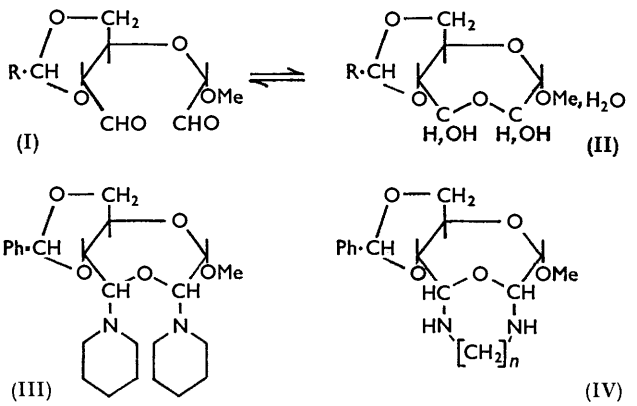
708. *Periodate Oxidation. Part V.*[1] *Further Reactions of Periodate-oxidised Methyl* 4,6-O-*Benzylidene-*α-D-*glucoside and of Some Related Compounds.**

By R. L. Colbran, R. D. Guthrie, and Margaret A. Parsons.

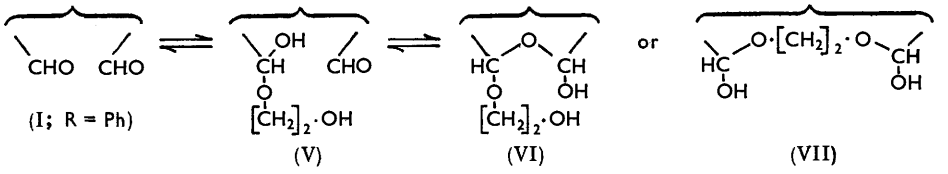
Reactions of periodate-oxidised methyl 4,6-*O*-benzylidene-α-D-glucoside with ethylene glycol, piperidine, ethylenediamine, and substituted hydrazines have confirmed that in solution there is an equilibrium between its dialdehyde and hemialdal forms. The periodate oxidation products of methyl 4,6-*O*-*o*- and 4,6-*O*-*p*-chlorobenzylidene- and methyl 4,6-*O*-*o*-bromobenzylidene-α-D-glucosides are similar to that from methyl 4,6-*O*-benzylidene-α-D-glucoside. A hemialdal structure has been proved for 2-(4-carboxy-5-methyl-2-furyl)diglycollic aldehyde and the corresponding 4-acetyl compound.

Reduction of periodate-oxidised methyl 4,6-*O*-benzylidene-α-D-glucoside gave the corresponding diprimary alcohol (XIV), whose analysis has led to a study of Gran's method [15] for methoxyl determination.

Reaction of periodate-oxidised methyl 4,6-*O*-benzylidene-α-D-glucoside with amines has shown that derivatives of either the dialdehyde (I; R = Ph) or the hemialdal hydrate (II; R = Ph) are formed.[2] These findings are now substantiated. Derivatives (III) of the hemialdal form have been obtained with piperidine, the first derivative obtained from this type of compound and a secondary amine, and (IV; $n = 2$) with ethylenediamine;



the latter compound, which contains a new heterocyclic system, was hydrolysed by picric acid to yield ethylenediamine picrate. The structures of these new derivatives and of others now reported were based on infrared and elemental analyses. Reaction of the periodate-oxidised sugar (II; R = Ph) with trimethylenediamine did not give the hetero-



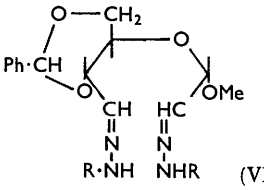
cyclic compound (IV; $n = 3$), but only starting compound, suggesting the possible instability of the fused ring system in the expected product. Reaction of the compound

* Part of this paper was presented at the 135th Meeting of the American Chemical Society, April, 1960, at Cleveland, Ohio.

[1] Part IV, Honeyman and Shaw, *J.*, 1959, 2454.
[2] Guthrie, Honeyman, and Parsons, *J.*, 1959, 2449.

(II; R = Ph) with ethylene glycol could give rise to two products (VI or VII), depending on the ring closure of the intermediate aldehydo-hemiacetal (V). Acetylation of the product gave a compound with two absorption bands in the >C=O stretching region at 1760 and 1743 cm.$^{-1}$. This is evidence in favour of formulation (VI), which would give a derivative with one primary and one glycosidic acetoxy-group, whereas formulation (VII) contains two of the latter. The diacetates of (II; R = Ph) and of periodate-oxidised methyl α-L-rhamnoside both have carbonyl absorption at a higher frequency than those quoted for aliphatic acetates (1750—1735 cm.$^{-1}$).[3] Hence the diacetate of (VII) should have carbonyl absorption at frequencies greater than 1750 cm.$^{-1}$, whilst the diacetate of (VI) would have one greater and one less than this value. Crystallisation of (VI) from water gave the hemialdal hydrate (II; R = Ph), a characteristic reaction of hemialdal alcoholates.[4]

The reaction of periodate-oxidised methyl 4,6-*O*-benzylidene-α-D-glucoside with substituted hydrazines was studied in an attempt to prepare compounds analogous to that obtained with phenylhydrazine.[4]



(VIII)

p-Nitrophenylhydrazine hydrochloride in water gave only the dialdehyde bis-*p*-nitrophenylhydrazone (VIII; R = *p*-NO_2·C_6H_4) even with a 1 : 1 proportion of reactants, or when the reaction was carried out in methanol. Similar results were obtained with excess of 2,4-dinitrophenylhydrazine and of isonicotinoylhydrazine, giving the products [VIII; R = 2,4-$(NO_2)_2$·C_6H_3] and [VIII; R = C_5H_4N·CO], respectively. The dialdehyde bis-semicarbazone (VIII; R = NH_2·CO) was obtained when (II; R = Ph) was treated with excess of semicarbazide hydrochloride in water or ethanol.

(II; R = Ph) dissolved readily in ethanolamine and a crystalline derivative was obtained whose structure has not yet been deduced. A molecular-weight determination by *X*-ray crystallography and elemental analysis indicated that one molecule of ethanolamine had condensed with one molecule of (II; R = Ph) with the elimination of three molecules of water. However, the infrared spectrum of the product had no ⁻OH, >NH, >C=O, or >C=N⁻ absorption. Reaction of (II; R = Ph) with ammonia or with hydrazine yielded derivatives whose structures are now being studied.

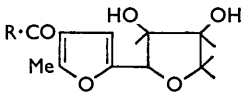
For *X*-ray study a series of analogues of (II; R = Ph) have been prepared, each containing a halogen atom in the arylidene group. Methyl 4,6-*O*-*o*- and 4,6-*O*-*p*-chlorobenzylidene- and methyl 4,6-*O*-*o*-bromobenzylidene-α-D-glucosides had infrared absorptions about 1600—1500 cm.$^{-1}$, due to the benzylidene group, whereas most 4,6-*O*-benzylidene derivatives of aldoses are anomalous in not absorbing in this region.[5] The three compounds reduced one molecular proportion of periodate and gave crystalline dialdehyde dihydrates to which hemialdal hydrate structures have been assigned (II; R = *o*-Cl·C_6H_4, *p*-Cl·C_6H_4, or *o*-Br·C_6H_4). The oxidations were carried out in aqueous methanol because of the insolubility of the starting compound in water. Isolation of the dialdehyde methanolates was avoided by removal of the methanol at the end of the reaction. Methylation, benzoylation, and reaction with methanol, cyclohexylamine, or aniline have shown that these products are similar to periodate-oxidised methyl 4,6-*O*-benzylidene-α-D-glucoside.[2,4]

On analytical and infrared spectral evidence a hemialdal structure has been suggested [6] for the periodate oxidation products (X; R^1 = OH or Me, R^2 = OH) of 5-(1,4-anhydro-D-*arabino*tetrahydroxybutyl)-2-methyl-3-furoic acid (IX; R = OH), and of 5-(1,4-anhydro-D-*arabino*tetrahydroxybutyl)-2-methyl-3-furyl methyl ketone (IX; R = Me). Polarographic data [7] show that equilibrium exists between reducible and non-reducible forms in

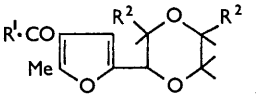
[3] Bellamy, " Infrared Spectra of Complex Molecules," Methuen, London, 1958.
[4] Guthrie and Honeyman, *J.*, 1959, 2441.
[5] Barker, Bourne, and Stephens, *Methods of Biochim. Analysis*, 1956, **3**, 213.
[6] García González, López Aparicio, and Ortiz Rizo, *Anales real Soc. espan. Fis. Quim.*, 1956, **52**, *B*, 717.
[7] López Aparicio and Piazza Molini, *ibid.*, p. 723.

solution. These periodate-oxidation products have now been methylated to yield products (X; R^1 = OMe or Me, R^2 = OMe) with two methyl ether groups, proving that these compounds have reacted in their hemialdal forms. As would now be expected, the hemialdals showed complex mutarotations in water and pyridine.

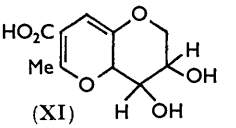
Jones [8] suggested structure (XI) for the compound formed by dehydration of the hydrolysed condensation product of D-glucose and ethyl acetoacetate, and hence (XII; R^1 = CO_2H, R^2 = CHO) for its periodate-oxidation product. The latter had the analysis of the anhydrous dialdehyde, and when methylated with Purdie's reagents gave a derivative which, on the basis of methoxyl content, was considered to be the triester (XII; R^1 = R^2 = CO_2Me). When García González *et al.*[9] later showed that the compound assumed by Jones to have structure (XI) was (IX; R = OH), it was assumed [9] that the methylated oxidation product was the corresponding triester (XIII). By means of elemental and infrared analysis we have shown that the methylation product is (X; R^1 = R^2 = OMe). The latter compound and (XIII) have similar methoxyl contents, but in the carbonyl region of the infrared spectrum the methylated oxidation product had only αβ-unsaturated ester absorption, and lacked saturated ester absorption expected for (XIII). The periodate-oxidation product of (IX; R = OH) has been found to be a "dialdehyde hydrate" by García González [9] and by the present authors, contrary to Jones's findings; [8] no anhydrous dialdehydes of this type have yet been isolated directly from a periodate oxidation.



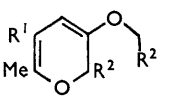
(IX)



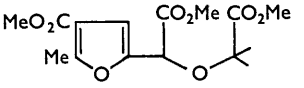
(X)



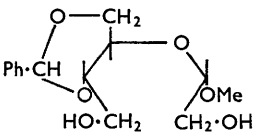
(XI)



(XII)



(XIII)



(XIV)

Reduction of periodate-oxidised methyl 4,6-*O*-benzylidene-α-D-glucoside with potassium borohydride has yielded the corresponding diprimary alcohol (XIV), further characterised as its diacetate. We have isolated the diprimary alcohol, previously reported to be anhydrous,[10] only as a crystalline monohydrate having the broad absorption band at 1640 cm.$^{-1}$ characteristic of hydrates.[5] Drying the compound to constant weight over phosphorus pentoxide caused a loss in weight equivalent to one molecule of water of crystallisation; exposing the dried solid to a damp atmosphere was followed by the appropriate increase in weight. The anhydrous compound had a different spectrum from that of the hydrate; in particular, the broad 1640 cm.$^{-1}$ band disappeared, and the hydroxyl band was narrower and shifted to a slightly higher frequency.

Methoxyl determinations on the reduced product (XIV) and its diacetate by a modification of Zeisel's method,[11] gave values much higher than expected. Smith and Van Cleve [12] have already drawn attention to similar abnormal methoxyl values in the case of D'- and L'-1'-hydroxymethyl-1-methoxydiethylene glycol and for D'- and L'-1-methoxydiethylene glycol [12] and suggested that these high values arose from the glycollaldehyde formed by

[8] Jones, *J.*, 1945, 116.
[9] García González, López Aparicio, and Vázquez, *Anales real Soc. espaň. Fís. Quím.*, 1948, **44**, *B*, 243.
[10] Lewis, Ph.D. Thesis, University of Minnesota, 1957.
[11] Samsel and McHard, *Ind. Eng. Chem. Anal.*, 1942, **14**, 750.
[12] Smith and Van Cleve, *J. Amer. Chem. Soc.*, 1955, **77**, 3091.

hydrolysis during the Zeisel determination. Later, evidence[13] was presented which suggested that the high values were due to the polyol, which is formed simultaneously with the glycollaldehyde, and which gives rise to a volatile higher alkyl iodide. von Rudloff[14] has also shown that several polyols including sorbitol and mannitol gave a considerable apparent methoxyl content by Zeisel's method. Acid hydrolysis of (XIV) and its diacetate would give rise to erythritol and glycollaldehyde. We have now shown that erythritol has an apparent methoxyl content of 11·3%, whereas glycollaldehyde has one of only 0·2%.

To overcome the abnormal methoxyl results a modified technique due to Gran[15] was used (cf. ref. 13) in which the volatile iodides from the Zeisel distillation are passed into a solution of trimethylamine in propan-2-ol. The alkyl iodides form quaternary ammonium salts with the trimethylamine, and Gran claimed that tetramethylammonium iodide alone is completely insoluble in propan-2-ol; it can thus be separated and determined independently of other volatile alkyl iodides. We have applied this method to vanillin and methyl α-D-glucoside, two substances not forming any other alkyl iodides, and in each case a methoxyl content slightly below the theoretical values was obtained. The discrepancy between the observed and the theoretical values could always be accounted for by titrating the propan-2-ol filtrate. On the basis of these experiments, and contrary to Gran's findings, it is suggested that tetramethylammonium iodide is slightly soluble in the trimethylamine–propan-2-ol solvent.

Because no fixed correction could be made, this difficulty was avoided by carrying out a series of methoxyl determinations for each substance, extending over a weight range of 20—120 mg. A plot of titre against sample weight should be a straight line passing through the origin, the slope of which should be directly proportional to the methoxyl content. The straight lines actually obtained were parallel to those expected, with small negative intercepts on the titre axis, equal to the experimentally observed titres of the propan-2-ol filtrates. Since the theoretical and experimentally observed slopes were equal, the true methoxyl content could be calculated from the latter.

Experimental

All solutions were concentrated *in vacuo*; those in chloroform and ether were previously dried with inorganic desiccants. The identity of compounds was proved where necessary by mixed m. p. determination and infrared spectrometry; all compounds had infrared spectra consistent with the assigned structures.

Reactions of 7,9-*Dihydroxy*-6α-*methoxy*-2-*phenyl*-trans-m-*dioxano*[5,4-e]-[1,4]-*dioxepan hydrate*[4] (II; R = Ph).—(a) *With ethylene glycol.* The hemialdal hydrate (2 g.) was heated with ethylene glycol (30 ml.) at 100° until dissolution occurred (about 30 min.). The solution was concentrated to about 4 ml. and cooled, and the resulting white mass was crystallised from chloroform–light petroleum. The gel-like solid was collected, washed thoroughly with water, and recrystallised from the same solvents to yield 7(or 9)-*hydroxy*-9(or 7)-(2-*hydroxyethoxy*)-6α-*methoxy*-2-*phenyl*-trans-m-*dioxano*[5,4-e]-[1,4]-*dioxepan* (VI) (58%), m. p. 141—144°, $[\alpha]_D^{21}$ +48·9° (5 min.) ⟶ +52·1° (21 hr.) constant for a further 24 hr. (*c* 2·65 in pyridine) (Found: C, 56·2; H, 6·3. $C_{16}H_{22}O_8$ requires C, 56·1; H, 6·5%). The product reduced Fehling's solution and on crystallisation from hot water yielded the hemialdal hydrate (II; R = Ph).

Acetylation of the product (VI) with pyridine–acetic anhydride at room temperature for 24 hr. gave a white solid when the reaction solution was poured into ice-water. Three recrystallisations gave a gel-like product, which when thoroughly dried was the 7(or 9)-*acetoxy*-9(or 7)-(2-*acetoxyethoxy*)-*derivative* (63%), m. p. 156—158°, $[\alpha]_D^{21}$ +65·6° (*c* 1·1 in chloroform) (Found: C, 56·8; H, 6·2. $C_{20}H_{26}O_{10}$ requires C, 56·3; H, 6·1%). The product had acetate absorptions at 1760 and 1743 cm.$^{-1}$.

(b) *With piperidine.* The hemialdal hydrate (5 g.) in freshly distilled piperidine (35 ml.)

[13] Cadotte, Dutton, Goldstein, Lewis, Smith, and Van Cleve, *J. Amer. Chem. Soc.*, 1957, **79**, 691.
[14] von Rudloff, *Analyt. Chim. Acta*, 1957, **16**, 294.
[15] Gran, *Svensk Papperstid.*, (*a*) 1952, **55**, 255; 1953, **56**, 179; (*b*) 1954, **57**, 702.

was heated on a steam-bath for 10 min. The clear solution obtained was poured, with stirring, into ice-cold dilute acetic acid, and the crystalline product which separated was collected, washed with sodium hydrogen carbonate solution and with water, and dried *in vacuo* (P_2O_5) (66%). Three recrystallisations from aqueous acetone gave needles of 6α-*methoxy*-2-*phenyl*-7,9-*dipiperidino*-trans-m-*dioxano*[5,4-e]-[1,4]-*dioxepan* (III), m. p. 130·5—131·5° (decomp.), $[\alpha]_D^{20}$ +46·9° (*c* 0·5 in pyridine) (Found: C, 66·7; H, 8·5; N, 6·1. $C_{24}H_{36}O_5N_2$ requires C, 66·6; H, 8·4; N, 6·5%).

(c) *With ethylenediamine.* The hemialdal hydrate (5 g.) was heated on a steam-bath with freshly distilled ethylenediamine (100 ml.). The clear solution obtained after 10 min. was concentrated until crystallisation began. The product was collected and a second crop was obtained on further concentration. The combined crops were suspended in water (20 ml.), filtered, washed with water, and dried. Two recrystallisations from methanol gave needles of *perhydro*-6α-*methoxy*-2-*phenyl*-trans-m-*dioxano*[5′,4′-5,6][1,4]-*dioxepano*[2,1,7-ag]-[1,3,6]-*oxadiazepine* (IV; $n = 2$), m. p. 148·5—149·5°, $[\alpha]_D^{21}$ +110° (*c* 0·3 in chloroform) (Found: C, 59·8; H, 6·6; N, 8·5. $C_{16}H_{22}O_5N_2$ requires C, 59·6; H, 6·9; N, 8·7%).

A solution of picric acid in methanol was added to a hot concentrated solution of the above compound (IV; $n = 2$) in methanol. On cooling, a yellow solid was deposited which after recrystallisation from ethanol was shown to be ethylenediamine picrate.

(d) *With trimethylenediamine.* The reaction was carried out as in (c), but evaporation of the solution gave a colourless syrup. When ethanol or methanol was added to a solution of the syrup in dilute acetic acid, the methanolate [4] or ethanolate [4] of the hemialdal was isolated; when t-butyl alcohol was added, the hemialdal hydrate (II; R = Ph) was isolated.

(e) *With ethanolamine.* The reaction was carried out as in (c) above, and evaporation of the clear solution gave a pale yellow syrup. Dilute acetic acid was added, and the solid collected, washed with sodium hydrogen carbonate solution and with water, and dried (P_2O_5). Three recrystallisations from aqueous methanol gave the product, m. p. 125—127°, $[\alpha]_D^{21}$ +116° (*c* 0·5 in pyridine), as needles [Found: C, 60·4; H, 6·7; N, 5·1%; *M* (*X*-ray), 326].

(f) *With* p-*nitrophenylhydrazine.* A hot aqueous solution of *p*-nitrophenylhydrazine hydrochloride (1·4 g., 1·2 mol.) and sodium acetate (4 g.) was added to a hot solution of the hemialdal hydrate (2 g., 1 mol.) in water (550 ml.). The orange solution was cooled rapidly and stored at 0° overnight. The solid (91%, based on the *p*-nitrophenylhydrazine hydrochloride) was collected. Three recrystallisations from ethanol gave orange-yellow needles of 2,4-O-*benzylidene*-3-O-(1-*methoxy*-2-*oxoethyl*)-D-*erythrose bis*-p-*nitrophenylhydrazone* (VIII; R = p-$NO_2{\cdot}C_6H_4$), m. p. 164—165° (decomp.) (Found: C, 56·6; H, 5·0; N, 15·5. $C_{26}H_{26}O_8N_6$ requires C, 56·7; H, 4·8; N, 15·3%).

The same product was obtained when using excess of *p*-nitrophenylhydrazine hydrochloride; or by adding *p*-nitrophenylhydrazine to a hot methanolic solution of the hemialdal hydrate, boiling under reflux for 10 min., and isolating the product as above.

(g) *With isonicotinoylhydrazine.* Isonicotinoylhydrazine (5 g.) was added to a hot solution of the hemialdal hydrate (5 g.) in water (1250 ml.) at 80—90°; a gel separated on rapid cooling, which was collected. This gel was difficult to dry thoroughly on the filter and hence it was crystallised from methanol whilst moist, yielding a more easily filterable gel, which after drying gave a white powder, m. p. 220—221° (decomp.) (60%). Two further recrystallisations gave 2,4-O-*benzylidene*-3-O-(1-*methoxy*-2-*oxoethyl*)-D-*erythrose bisisonicotinoylhydrazone* (VIII; R = $CO{\cdot}C_5H_4N$), m. p. 221—222° (decomp.) (Found: C, 60·6; H, 5·4; N, 16·5. $C_{26}H_{26}O_6N_6$ requires C, 60 2; H, 5·1; N, 16·2%).

The same product was obtained when isonicotinoylhydrazine was added to a hot methanolic solution of the hemialdal hydrate.

(h) *With* 2,4-*dinitrophenylhydrazine.* A solution of the hemialdal hydrate (2 g.) and 2,4-dinitrophenylhydrazine (2·5 g.) in *NN*-dimethylformamide (50 ml.) was heated at 80° for 5 min. and then poured into ice-water. The orange-red precipitate was dissolved in chloroform, and the solution chromatographed on bentonite–kieselguhr (4 : 1). Elution with chloroform and two crystallisations from n-butanol gave 2,4-O-*benzylidene*-3-O-(1-*methoxy*-2-*oxoethyl*)-D-*erythrose bis*-2,4-*dinitrophenylhydrazone* [VIII; R = 2,4-$(NO_2)_2C_6H_3$], m. p. 114—119° (decomp.) (Found: C, 49·2; H, 4·2; N, 18·2. $C_{26}H_{24}O_{12}N_8$ requires C, 48·8; H, 3·8; N, 17·5%).

(i) *With semicarbazide.* A hot solution of semicarbazide hydrochloride (2 g.) and sodium acetate (5 g.) in water (10 ml.) was added to a solution of the hemialdal hydrate (2 g.) in ethanol (150 ml.) which was boiling under reflux; heating was continued for a further 10 min. The

solution was cooled rapidly, and stored at 0° overnight; the deposited solid (60%) was recrystallised from a large volume of acetone to give 2,4-O-*benzylidene*-3-O-(1-*methoxy*-2-*oxoethyl*)-D-*erythrose bis-semicarbazone* (VIII; R = $CO{\cdot}NH_2$), m. p. 185—189° (decomp.) (Found: C, 48·2; H, 5·3; N, 21·5. $C_{16}H_{22}O_6N_6$ requires C, 48·7; H, 5·6; N, 21·3%). A less pure product was obtained by using an aqueous solution of the hemialdal hydrate.

(j) *With potassium borohydride.* To a suspension of the hemialdal hydrate (7·5 g.) in water (350 ml.) was added potassium borohydride (1·25 g.). The clear solution which resulted after shaking for 45 min. was adjusted to pH 5 with dilute hydrochloric acid. The solution was evaporated to dryness (bath temp. <40°), the solid that separated being removed from the mixture from time to time. The crude product (90%) had m. p. 54—56°. Two recrystallisations from cold chloroform–light petroleum [10] gave 2,4-O-*benzylidene*-3-O-(2-*hydroxy*-1-*methoxyethyl*)-D-*erythritol monohydrate* (as XIV), m. p. 56—57°, $[\alpha]_D^{21}$ −49·2° (*c* 1·66 in water), $[\alpha]_D^{21}$ −30° (*c* 1·4 in ethanol) [Found: C, 55·9; H, 7·4; OMe, 17·9 (Zeisel), 10·2 (modified Gran); H_2O (*in vacuo* over P_2O_5), 5·8. $C_{14}H_{20}O_6,H_2O$ requires C, 55·6; H, 7·3; OMe, 10·3; H_2O, 6·0%]. The loss in weight on drying was reversible. The dried compound was (XIV), m. p. 40—42° (Found: C, 59·8; H, 7·2. Calc. for $C_{14}H_{20}O_6$: C, 59·1; H, 7·1%). Lewis [10] reported m. p. 55—55·5°, $[\alpha]_D$ −31° (*c* 1·8 in ethanol).

The monohydrate (as XIV) was acetylated with acetic anhydride–pyridine at 0° for 18 hr. Pouring into ice-water gave a white solid which, after three recrystallisations from aqueous ethanol gave 2,4-O-*benzylidene*-3-O-(2-*acetoxy*-1-*methoxyethyl*)-D-*erythritol* 1-*acetate* as needles, m. p. 49·5—50·5°, $[\alpha]_D^{21}$ −53·4° (*c* 2·17 in chloroform) [Found: C, 58·8; H, 6·5; OMe, 15·1 (Zeisel), 8·35 (modified Gran). $C_{18}H_{24}O_8$ requires C, 58·7; H, 6·6; OMe, 8·4%].

Methyl 4,6-O-p-*Chlorobenzylidene*-α-D-*glucoside*.—Methyl α-D-glucoside (14 g.), anhydrous zinc chloride (11 g.), and *p*-chlorobenzaldehyde (50 g.) were shaken at 55° for 6·5 hr., and then left overnight at room temperature. The reaction mixture was extracted with hot ether (3 × 150 ml.), and the residue was washed with hot water (80 ml.) before being dissolved in methanol–water (200 ml., 1 : 1). The solution was concentrated until crystals separated. After cooling, the product (26%) was dried. Three recrystallisations from aqueous methanol gave *methyl* 4,6-O-p-*chlorobenzylidene*-α-D-*glucoside* (13%), as needles, m. p. 166—167°, $[\alpha]_D^{21}$ +54·5° (*c* 0·5 in pyridine) (Found: C, 52·5; H, 5·5. $C_{14}H_{17}O_6Cl$ requires C, 53·1; H, 5·4%).

Benzoylation with benzoyl chloride in pyridine for 24 hr. at 0° gave a pale yellow sticky solid after excess of benzoyl chloride had been decomposed and the reaction mixture poured into ice-water. The solid was washed with water and recrystallised twice from ethanol to give needles of *methyl* 4,6-O-p-*chlorobenzylidene*-α-D-*glucoside* 2,3-*dibenzoate* (61%), m. p. 130—131° (Found: C, 64·4; H, 5·2. $C_{28}H_{25}O_8Cl$ requires C, 64·0; H, 4·8%).

Periodate Oxidation of Methyl 4,6-O-p-*Chlorobenzylidene*-α-D-*glucoside*.—(a) *Quantitative.* The glucoside (0·11 g.) was oxidised in methanol–water (1 : 4) which was 0·004M with respect to sodium metaperiodate. The consumption of periodate [1] was 0·75 (65 hr.), 0·95 (89 hr.), 1·05 (110 hr.), and 1·08 mol. (131 hr.). The product crystallised as the reaction proceeded.

(b) *Preparative.* The glucoside (1 g.) was dissolved in warm methanol (250 ml.), and water (about 450 ml.) added almost to turbidity. Sodium metaperiodate (0·7 g.) was added, and the solution set aside in the dark at room temperature for 10 days. The methanol was removed *in vacuo*, and the product collected, washed with water, and dried. Two recrystallisations from aqueous acetone gave needles of 2-p-*chlorophenyl*-7,9-*dihydroxy*-6α-*methoxy*-trans-m-*dioxano*-[5,4-e]-[1,4]-*dioxepan hydrate* (II; R = *p*-$Cl{\cdot}C_6H_4$) (81%), m. p. 152—153° (Found: C, 47·6; H, 5·5. $C_{14}H_{17}O_7Cl,H_2O$ requires C, 47·9; H, 5·4%).

This was boiled under reflux with methanol, and the clear solution concentrated and then cooled to give 2-p-*chlorophenyl*-7(or 9)-*hydroxy*-6α,9(or 7)-*dimethoxy*-trans-m-*dioxano*[5,4-e]-[1,4]-*dioxepan*, m. p. 158—160° (Found: C, 51·5; H, 5·4. $C_{15}H_{19}O_7Cl$ requires C, 51·9; H, 5·5%).

The oxidation product (II; R = *p*-$Cl{\cdot}C_6H_4$) (0·23 g.) and aniline (5 ml.) were warmed on a steam-bath for 15 min. Water was added to the cooled solution, followed by acetic acid. The syrup that separated was washed by decantation with sodium hydrogen carbonate solution and with water. Two crystallisations from aqueous acetone gave needles of 7,9-*dianilino*-2-p-*chlorophenyl*-6α-*methoxy*-trans-m-*dioxano*[5,4-e]-[1,4]-*dioxepan* (32%), m. p. 167—168°, $[\alpha]_D^{21}$ +9·2° (*c* 0·3 in pyridine) (Found: C, 64·1; H, 5·5; N, 5·5. $C_{26}H_{27}O_5ClN_2$ requires C, 64·7; H, 5·6; N, 5·8%).

A solution of the oxidation product (II; R = *p*-$Cl{\cdot}C_6H_4$) (0·1 g.) in cyclohexylamine (4 ml.)

was heated on a steam-bath for 15 min., cooled, and poured into ice-water (50 ml.). The product was washed with water, dried, and recrystallised twice from light petroleum (b. p. 40—60°), giving needles of 2,4-O-p-*chlorobenzylidene*-3-O-(1-*methxoy*-2-*oxoethyl*)-D-*erythrose bis*-N-*cyclohexylaldimine* (81%), m. p. 134—136°, $[\alpha]_D^{21}$ −41·0° (*c* 0·3 in pyridine) (Found: C, 65·6; H, 7·7; N, 6·1. $C_{26}H_{37}O_4ClN_2$ requires C, 65·5; H, 7·8; N, 5·9%).

Methyl 4,6-O-o-*Chlorobenzylidene*-α-D-*glucoside*.—Methyl α-D-glucoside (14 g.), anhydrous zinc chloride (10 g.), and *o*-chlorobenzaldehyde (38 ml.) were shaken at room temperature in a dark, stoppered bottle for 7·5 hr. After storage at 0° overnight, the solution was mixed with a small volume of ice-cold water, and filtered. The residue was washed quickly with ice-cold 10% aqueous sodium hydrogen sulphite, sodium hydrogen carbonate solution, and water. It was then suspended in ether, stirred, and collected. The solid was dissolved in methanol–water (1 : 1), the solution was concentrated until crystals separated, and after cooling, the product (56%) was collected and dried. Recrystallisation from aqueous methanol gave needles of *methyl* 4,6-O-o-*chlorobenzylidene*-α-D-*glucoside* (40%), m. p. 190—191°, $[\alpha]_D^{21}$ +85·4° (*c* 0·5 in pyridine) (Found: C, 53·0; H, 5·3. $C_{14}H_{17}O_6Cl$ requires C, 53·1; H, 5·4%).

Benzoylation as described above gave needles of the 2,3-*dibenzoate* (57%), m. p. 99—100° (Found: C, 63·7; H, 4·8. $C_{28}H_{25}O_8Cl$ requires C, 64·0; H, 4·8%).

Acetylation as described above gave, after two crystallisations from aqueous ethanol, the 2,3-*diacetate* (40%), m. p. 174° (Found: C, 54·1; H, 5·6. $C_{18}H_{21}O_8Cl$ requires C, 53·9; H, 5·3%).

Periodate Oxidation of Methyl 4,6-O-o-*Chlorobenzylidene*-α-D-*glucoside*.—(a) *Quantitative*. The consumption of periodate by the compound (0·1 g.) in aqueous 0·004M-sodium metaperiodate (250 ml.) was 0·40 (25 hr.), 0·53 (42 hr.), 0·76 (90 hr.), 0·95 (187 hr.), 0·99 (258 hr.), and 1·00 mol. (306 hr.). The product crystallised as the reaction proceeded.

(b) *Preparative*. The oxidation product, isolated as described above after 12 days at room temperature, was 2-o-*chlorophenyl*-7,9-*dihydroxy*-6α-*methoxy*-trans-m-*dioxano*[5,4-e][1,4]-*dioxepan hydrate* (II; R = *o*-Cl·C_6H_4) (54%), m. p. 141—142° (Found: C, 48·4; H, 5·6. $C_{14}H_{17}O_7Cl,H_2O$ requires C, 47·9; H, 5·4%).

Benzoylation of the methanolate (prepared as above but not characterised) gave, after recrystallisation from ethanol, 7(or 9)-*benzoyloxy*-2-o-*chlorophenyl*-6α,9(or 7)-*dimethoxy*-trans-m-*dioxano*[5,4-e][1,4]-*dioxepan*, m. p. 256—257°, $[\alpha]_D^{21}$ +13·5° (*c* 0·29 in pyridine) (Found: C, 58·6; H, 5·1. $C_{22}H_{23}O_8Cl$ requires C, 58·6; H, 5·1%).

Benzoylation of the oxidation product (II; R = α-Cl·C_6H_4) gave, after two crystallisations from ethanol, 7,9-*dibenzoyloxy*-2-o-*chlorophenyl*-6α-*methoxy*-trans-m-*dioxano*[5,4-e][1,4]-*dioxepan*, m. p. 166—168°, $[\alpha]_D^{21}$ +22·3° (*c* 0·29 in pyridine) (Found: C, 62·2; H, 4·8. $C_{28}H_{25}O_9Cl$ requires C, 62·2; H, 4·6%).

Methylation of the oxidation product with Purdie's reagents gave, after crystallisation from methanol, 2-o-*chlorophenyl*-6α,7,9-*trimethoxy*-trans-m-*dioxano*[5,4-e][1,4]-*dioxepan* (49%), m. p. 239—240°, $[\alpha]_D^{21}$ +77·6° (*c* 0·3 in pyridine) (Found: C, 53·0; H, 6·0. $C_{16}H_{21}O_7Cl$ requires C, 53·3; H, 5·8%).

Methyl 4,6-O-o-*Bromobenzylidene*-α-D-*glucoside*.—*o*-Bromobenzaldehyde (30 g.) was condensed with methyl α-D-glucoside (10 g.) by the method described for *o*-chlorobenzaldehyde. *Methyl* 4,6-O-o-*bromobenzylidene*-α-D-*glucoside* was obtained as needles (26%), m. p. 205—206°, $[\alpha]_D^{21}$ +91·5° (*c* 0·5 in pyridine) (Found: C, 46·1; H, 4·9. $C_{14}H_{17}O_6Br$ requires C, 46·5; H, 4·7%).

Benzoylation as described above gave the 2,3-*dibenzoate*, m. p. 95—96°, $[\alpha]_D^{21}$ +106° (*c* 1·02 in chloroform) (Found: C, 58·4; H, 4·7. $C_{28}H_{25}O_8Br$ requires C, 59·1; H, 4·4%).

Periodate Oxidation of Methyl 4,6-O-o-*Bromobenzylidene*-α-D-*glucoside*.—(a) *Quantitative*. The consumption of periodate by the compound (0·1 g.) in aqueous 0·002M-sodium metaperiodate solution (500 ml.) was 0·37 (72 hr.), 0·63 (190 hr.), 0·82 (245 hr.), 0·97 (509 hr.), 1·02 (598 hr.), and 1·02 mol. (667 hr.). The product crystallised as the reaction proceeded.

(b) *Preparative*. The compound (1·5 g.), oxidised as described above but by use of water–methanol (1 : 2) and a reaction time of 21 days, gave 2-o-*bromophenyl*-7,9-*dihydroxy*-6α-*methoxy*-trans-m-*dioxano*[5,4-e][1,4]-*dioxepan hydrate* (II; R = *o*-Br·C_6H_4) (55%), m. p. 134—136° (Found: C, 42·7; H, 4·5. $C_{14}H_{17}O_7Br,H_2O$ requires C, 42·5; H, 4·8%).

Methylation of the oxidised compound with Purdie's reagents gave, after two crystallisations from methanol, 2-O-o-*bromophenyl*-6α,7,9-*trimethoxy*-trans-m-*dioxano*[5,4-e][1,4]-*dioxepan*, m. p. 241·5—243·5° (Found: C, 47·7; H, 5·2; OMe, 22·0. $C_{16}H_{21}O_7Br$ requires C, 47·4; H, 5·2; OMe, 23·0%).

Periodate Oxidation of 5-(1,4-*Anhydro*-D-arabino*tetrahydroxybutyl*)-2-*methyl*-3-*furoic Acid* (IX; R = OH).—This compound was prepared and oxidised as previously described.[16] The 2-(4-carboxy-5-methyl-2-furyl)-3,5-dihydroxy-1,4-dioxan (X; $R^1 = R^2 = OH$), m. p. 134—140°, had an infrared spectrum and m. p. identical with those recorded in the literature;[6] $[\alpha]_D^{21}$ −0·5° (7 min.) ⟶ −51·0° (4 hr.) ⟶ −10·4° (335 hr.) (*c* 1·0 in pyridine); the solution darkened after 12 hr.; $[\alpha]_D^{21}$ −18·7° (19 min.) ⟶ −9·8° (311 hr.) (*c* 0·25 in water) (Found: C, 49·3; H, 5·1. Calc. for $C_{10}H_{12}O_7$: C, 49·2; H, 5·0%).

The oxidation product was methylated with Purdie's reagents to give a pale yellow syrup that crystallised on trituration with light petroleum. Three crystallisations from aqueous methanol gave 3,5-*dimethoxy*-2-(4-*methoxycarbonyl*-5-*methyl*-2-*furyl*)-1,4-*dioxan* (X; $R^1 = R^2 = OMe$), m. p. 128—129°, $[\alpha]_D^{21}$ +16·9° (*c* 1·0 in chloroform) (Found: C, 54·7; H, 6·2; OMe, 32·4. $C_{13}H_{18}O_7$ requires C, 54·5; H, 6·3; OMe, 32·5%). Jones's methylation product [8] had m. p. 119°.

Periodate Oxidation of 5-(1,4-*Anhydro*-D-arabino*tetrahydroxybutyl*)-2-*methyl*-3-*furyl Methyl Ketone* (IX; R = Me).—Periodic acid (19 ml.; 0·28M) was added to a solution of the above compound [6] (13 g.) in water (25 ml.) at <5° and the solution was kept at 0° for 50 min. The resulting white solid (8·5 g., 61%) was crystallised three times from acetone–light petroleum to yield 2-(4-*acetyl*)-5-*methyl*-2-*furyl*)-3,5-*dihydroxy*-1,4-*dioxan* (X; $R^1 = Me$, $R^2 = OH$), m. p. 126—127·5°, $[\alpha]_D^{21}$ −40·0° (6 min.) ⟶ −54·2° (25 hr.) ⟶ −47·9° (53 hr.) (*c* 1·0 in pyridine) (Found: C, 54·1; H, 5·9. Calc. for $C_{11}H_{14}O_6$: C, 54·5; H, 5·8%). Jones [8] reported m. p. 128—129°.

Methylation of this oxidation product as described above, followed by crystallisation from methanol–light petroleum, gave 2-(4-*acetyl*-5-*methyl*-2-*furyl*)-3,5-*dimethoxy*-1,4-*dioxan* (X; $R^1 = Me$, $R^2 = OMe$), m. p. 101·5—102·5°, $[\alpha]_D^{20}$ +25·2° (*c* 1·0 in chloroform) (Found: C, 57·5; H, 6·2. $C_{13}H_{18}O_6$ requires C, 57·8; H, 6·7%).

Methoxyl Determinations.—Gran's method [15b] was used. For a given substance a weight of 20—120 mg. was used and a graph of titre (from the precipitate only) against sample weight was plotted. 0·1N-Sodium thiosulphate was used in the final titrations, so that the methoxyl content equals 0·0517 × slope.

(a) *Methyl* α-D-*glucoside.* By use of the above method a line was obtained approximately parallel to the theoretical line, but with a small negative intercept on the titre axis. If the small titre (*ca.* 0·5 ml.) obtained from the filtrate was added to that from the precipitate the points then fitted on to the theoretical line quite well. An example of such a run is shown below.

Weight of sample (mg.)	22·1	40·8	57·4	75·1
Titre from precipitate (ml.)	6·42	12·08	17·27	22·31
Titre from filtrate (ml.)	0·50	0·50	0·51	0·74

The methoxyl content found from the slope of the plot of titre (from the precipitate) against sample weight was 15·9% [Calc. for $C_6H_{11}O_5(OMe)$: 16·0%].

(b) *Vanillin.* The results obtained were similar to those in (a) (Found: OMe, 20·3. Calc. for $C_8H_8O_3$: OMe, 20·4%).

(c) *Monohydrate of* (XIV) *and its diacetate.* Results calculated from the graphical method have been listed above.

(d) *Erythritol.* No precipitate was obtained, but titration of the propan-2-ol filtrate gave an apparent methoxyl content of 11·3%.

(e) *Glycollaldehyde.* An apparent methoxyl content of 0·2% was found as in (d).

The authors thank Miss A. M. Dodge and Mr. B. Hesp for assistance with the experimental work. The molecular weight (*X*-ray method) was kindly determined by Dr. J. O. Warwicker. Part of this work was sponsored by the Office, Chief of Research & Development, U.S. Department of Army, through the European Office.

SHIRLEY INSTITUTE, DIDSBURY, MANCHESTER, 20. [*Received, November 30th*, 1959].

[16] García González, *Adv. Carbohydrate Chem.*, 1956, **11**, 97.