Deoxy-sugars. Part XXIX. A Further Contribution to the Chemistry of the Glycal Reaction.*

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The conversion of D-glucal into 2-deoxy-D-glucose is accompanied by a dehydration process and some 3-hydroxy-2-hydroxymethyl-2-pyran is also formed. It has been shown that treatment of glycals with ion-exchange resins in the acid form results in the production of impure 2-deoxy-sugars.

IN previous communications (Deriaz, Overend, Stacey, Teece, and Wiggins, *J.*, 1949, 1879; Overend, Shafizadeh, and Stacey, *J.*, 1951, 992; Shafizadeh and Stacey, *J.*, 1952, 3608) results obtained during a comprehensive study of the glycal reaction (cf. Helferich, *Adv. Carbohydrate Chem.*, 1952, **7**, 209) have been outlined. In addition to improving the overall yield of deoxy-sugar from the glycal, side reactions have been investigated; *e.g.*, it has been demonstrated that D-glucal on treatment with methanolic hydrogen chloride affords not only methyl 2-deoxy-αβ-D-glucoside, but also other compounds amongst which 2-hydroxymethyl-5-methoxymethylfuran was identified (Shafizadeh and Stacey, *loc. cit.*). We also have some evidence that 4 : 5-dihydro-4-hydroxy-2 : 5-bismethoxymethylfuran is formed. Further examination of the products of side-reactions has led to the isolation of a pyran derivative.

Separation of 2-deoxy-D-glucose from the mixture obtained by the action of dilute sulphuric acid on D-glucal left a residue from which an ether-soluble $C_6H_8O_3$ syrup (*A*) was isolated. This unsaturated compound was recognised as 3-hydroxy-2-hydroxymethyl-2-pyran on the following evidence. The ultraviolet absorption spectrum was similar to that of furfuryl alcohol and 2-hydroxymethyl-5-methoxymethylfuran, showing a maximum absorption at 215 mμ (two conjugated double bonds; cf. Braude, *Ann. Reports*, 1945, **42**, 105). Catalytic hydrogenation resulted in the uptake of 2 mols. of hydrogen and afforded a saturated product (*B*) characterised as its crystalline bis-3 : 5-dinitrobenzoyl derivative. The initial compound (*A*) also afforded a crystalline di-*O*-benzoate. At this stage the possibility was considered that dilute sulphuric acid converts glucal into 2 : 5-bishydroxymethylfuran [cf. conversion of glucal into 2-hydroxymethyl-5-methoxymethylfuran by methanolic hydrogen chloride (Shafizadeh and Stacey, *loc. cit.*)]. However, compound (*A*)

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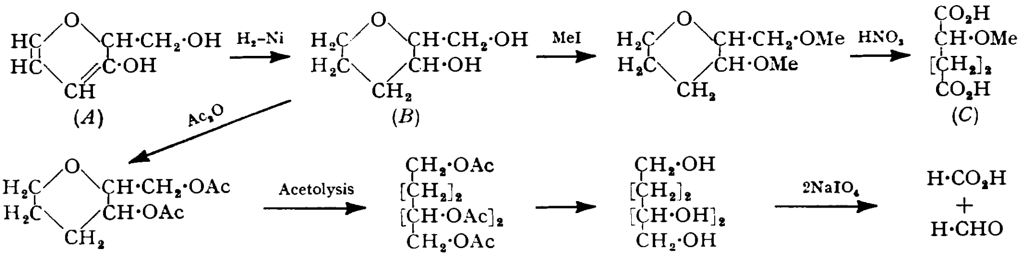
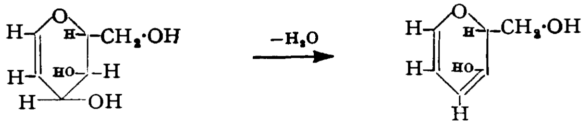
was optically active and its di-*O*-benzoate differed from that obtained from authentic 2 : 5-bishydroxymethylfuran (cf. Wiggins and Newth, *Research*, 1950, **3**, 50). Moreover, the bis-3 : 5-dinitrobenzoate of the reduction product (*B*) differed from the corresponding derivative of tetrahydro-2 : 5-bishydroxymethylfuran [prepared from hydroxymethylfurfuraldehyde (Haworth, Jones, and Wiggins, *J.*, 1945, 1)].

The di-*O*-methyl derivative of product (*B*), when treated with boiling 2N-nitric acid followed by concentrated nitric acid at 0° [conditions required for the oxidation of tetrahydrofuran and tetrahydropyran (Jones and Taylor, *Quart. Rev.*, 1950, **4**, 195) and dihydropyran (*Org. Synth.*, 1950, **30**, 48)], afforded an optically inactive methoxyglutaric acid (*C*). Acetolysis of the di-*O*-acetate of compound (*B*) (cf. Wiggins *et al.*, *loc. cit.*; Hudson *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 1898) furnished a tetra-*O*-acetate, which on deacetylation gave a 2 : 3-dideoxyhexitol. The structure of the last compound was established by periodate oxidation: the dideoxyhexitol consumed 2 mols. of oxidant and afforded 1 mol. of formaldehyde and somewhat less than 1 mol. of formic acid (cf. Hirst and Jones, *J.*, 1949, 1659, who report a similar deficiency of formic acid on like treatment of inositol). It follows that acid (*C*) was not internally compensated, but rather that its racemic nature was responsible for the lack of optical activity, and that it was an α-methoxyglutaric acid. The sequence of reactions described may be depicted :



α-Methoxyglutaric acid (*C*) would be derived from tetrahydro-3-hydroxy-2-hydroxymethylpyran (*B*) by methylation and subsequent oxidation. Compound (*B*) would result from the hydrogenation of 3-hydroxy-2-hydroxymethylpyran (*A*). Any other sequence of conjugated double bonds in (*A*) would result in the compound's being optically inactive. Furthermore, it is a reasonable expectation that the double bond present in glucal would remain fixed, since any initial migration of this bond requires the hydroxyl group at $C_{(3)}$ to undergo an anionotropic migration to $C_{(1)}$ (cf. Braude, *Quart. Rev.*, 1950, **4**, 404); this would result in compound (*A*) having a $C_{(4)}$ double bond and a $C_{(5)}$ hydroxyl group. Such a compound would yield glutaric acid in the reactions described.

Treatment of D-galactal with dilute sulphuric acid in addition to affording 2-deoxy-D-galactose, likewise gave some of the pyran derivative (*A*), but in less amount. In this case the limited nature of the side reaction may account for the greater yields of 2-deoxy-D-galactose, compared with 2-deoxy-D-glucose, in the glycal reaction. Presumably the pyran derivative (*A*) is formed by a simple dehydration process involving the hydroxyl group adjacent to the allylic system, and this reaction proceeds more readily with glucal than with galactal.



Attempts have been made to convert glycals into deoxy-sugars by means of ion-exchange resins in acidic form (cf. Wadman, *J.*, 1952, 3051; Cadotte, Smith, and Spriestersbach, *J. Amer. Chem. Soc.*, 1952, **74**, 1501; for the use of cation-exchange resins in promoting the formation of glycosides from pentoses, hexoses, uronic acids, and methylated sugars, and of *iso*propylidene derivatives of sugars and methyl glycosides). Glucal and galactal were treated separately with Amberlite IR-100(H) and IR-120(H). In one series of experiments the resin was packed in a cooled glass column, but since continuous re-cycling of the glycal solution was required this method was abandoned in favour of stirring the resin in a cooled aqueous solution of the glycal. The low temperatures reduced the formation of tarry materials. In all cases the progress of the reaction was followed by examining aliquot parts by paper ionophoresis (Foster, *Chem. and Ind.*, 1952, 1050). It could be demonstrated that the glycal was progressively converted to the 2-deoxy-sugar, but that undesirable side products were also formed, and that by merely evaporating a filtered solution it was not possible to obtain the deoxy-sugar crystalline. The syrupy products could be characterised by formation of the crystalline diethylmercaptals (cf. Overend, Stacey, and Staněk, *J.*, 1949, 2841). The ionophoresis results, which indicated a progressive diminution of the amount of glycal in the solution concurrent with the increase in amount of deoxy-sugar, precluded the possibility of formation of the mercaptal directly from the glycal.

EXPERIMENTAL

3-Hydroxy-2-hydroxymethylpyran.—(a) *From* D-*glucal.* A solution of D-glucal (25 g.) in sulphuric acid (5%; 200 c.c.) was kept at 0° for 15 hr. and then neutralised with barium hydroxide. The mixture was separated at the centrifuge, the supernatant liquid filtered through charcoal, and the filtrate concentrated to a thick syrup which was dissolved in dry methanol (4 vol.). The solution was refiltered and then evaporated to dryness and the residue treated with amyl alcohol (120 c.c.). 2-Deoxy-D-glucose (11·7 g.; m. p. 145—146°) crystallised. The mother liquors were concentrated (to 30 c.c.) and ether (60 c.c.) was then added. A resinous material was discarded. Evaporation of the remaining solution afforded a syrupy residue from which *3-hydroxy-2-hydroxymethylpyran* (3·6 g.) was obtained, b. p. 120—130° (bath temp.)/0·01 mm., n^{21} 1·507 (Found: C, 56·3; H, 6·1. $C_6H_8O_3$ requires C, 56·2; H, 6·2%).

(b) *From* D-*galactal.* D-Galactal (40 g.) was treated with ice-cold sulphuric acid, and 2-deoxy-D-galactose (35 g.) isolated as described by Overend, Shafizadeh, and Stacey (*J.*, 1951, 998). The mother liquors were concentrated (to 30 c.c.) and ether (60 c.c.) was added. Thereafter the pyran derivative (0·37 g.), $[\alpha]_D^{18}$ $+15°$ (*c*, 7 in MeOH), was isolated as described previously. Treatment of 3-hydroxy-2-hydroxymethylpyran with benzoyl chloride and pyridine gave a good yield of *di-*O*-benzoate* as needles, m. p. 85°, $[\alpha]_D$ $+64°$ (*c*, 1·6 in MeOH) (Found: C, 71·6; H, 4·8. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%).

Tetrahydro-3-hydroxy-2-hydroxymethylpyran.—A solution (30 c.c.) of 3-hydroxy-2-hydroxymethylpyran (1·189 g.) in aqueous ethanol was shaken with Raney nickel (0·7g.) in an atmosphere of hydrogen at a slight overpressure, at room temperature. When the uptake of hydrogen was complete the filtered solution was evaporated to dryness. *Tetrahydro-3-hydroxy-2-hydroxymethylpyran* (0·91 g.) formed a syrup, n^{19} 1·478 (Found: C, 54·9; H, 8·9. $C_6H_{12}O_3$ requires C, 54·5; H, 9·1%). The 3 : *5-dinitrobenzoyl* derivative had m. p. 172° (Found: C, 46·0; H, 3·0; N, 10·8. $C_{20}H_{16}O_{13}N_4$ requires C, 46·1; H, 3·1; N, 10·8%).

Tetrahydro-3-methoxy-2-methoxymethylpyran.—To tetrahydro-3-hydroxy-2-hydroxymethylpyran (3 g.) in liquid ammonia (250 c.c.), sodium (1·6 g.) was added portionwise slowly. The mixture was stirred under anhydrous conditions for 6 hr. and then methyl iodide (4·3 c.c.) was added. This procedure was repeated four times and then the product was isolated in the usual fashion. *Tetrahydro-3-methoxy-2-methoxymethylpyran* (2·4 g.) formed a liquid, b. p. 100° (bath temp.)/12 mm., n^{18} 1·437 (Found: C, 60·0; H, 10·0; OMe, 38·3. $C_8H_{16}O_3$ requires C, 60·0; H, 10·0; OMe, 38·7%).

Oxidation of Tetrahydro-3-methoxy-2-methoxymethylpyran.—The tetrahydropyran (2·1 g.) and 0·2N-nitric acid (6 c.c.) were heated at 100° for 2 hr. Thereafter the product was cooled in ice-salt and gradually added to ice-cold nitric acid (*d*, 1·42; 9 g.) containing sodium nitrite (0·1 g.). The mixture was stirred continuously at 0° for 2 hr. before the temperature was slowly raised to that of the room. When the solution became pale yellow it was diluted with water and evaporated under diminished pressure. This procedure was repeated until most of the excess of nitric acid had been removed. The syrupy residue was dissolved in water, neutralised with potassium hydrogen carbonate, and re-evaporated. The dry residue was extracted with dry methanol and after concentration (to 10 c.c.) the extract was heated under reflux for 8 hr. with methyl iodide (5 c.c.). After removal of solvents the residue was extracted with warm ether. The residue from this extraction was re-treated with dry methanol and methyl iodide and again extracted with ether. The combined ethereal extracts were evaporated and the syrupy residue was distilled. Besides starting material (0·47 g.) [b. p. 110—120° (bath temp.)/15 mm.], racemic *dimethyl α-methoxyglutarate* (0·9 g.) was obtained, b. p. 125—135° (bath temp.)/0·05 mm., n^{19} 1·4459 (Found: C, 50·9; H, 7·6. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4%).

3-Acetoxy-2-acetoxymethyltetrahydropyran.—A solution of tetrahydro-3-hydroxy-2-hydroxymethylpyran (2·63 g.) in a mixture of dry pyridine (10 c.c.) and freshly distilled acetic anhydride (15 c.c.) was kept at 0° for 3 days. Thereafter the product was isolated according to the standard procedure and *3-acetoxy-2-acetoxymethyltetrahydropyran* (3·7 g.) was obtained; it had b. p. 183° (bath temp.)/15 mm., n^{22} 1·4465 (Found: C, 55·2; H, 7·6. $C_{10}H_{16}O_5$ requires C, 55·5; H, 7·4%).

This di-*O*-acetate (3·5 g.) was dissolved in a mixture of acetic anhydride (35 c.c.), glacial acetic acid (15 c.c.), and concentrated sulphuric acid (1 c.c.) at 0°. The mixture was kept at room temperature for 10 days and was then poured into ice-water and extracted with chloroform. The extract was washed successively with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated to dryness. From the residue there was obtained a 1 : 4 : 5 : 6-*tetra-*O*-acetyl-*2 : 3-*dideoxyhexitol* (4 g.), b. p. 170° (bath temp.)/0·02 mm., n^{24} 1·4436 (Found: C, 52·6; H, 7·1. $C_{14}H_{22}O_8$ requires C, 52·8; H, 6·9%).

2 : 3-*Dideoxyhexitol.*—1 : 4 : 5 : 6-Tetra-*O*-acetyl-2 : 3-dideoxyhexitol (1·5 g.) was added to barium hydroxide (6·2 g.) in water (40 c.c.) and the mixture was heated at 90° for 2 hr. After addition of solid carbon dioxide the mixture was centrifuged and then filtered, the filtrate was evaporated to dryness, and the residue was extracted with methanol. Evaporation of the extract yielded a 2 : 3-*dideoxy*-DL-*hexitol* (0·4 g.) as a hygroscopic syrup, b. p. 220—225° (bath temp.)/0·02 mm., n^{24} 1·495 (Found: C, 47·8; H, 9·4. $C_6H_{14}O_4$ requires C, 48·0; H, 9·3%). A solution of this compound (25·4 mg.) in water (5 c.c.) was treated with sodium metaperiodate (0·075M, 10 c.c.) and water was added to give a final volume of 25 c.c. At intervals, aliquot parts (2 c.c.) were withdrawn and the uptake of oxidant determined. Likewise the amounts of formic acid and formaldehyde produced during the oxidation were estimated. The latter was weighed as its dimedone derivative (m. p. 189—190°), and it was shown that 1·15 mol. of formaldehyde were formed. 2-Deoxy-D-sorbitol behaved as expected in control experiments as a model compound.

Treatment of Glycals with Ion-exchange Resins.—D-Glucal (1 g.) in water (50 c.c.) was passed 25 times through a column (65 cm. × 15 mm.) of Amberlite resin IR-120(H) (30 g.) which was cooled to 1—2°. The resin was washed with water (200 c.c.), and the combined eluate and washings were concentrated and then examined by ionophoresis (apparatus as described by Foster, *Chem. and Ind.*, 1952, 1050). It was demonstrated that the amount of D-glucal decreased progressively during the cyclisation process and the amount of 2-deoxy-D-glucose correspondingly increased. Essentially similar results were obtained by using IR-100(H) resin. In neither case could the syrup obtained on evaporation of the solutions be induced to crystallise satisfactorily.

In another experiment D-glucal (1 g.) was stirred for 3 hr. at 0° with Amberlite resin IR-120 (H) (20 g.) in water (50 c.c.). Samples were examined every 15 min. ionophoretically. After 3 hr. the glucal had been practically completely converted into 2-deoxyglucose. Evaporation of the solution afforded a syrup which would not crystallise, but readily afforded 2-deoxy-D-glucose diethylmercaptal (0·25 g.) as white plates, m. p. and mixed m. p. 134—135°, on treatment with ethanethiol (2 c.c.) and hydrochloric acid (1·25 c.c.).

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