568. *The Degradation of Carbohydrates by Alkali. Part XIII.** 2 : 3-*Di-O-methylglucose and its Conversion into 5-Hydroxymethylfurfuraldehyde.*

By J. Kenner and G. N. Richards.

Degradation of 2 : 3-di-*O*-methyl-D-glucose by lime-water at room temperature does not yield saccharinic acids, owing to the formation of an alkali-stable intermediate which is very readily converted into 5-hydroxymethylfurfuraldehyde in acid solution.

It is a consequence of the mechanism[1] of formation of saccharinic acids from αβ-dihydroxy- or α-hydroxy-β-alkoxy-carbonyl systems :

$$\text{–CO·CH(OH)·CH(OR)–} \longrightarrow \text{–CO·C(OH):CH–} \longrightarrow \text{Saccharinic acid}$$

that alkylation of the α-hydroxyl group should arrest the reaction at an intermediate stage, and it was thus of interest to examine a case of this kind.

2 : 3 : 4 : 6-Tetra-*O*-methylglucose is one instance, and, in fact, a careful kinetic study

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* Part XII, preceding paper.

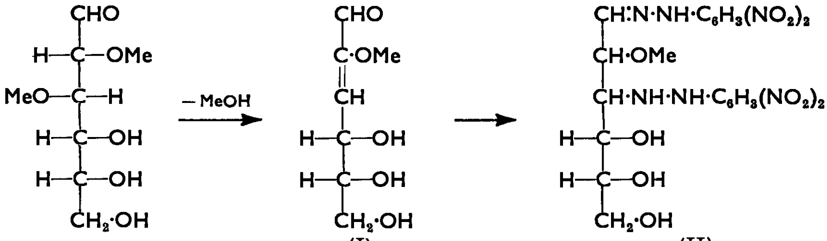
[1] Kenner, *Chem. and Ind.*, 1955, 727.

of its behaviour at 35° towards lime-water by Simons and Struck [2] led them to formulate the following scheme of reactions :

$$\begin{tikzcd}
G + OH^- = GOH^- \arrow[r, rightleftharpoons] & G' + OH^- \arrow[r, rightleftharpoons] \arrow[d, rightleftharpoons] & MOH^- = M + OH^- \\
& G'OH^- \arrow[r, rightleftharpoons] & G'' + OH^-
\end{tikzcd}$$

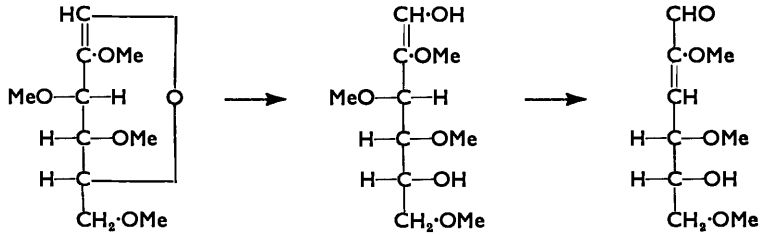
(G = Tetra-*O*-methylglucose; M = Tetra-*O*-methylmannose)

They were unable to identify G′ and G″, but we have now shown that in the analogous case of 2 : 3-di-*O*-methylglucose the action of lime-water at 25° causes the gradual formation of an absorption band at 2140 Å corresponding to the formation of an αβ-unsaturated carbonyl derivative (I).[3] In agreement with the observations of Simons and Struck, the reaction in the present instance also did not go to completion. As a result, the unsaturated product was not obtained pure even by chromatography and it was at best only concentrated by extraction with ether. Nevertheless the structure (I) is assigned on the basis of its ultraviolet absorption and of its degradation by ozone to a derivative of glyoxylic acid. Paper chromatography also gave evidence of the formation of erythrose in the latter reaction. Treatment of the product (I) with 2 : 4-dinitrophenylhydrazine yielded a hydrazone of composition (II), verified by acetylation. Two other unidentified hydrazones were obtained in smaller amount from this reaction.



(I) (II)

Acidification of the original reaction mixture at room temperature left the di-*O*-methylglucose unchanged and possibly also 2 : 3-di-*O*-methylmannose, which could not be distinguished by paper chromatography, but the absorption band at 2140 Å was gradually replaced by a transient one at 2300 Å and finally by another at 2850 Å, representing 5-hydroxymethylfurfuraldehyde [4] (VII), methyl alcohol being liberated.



(III) (IV)

The facility of this reaction corresponds to that of the conversion of tetramethylglucoseen (III) into 5-methoxymethylfurfuraldehyde (VIII) by 3N-hydrochloric acid,[5] and indeed this reaction probably involves the 4 : 6-di-*O*-methyl ether (IV) of (I) as an intermediate. Acid hydrolysis of the vinyl ethers (I) and (IV) followed by elimination of water and of methyl alcohol respectively would yield the unsaturated dicarbonyl derivatives (V)

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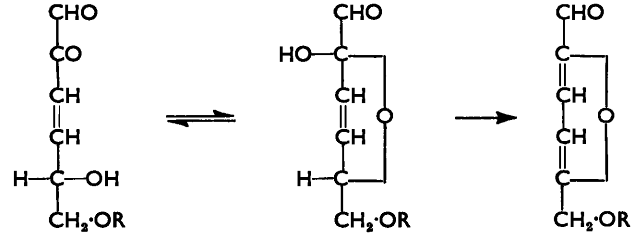
[2] Simons and Struck, *J. Amer. Chem. Soc.*, 1934, **56**, 1947.

[3] Braude, *Ann. Reports*, 1945, **42**, 105.

[4] Scallet and Gardner, *J. Amer. Chem. Soc.*, 1945, **67**, 1934.

and (VI), which would be expected to cyclise and lose water readily, yielding 5-hydroxymethylfurfuraldehyde (VII) and its methyl ether (VIII). The compound (VI) was characterised by Wolfrom, Wallace, and Metcalf [5] as an intermediate in the acid conversion of tetramethylglucoseen into 5-methoxymethylfurfuraldehyde (VIII), and later the compound (V) was postulated [6] as an intermediate in the acid degradation of glucose. The absorption band at 2300 Å may provide additional evidence for (V).



(V) : R = H
(VI) : R = Me

(VII) : R = H
(VIII) : R = Me

The results of Neher and Lewis [7] on the behaviour of methylated hexoses and pentoses agree with the above hypothesis, and it would be expected that the pentoses should undergo corresponding reactions.

EXPERIMENTAL

The following solvents and sprays were used for chromatography with Whatman No. 1 paper at 27°. Solvent *a*, butan-1-ol–pyridine–benzene–water (4 : 2 : 1 : 1); sprays: *a*, *p*-anisidine hydrochloride; [8] *b*, silver nitrate–sodium hydroxide.[9]

Alkaline Degradation of 2 : 3-*Di*-O-*methyl*-D-*glucose*.—2 : 3-Di-*O*-methyl-D-glucose was prepared by Irvine and Scott's method,[10] except that methylation was carried out with dimethyl sulphate in acetone,[11] and the benzylidene and the glycosidic alkyl group were removed in one step. The properties of the product, after recrystallisation, were the same as those recorded by Irvine and Scott, and it was further characterised as its p-*nitrophenylhydrazone*, m. p. 164—165° (Found: C, 48·6; H, 6·15; N, 12·3; OMe, 17·9. $C_{14}H_{21}O_7N_3$ requires C, 48·95; H, 6·2; N, 12·2; OMe, 18·0%), and p-*toluidide*, m. p. 156—157°, $[\alpha]_D^{20}$ $-88°$ (initial) ⟶ $+38°$ (48 hr.) (*c* 1 in EtOH) (Found: N, 4·8. $C_{15}H_{23}O_5N$ requires N, 4·7%).

Reaction of 2 : 3-*Di*-O-*methyl*-D-*glucose with Lime-water*.—(a) *Ultraviolet absorption*. The formation of an absorption band at 2140 Å in a solution of 2 : 3-di-*O*-methyl-D-glucose (0·0208 g.) in oxygen-free 0·04N-lime-water (50 ml.) at room temperature (15—20°) was observed as follows:

Time (hr.)	0·25	1·0	3·0	5·0	23	29	47	72
ε at 2140 Å	216	256	301	351	542	552	662	667

After 72 hr. the solution was acidified by 2N-hydrochloric acid (2 ml.), and the following three absorption bands were observed:

Time	0·25 hr.	6·5 hr.	4 days	6 days	10 days
ε_{2140}	670	*	530	*	*
ε_{2300}	187	>2000	960	830	*
ε_{2850}	*	320	3675	3850	3800

* Not observed.

The final absorption corresponds to a yield of 23% of 5-hydroxymethylfurfuraldehyde, calculated [4] on the original amount of 2 : 3-di-*O*-methyl-D-glucose.

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[5] Wolfrom, Wallace, and Metcalf, *J. Amer. Chem. Soc.*, 1942, **64**, 265.
[6] Wolfrom, Schuetz, and Cavalieri, *ibid.*, 1948, **70**, 514.
[7] Neher and Lewis, *ibid.*, 1931, **53**, 4411, and references therein.
[8] Hough, Jones, and Wadman, *J.*, 1950, 1702.
[9] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[10] Irvine and Scott, *J.*, 1913, **103**, 575.
[11] Glen, Myers, and Grant, *J.*, 1951, 2568.

(b) The optical rotation of a solution of 2 : 3-di-*O*-methyl-D-glucose (5·00 g.) in oxygen-free 0·04N-lime-water (500 ml.) at room temperature varied as follows :

Time (hr.)	1·0	2·0	4·0	5·5	7·5	24	31	50	72
$[\alpha]_D^{20}$	+45°	+38°	+33°	+27·5°	+22°	+11°	+8°	+8°	+8°

During this period the alkalinity of the solution measured by the usual method remained constant. When finally the resulting solution was saturated with carbon dioxide and concentrated, the distillate, collected in a liquid-air trap, gave a strong test for methanol.[12] After filtration from calcium carbonate, the solution was evaporated to dryness, leaving a colourless syrup (4·90 g.) which gave two spots when examined by paper chromatography in solvent *a*. The first was identical in R_F value (0·58) with 2 : 3-di-*O*-methyl-D-glucose and -mannose, reacted when heated with spray *a*, and showed the same lack of reactivity with spray *b*. In this connection we have found that a " normal " reactivity (comparable with that of the parent aldose) towards spray *a*, together with a very slow and faint reaction with spray *b*, is a characteristic of all 2-ethers of the aldoses. The second spot (compound A) (R_F 0·62) reacted strongly with spray *b* and gave a yellow colour at room temperature with spray *a*. Attempts to separate this mixture both by cellulose and carbon column chromatography were unsuccessful, but repeated extraction of the syrup with boiling ether and evaporation of the extract yielded a colourless syrup (S) (0·40 g.) in which the compound (A) predominated. The bulk of the material (R) was insoluble in ether.

Addition of the syrup (0·20 g.) to a saturated solution (100 ml.) of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid at room temperature caused the rapid formation of an orange precipitate (0·31 g.). This, when filtered, extracted with boiling ethanol, and recrystallised from nitrobenzene, had m. p. 266° (decomp.) (Found : C, 41·2; H, 3·7; N, 20·2. $C_{19}H_{22}O_{12}N_8$ requires C, 41·1; H, 4·0; N, 20·2%). Treatment with acetic anhydride in pyridine furnished a *triacetate*, which separated from aqueous dioxan as orange needles, m. p. 179—181° (Found : C, 44·5; H, 4·5; N, 16·1. $C_{25}H_{28}O_{15}N_8$ requires C, 44·1; H, 4·1; N, 16·5%).

The ethanol extract from the above crude 2 : 4-dinitrophenylhydrazone, on evaporation, yielded a solid residue (0·15 g.) which appeared to be a mixture and was chromatographed on bentonite–kieselguhr.[13] Elution with chloroform containing decreasing amounts of ether yielded two pure fractions : (i) An unidentified *substance*, m. p. 182—183°, unchanged by recrystallisation as yellow needles from aqueous ethanol (Found : C, 48·0; H, 4·9; N, 15·4%). (ii) A *substance*, m. p. 211—212°, orange needles from aqueous dioxan, and apparently isomeric with the corresponding 5-hydroxymethylfurfuraldehyde derivative, whose m. p. it depressed on admixture (Found : C, 46·6; H, 3·3; N, 18·5%).

A solution of a further portion of the syrup (S) (0·40 g.) in dry chloroform (50 ml.) was subjected at 0° to a stream of ozonised oxygen until no more ozone was absorbed. After addition of water (1 ml.) the solution was evaporated to dryness, and examination of the residue by paper chromatography (solvent *a*) indicated the presence of erythrose (R_F 0·41). In order to separate the acidic portion of the residue, its solution in water (20 ml.) was passed through excess of Amberlite resin IR-4B (OH), and the resin then washed with water (100 ml.) and finally eluted with N-hydrochloric acid (20 ml.). Addition of the acidic eluate to a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid (20 ml.) was followed by separation of yellow needles. After collection and recrystallisation from ethanol–water, these showed m. p. 190—191° (decomp.) alone or in admixture with glyoxylic acid 2 : 4-dinitrophenylhydrazone.

Action of Acid on Compound A.—The solution of a portion (0·501 g.) of the insoluble residue (R) from the above ether-extraction in N-sulphuric acid (10 ml.) underwent the following changes in optical rotation at 25° :

Time (hr.)	4·0	5·5	24	50	72
$[\alpha]_D^{25}$	−0·4°	+1·6°	+7·6°	+8·4°	+8·4°

Paper chromatography in solvent *a* of de-ionised samples taken during the reaction indicated the disappearance of compound (A) (R_F 0·62), the intermediate formation and subsequent decay of small amounts of another component (compound B, R_F 0·72), and the formation of 5-hydroxymethylfurfuraldehyde (R_F 0·81). The spot corresponding to 2 : 3-di-*O*-methyl-D-glucose (R_F 0·58) was observed in every case. Evaporation of part of the residual solution under

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[12] Deniges, *Compt. rend.*, 1915, **150**, 832.

[13] Elvidge and Whalley, *Chem. and Ind.*, 1955, 589.

reduced pressure yielded a distillate which gave a strong positive test for methanol [12] and treatment of the remainder with a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid resulted in the immediate formation of a red precipitate, which, when recrystallised from ethanol–water, had m. p. 195—196° (sintered at 186°) [14] alone or in admixture with 5-hydroxymethylfurfuraldehyde 2 : 4-dinitrophenylhydrazone.

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[14] Wahhab, *J. Amer. Chem. Soc.*, 1948, **70**, 3580.