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SOLID-PHASE SYNTHESIS OF OLIGOSACCHARIDES.

II.* SYNTHESIS OF 2-ACETAMIDO-6-O-(2-ACETAMIDO-2-DEOXY-β-D-GLUCOPYRANOSYL)-2-DEOXY-D-GLUCOSE.

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The use of a solid support for the stepwise synthesis of oligosaccharides is, in principle, a promising technique, but it has only been attempted quite recently[1-4] and is subject to numerous difficulties.

As part of a general study[5] on the adaptation of the Merrifield type of synthesis on a polymer support[6] for use in sugar chemistry, we describe here the synthesis, by use of an insoluble, modified, polystyrene resin, of the known[7-9] disaccharide 2-acetamido-6-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-D-glucose (8).

Following the procedure of Letsinger[10], a 0.17% cross linked styrene-divinylbenzene "popcorn" polymer (1 g) having acid chloride functional groups (1.7 mmole/g of resin) was treated in a dry mixture of benzene (10 ml) and pyridine (2 ml) for 48 h at room temperature with benzyl-2-acetamido-2-deoxy-4,6-O-benzylidene-α-D-glucopyranoside[11] (1, 0.452 g) to attach the polymer to 1 through O-3 ; after washing the resin successively with benzene, chloroform, dioxane, 1:1 dioxane-water, acetone, methanol and ether, product 2 contained (according to the gain in weight) 1 mmole of 1 per g of resin. Residual acid chloride groups were esterified with methanol (1 ml) for 12 h. The benzylidene groups were split off by treating 2 with 9:1 trifluoroacetic acid-water[12] to give the polymer-fixed derivative 3 having O-4 and O-6 free. Glycosylation of 3 was effected either (a) with 2-methyl-4,5-(3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyrano)-2-oxazoline[13] (4, 3 moles per mole of 3) in a mixture of nitromethane (7 ml) and toluene (10 ml) containing a catalytic amount of p-toluenesulfonic acid (20 mg) for 1.5 h at 120° (conditions of Zurabyan[14]) or (b) with 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride[15]

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[*] Part I, see ref. 5.

(**5**, 2 moles per mole of **3**) in benzene containing mercuric cyanide (1 mole per mole of **5**) for 48 h at 60°. The resulting product was presumed to be the polymer-fixed, protected β-*D*(1⟶6)-linked dissacharide **6**, on the basis of the favored stereochemistry of glycosylation reactions[16] of **4** and **5**, and the higher reactivity of primary hydroxyl groups (6-OH) over secondary ones (4-OH). At the elevated temperature of procedure (*a*) the polymer tended to become partially solubilized, decreasing the net yield, but three successive treatments led to a product whose gain in weight, allowing for loss of polymer by solubilization, indicated a yield of 80% in the coupling reaction.

Detachment of the protected disaccharide from the resin was effected by suspending **6** in 1:1 methanol-toluene saturated with ammonia or, more effectively, by use of 0.5 M sodium methoxide in methanol (2 ml) in 1:1 methanol-*p*-dioxane* (8 ml) for 1.5 h at 40°C ; sodium ions were subsequently removed with Amberlite IR-120 (H^+). The mixture was filtered, the filtrate evaporated, and the chloroform insoluble portion of the residue was acetylated (acetic anhydride-pyridine) to give benzyl 2-acetamido-6-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-2-deoxy-α-*D*-glucopyranoside (**7**) yield 420 mg (58% based on **1**), m.p. 242° (from chloroform-ether), $[\alpha]_D^{25}$ +65°(*c* 1 in chloroform); m/e 364 (1.1% of base peak m/e 330) attributable[17] to ion **A** ; n.m.r. ($CDCl_3$: δ 5.65 and 5.99 bd, $J_{2,NH}$ 8.5 and 9.5 Hz, disappear slowly on deuteration (NHAc of disaccharide) ; 4.9 d, $J_{1,2}$ 3.5 Hz (H-1 equatorial of benzyl glycoside moiety) ; 4.5 d, $J_{1',2'}$ 8 Hz (H-1' axial of interglycosidic link) ; 4.93-5.4 (triplets, J 8-9 Hz, 4 protons diaxially disposed, H-3, H-4, H-3', H-4').

Anal. Calc. for $C_{33}H_{44}N_2O_{16}$: C 54.68, H 6.13, N 3.87, O 35.32.
Found : 54.70, 5.98 3.98 35.33.

These data in comparison with previous n.m.r. spectral analyses of amino sugar derivatives[18], indicate that the interglycosidic link in **7** is β-*D* through position *O*-6 (and not through *O*-4).

A second product formed in the coupling reaction by procedure (*b*) appeared to be a trisaccharide derivative, presumably the product glycosylated at *O*-6 and *O*-4.

Conventional *O*-deacetylation of **7** with methanolic ammonia, followed by hydrogenolytic cleavage of the benzyl glycoside group, gave the known disaccharide **8**[7-9] m.p. 200° (from ethanol), $[\alpha]_D^{25}$ +8° (equilibrium) (*c* 0.3 in water).

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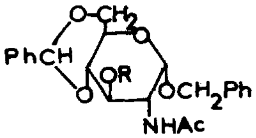
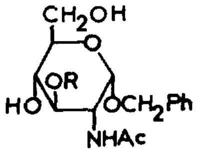
* As some carboxyl groups of the functionalized polymer were not transformed into acid chlorides, an excess of sodium over the usual quantities had to be used.

Although the yields here recorded are probably considerably lower than optimal yields achievable, the results do show that the solid-support technique does provide a valid procedure for stepwise oligosaccharide synthesis applicable with amino sugars.

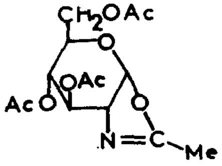


1 R = H

2 R = polymer-CO-



3 R = polymer-CO-



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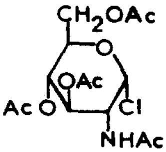

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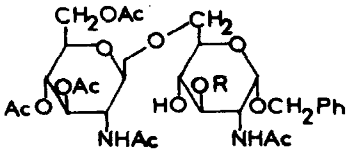
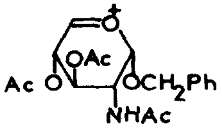
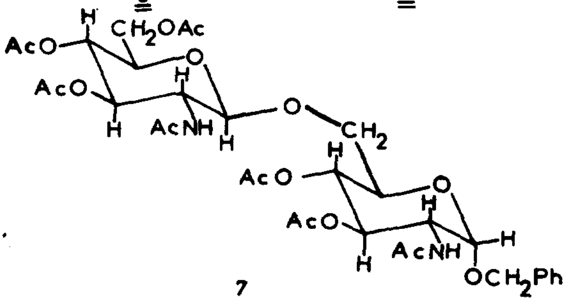


6 R = polymer-CO-



A: m/e 364



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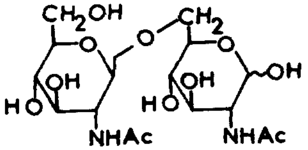

8

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