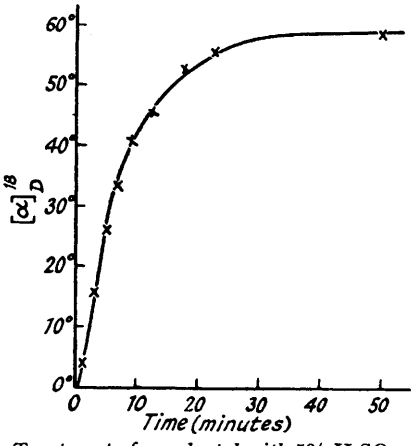
221. *Deoxy-sugars. Part XVII. An Investigation of the Glycal Method for the Preparation of Derivatives of 2-Deoxy-D-galactose.*

By W. G. Overend, F. Shafizadeh, and M. Stacey.

The glycal method for the preparation of derivatives of 2-deoxy-D-galactose has been investigated. No evidence has been obtained for the formation of a stable intermediate ester when D-galactal is converted into 2-deoxy-D-galactose by treatment with dilute sulphuric acid. It is shown that the addition of methanol to galactal and triacetyl galactal follows the same course (cf. Fischer, Bergmann, and Schotte, *Ber.*, 1920, **53**, 517).

Recently the preparation and properties of some derivatives of 2-deoxy-D-galactose were described (Overend, Shafizadeh, and Stacey, *J.*, 1950, 671). For these experiments 2-deoxy-β-D-galactose was prepared from D-galactose by the well-known glycal method. Levene and Tipson (*J. Biol. Chem.*, 1931, **93**, 644) first used this procedure for the preparation of 2-deoxy-D-galactose and more recently it was likewise employed by Pigman and Isbell (*J. Res. Nat. Bur. Stand.*, 1939, **22**, 397). The latter workers assumed that on treatment of D-galactal with dilute sulphuric acid the deoxy-sugar was formed *via* an intermediate ester which was hydrolysed when heated with barium carbonate at 60° for a relatively long period. We originally adopted



Treatment of D-*galactal with* 5% H_2SO_4.

this method but now have found that 2-deoxy-D-galactose can be obtained in considerably improved yield by introducing a rapid neutralisation of the reaction mixture with barium hydroxide at room temperature. Moreover, potentiometric titrations with N-potassium carbonate of 5% aqueous sulphuric acid containing D-galactal or D-glucal did not materially differ from those of 5% aqueous sulphuric acid alone, thereby indicating that the acid concentration was not decreased by entering into stable ester formation with the glycal. Polarimetric observation of a solution of D-galactal in dilute sulphuric acid indicated that the reaction yielded directly 2-deoxy-D-galactose since the final value for the optical rotation of the solution was the same as that of the deoxy-sugar in similar sulphuric acid solution (see figure). Whether an unstable transient ester is formed is not known, but it would appear that the process described by Pigman and Isbell (*loc. cit.*) as hydrolysis by barium carbonate was merely slow heterogeneous-phase neutralisation of sulphuric acid by barium carbonate.

Fischer, Bergmann, and Schotte (*Ber.*, 1920, **53**, 517) recorded that triacetyl D-glucal and hydrogen bromide in acetic acid gave a crystalline " diacetyl D-glucal hydrobromide " which on re-acetylation yielded " triacetyl D-glucal hydrobromide." The bromine atoms in these compounds were stated to be inert towards silver nitrate, a behaviour which supported Fischer's view that these were 2-bromo-2-deoxy-sugar derivatives. This opinion seemed to be difficult to accept since, in the above-described " glycal procedure " the addition of water to glycals in the presence of dilute sulphuric acid to give 2-deoxy-sugars, the opposite type of orientation is obtained, the anion becoming attached to $C_{(1)}$. Repetition of this work by Davoll and Lythgoe

(*J.*, 1949, 2526) yielded a syrup which behaved as 3 : 4 : 6-triacetyl 1-bromo-1 : 2-dideoxy-glucose since on condensation with silver theophylline followed by deacetylation they obtained 2′-deoxy-D-glucopyranosidyltheophylline identical with that first obtained by Levene (*J. Biol. Chem.*, 1931, **92**, 53). Consequently they concluded that additions to glycals and acetylated glycals follow identical courses. Before publication of this result we had carried out some experiments which supported this conclusion (cf. *Chem. and Ind.*, 1949, 466).

When D-galactal was treated with 0·2% methanolic hydrogen chloride, α-methyl-2-deoxy-D-galactopyranoside (Overend *et al.*, *loc. cit.*) was obtained. The use of 3% methanolic hydrogen chloride resulted in a decreased yield of the glycoside (*i.e.*, 32% compared with 47%). Treatment of 3 : 4 : 6-triacetyl D-galactal with 2% methanolic hydrogen chloride, followed by deacetylation also yielded directly crystalline α-methyl-2-deoxy-D-galactopyranoside, thereby showing that in this instance addition of methanol to galactal and its triacetate followed the same course. However, in neither case was the reaction simple, since the glycosidic product was invariably accompanied by a liquid which is unidentified as yet. This material is optically inactive, readily absorbs bromine, and contains methoxyl residues. It would appear to be a degradation product, since it has been noticed that, as the concentration of hydrogen chloride in the methanol is increased, so the yield of liquid increases.

Experimental.

2-Deoxy-D-galactose.—D-Galactal (6·1 g.) was dissolved in ice-cold 5% sulphuric acid (85 c.c.), and the solution was kept at 0° for 24 hours. The solution was then neutralised with barium hydroxide at room temperature, and filtered through a charcoal pad. The filtrate was concentrated under diminished pressure to a syrup which was taken up in methanol (3 vols.) and set aside. 2-Deoxy-D-galactose crystallised from solution and was recrystallised from methanol in colourless cubes (4·9 g., 73%) which had m. p. 110°, $[\alpha]_D^{21}$ +57° ± 2° (equilibrium, *c*, 1·0 in water) (Found : C, 43·9; H, 7·1. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·3%) [cf. Pigman and Isbell, *J. Res. Nat. Bur. Stand.*, 1939, **22**, 397, who give m. p. 120—121° and $[\alpha]_D$ +41° ⟶ +60·5° (equilbrium in 30 minutes; *c*, 4·0 in 0·001N-potassium hydrogen phthalate buffer); Tamm and Reichstein (*Helv. Chim. Acta*, 1948, **31**, 1630) give m. p. 105—106° and $[\alpha]_D^{18}$ +60·7° in water; Overend, Shafizadeh, and Stacey, *J.*, 1950, 671, report a 50% yield of this compound].

Potentiometric Titrations.—The following solutions were titrated potentiometrically with N-potassium carbonate : (i) 5% sulphuric acid (15 c.c.), (ii) 5% sulphuric acid (15 c.c.) containing glucal (1·4 g.) (this solution was kept for 2 hours before titration), (iii) 5% sulphuric acid (15 c.c.) containing glucal (1·6 g.) (this solution was kept at 0° for 20 hours before titration), and (iv) 5% sulphuric acid (15 c.c.) containing galactal (0·98 g.) (this solution was kept at 0° for 22 hours before titration). Results were the same in all cases.

Treatment of D-Galactal with Methanolic Hydrogen Chloride.—(a) 0·2% *Methanolic hydrogen chloride.* D-Galactal (35 g.) was treated with 0·2% methanolic hydrogen chloride (300 c.c.) at room temperature. After 1·5 hours (optical rotation constant) the solution was neutralised with silver carbonate and filtered. The filtrate was evaporated under diminished pressure, and ethyl acetate was added to the syrupy residue. Part of it crystallised and was separated. Repeated recrystallisation from ethyl acetate gave α-methyl-2-deoxy-D-galactopyranoside (19·8 g., 47%), m. p. 112—113°, $[\alpha]_D^{20}$ +170° (*c*, 0·32 in methanol) (Found : C, 47·2; H, 8·4. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·8%) (Overend *et al.*, *loc. cit.*, give m. p. 112—113°; Tamm and Reichstein, *loc. cit.*, report m. p. 109—110°). The syrupy material remaining was re-treated with methanolic hydrogen chloride (75 c.c.) and yielded a further amount (3·4 g.) of the above glycoside. The syrupy material finally obtained was mobile, showed no optical activity, appeared to be unsaturated, and yet contained some methoxyl residues (Found : OMe, 32%).

(b) 3% *Methanolic hydrogen chloride.* Treatment of galactal with 3% methanolic hydrogen chloride resulted in a very rapid reaction, and gave the same products, but the yield of the glycoside was reduced to 31·6%.

Treatment of Triacetyl Galactal with Methanolic Hydrogen Chloride.—3 : 4 : 6-Triacetyl galactal (5 g.) in solution in 2% methanolic hydrogen chloride (20 c.c.) was kept for 24 hours and then neutralisation was effected with silver carbonate. The silver residues were filtered off through a charcoal pad, and the filtrate was evaporated to a syrup. Distillation of this afforded a colourless mobile oil (0·6 g.), b. p. 120—130° (bath-temp.)/0·1 mm. (Found : OMe, 29·2%), which is unidentified. The still residue was dissolved in dry methanol (10 c.c.), and sodium (15 mg.) was added. After 12 hours the solution was evaporated to dryness and extracted with ethyl acetate. Evaporation of the extract afforded crystalline α-methyl-2-deoxy-D-galactopyranoside (0·5 g.), m. p. 112—113° alone or on admixture with an authentic specimen.

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