AMINOSACCHARIDES

PART V*. KOENIGS–KNORR REACTION OF THE ACETOBROMO DERIVATIVES OF 2-DEOXY-2-(2,4-DINITROANILINO)-D-GLUCOPYRANOSE AND ITS MONOMETHYL ETHERS**

P. F. LLOYD, B. EVANS, AND R. J. FIELDER

Department of Chemistry, University College of North Wales, Bangor, Caernarvonshire (Great Britain)

(Received September 8th, 1971; accepted for publication, October 21st, 1971)

ABSTRACT

Syntheses of 4,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-3-*O*-methyl-α-D-glucopyranosyl bromide (**3**) and the isomeric 3,6-di-*O*-acetyl-4-*O*-methyl (**4**) and 3,4-di-*O*-acetyl-6-*O*-methyl (**2**) derivatives are described. 2-Deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-D-glucose (**7**) was synthesised *via* ethyl 3,4-di-*O*-benzoyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-trityl-α-D-glucopyranoside (**14**) and its de-*O*-tritylated derivative (**15**). When **15** and its β-anomer **26** were methylated, little migration of benzoyl groups from C-4 to C-6 occurred. Compounds **3**, **4**, and **2** reacted with ethanol, in nitromethane solution with silver carbonate present, to form mainly β-D-glycopyranosides. In chloroform solution with pyridine as catalyst, **3** and **4** reacted rapidly with ethanol to give α-D-glycopyranosides as the major products, but **2** reacted slowly to give low yields of both glycosides. A possible mechanism for the pyridine-catalysed ethanolysis of **3**, **4**, and the unmethylated halide **1**, involving participation of AcO-6, is discussed.

INTRODUCTION

It has been shown that 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide (**1**), a stable aminoglycosyl halide with a non-participating group at C-2, reacts with alcohols (Koenigs–Knorr reaction) to give both α- and β-D-glycopyranosides, the proportions of which are dependent upon both the catalyst and the solvent employed[1–3]. Condensation of **1** with alcohols in polar solvents in the presence of silver carbonate gave high yields of β-D-glycosides, but when the reaction was carried out in non-polar solvents with pyridine as catalyst the products were predominantly α-D-glycosides. These reactions have been extended to the synthesis of oligosaccharides[4], thioglycosides[5], and nucleosides[6], with the distinctive colour of the Dnp (2,4-dinitrophenyl) derivatives facilitating both analytical and preparative chromatography.

In order to rationalise the pyridine-catalysed formation of α-D-glycosides, it

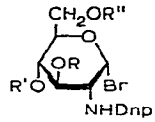
*Part IV: P. F. Lloyd, B. Evans, and R. J. Fielder, *Carbohyd. Res.*, 9 (1969) 471.

**Dedicated to Professor M. Stacey, C.B.E., F.R.S., in honour of his 65th birthday.

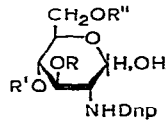
was tentatively suggested[3] that a pyridine-stabilised intermediate-complex involving AcO-6 was formed, nucleophilic attack upon which furnished α-D-glycosides. In this paper, we describe the way in which the reactivity of the glycosyl halide is affected by replacement, in turn, of each of the three *O*-acetyl groups in **1** by the non-participating *O*-methyl group. This study was undertaken not only in the hope that it would shed light on the mechanism of the reaction but also to give information on the applicability of the method to other substituted amino-sugar derivatives, especially those which bear glycosyl substituents on primary or secondary hydroxyl groups in the ring.

RESULTS AND DISCUSSION

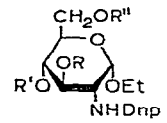
The starting materials for the synthesis of the glycosyl halides **3**, **4**, and **2** were the 3-, 4-, and 6-mono-methyl ethers of 2-deoxy-2-(2,4-dinitroanilino)-D-glucose, syntheses of which have been reported[7]. The 3-methyl (**5**) and 4-methyl (**6**) ethers were obtained as described[7]. The method for preparing the 6-methyl ether (**7**), which involved methylation of the intermediate ethyl 3,4-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranoside (**8**), was known to be unsatisfactory because extensive migration (76%) of the acetyl group from C-4 to C-6 leads to the 4-*O*-methyl (**10**) rather than the 6-*O*-methyl (**9**) derivative.



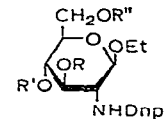
1 R=R'=R"=Ac
2 R=R'=Ac, R"=Me
3 R=Me, R'=R"=Ac
4 R=R"=Ac, R'=Me



5 R=Me, R'=R"=H
6 R=R"=H, R'=Me
7 R=R'=H, R"=Me



8 R=R'=Ac, R"=H
9 R=R'=Ac, R"=Me
10 R=R"=Ac, R'=Me
11 R=Me, R'=R"=Ac
12 R=R'=R"=H
13 R=R'=H, R"=Tr
14 R=R'=Bz, R"=Tr
15 R=R'=Bz, R"=H
16 R=R'=Bz, R"=Me
17 R=R"=Bz, R'=Me
18 R=R'=H, R"=Me
19 R=R"=H, R'=Me
20 R=Me, R'=R"=H



21 R=R'=H, R"=Me
22 R=R'=R"=Ac
23 R=R'=R"=H
24 R=R'=H, R"=Tr
25 R=R'=Bz, R"=Tr
26 R=R'=Bz, R"=H
27 R=R'=Bz, R"=Me
28 R=R"=H, R'=Me
29 R=R'=Ac, R"=Me
30 R=R"=Ac, R'=Me
31 R=Me, R'=R"=Ac

For the present synthesis, an alternative route to **7** (**12** → **13** → **14** → **15** → **16** → **18** → **7**) was investigated, which parallelled that described earlier except that benzoyl rather than acetyl groups were used. All the intermediates in this scheme were crystalline and yields were high; the products at each stage were purified by column chromatography on silica gel, a rapid procedure that could be followed visually. Detritylation of the 6-*O*-trityl derivative **14** afforded ethyl 3,4-di-*O*-benzoyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranoside (**15**) in 74% yield. Methylation of **15** gave a crystalline, chromatographically homogeneous product (81% yield) designated as **16**. However, this evidently contained a small amount of the isomeric 3,6-di-*O*-

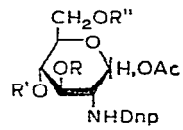
benzoyl-4-*O*-methyl derivative **17**, since at the next (debenzoylation) stage the isomeric 6- and 4-methyl ethers (**18** and **19**) were separated chromatographically in yields, respectively, of 73 and 3%. Clearly, the extent of acyl migration occurring at stage **15** → **16** in this benzoyl series was very much less than in the acetyl series already cited[7].

The anomeric ethyl 2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-β-D-glucopyranoside (**21**) was also required as a reference compound. It was synthesised definitively by deacetylating ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranoside (**22**) of established structure to give **23**, and then following a parallel route to that above, **23** → **24** → **25** → **26** → **27** → **21**. Benzoyl migration (**26** → **27**) during methylation occurred to a smaller extent than in the α-series. When **27** was debenzoylated and the product analysed chromatographically, only a faint band (<1%) migrating at the rate expected for the isomeric 4-methyl ether **28** was observed.

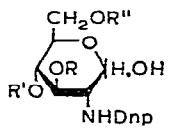
Acetylation of the 6-*O*-methyl-β-D-glycoside **21** and the 6-, 4-, and 3-*O*-methyl-α-D-glycosides (**18**, **19**, and **20**) gave crystalline, reference diacetates (**29**, **9**, **10**, and **11**). Ethyl 3,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-4-*O*-methyl-β-D-glucopyranoside (**30**) and the corresponding 3-*O*-methyl isomer **31** were not synthesised definitively. It seemed likely that these would be the major products when their bromo derivatives, **4** and **3**, were treated with ethanol and silver carbonate (as described below), and, indeed, the products so obtained were not identical with the α-D anomers of established structure but were characterised as ethyl glycopyranosides by their analyses, chromatographic mobilities, and behaviour on acid hydrolysis. N.m.r. spectroscopy[8] might have been expected to provide useful confirmatory data, but satisfactory signals were not obtained with these compounds which were available only in small amounts. In the 2-deoxy-2-(2,4-dinitroanilino)-D-glucose series, the highly polarised Dnp group causes anomalous, optical rotational effects[9,10], and the sign and magnitude of the rotations cannot be taken as a guide to anomeric configuration.

The three reducing monoethers **5**, **6**, and **7** were converted into their crystalline triacetates, **34**, **33**, and **32**, and then by treatment with hydrogen bromide into the corresponding glycosyl bromides. High yields of crystalline 3,4-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-α-D-glucopyranosyl bromide (**2**) and the 4-*O*-methyl compound **4** were obtained, but **34** underwent halogenation at a slower rate, as shown by t.l.c.-monitoring of the reaction, and a crystalline bromo compound could not be obtained. The yellow glass finally isolated was shown to consist substantially of a component of high chromatographic mobility which, on the basis of qualitative tests, was assigned the structure 4,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-3-*O*-methyl-α-D-glucopyranosyl bromide (**3**); smaller quantities of **34** and **37** and traces of unidentified compounds were present. Because **3** underwent decomposition when a chromatographic purification was attempted, the freshly prepared glass was used for the Koenigs–Knorr reactions; the impure nature of this preparation is reflected in the lower yields of 3-*O*-methylglycosides obtained.

The three glycosyl halides underwent rapid hydrolysis, in the presence of water and silver carbonate, furnishing diacetates **35**, **36**, and **37**. These were invariably present to some extent as minor products of the Koenigs–Knorr reactions.



32 R=R'=Ac, R''=Me
33 R=R''=Ac, R'=Me
34 R=Me, R'=R''=Ac



35 R=R'=Ac, R''=Me
36 R=R''=Ac, R'=Me
37 R=Me, R'=R''=Ac

For the main study, ethanol was used as the aglycon and the two sets of conditions selected were those shown earlier[3] to be optimal for α- or β-glycoside formation using the unmethylated glycosyl bromide **1**. The reactions were monitored by using t.l.c., and the products were separated by preparative layer chromatography. Like **1**, each of the three mono-*O*-methylglycosyl halides **3**, **4**, and **2** reacted with ethanol, in nitromethane in the presence of silver carbonate, to give the ethyl β-D-glycoside as the main product (Table I). Smaller amounts of α-D-glycoside were present in the reaction products from the 4- and 3-methyl halides but, although several solvent systems were employed, the α-D-glycoside could not be detected chromatographically in the products from **2**.

TABLE I

REACTION OF SUBSTITUTED 2-DEOXY-2-(2,4-DINITROANILINO)-α-D-GLUCOPYRANOSYL BROMIDES WITH ETHANOL

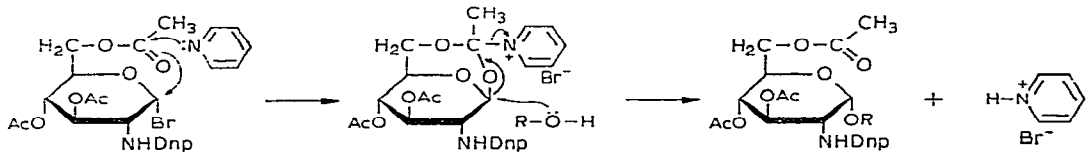
Glycosyl bromide	*Solvent*	*Acid acceptor*	*Products (%)*[b]		
			α-Glycoside	*β-Glycoside*	*Hydrolysis product*
1[a]	nitromethane	Ag_2CO_3	2	83	20
3	nitromethane	Ag_2CO_3	(2)	43	(30)
4	nitromethane	Ag_2CO_3	9	60	(10)
2	nitromethane	Ag_2CO_3	0	69	13
1[a]	chloroform	pyridine	82	9	4
3	chloroform	pyridine	37	6	(35)
4	chloroform	pyridine	72	(2)	12
2 (run 1)	chloroform	pyridine	(<2)	12	30
2 (run 2)	chloroform	pyridine	5	9	(30)

[a]Values calculated from data given by Lloyd and Roberts[3]. [b]Values given in brackets are values estimated from visual examination of thin-layer chromatograms; other values relate to products isolated and characterised.

When pyridine was employed as catalyst and chloroform as solvent, the 3- and 4-methyl halides (**3** and **4**) reacted with ethanol in the manner expected from the earlier study[3], giving the α-D-glycoside as the major product together with a smaller amount of the β-D-glycoside. The 6-*O*-methylglycosyl halide **2** did not follow this reaction pattern, there being two main differences. Firstly, whereas **3**, **4**, and **1** had reacted rapidly with the alcohol at 50° (reaction being completed within 24 h), **2**

reacted at a much slower rate; after 24 h, it was largely unchanged and even after 4 days, when the reaction products were worked up, the main component was the starting compound **2**. Secondly, although small amounts of glycoside could be isolated from the products, the proportion of β-D-glycoside was substantially greater than that of α-D-glycoside (Table I). The appreciable quantity of hydrolysis product **34** isolated was attributable, in part at least, to reaction of **2** with moisture during evaporation and separation.

Earlier work from our laboratories[3] established that the pyridine-catalysed formation of α-D-glycosides from **1** occurred with greater facility in non-polar solvents, and suggested that this was not an S_N1 reaction. A more likely mechanism was described, with the intermediate formation of a resonance-stabilised cation, which involved AcO-6, as shown in Scheme 1 (step 1); nucleophilic attack upon this intermediate could furnish an α-D-glycoside (step 2). The data presented in this paper are consistent with such a mechanism, with **2**, **3**, and **4** reacting as expected. But whether the suggested mechanism is correct or not (and some related and alternative schemes are possible), the lack of reactivity of **2** in contrast to **1**, **3**, and **4** points to a high degree of anchimeric assistance by AcO-6. Other steric or electronic effects associated with the location of the small methyl group would not be expected to account for these differences.



Scheme 1 Step 1 Step 2

If our interpretation is correct, it follows that non-participating groups at C-6 (such as ether, deactivated ester, probably glycosyl, and possibly bulky groups) could cause the reaction to fail, but participating groups, especially small, strong nucleophiles, would be expected to promote α-D-glycoside formation. In view of the fact that α-D-glycoside formation, from α and β halides, may proceed by a different mechanism involving anomerisation when *p*-nitrobenzoyl groups are present[11], it is more difficult to predict the effect of activated aromatic substituents, such as *p*-methoxybenzoyl at C-6. It may be possible to extend the pyridine-catalysed reaction, as described for **1**, **3**, and **4**, to other sugar series, including not only amino and diamino sugars but also aldohexoses, by selecting suitable derivatives such that groups which lend powerful anchimeric assistance are located at C-6 and non-participating groups (*e.g.* nitro[12], benzyl[11,13], and trichlorosulphate[14]) at C-2.

EXPERIMENTAL

Solvents and reagents. — Acetone (Analar) was purified by drying over anhydrous calcium sulphate and fractional distillation. Chloroform was shaken with six changes of water (0.5 vol.), dried with calcium chloride, and distilled. Ethanol was

dried by being refluxed with magnesium ethoxide and distilled. Nitromethane was thrice distilled from phosphorus pentoxide and then fractionally distilled. Pyridine was refluxed over sodium hydroxide for 1 h and then distilled. Traces of water were removed immediately before use by allowing the pyridine to percolate through a column containing molecular sieve (B.H.D. type 4a, 8–12 mesh beads) protected by a calcium chloride drying-tube. The column was regenerated by draining off the pyridine and flushing the heated column (250–300°) with dry nitrogen. Silver carbonate was prepared shortly before use by mixing a 10% solution of silver nitrate with an equivalent amount of sodium hydrogen carbonate. The precipitate was washed with water and then methanol, and kept in the dark over phosphorus pentoxide.

Thin-layer chromatography (t.l.c.), preparative layer chromatography, and column chromatography were performed with Kieselgel G (Merck 7731) and (*A*) chloroform–nitromethane, 9:1 v/v; (*B*) chloroform–ethanol, 9:1 v/v; or (*C*) chloroform–ethanol, 19:1 v/v.

All evaporation was carried out under diminished pressure unless otherwise stated. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. Melting points are uncorrected. Light petroleum (b.p. 60–80°) was used.

*Ethyl 2-deoxy-2-(2,4-dinitroanilino)-β-*D*-glucopyranoside* (**23**). — Ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranoside[3] (**22**) (9.0 g) was added to methanol (250 ml) which had been saturated at 0° with ammonia, and shaken for 24 h. The solvent was removed by evaporation, and the residue was recrystallised from ethanol to give **23** (6.4 g, 94%), m.p. 194°, $[\alpha]_D^{19}$ +13.9° (*c* 0.2, acetone) (Found: C, 44.9; H, 5.3; N, 10.7. $C_{14}H_{19}N_3O_9$ calc.: C, 45.1; H, 5.2; N, 11.3%).

*Ethyl 2-deoxy-2-(2,4-dinitroanilino)-6-*O*-trityl-α-*D*-glucopyranoside* (**13**). — Ethyl 2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranoside[3] (**12**) (10.0 g) and trityl chloride (8.0 g, 1.1 mol.) in dry pyridine (100 ml) were shaken to effect complete dissolution and then heated under reflux for 8 h with the exclusion of moisture. The mixture was poured into ice–water (1 litre), and the suspension was extracted with chloroform. The chloroform extract, after washing (aqueous sodium hydrogen sulphate and water) and drying ($MgSO_4$), gave, on evaporation, a thick syrup which was fractionated by column chromatography with solvent *A* to give unchanged **12**, a small amount of unidentified material believed to be a ditrityl compound, and **13** (8.6 g, 51%), m.p 75–77°, $[\alpha]_D^{20}$ −25.6° (*c* 0.5, chloroform) (Found: C, 64.0; H, 5.4; N, 6.8. $C_{33}H_{33}N_3O_9$ calc.: C, 64.4; H, 5.4; N, 6.8%).

The 3,4-dibenzoate (**14**) had m.p. 106–107° (from ethanol), $[\alpha]_D^{20}$ +95.2° (*c* 0.2, chloroform) (Found: C, 68.6; H, 5.1; N, 5.2. $C_{47}H_{41}N_3O_{11}$ calc.: C, 68.9; H, 5.3; N, 5.4%).

*Ethyl 2-deoxy-2-(2,4-dinitroanilino)-6-*O*-trityl-β-*D*-glucopyranoside* (**24**). — Compound **24** was prepared from **23** (5.0 g) by the method used for the preparation of **13**. The crude product, when fractionated on a column of Kieselgel G (Solvent *A*), gave some unchanged **23** and the trityl ether **24** (3.0 g, 37%) as a yellow glass, $[\alpha]_D^{20}$ −25.3° (*c* 0.2, chloroform) (Found: C, 63.4; H, 5.4; N, 6.8. $C_{33}H_{33}N_3O_9$ calc.: C, 64.4; H, 5.4; N, 6.8%).

The 3,4-dibenzoate (**25**) had m.p. 98–99° (from ethanol), $[\alpha]_D^{20}$ +10.8° (*c* 0.2, chloroform) (Found: C, 69.0; H, 5.1; N, 5.3. $C_{47}H_{41}N_3O_{11}$ calc.: C, 68.9; H, 5.3; N, 5.4%).

*Ethyl 3,4-di-*O*-benzoyl-2-deoxy-2-(2,4-dinitroanilino)-α-*D*-glucopyranoside* (**15**). — To a solution of **14** (10.0 g) in glacial acetic acid (400 ml) at 10° was added hydrobromic acid in glacial acetic acid (50%, 10 ml) and the mixture was shaken for 45 sec. The precipitate was immediately removed by filtration, under suction, and the filtrate was poured into ice–water (1.5 l). The resulting suspension was extracted with chloroform, and the extract, after washing (water) and drying ($MgSO_4$), was evaporated. Examination of the crude product by t.l.c. indicated that it was contaminated with small amounts of starting material and decomposition products. It was purified by passage through a Kieselgel column (solvent *A*) and recrystallised from ethanol. The yellow product **15** (6.0 g, 74%) had m.p. 239°, $[\alpha]_D^{20}$ +14.2° (*c* 0.2, chloroform) (Found: C, 57.8; H, 4.6; N, 7.2. $C_{28}H_{27}N_3O_{11}$ calc.: C, 57.8; H, 4.8; N, 7.2%).

*Ethyl 3,4-di-*O*-benzoyl-2-deoxy-2-(2,4-dinitroanilino)-β-*D*-glucopyranoside* (**26**). — Compound **26**, when prepared (61% yield) from **25** and purified by chromatography by the method given above, had m.p. 204° (from ethanol–light petroleum), $[\alpha]_D^{20}$ +10.4° (*c* 0.2, chloroform) (Found: C, 57.7; H, 4.6; N, 7.3. $C_{28}H_{27}N_3O_{11}$ calc.: C, 57.8; H, 4.8; N, 7.2%).

*Ethyl 3,4-di-*O*-benzoyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-α-*D*-glucopyranoside* (**16**). — Compound **15** (5.4 g) dissolved in methyl iodide (80 ml) was stirred with silver oxide (freshly prepared, 20 g) and heated under reflux for 24 h, after which time methylation was complete (t.l.c.). The silver residues were removed by filtration and washed (dry chloroform) and the combined filtrate and washings were evaporated to dryness. The crude product was dissolved in chloroform, precipitated by addition of a large excess of pentane, and recrystallised from ethanol. This product (**16**) (4.4 g, 81%) was chromatographically homogeneous (solvents *A* and *B*) but contained a small amount (see below) of the isomeric 4-methyl ether **17**. It had m.p. 211–212°, $[\alpha]_D^{20}$ +144° (*c* 0.2, chloroform) (Found: C, 58.8; H, 5.1; N, 7.1. $C_{29}H_{29}N_3O_{11}$ calc.: C, 58.5; H, 5.0; N, 7.1%).

*Ethyl 3,4-di-*O*-benzoyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-β-*D*-glucopyranoside* (**27**). — Methylation of **26** by the above method gave **27** in 86% yield. Recrystallised from ethanol, it had m.p. 91°, $[\alpha]_D^{20}$ +17.8° (*c* 0.3, chloroform) (Found: C, 58.2; H, 4.9; N, 7.0. $C_{29}H_{29}N_3O_4$ calc.: C, 58.5; H, 5.0; N, 7.1%).

*Ethyl 2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-α-*D*-glucopyranoside* (**18**). — Compound **16** (4.00 g) was dissolved in dry methanol (300 ml) which had previously been reacted with sodium (7.5 g). After shaking for 6 h, debenzoylation was complete (t.l.c., solvent *B*). The solution was neutralised with solid carbon dioxide, and the precipitate was removed by filtration and washed with acetone. The combined filtrate and washings were evaporated to give a yellow solid, the two components of which were separated by column chromatography (solvent *B*). The first component to be eluted was recrystallised from ethanol–light petroleum to give **18** (1.90 g, 73%), m.p. 167°, $[\alpha]_D^{20}$ −29.5° (*c* 0.5, chloroform) (Found: C, 46.7; H, 5.6; N, 10.7; OMe, 8.1. $C_{15}H_{21}N_3O_9$ calc.: C, 46.5; H, 5,5; N, 10.8; OMe, 8.0%).

The 3,4-diacetate (**9**) of **18** had m.p. 205°, $[\alpha]_D^{20}$ +33.5° (*c* 0.1, chloroform) (Found: C, 48.2; H, 5.5; N, 8.8. $C_{19}H_{25}N_3O_{11}$ calc.: C. 48.4; H, 5.4; N, 8.9%).

The second component from the column, purified in a similar way to **18**, was the isomeric compound ethyl 2-deoxy-2-(2,4-dinitroanailino)-4-*O*-methyl-α-D-glucopyranoside (**19**) (0.08 g, 3%), m.p. and mixed m.p. 176°, $[\alpha]_D^{20}$ +5.5° (*c* 0.2, chloroform); lit.[7] m.p. 176–177°, $[\alpha]_D^{20}$ +10.4° (chloroform) (Found: C, 47.1; H, 5.3; N, 11.0).

The 3,6-diacetate (**10**) of **19** had m.p. 206–207°, $[\alpha]_D^{20}$ +39.7° (*c* 0.2, chloroform) (Found: C, 48.7; H, 5.5; N, 8.9%).

Ethyl 2-deoxy-2-(2,4-dinitroanilino)-6-O-methyl-β-D-glucopyranoside (**21**). — Debenzoylation of **27** to furnish **21** was effected by the method described above. The crude product on fractionation (column chromatography, solvent *A*) gave **21** (85%), m.p. 154–155°, $[\alpha]_D^{20}$ +29.9° (*c* 0.2, chloroform) (Found: C, 46.5; H, 5.4; N, 10.3; OMe, 7.7. $C_{15}H_{21}N_3O_9$ calc.: C, 46.5; H, 5.4; N, 10.8; OMe, 8.0%).

The 3,4-diacetate (**29**) of **21** had m.p. 185°, $[\alpha]_D^{20}$ +23.6° (*c* 0.1, chloroform) (Found: C, 48.3; H, 5.4; N, 8.8. $C_{19}H_{25}N_3O_{11}$ calc.: C, 48.4; H, 5.4; N, 8.9%).

Also eluted from the column were unchanged **27** and two other compounds (in trace amounts) believed (t.l.c. data) to be the isomeric 4-methyl ether **28** and a monobenzoyl derivative.

2-Deoxy-2-(2,4-dinitroanilino)-6-O-methyl-D-glucose (**7**). — Hydrolysis of **18** with with 3M hydrochloric acid at 100° gave **7** (60%), m.p. 211°, $[\alpha]_D^{20}$ +4.6° (*c* 0.2, chloroform); lit.[7] m.p. 188–195°, $[\alpha]_D^{20}$ +6.6° (acetone) (Found: C, 43.5; H, 5.0; N, 11.7. $C_{13}H_{17}N_3O_9$ calc.: C, 43.5; H, 4.8; N, 11.7%). Hydrolysis of the anomeric glycoside **21** gave the same product.

Acetylation of **7**, **6**, *and* **5**. — Compound **7** (0.50 g) was dissolved in pyridine (12 ml) and acetic anhydride (6 ml). After being kept at room temperature for 24 h, the mixture was poured into ice–water, and the precipitate was collected by filtration, washed, and recrystallised from ethanol. The resulting 1,3,4-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-D-glucose (**32**) (0.31 g, 58%) had m.p. 202°, $[\alpha]_D^{21}$ +46.5° (*c* 0.1, chloroform) (Found: C, 47.0; H, 4.7; N, 8.6. $C_{19}H_{23}O_{12}N_3$ calc.: C, 47.0; H, 4.8; N, 8.7%).

In a similar way **6**[7], was converted into the isomeric 1,3,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-4-*O*-methyl-D-glucose (**33**), m.p. 196°, $[\alpha]_D^{20}$ +45.5° (*c* 0.1, chloroform) (Found: C, 46.7; H, 5.0; N, 8.4%); and **5**[7] gave 1,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-3-*O*-methyl-D-glucose (**34**), m.p. 124°, $[\alpha]_D^{20}$ −9.9° (*c* 0.1, chloroform) (Found: N, 8.3%).

Synthesis of 1-bromo derivatives **2**, **4**, *and* **3**. — To a solution of **32** (0.150 g) in chloroform (1.5 ml) was added a solution of hydrogen bromide in acetic acid (50% w/v, 1.5 ml); the solutions were cooled to 0° before mixing, and anhydrous conditions were maintained. The mixture was kept at room temperature for 5 h, dry toluene (3 ml) was then added, and the solution evaporated to dryness. Addition of toluene (3 ml) and evaporation was repeated three more times, and the solid obtained was recrystallised from dry ethyl acetate. 3,4-Di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-α-D-glucopyranosyl bromide (**2**) (0.135 g, 78%) thus obtained had m.p.

135°, $[\alpha]_D^{22}$ +28.0° (*c* 0.1, chloroform) (Found: C, 40.7; H, 3.9; Br, 15.9; N, 8.4. $C_{17}H_{20}BrN_3O_{10}$ calc.: C, 40.3; H, 3.9; Br, 15.8; N, 8.3%).

In a similar way **33** was converted into 3,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-4-*O*-methyl-α-D-glucopyranosyl bromide (**4**, 70%), m.p. 150–152°, $[\alpha]_D^{20}$ +67.8° (*c* 0.1, chloroform) (Found: C, 40.5; H, 4.1; Br, 15.8; N, 8.4%).

When the above method was applied to the 3-*O*-methyl derivative **34**, a syrupy product was obtained which, as shown by t.l.c. (solvent *C*), contained unchanged **34**. This product was treated with a further quantity of hydrogen bromide in acetic acid for a further 5 h and the product isolated as before. The 4,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-3-*O*-methyl-α-D-glucopyranosyl bromide (**3**) thus obtained as a yellow glass, $[\alpha]_D^{20}$ −5.0° (*c* 0.1, chloroform), R_F 0.47 (solvent *C*), still contained a small amount of unchanged triacetate (**34**), R_F 0.36, and also some diacetate **37**.

*Ethyl 4,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-3-*O*-methyl-α-D-glucopyranoside* (**11**). — Conventional treatment of ethyl 2-deoxy-2-(2,4-dinitroanilino)-3-*O*-methyl-α-D-glucopyranoside[7] (**20**) with acetic anhydride–pyridine gave **11**, m.p. 107°, $[\alpha]_D^{20}$ +2.9° (*c* 0.2, chloroform) (Found: C, 48.8; H, 5.5; N, 8.9. $C_{19}H_{25}N_3O_{11}$ calc.: C, 48.4; H, 5.4; N, 8.9%).

Reactions of the acetobromo compounds **2**, **4**, *and* **3** *with water.* — 3,4-Di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-α-D-glucopyranosyl bromide (**2**, 30 mg) was dissolved in acetone (40 ml) containing water (50 μl) and shaken with silver carbonate (0.25 g) in the dark for 5 days. The solution was filtered and evaporated to dryness. The residue was purified by p.l.c. (solvent *A*). The main component (R_F 0.41), extracted with acetone, was 3,4-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-D-glucose (**35**) (21 mg, 77%), m.p. 194–196° (from ethanol), $[\alpha]_D^{20}$ −6.5° (*c* 0.1, chloroform) (Found: C, 46.4; H, 4.6; N, 9.3. $C_7H_{21}N_3O_{11}$ calc.: C, 46.1; H, 4.8; N, 9.4%).

In a similar way, **4** was converted into 3,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-4-*O*-methyl-D-glucose (**36**, 68%), melting unsharply, $[\alpha]_D^{20}$ +14.9° (*c* 0.1, chloroform), R_F 0.17 (Solvent *C*) (Found: C, 46.2; H, 5.0; N, 9.2%); and **3** gave 4,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-3-*O*-methyl-D-glucose (**37**, 50%) which was chromatographically homogeneous in several solvents but could not be crystallised. It was isolated as a yellow glass, $[\alpha]_D^{20}$ −15.2° (*c* 0.2, chloroform), R_F 0.18 (Solvent *C*) (Found: C, 45.4; H, 5.1; N, 8.7%).

Reactions of the acetobromo Compounds **2**, **4**, *and* **3** *with ethanol.* — (*1*) *In the presence of silver carbonate in nitromethane.* (*a*) Compound **2** (60 mg) was dissolved in nitromethane (2.5 ml) and ethanol (2.5 ml) and stirred with silver carbonate (1.10 g) and anhydrous calcium sulphate (0.80 g) with exclusion of light and moisture, at room temperature for 5 days. That all the bromo compound had reacted was indicated by t.l.c. The reaction mixture was filtered and the residues were washed with chloroform. The combined filtrate and washings were evaporated to dryness and the components of the yellow solid thus obtained were separated by p.l.c. (solvent *B*). The faster band (R_F 0.60) furnished ethyl 3,4-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-β-D-glucopyranoside (**29**) (38 mg, 69%), m.p. and mixed m.p. 183°,

$[\alpha]_D$ +23.3° (*c* 0.1, chloroform). The slower band (R_F 0.23) yielded 3,4-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-D-glucose (**35**) (6 mg, 13%), m.p. and mixed m.p. 193–195°, $[\alpha]_D^{20}$ −6.0° (*c* 0.05, chloroform). No trace of the α-D-glycoside **9** (R_F 0.63) was present.

(*b*) Compound **4** (60 mg) was treated with ethanol as in (*a*), and the products were isolated by t.l.c. (solvent *C*). The following products were obtained. Ethyl 3,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-4-*O*-methyl-β-D-glucopyranoside (**30**) (35 mg, 60%), m.p. 127°, $[\alpha]_D^{20}$ +40.4°, R_F 0.37 (solvent *C*) (Found: C, 48 5; H, 5.5; N, 9.2. $C_{19}H_{25}N_3O_{11}$ calc.: C, 48.4; H, 5.4; N, 8.9%). Ethyl 3,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-4-*O*-methyl-α-D-glucopyranoside (**10**) (5 mg, 9%), m.p. and mixed m.p. 207°, $[\alpha]_D^{20}$ +40.4° (*c* 0.1, chloroform), R_F 0.49 (solvent *C*). A small amount of a compound chromatographically identical (R_F 0.17, solvent *C*) with 3,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-4-*O*-methyl-D-glucose (**36**) was also present.

(*c*) Compound **3** (60 mg) was treated with ethanol as in (*a*), and the products were isolated by t.l.c. (solvent *C*). Several weak, unidentified bands were present, but the main product was 4,6-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-3-*O*-methyl-β-D-glucopyranoside (**31**) (25 mg, 43%), which was obtained as a yellow glass after purification by t.l.c. using several different solvents. It had $[\alpha]_D^{20}$ +4.0° (*c* 0.1, chloroform), R_F 0.40 (solvent *C*) (Found: C, 48.7; H, 5.5; N, 8.6. $C_{19}H_{25}N_3O_{11}$ calc.: C, 48.4; H, 5.4; N, 8.9%). The hydrolysis product (**37**), R_F 0.18, was also present in ~30% yield and the α-D-glycoside **11**, R_F 0.44, in <2% yield, as judged by the intensities of the coloured bands on t.l.c. (solvent *C*), but these were not isolated.

(*2*) *In the presence of pyridine in chloroform.* (*a*) A solution of **2** (60 mg) in chloroform (2.5 ml) containing pyridine (30 μl) was mixed with ethanol (2.5 ml) and heated at 50° with exclusion of moisture. The reaction was monotored by t.l.c. (solvent *B*). After 24 h, the main component was unreacted **2** (R_F 0.70) which underwent some decomposition on the chromatogram (streaking) and which was readily converted into the diacetate **35** (R_F 0.23) on treatment with water. After 4 days, the mixture was evaporated to dryness and the residue was fractionated by t.l.c. (solvent *B*. The main component was unchanged **2** (~60%) which could not be isolated in pure form because it underwent hydrolysis. The following compounds were isolated and recrystallised from ethanol. Ethyl 3,4-di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-β-D-glucopyranoside (**29**) (7 mg, 12%), m.p. and mixed m.p. 186–187°, $[\alpha]_D^{19}$ +22.6° (*c* 0.1, chloroform), R_F 0.63 (solvent *B*). 3,4-Di-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-6-*O*-methyl-D-glucose (**35**) (15 mg, 30%), m.p. and mixed m.p. 194–195°, $[\alpha]_D^{20}$ −6.8° (*c* 0.2, chloroform), R_F 0.23 (solvent *B*). The α-D-glycoside **9** (R_F 0.63) was present in trace amount.

In a second experiment, **2** (60 mg) was treated with ethanol as described above, and the following compounds were isolated: **29** (9%), **9** (5%), m.p. and mixed m.p. 200–201°, $[\alpha]_D^{20}$ +28.0° (*c* 0.05, chloroform); also present, but not isolated, were unchanged **2** (~50% yield) and **35** (~30% yield).

(*b*) Compound **4** (60 mg) was treated with ethanol as in (*a*). After 24 h at 50°, all the bromo compound had reacted. After 4 days at 50°, the following products

were isolated by t.l.c. (solvent *C*): the α-D-glycoside **10** (41 mg, 72%), m.p. and mixed m.p. 205–206°, $[\alpha]_D^{20}$ +38.5° (*c* 0.1, chloroform) (Found: C, 48.1; H, 5.3; N, 8.9%); and the diacetate **36** (6 mg, 12%), R_F 0.17 (solvent *C*). The β-D-glycoside **30** (R_F 0.37) was also present in a trace amount.

(*c*) Compound **3** (60 mg) was treated with ethanol in the same way to furnish an initial product mixture which, on fractionation by t.l.c. (solvent *B*) followed by a second t.l.c. fractionation with solvent *C* (to achieve complete separation of the anomeric glycosides), gave the following compounds: the α-D-glycoside **11** (21 mg, 37%), m.p. and mixed m.p. 108–110° (Found: C, 48.5; H, 5.4; N, 9.0%), and the β-D-glycoside **31** (3 mg, 6%) identified chromatographically. The hydrolysis product **37** (R_F 0.18, solvent *C*) was also present (~35% yield, as judged by the intensity of the band). Several unidentified weaker bands were also present.

ACKNOWLEDGMENTS

The award of studentships by the Science Research Council (to B. E. and R. J. F.) and an Imperial Chemical Industries Fellowship tenable in the University of Wales (to B. E.) are gratefully acknowledged, as is valuable technical assistance by Mrs. Olive Owen.

REFERENCES

1 P. F. Lloyd and M. Stacey, *Chem. Ind. (London)*, (1955) 917.
2 P. F. Lloyd and M. Stacey, *Tetrahedron*, 9 (1969) 116.
3 P. F. Lloyd and G. P. Roberts, *J. Chem. Soc.*, (1963) 2962.
4 P. F. Lloyd and G. P. Roberts, *J. Chem. Soc.*, (1965) 6910; S. Umezawa and S. Koto, *J. Antibiot., Ser. A*, 19 (1966) 88.
5 D. Horton and M. L. Wolfrom, *J. Org. Chem.*, 27 (1967) 194.
6 M. L. Wolfrom, H. G. Garg, and D. Horton, *J. Org. Chem.*, 30 (1965) 1556; M. L. Wolfrom and H. B. Bhat, *ibid.*, 32 (1967) 2757.
7 P. F. Lloyd, B. Evans, and R. J. Fielder, *Carbohyd. Res.*, 9 (1969) 471.
8 D. Horton, J. B. Hughes, J. S. Jewell, K. D. Philips, and W. N. Turner, *J. Org. Chem.*, 32 (1967) 1073.
9 Y. Wang and H. Tai, *Acta Chim. Sinica*, 24 (1958) 368.
10 D. Horton, *J. Org. Chem.*, 29 (1964) 1776.
11 T. Ishikawa and H. G. Fletcher, Jr., *J. Org. Chem.*, 34 (1969) 563.
12 M. L. Wolfrom, A. O. Pittet, and I. C. Gillam, *Proc. Nat. Acad. Sci. U. S.*, 47 (1961) 700.
13 C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, 29 (1964) 3286.
14 H. J. Jennings, *Chem. Commun.*, 14 (1967) 722.