The Degradation of Carbohydrates by Alkali. Part XI. 4-O-Methyl Derivatives of Glucose and Fructose.*

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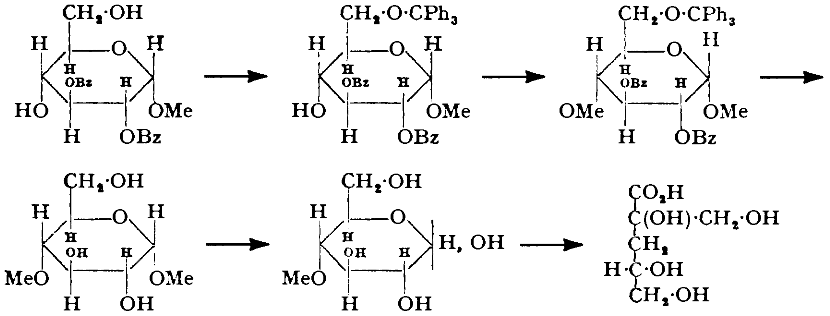
The prediction that D-gluco*iso*saccharinic acids should result from the alkaline degradation of 4-*O*-methyl-D-glucose or -fructose is confirmed.

Evidence has been adduced (*J.*, 1954, 278) that alkaline decomposition of 3-*O*-derivatives of glucose will always furnish the stereoisomeric D-gluco*meta*saccharinic acids and it was suggested that the two D-gluco*iso*saccharinic acids should similarly be produced from the corresponding 4-*O*-derivatives.

This has now been substantiated by the behaviour of 4-*O*-methyl-D-glucose, prepared from methyl 2 : 3-di-*O*-benzyl-α-D-glucoside (Bell and Lorber, *J.*, **1940**, **453**) by a series of reactions corresponding to that employed by McGilvray (*J.*, 1952, **3648**) for the preparation of the 4-*O*-methyl-β-D-glucoside. The simultaneous removal of triphenylmethyl and benzyl groups, as represented in the scheme, is noteworthy and was conveniently effected by use of Raney nickel. As expected, the same D-gluco*iso*saccharinic acids were also obtained, and more rapidly, by treatment of 4-*O*-methyl-D-fructose with lime-water. Further, the experimental data tabulated below show that acid is not formed from 4-*O*-methyl-D-glucose until conversion into 4-*O*-methyl-D-fructose has set in (cf. *J.*, 1953, 2245).



The generalisation thus confirmed may be applied to the structural investigation of carbohydrate materials. Thus, alkaline degradation of maltose and lactose to D-gluco*iso*saccharinic acids (Dubrunfaut, *Moniteur Scient.*, 1882, 521; Cuisinier, *ibid.*, p. 522), and respectively glucose and galactose (Lobry de Bruyn and van Ekenstein, *Rec. Trav. chim.*, 1896, **15**, 96; 1899, **18**, 147) would have revealed that the disaccharides were the 4-*O*-glucosyl- and the 4-*O*-galactosyl-D-hexose respectively had the reaction been then understood. Similarly, the formation of D-gluco*iso*saccharinic acids by the action of lime-water on hydro- and oxy-celluloses (Faber and Tollens, *Ber.*, 1899, **32**, 2596; Murumow, Sack, and Tollens, *ibid.*, 1901, **34**, 1427; Tollens, *ibid.*, p. 1434) would have indicated the chain structure and, almost certainly, also the pyranosidic ring structure which was not assigned to cellulose until later.

Formation of the ordinary, the *meta*-, and the *iso*-type of D-glucosaccharinic acids is in fact diagnostic of 1-, 3-, and 4-*O*-substituted glucose derivatives respectively. Doubtless the same will apply to the acids derived from other monoses, and saccharinic acids are thus to be regarded as reference compounds in carbohydrate chemistry. Although some duplication will occur, *e.g.*, the same *meta*-acids will be derived from glucose, allose, mannose, and altrose, each monose should in general provide a distinct set of acids individually accessible by use of the above generalisation.

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* Part X, *J.*, 1955, 1709.

EXPERIMENTAL

The following solvents and sprays were used in paper chromatography: solvent a, butanol–pyridine–water (6 : 4 : 3); spray a, silver nitrate–sodium hydroxide (Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444); spray b, naphtharesorcinol (Hough, Jones, and Wadman, *J.*, 1950, 1702).

Methyl 2 : 3-*Di*-O-*benzyl*-6-O-*triphenylmethyl*-α-D-*glucoside* was prepared by treating a solution of methyl 2 : 3-di-*O*-benzyl-α-D-glucoside (22·0 g.) in dry pyridine (400 ml.) with triphenylmethyl chloride (16·0 g.) at 100° for 2½ hr. The resulting solution, cooled to 0°, was diluted with water (100 ml.) and, after several hours at room temperature, then poured into water. By extraction with water and isolation in the usual way, the 6-O-*triphenylmethyl ether* was obtained as an amorphous solid, $[\alpha]_D^{26}$ +14·5° (*c* 3 in $CHCl_3$) (Found: C, 77·4; H, 6·7; OMe, 5·1. $C_{40}H_{40}O_6$ requires C, 77·9; H, 6·5; OMe, 5·0%). Four successive treatments with silver oxide and methyl iodide in the usual manner converted it into its 4-O-*methyl ether*, a yellow glass, $[\alpha]_D^{20}$ +13° (*c* 2 in $CHCl_3$) (Found: C, 77·8; H, 7·0; OMe, 10·2. $C_{41}H_{42}O_6$ requires C, 78·1; H, 6·7; OMe, 9·8%).

Methyl 4-O-*methyl*-α-D-*glucoside* resulted when the foregoing ether (23·20 g.) in ethanol (200 ml.) was stirred with a suspension of Raney nickel (80 g.) in ethanol (100 ml.) at 60°, rising during 6 hr. to 85°. The solution, after 2 hours' further refluxing, was filtered and evaporated nearly to dryness. Filtration of a solution of the residue in a mixture of water (100 ml.) and chloroform (100 ml.), and evaporation of the aqueous solution after further washing with chloroform (2 × 50 ml.), afforded a colourless syrup (6·17 g.) which, after distillation at 163—165° (bath-temp.)/0·03 mm., had n_D^{18} 1·4810, $[\alpha]_D^{20}$ +15° (*c* 3 in H_2O) (Found: OMe, 30·6. $C_8H_{16}O_6$ requires OMe, 29·8%).

4-*O*-Methyl-D-glucose was produced by heating a solution of the glucoside (2·00 g.) in N-sulphuric acid (25 ml.) 20 hr. at 100°, but the amorphous product (1·43 g.) was found on chromatographic analysis to contain, besides the 4-*O*-methyl-D-glucose (R_F 0·49, solvent a, spray a), traces of glucose (R_F 0·29), and 4 : 6-di-*O*-methyl-D-glucose (R_F 0·62). Elution of the crude product from a cellulose column with *n*-butanol half-saturated with water removed first a very small amount of, probably, a tri-*O*-methyl derivative (R_F 0·72), and then 4 : 6-di-*O*-methyl-D-glucose (m. p. and mixed m. p. 162—163°); further elution with the same solvent and then with 90% methanol yielded pure 4-*O*-methyl-D-glucose as a colourless syrup, $[\alpha]_D^{20}$ +60·8° (*c* 5 in H_2O) (Found: OMe, 15·6. Calc. for $C_7H_{14}O_6$: OMe, 16·0%). Pacsu (*Ber.*, 1925, **58**, 1455; cf. Schinle, *Ber.*, 1932, **65**, 315) reported $[\alpha]_D$ +61°. The p-*toluidide*, recrystallised from ethanol–water, had m. p. 159—160° (Found: N, 5·3. $C_{14}H_{21}O_5N$ requires N, 4·95%). The phenylosazone had m. p. 156—157° (Found: N, 14·9. Calc. for $C_{19}H_{24}O_4N_4$: N, 15·05%).

Action of Lime-water on 4-O-*Methyl*-D-*glucose*.—(a) *Qualitative*. A solution of 4-*O*-methyl-D-glucose (1·90 g.) in oxygen-free 0·04N-lime-water (600 ml.) was kept at 35° for 4 days and then at 100° for 1 hr., then saturated with carbon dioxide, boiled for a few minutes, and filtered. Evaporation of the filtrate to dryness yielded a white powder (1·84 g.) which was dissolved in hot water (5 ml.) and fractionally precipitated with ethanol (cf. Corbett and Kenner, *J.*, 1954, 1789), to yield first of all calcium α-D-gluco*iso*saccharinate (0·53 g., from 75% alcohol), $[\alpha]_D^{20}$ −2° (*c* 1 in H_2O), and, after separation of intermediate fractions, calcium β-D-gluco*iso*saccharinate (0·29 g., from 100% alcohol), $[\alpha]_D^{20}$ +3° (*c* 1 in H_2O).

The α-form was readily converted into the crystalline α-D-gluco*iso*saccharinolactone (cf. Corbett and Kenner, *loc. cit.*), m. p. and mixed m. p. 94—96°, while the β-form, treated in the usual manner, yielded the corresponding brucine salt, m. p. 190—195° (decomp.), and, after recrystallisation from ethanol, $[\alpha]_D^{20}$ −20° (*c* 1 in H_2O). Nef (*Annalen*, 1910, **376**, 1) reported m. p. 200—210° (decomp.), $[\alpha]_D^{20}$ −20°.

(b) *Quantitative*. A solution of 4-*O*-methyl-D-glucose (0·275 g.) in oxygen-free 0·0398N-lime-water (100 ml.) was kept at 25°; at intervals samples (5 ml.) were withdrawn, added to 0·05N-sulphuric acid (5 ml.), and then titrated with 0·025N-potassium hydroxide (phenolphthalein). The neutralised solutions were subsequently diluted to 25 ml. and the optical rotations observed in a 4-dm. tube (see Table).

4-O-*Methyl*-D-*fructose*.—The sample of methyl derivative used, kindly supplied by Dr. J. Oldham, had $[\alpha]_D^{21}$ −91·5° (*c* 1 in H_2O) and readily yielded 4-*O*-methylglucose phenylosazone, m. p. and mixed m. p. 156—157°. Hirst, Mitchell, Percival, and Percival give $[\alpha]_D^{18}$ (equil.) −97° (*c* 1 in H_2O), and phenylosazone, m. p. 157—158°. We are also indebted to Dr. E. Percival for another sample.

(a) *Qualitative.* A solution of 4-*O*-methyl-D-fructose (2·20 g.) in oxygen-free water (100 ml.) was heated with calcium hydroxide (2 g.) on the boiling-water bath in a stream of nitrogen for 2 hr. After filtration the pale yellow solution was saturated with carbon dioxide, brought to the b. p., again filtered, and evaporated to dryness. Fractional precipitation of an aqueous solution of the residue (2·21 g., 98%) with ethanol yielded pure calcium α-D-gluco*iso*saccharinate which was converted into the corresponding brucine salt, m. p. and mixed m. p. 160—161°, and into the crystalline lactone, m. p. and mixed m. p. 94—96°. Later fractions from the precipitation of the calcium salts yielded calcium β-D-gluco*iso*saccharinate, from which was prepared the brucine salt, m. p. and mixed m. p. 190—195°, $[\alpha]_D^{20}$ $-22.5°$ (*c* 2 in H_2O).

Time (hr.)	$[\alpha]_D^{20}$	Acid formed (equiv./mole)	Paper chromatography *		
			G	F	S
0	+60·8°	0	10	—	—
0·5	+50	0	10	—	—
1·0	+45	0	8	1	—
2·0	+38	0	7	2	—
3·0	+34	0	6	3	—
5·0	+27	0	5	5	—
7·5	+23	0·03	5	5	—
24	−11	0·16	4	5	—
31	−13	0·19	3	5	—
48	−13°	0·33	3	4	1
72	−11	0·46	2	3	2
144	− 2	0·67	2	2	3
221	− 2	0·75	1	1	4
337	− 2	0·80	—	—	5
485	− 2	0·83	—	—	5
650	− 2	0·86	—	—	5
805	− 2	0·89	—	—	5

* G = 4-*O*-methyl-D-glucose (R_F 0·48) (solvent a, sprays a, b). F = 4-*O*-methyl-D-fructose (R_F 0·55). S = saccharinic acid ($R_F < 0.05$). Numbers denote relative intensity of spots (10 maximum).

(b) *Quantitative.* A solution of 4-*O*-methyl-D-fructose (0·0790 g.) in oxygen-free 0·0393N-lime-water (25 ml.) was kept at 25° and the fall in alkalinity measured as described for 4-*O*-methyl-D-glucose. The change in optical rotation of the alkaline solution was observed in a separate experiment. Paper chromatography on intermediate samples was carried out as for 4-*O*-methyl-D-glucose (see Table); as also in that case no spot corresponding to 4-*O*-methyl-D-mannose was detected, but this does not exclude the possibility that a trace of this compound, probably having an R_F value very similar to that of 4-*O*-methyl-D-fructose, may be present.

Time (hr.)	$[\alpha]_D^{20}$	Acid formed (equiv./mole)	Paper chromatography *			
			F	G	P	S
0·25	−90°	0·03	10	—	—	—
0·5	−88	0·04	10	—	—	—
1·0	−84·5	0·06	10	—	—	—
2·0	−81	0·08	10	—	—	—
4·5	−66·5	0·12	8	1	—	1
7·5	−56	0·16	7	1	1	1
24	−27°	0·35	5	1	1	2
48	−16	0·48	4	1	1	2
150	− 7	0·83	1	1	1	3
240	− 2	0·91	—	—	—	3
480	− 2	0·92	—	—	—	3

• F = 4-*O*-methyl-D-fructose (R_F 0·55) (solvent a, sprays a, b). G = 4-*O*-methyl-D-glucose (R_F 0·49). P = supposed 4-*O*-methyl-D-psicose (R_F 0·61). S = saccharinic acids ($R_F < 0.05$).

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