712. *The Reaction Between 3,4,6-Tri-O-acetyl-D-glucal and p-Nitrophenol.*

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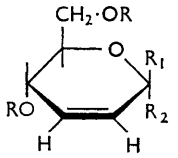
From the reaction between 3,4,6-tri-*O*-acetyl-D-glucal and *p*-nitrophenol two forms of *p*-nitrophenyl 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*-hexoside, which are believed to be anomeric, have been obtained. Treatment of these acetylated unsaturated glycosides with permanganate in aqueous acetone affords hexoside derivatives with a 2,3-*cis*-diol grouping which is *trans* to the aglycone residue. Hydrogenolysis of the α-anomer results in both saturation of the olefinic linkage and cleavage of the *O*-glycosyl bond to yield 4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-glucitol.

Acid-catalysed addition of methanol to the olefinic linkage in D-glucal,[1] D-galactal,[2] and tri-*O*-acetyl-D-galactal [2] has been shown to afford the corresponding methyl 2-deoxy-α-glycoside as the main product. It has now been demonstrated that the action of a phenol on tri-*O*-acetyl-D-glucal leads not to an aryl 2-deoxyglycoside triacetate, but to an acetylated unsaturated glycoside. This is in contrast to the results of Wallenfels and Lehmann [3] who found that treatment of tri-*O*-acetyl-D-galactal with phenol in the presence of toluene-*p*-sulphonic acid afforded phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactoside.

When D-glucal and *p*-nitrophenol were heated in dioxan, initially without the addition of catalyst and subsequently with zinc chloride and hydrochloric acid, glycoside was not detected on chromatographic analysis of the products. However, a crystalline product was obtained when 3,4,6-tri-*O*-acetyl-D-glucal and *p*-nitrophenol were heated in boiling benzene, and this substance was shown to be *p*-nitrophenyl 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-α-D-*erythro*-hexoside (I). From a subsequent preparation, the β-isomer (II) was isolated together with lower-melting crystalline material (A) which was resolved by fractional crystallisation into pure hexosides (I) and (II). Optical rotation and infrared spectral measurements indicated that the material (A) was an equimolecular mixture of hexosides (I) and (II). That compounds (I) and (II) are likely to be a pair of anomeric glycosides is supported by the fact that both on treatment with methanolic hydrogen chloride gave solutions with the same equilibrium optical rotation. It is assumed that hexoside (I), having the higher positive specific rotation, is the α-form. The diacetates (I and II) readily underwent deacetylation with barium methoxide in methanol [4] to yield the unsaturated glycosides (III and IV).



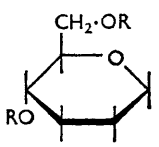
(I; R = Ac, R_1 = H, R_2 = O·C_6H_4·NO_2)
(II; R = Ac, R_1 = O·C_6H_4·NO_2, R_2 = H)
(III; R = R_1 = H, R_2 = O·C_6H_4·NO_2)
(IV; R = R_2 = H, R_1 = O·C_6H_4·NO_2)
(VIII; R = R_1 = H, R_2 = Ph)

The structure of the glycoside diacetate (I) is revealed by the following evidence. Although non-reducing towards Fehling's solution, the compound did reduce aqueous potassium permanganate. Hydrolysis with methanolic hydrogen chloride (0·005N) yielded *p*-nitrophenol in amount (spectrophotometric determination) which indicated that one mol. of the phenol had undergone reaction with one mol. of the acetylated glycal. Acetyl determination showed that two groups per molecule were present. From treatment of compound (I) with potassium permanganate in aqueous acetone (a reagent [5] leading to a *cis*-diol from an olefin) and subsequent acidic hydrolysis, D-mannose was obtained

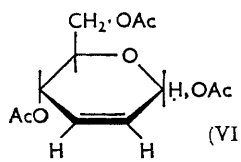
[1] Hughes, Overend, and Stacey, *J.*, 1949, 2846.
[2] Overend, Shafizadeh, and Stacey, *J.*, 1951, 992.
[3] Wallenfels and Lehmann, *Annalen*, 1960, **635**, 166.
[4] Mitchell, *J. Amer. Chem. Soc.*, 1941, **63**, 3534.
[5] Raphael and Roxburgh, *J.*, 1955, 3405.

together with a trace of a compound having the chromatographic mobility of D-allose. The mannose was characterised by conversion into its phenylhydrazone and into *N*-*p*-nitrophenyl-D-mannosylamine: these derivatives were identified with authentic samples. Similar permanganate and subsequent acid treatment of compound (II) yielded allose together with a small amount of mannose. The allose was identified by its optical rotation and by chromatographic properties which in acidic, basic, and neutral solvents were identical with those of an authentic sample. In these solvents this sugar was not readily distinguishable from glucose but in a solvent containing boric acid [6] the two sugars were resolvable. The difference in the hydroxylation of hexosides (I) and (II) must arise from differences in the accessibility of the double bond to attack by the permanganate ion. The side of the double bond *trans* to the aglycone is apparently more accessible.

On hydrogenation of compound (I) in methanol over platinum oxide 5 mol. of hydrogen were consumed rapidly. This uptake can be accounted for as follows: 3 mol. for the reduction of the nitro-group (a control experiment indicated that *p*-nitrophenol rapidly consumed 3 mol. of hydrogen under identical conditions), and 1 mol. each for saturation of the olefinic linkage and for hydrogenolysis of the glycosidic bond. Although hydrogenolysis of aryl glycosides generally occurs with fission of the aryl–oxygen bond [7] we were unable to detect, either by chromatography or by tests for a reducing group, any 4,6-di-*O*-acetyl-2,3-dideoxy-D-glucose (an authentic sample was prepared for reference purposes) or other reducing sugar amongst the products of the action of hydrogen on compound (I). Qualitative tests indicated that the aromatic product of the hydrogenolysis was *p*-aminophenol, removal of which afforded a distillable oil (B) which could be readily deacetylated to another oil (C). Compound (C) yielded a crystalline mono-*O*-benzylidene derivative identical with 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-D-glucitol as described by Bergmann and Breuers.[8] Compound (C) is therefore considered to be 1,5-anhydro-2,3-dideoxy-D-glucitol (V) and (B) is the 4,6-di-*O*-acetyl derivative (VI). Obviously in the hydrogenolysis of compound (I) cleavage of the glycosyl–oxygen bond had occurred. It is noteworthy that Bergmann and Breuers [8] obtained 4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-glucitol (VI) by hydrogen treatment of 1,4,6-tri-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*-hexose (VII) (" triacetyl-pseudoglucal "), another example of glycosyl–oxygen bond fission in this series. Finally, further support for the structure of the glycoside (I) follows from the synthesis of the compound from 1,4,6-tri-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*-hexose (VII) (prepared by Fischer's [9] and Bergmann's [10] methods) and *p*-nitrophenol by the Helferich and Schmitz-Hillebrecht method.[11]



(V; R = H)
(VI; R = Ac)



(VII)

Phenol underwent reaction with 3,4,6-tri-*O*-acetyl-D-glucal in benzene more slowly than did its *p*-nitro-derivative, but convenient reaction was obtained in chlorobenzene to give a distillable oil, which on deacetylation afforded crystalline phenyl 2,3-didehydro-2,3-dideoxy-α(?)-D-*erythro*-hexoside (VIII). (The value of the specific rotation indicates the α-configuration as the more probable.)

It is envisaged that the reactions proceed *via* attack by the (substituted) phenoxide ion at $C_{(1)}$ of the glycal triacetate together with displacement of the acetoxy-group at $C_{(3)}$ and

[6] Rees and Reynolds, *Nature*, 1958, **181**, 767.
[7] Richtmyer, *J. Amer. Chem. Soc.*, 1934, **56**, 1633.
[8] Bergmann and Breuers, *Annalen*, 1929, **470**, 51.
[9] Fischer, *Ber.*, 1914, **47**, 196.
[10] Bergmann, Kobel, Schotte, Rennert, and Ludewig, *Annalen*, 1923, **434**, 79.
[11] Helferich and Schmitz-Hillebrecht, *Ber.*, 1933, **66**, 378.

allylic migration of the double bond. Attack at the other end of the allylic system by the *p*-nitrophenoxide ion would produce 4,6-di-*O*-acetyl-3-*O*-*p*-nitrophenyl-D-glycal. That compounds (I) and (II) did not have this type of structure is indicated by the production of unsubstituted hexoses after oxidation in neutral solution and subsequent acid hydrolysis. Moreover, although compounds (I) and (II) are non-reducing towards Fehling's solution, both 3,4,6-tri-*O*-acetyl-D-glucal and 4,6-di-*O*-acetyl-3-*O*-methyl-D-glucal reduce the reagent readily.

When the double bond is between $C_{(2)}$ and $C_{(3)}$, as in 1,4,6-tri-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*-hexose, reaction with *p*-nitrophenol proceeds by direct attack at $C_{(1)}$ without allylic change. The electron-withdrawing influence of the hetero-oxygen atom is most likely to cause this effect.

Experimental

p-*Nitrophenyl* 4,6-*Di*-O-*acetyl*-2,3-*didehydro*-2,3-*dideoxy*-α-D-erythro-*hexoside*.—3,4,6-Tri-*O*-acetyl-D-glucal (10 g., 1 mol.) and freshly recrystallised *p*-nitrophenol (20 g., 3·9 mol.) in benzene (50 ml.) were heated under reflux for 4 hr. The solution was extracted with 5% sodium hydroxide (3 × 30 ml.) and water (3 × 25 ml.), and dried ($MgSO_4$). Removal of the solvent and crystallisation from ethanol afforded p-*nitrophenyl* 4,6-*di*-O-*acetyl*-2,3-*didehydro*-2,3-*dideoxy*-α-D-erythro-*hexoside* (I) (5·5 g., 43%), m. p. 96—97°, $[\alpha]_D^{20}$ +174° (*c* 0·2 in benzene) (Found: C, 54·9; H, 4·8; N, 4·2; Ac, 24·6. $C_{16}H_{17}NO_8$ requires C, 54·7; H, 4·8; N, 4·0; Ac, 24·5%).

Repetition of this experiment except that half-scale quantities and unpurified *p*-nitrophenol were used yielded p-*nitrophenyl* 4,6-*di*-O-*acetyl*-2,3-*didehydro*-2,3-*dideoxy*-β-D-erythro-*hexoside* (II) which was recrystallised from ethanol (1·5 g., 23%), m. p. 102—103°, $[\alpha]_D^{20}$ +51° (*c* 0·6 in benzene) (Found: C, 54·7; H, 4·9; N, 4·0; Ac, 24·5%). A further crop of crystals (A) (0·4 g.), m. p. 82—86°, $[\alpha]_D$ +117° (*c* 0·4 in benzene), was collected. No purification resulted from a recrystallisation from ethanol, but on recrystallisation from 5% aqueous ethanol two fractions corresponding to compounds (I) and (II) were obtained and identified by melting and mixed melting point determinations. [Infrared spectral evidence indicated that before separation fraction (A) contained equimolecular amounts of compounds (I) and (II).] A third crop of crystals (0·1 g.) precipitated from the mother liquors was identical with compound (I).

p-*Nitrophenyl* 2,3-*Didehydro*-2,3-*dideoxy*-α-D-erythro-*hexoside*.—*p*-Nitrophenyl 4,6-di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-α-D-*erythro*-hexoside (1 g.) was dissolved in dry methanol (25 ml.) at 0° and a solution of barium methoxide in methanol (0·3 ml.; 1·5N) was added. After 48 hr. at 0°, the solution was neutralised (carbon dioxide), filtered, and evaporated to dryness, to give after recrystallisation from benzene hygroscopic p-*nitrophenyl* 2,3-*didehydro*-2,3-*dideoxy*-α-D-erythro-*hexoside* (0·2 g., 26%), m. p. 109—110°, $[\alpha]_D^{20}$ +270° (*c* 1·0 in ethanol) (Found: C, 53·6; H, 4·9; N, 5·2. $C_{12}H_{13}NO_6$ requires C, 53·9; H, 4·9; N, 5·2%). Deacetylation with sodium methoxide in methanol (0·01N) resulted in cleavage of the glycosidic bond.

Treatment of Compound (I) *with Neutral Permanganate*.—2% Aqueous potassium permanganate (20 ml.) was added during 1 hr. to a vigorously stirred suspension of the compound (1 g.) in aqueous acetone (50% v/v; 20 ml.) maintained at 0—5° under an atmosphere of carbon dioxide. The temperature was allowed to rise to 7° and then ethanol (50 ml.) was added. The filtered solution was treated with ion-exchange resin (IRC 50) and evaporated to dryness. Nothing crystalline could be isolated from the syrupy product which was heated with sulphuric acid (25 ml.; 1N) for 2 hr. at 100°. After neutralisation ($BaCO_3$), the filtered solution was evaporated to dryness. An ethanolic extract of the residue was shown by paper chromatography to contain mannose and a trace of a sugar with a mobility identical to that of allose (Solvent system: benzene–n-butanol–pyridine–water 1 : 5 : 3 : 3. Spray reagent: silver nitrate in acetone and then 0·5N-sodium hydroxide in ethanol).

A portion (0·1 g.) of the syrup, obtained on evaporation of the ethanolic extract, and *p*-nitroaniline (0·1 g.) were heated for 5—10 min. in boiling methanol (2 ml.) containing hydrochloric acid (0·07%). On cooling *N*-*p*-nitrophenyl-D-mannopyranosylamine separated as yellow needles, m. p. 211° (after two recrystallisations from ethanol) alone or in admixture with authentic material prepared from D-mannose under identical conditions. To another portion of the syrup (0·1 g.) in water (1 ml.) and acetic acid (0·5 ml.) at 10°, phenylhydrazine (0·05 ml.) was added. After 10 min. crystals of D-mannose phenylhydrazone separated. Crystallisation from water afforded a product with m. p. 188—189°; on admixture with

D-mannose phenylhydrazone, similarly prepared from authentic D-mannose, the m. p. was 188—190°.

4,6-*Di*-O-*acetyl*-1,5-*anhydro*-2,3-*dideoxy*-D-*glucitol*.—Compound (I) (1·5 g.) in methanol (40 ml.) was shaken with hydrogen at a slight overpressure at room temperature in the presence of platinum oxide (0·1 g.). When hydrogen uptake was complete (5·1 mol.), the catalyst was filtered off, and the filtrate evaporated to dryness. A solution of the residue in ethyl acetate (35 ml.) was extracted with N-hydrochloric acid (3 × 15 ml.), washed with water, dried (Na_2SO_4), and evaporated to a non-reducing syrup, which on distillation gave 4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-glucitol (0·32 g., 35%), b. p. 78° (bath temp.)/0·15 mm., $[\alpha]_D^{20}$ +2·6° (*c* 0·8 in ethanol), $n_D^{19.5}$ 1·4518. [Bergmann and Breuers [8] give b. p. 102—103°/0·7 mm., $[\alpha]_D^{20}$ +2·2° (in ethanol), n_D^{18} 1·4511.] Deacetylation of the di-*O*-acetate (0·2 g.) in methanol (10·1 ml.) with barium methoxide (0·01N) at 0° for 18 hr. afforded 1,5-anhydro-2,3-dideoxy-D-glucitol (0·07 g., 58%), b. p. 104°/0·1 mm. (Bergmann and Breuers [8] report b. p. 122°/1·5 mm.)

1,5-*Anhydro*-4,6-O-*benzylidene*-2,3-*dideoxy*-D-*glucitol*.—1,5-Anhydro-2,3-dideoxy-D-glucitol (0·07 g.), zinc chloride (0·05 g.), and freshly distilled benzaldehyde (3 ml.) were heated at 100° for 0·5 hr. The product was isolated in standard fashion and the 4,6-*O*-benzylidene derivative was recrystallised thrice from ethanol. It had m. p. 135°. (Bergmann and Breuers [8] give m. p. 137°.)

Phenyl 4,6-*Di*-O-*acetyl*-2,3-*didehydro*-2,3-*dideoxy*-α-D-erythro-*hexoside*.—3,4,6-Tri-*O*-acetyl-D-glucal (3·0 g.) and phenol (10 g.) were heated in boiling chlorobenzene (30 ml.) for 3 hr. The product was isolated as a syrup which could not be crystallised even after purification on alumina, or by fractional distillation. *Phenyl* 4,6-*di*-O-*acetyl*-2,3-*didehydro*-2,3-*dideoxy*-α-D-erythro-*hexoside* (0·9 g., 35%) was obtained as a syrup, b. p. 170° (bath temp.)/1 mm., $[\alpha]_D^{20}$ +131·7° (*c* 1·5 in ethanol) (Found: C, 61·8; H, 6·0; Ac, 28·0. $C_{16}H_{18}O_6$ requires C, 62·7; H, 5·9; Ac, 28·1%).

Deacetylation of the 4,6-diacetate (0·8 g.) with barium methoxide in methanol and crystallisation of the product from ethanol gave *phenyl* 2,3-*didehydro*-2,3-*dideoxy*-α-D-erythro-*hexoside* (0·2 g., 34%), m. p. 81—82°, $[\alpha]_D^{20}$ +175° (*c* 0·3 in ethanol) (Found: C, 64·8; H, 6·4. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%).

1,4,6-*Tri*-O-*acetyl*-2,3-*didehydro*-2,3-*dideoxy*-D-erythro-*hexose*.—4,6-Di-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*-hexose {b. p. 140°/0·15 mm., $[\alpha]_D^{20}$ +45° (*c* 1·7 in ethanol)} (1·3 g.), prepared from 3,4,6-tri-*O*-acetyl-D-glucal by Fischer's method,[9] was heated at 100° for 2 hr. with acetic anhydride (10 ml.) and sodium acetate (1·0 g.). Excess of acetic anhydride was removed by repeated evaporation with ethanol, and the residue was washed in ether (25 ml.), with saturated sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). After evaporation of the ether the residue was distilled to give 1,4,6-tri-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*-hexose (1·26 g., 82%), b. p. 136—137° (bath temp.)/0·09 mm., $[\alpha]_D^{20}$ +112° (*c* 2 in benzene). (Bergmann *et al.*[10] give b. p. 150—165°/0·2—0·3 mm.)

Preparation of Compound (I) *from* 1,4,6-*Tri*-O-*acetyl*-2,3-*didehydro*-2,3-*dideoxy*-D-erythro-*hexose*.—1,4,6-Tri-*O*-acetyl-2,3-didehydro-2,3-dideoxy-D-*erythro*-hexose (0·5 g.) and *p*-nitrophenol (1 g.) were heated in boiling benzene (25 ml.) for 2·5 hr. (to constant optical rotation). Compound (I) (0·15 g., 23%) was isolated as before and after recrystallisation from ethanol had m. p. 96—97°, alone or when admixed with the material obtained in the alternative synthesis, $[\alpha]_D^{20}$ +166° (*c* 0·4 in benzene).

Acidic Hydrolysis of Compounds (I) *and* (II).—The compounds were kept at room temperature in methanolic hydrogen chloride (1N) and the optical rotations of the solutions were noted at intervals.

	Compound (I) (*c* 0·54)					
Time (hr.)	0	0·66	1·2	2·66	17	
α_D	+0·68°	+0·54°	+0·44°	+0·29°	−0·03°	(const.)

	Compound (II) (*c* 0·6)					
Time (hr.)	0	0·33	0·5	0·75	1·0	17
α_D	+0·08°	+0·26°	+0·32°	+0·38°	+0·44°	−0·02° (const.)

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