharide mixture, benzyl 2-acetamido-3-*O*-[3,4,6-tri-*O*-acetyl-2-diphenoxyphosphinylamino-2-deoxy-αβ-D-glucosyl)-4,6-*O*-benzylidene-2-deoxy-α-D-glucoside (V), yield 30%, containing approximately 85% of the β-form. The pure anomers are β (Vb), m.p. 102·5—103·5°, $[\alpha]_D^{23}$ + 68° (*c*, 0·8, in chloroform) and α (Va), m.p. 147—149° $[\alpha]_D^{23}$ + 81° (*c*, 0·8, in chloroform). The anomeric mixture (V) was treated with ammonia in benzyl alcohol, causing de-*O*-acetylation and trans-esterification of the diphenoxyphosphinyl group to dibenzyloxyphosphinyl, to give benzyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(2-dibenzyloxyphosphinylamino-2-deoxy-β-D-glucosyl)-2-deoxy-α-D-glucoside (VIb), yield 34%, m.p. 179—180°, $[\alpha]_D^{23} + 49°$ (c, 0·5, in pyridine), and the $\alpha\alpha$-anomer (VIa), m.p. 216—217°, $[\alpha]_D^{23} + 75°$ (*c*, 0·5, in pyridine). Treatment of the β-linked disaccharide (VIb) with acetic acid removed the benzylidene group, hydrogenolysis removed the *N*-dibenzyloxyphosphinyl and *O*-benzyl groups and *N*-acetylation produced the desired crystalline disaccharide (I), yield from (VIb), 26%, m.p. 198—199°, $[\alpha]_D^{23} + 8·7$ (*c*, 1, in water).

The synthesis of (II) involved condensation of bromide (III) with the acyclic compound (VII) to give the fully-blocked α-disaccharide (VIIIa), yield 35%, m.p. 116—118°, $[\alpha]_D^{23} + 29°$ (*c*, 1·0, in chloroform), and the β-anomer (VIIIb), yield 10%, m.p. 93—95°, $[\alpha]_D^{23} - 23°$ (*c*, 0·75, in chloroform). Treatment of (VIIIa) with ammonia in benzyl alcohol gave 2-amino-4-*O*-(2-dibenzyloxyphosphinylamino-2-deoxy-α-D-glucosyl)-2-deoxy-5,6-*O*-isopropylidene-D-glucose 2,3-carbonate diethyl acetal (IX), yield 60%, m.p. 112—115°, $[\alpha]_D^{23} + 19°$ (*c*, 0·9, in chloroform). The α-anomer (IX) was deblocked and *N*-acetylated to give, *via* a series of crystalline derivatives, the α-1$\rightarrow$4-linked disaccharide (II), yield from (IX) 20%, m.p. 170° (decomp.), $[\alpha]_D^{23} + 108°$ (*c*, 1·0, in water). The investigations show that the above described method constitutes a generally applicable procedure for the synthesis of amino-sugar disaccharides.

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