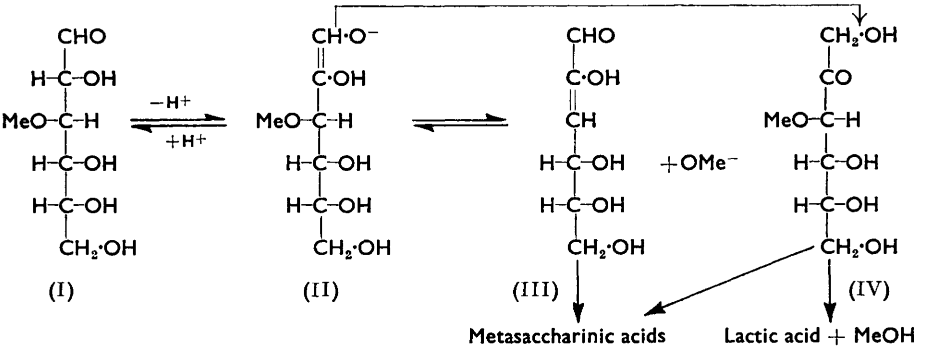
588. *The Degradation of Carbohydrates by Alkali. Part XV.* Factors in the Formation of Metasaccharinic Acids from* 3-O-*Derivatives of Glucose.*

By J. Kenner and G. N. Richards.

The significance of the medium, the alkali employed, and the substituent groups involved, as factors in the action of alkali on carbohydrates, is illustrated in a study of the behaviour of 3-*O*-derivatives of D-glucose. This provides a quantitative comparison of alkyl groups in respect of their inductive effects and has revealed the 3-*O*-toluene-*p*-sulphonate as an excellent source of 2-deoxy-D-ribose.

The collective results of this series of papers confirm the view that the type of saccharinic acid formed by the action of lime-water on 1-, 3-, or 4-*O*-alkylhexoses is determined by the site of the alkyl group. This was attributed to the greater receptivity of the aqueous alkaline medium for alkoxyl than for hydroxyl anion,[1] and it has now been shown that conversely the decomposition of 0·02m-solutions of 3-*O*-methyl-D-glucose (I) by 0·1N-alkali at 25° is faster in water or ethyl alcohol than in methyl alcohol. Apparent first-order velocity constants for 0·1N-alkali were: NaOH 4·0, NaOMe 0·7, NaOEt 6·3, $\times 10^{-2}$ hr.$^{-1}$. Evidently the conversion of the ion (II) into the acid (III) is a rate-controlling step. Further, the retardation of this reaction in methyl alcohol affords greater opportunity for isomerisation to 3-*O*-methyl-D-fructose (IV) and accordingly under these conditions the formation of traces of lactic acid was detected.[1, 2]



The tolerance of the alkoxy-anion for its charge, another factor in these reactions, should reflect and provide a quantitative relative measure of the inductive effect of the alkyl group; so apparent first-order velocity constants have been determined for the reaction with saturated lime-water at 25° of 3-*O*-benzyl- and a series of 3-*O*-alkyl-D-glucoses. These are well adapted to comparative measurement since in the conversion

---

* Part XIV, *J.*, 1957, 927.

[1] Kenner and Richards, *J.*, 1954, 278.

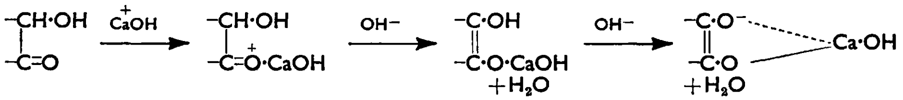
[2] Cf. Kenner and Richards, *J.*, 1954, 1784.

of 3-*O*-methyl-D-glucose into metasaccharinic acids in water there were no perceptible side reactions such as the formation of lactic acid noted above. The experimental results accord with current qualitative conceptions, *viz.*, $10^2k'$ (hr.$^{-1}$) for CH_2Ph 10·1, Me 5·3 (5·4 calc. from determinations of reducing power[1]), Et 3·0, Pr^n 2·9, Pr^i 1·7, Bu^n 2·9.

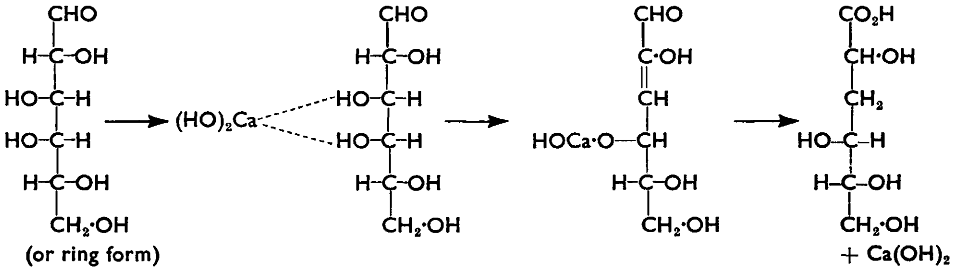
The cation of the alkali employed is also an important factor in this reaction. Evidence for the inefficiency of potassium hydroxide relative to lime-water[1] is now supplemented by the following table of apparent first-order velocity constants for the action on 3-*O*-methyl-D-glucose in 0·02m-solution at 25° of 0·05N-sodium hydroxide alone and after addition of metallic nitrates in the proportions indicated :

		Li^+–	Ba^{++}	Sr^{++}	Ca^{++}			
Metal nitrate added to 0·05N-NaOH (equiv./mole of aldose)	0	1·0	1·0	1·0	1·0	1·5	2·0	2·5
$10^2k'$ (hr.$^{-1}$)	1·9	2·1	2·0	2·8	4·8	5·5	6·6	6·2

The slight accelerative influence of lithium cations accords with their superior co-ordinating power,[3] but the markedly greater effect of strontium, and especially of calcium, ions points to internal complex formation as a much more potent supplement in this reaction than basicity of the reagent. Further, formic being stronger than glycollic acid, a greater electron-availability and consequent superior co-ordinating power would be expected on the carbonyl-oxygen atom of a ketose than on that of the isomeric aldose. Thus formation of their common dienolate ion according to the following scheme might occur more readily from the ketose :



This agrees with the somewhat faster formation of metasaccharinic acids from 3-*O*-methyl-D-fructose than from 3-*O*-methyl-D-glucose[1] and with the observation by Bamford, Bamford, and Collins[4] of the faster epimerisation of fructose than of glucose by sodium hydroxide. We thus also have a certain variation with the alkali employed, in the character of the entity (II).



(V) (VI)

An alternative mode of complex formation, long familiar in connection with the use of calcium and strontium hydroxides for the purification of cane-sugar, is probable in the action of lime-water on galactose as represented in (V). This would be inimical to the type of process by which D-glucose is converted into D-psicose and α-D-saccharinic acid.[2] Thus, if dissociation of the complex is avoided by operation at the ordinary temperature, D-galactose yields D-galactometasaccharinic acid[5] (VI).

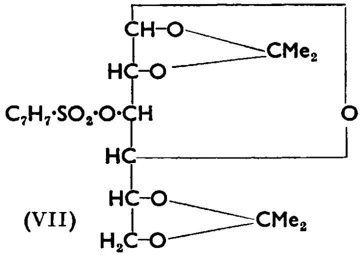
---

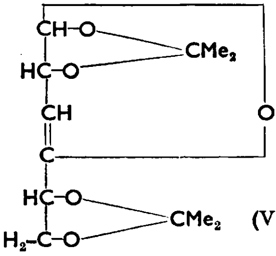
[3] Cf. Meerwein and Burneleit, *Ber.*, 1928, **61**, 1840.

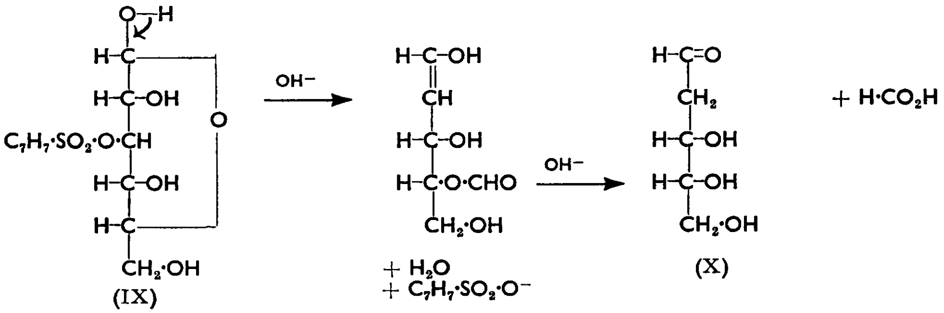
[4] Bamford, Bamford, and Collins, *Proc. Roy. Soc.*, 1950, **204**, *A*, 85; cf. Bamford and Collins, *ibid.*, 1955, **228**, *A*, 100.

[5] Kiliani and Sanda, *Ber.*, 1893, **26**, 15649.

The circumstances of the decomposition of 3-*O*-toluene-*p*-sulphonyl-D-glucose (IX) by lime-water are quite different from those of the foregoing reactions, because sulphonic esters exhibit their own inherent tendency to decomposition on treatment with alkali. Thus Freudenberg and Braun,[6] and Weygand and Wolz,[7] converted 1 : 2-5 : 6-di*iso*propylidene-3-*O*-toluene-*p*-sulphonyl-D-glucose (VII) into the unsaturated derivative (VIII) by heating it with hydrazine and with sodium hydroxide respectively. Weygand and Wolz justified the assumption by Freudenberg and Braun of the 3 : 4-site of the double bond, but the alternative 2 : 3-position becomes involved when 3-*O*-toluene-*p*-sulphonyl-D-glucose (IX) [derived from (VII) by acid hydrolysis, most satisfactorily in presence of toluene-*p*-sulphonic acid] is decomposed by gradual addition of lime-water at 25°. The product of the ensuing rapid reaction, 2-deoxy-D-ribose (X), is thus protected as far as possible from the effects of alkali and temperature, and the yield (76% of crystalline material) is gratifying. Simultaneously with these experiments Smith reported a similar result (55% yield of amorphous product) on decomposition of 3-*O*-methanesulphonyl-D-glucose by sodium hydroxide,[8] relating his result to the reaction scheme of English and Brutcher: [9]

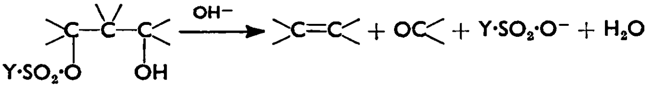

(VII)


(VIII)



(IX)

(X)



$$\gt C(OSO_2Y)-C\lt-C(OH)\lt \xrightarrow{OH^-} \gt C{=}C\lt + OC\lt + Y{\cdot}SO_2{\cdot}O^- + H_2O$$

This expresses the fact that removal of proton by alkali is easier from hydroxyl than from ⪢CH and equally effective for olefin formation if it is attached to carbon in the β-position to the ester grouping. Although the action of lime-water (0·04N) was found to be more rapid than that of sodium hydroxide (2N) and Smith's ester suffered decomposition more readily than the toluene-*p*-sulphonate, it nevertheless furnishes only a 65% yield of crystalline deoxy-compound on treatment with lime-water.

[6] Freudenberg and Braun, *Ber.*, 1922, **55**, 3236.
[7] Weygand and Wolz, *Chem. Ber.*, 1952, **85**, 256.
[8] D. C. C. Smith, *Chem. and Ind.*, 1955, 92.
[9] English and Brutcher, *J. Amer. Chem. Soc.*, 1952, **74**, 4279.

The review, in this and previous papers of this series, of the action of alkali on carbohydrates now appears sufficiently complete for guidance in future study of particular instances.

EXPERIMENTAL

The following solvents and sprays were used for paper chromatography on Whatman No. 1 paper at 27°. Solvents: " a "[11] butan-1-ol–pyridine–water, 6 : 4 : 3; " b "[12] ethyl acetate–acetic acid–water, 10 : 1·3 : 1; " c " butan-1-ol–pyridine–benzene–water (4 : 2 : 1 : 1); " d "[13] butan-1-ol–ethanol–water (40 : 11 : 19). Sprays: " a "[14] silver nitrate–sodium hydroxide; " b "[15] hydroxylamine–ferric chloride; " c "[16] sodium metaperiodate–potassium permanganate; " d "[17] B.D.H. " 4·5 " indicator.

Preparation of 3-O-*Alkyl*-D-*glucoses*.—The method of Glen *et al.*[18] yielded 3-*O*-methyl-, -ethyl-, -*n*-propyl-, and -*n*-butyl-D-glucose, with the properties recorded by these authors, but each compound required additional purification on either powdered cellulose or carbon–Celite columns to remove traces of glucose. Repeated recrystallisation from absolute ethanol achieved the same effect on the large scale, but was otherwise too wasteful. It was normally preferable to avoid distillation of the 3-*O*-alkyl-1 : 2-5 : 6-di-*O*-*iso*propylidene-D-glucose and, instead, to remove acetone polymers by chloroform extraction after hydrolysis, since, even with careful fractional distillation at this stage, the final product always contained glucose.

As expected from the limited accessibility of the hydroxyl group in 1 : 2-5 : 6-di-*O*-*iso*propylidene-D-glucose, the yields were drastically reduced as the size of the alkyl group increased and with *iso*propyl bromide only 5—10% of 3-O-iso*propyl*-D-*glucose* was ultimately obtained, showing m. p. 159—162°, $[\alpha]_D^{20}$ +25° (10 min.), +44·5° (5 hr., equil.) (*c* 3 in H_2O) (Found: C, 48·8; H, 8·3. $C_9H_{18}O_6$ requires C, 48·6; H, 8·2%). A similar experiment with *tert.*-butyl bromide yielded only traces of the supposed 3-*O*-*tert.*-butyl-D-glucose (R_F 0·54; solvent " a ", spray " a "), which was not isolated in the pure state.

3-*O*-Benzyl-D-glucose was prepared by the method of Adams *et al.*[19], purified by chromatography on powdered cellulose, and showed the properties recorded by these authors.

Certain of the alkylated glucoses were characterised as the N-3-O-*alkyl*-D-*glucosyl*-p-*toluidines* by treatment of a concentrated alcoholic solution with the theoretical amount of *p*-toluidine at room temperature overnight. Evaporation of the resulting solution and recrystallisation of the residue from ethanol yielded derivatives as tabulated.

Alkyl group	M. p.	Found: N (%)	Required: N (%)
Et	155·5—157·5°	5·0	4·7
Pr^n	124—125	4·9	4·5
Bu^n	137—139	4·1	4·3
CH_2Ph	130—131	3·8	3·9

Treatment of 3-O-*Alkyl*-D-*glucoses with Lime-water*.—A 0·02M-solution of the glucose derivative in oxygen-free 0·040N-lime-water was kept at 25° ± 0·1°, while the formation of acid was determined as in earlier work.[1] Plotting $\log_{10}$ [1—(equivs. of acid/mole of glucose derivative)] against time gave, after an induction period of *ca.* 1 hr., a linear curve up to *ca.* 70—80% completion; the velocity constant for 3-*O*-methyl-D-glucose [1] was almost the same as that given by plotting $\log_{10}$ (unchanged 3-*O*-methylhexose) against time for the same phase of the reaction. The apparent first-order rate constants, determined by the former method, have been listed.

Effect of Metallic Ions on the Alkaline Degradation of 3-O-*Methyl*-D-*glucose*.—An aqueous solution (25 ml.) containing 3-*O*-methyl-D-glucose (0·194 g.) and the required amount of the

---

[11] Jeanes, Wise, and Dimler, *Analyt. Chem.*, 1951, **23**, 415.
[12] Moilanen and Richtzenhain, *Acta Chem. Scand.*, 1954, **8**, 704.
[13] Hough, Jones, and Wadman, *J.*, 1950, 1702.
[14] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[15] Abdel-Akher and F. Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859.
[16] Lemieux and Bauer, *Analyt. Chem.*, 1954, **26**, 920.
[17] Nair and Muthe, *Naturwiss.*, 1956, **43**, 106.
[18] Glen, Myers, and Grant, *J.*, 1951, 2568.
[19] Adams, Reeves, and Goebel, *J. Biol. Chem.*, 1941, **140**, 653.

metallic nitrate was saturated with nitrogen and treated with oxygen-free 0·100N-sodium hydroxide (25 ml.) at 25° ± 0·1°. The observed rates, calculated as above, have been listed.

Treatment of 3-O-*Methyl*-D-*glucose with Sodium Hydroxide and with Sodium Alkoxides*.—(*a*) A 0·02M-solution of 3-*O*-methyl-D-glucose in oxygen-free sodium hydroxide of required normality was kept at 25° ± 0·1°. The rate constants were calculated as above:

NaOH (N)	0·05	0·1	0·2	0·4
$10^2k'$ (hr.$^{-1}$)	1·9	4·0	6·0	9·7

(*b*) 3-*O*-Methyl-D-glucose (0·194 g.) was dissolved with warming in anhydrous ethanol (20 ml.), 0·20N-ethanolic sodium ethoxide (25 ml.) added, and the volume of the solution adjusted to 50 ml. with ethanol. All solutions were oxygen-free. The rate of development of acidity at 25° ± 0·1° was determined in the usual way. The results of this and a similar experiment with sodium methoxide in methanol have been given.

After 24 hr. each alcoholic solution was diluted with water (50 ml.) and immediately passed through columns of Amberlite resin IR-120(H) (5 g.) and IR-4B (3 g.). The neutral effluent, when examined by paper chromatography in solvent " a ", with sprays " a " and " c ", showed in each case, 3-*O*-methyl-D-fructose (R_F 0·59) and -glucose (R_F 0·51). The basic resin was washed with water and eluted with 2% sodium carbonate solution (120 ml.), and the effluent stirred with Amberlite resin IR-120(H) (20 g.) for 2 hr. The filtered solution was evaporated to dryness and the residue examined by paper chromatography in solvent " b ", with sprays " b ", " c ", and " d ". In both cases the main product was β-D-glucometasaccharinolactone (R_L 0·42), together with smaller amounts of the α-isomer (R_L 0·47, lactone), but in the case of the reaction originally carried out in methanol a trace of lactic acid (R_L 1·00) was detected (R_L = rate relative to lactic acid).

2-*Deoxy*-D-*ribose*.—(*a*) A solution of 1 : 2-5 : 6-di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-D-glucose [20] (20·95 g.) in dioxan (132 ml.) and water (68 ml.) was boiled under reflux for 1·5 hr. with toluene-*p*-sulphonic acid (17·2 g.), then, after cooling, passed through Amberlite resin IR-4B(OH) and evaporated to a colourless syrup (13·44 g., 79·5%) which crystallised slowly and showed m. p. 75—77°, $[\alpha]_D^{21}$ +40·5°, (*c* 1 in H_2O). This material proved difficult to recrystallise, but gave a single spot on the paper chromatogram (solvent " c ", spray " a ", R_F 0·76) and was used without further purification. Freudenberg and Ivers [20] reported m. p. 70—71°, $[\alpha]_D$ +39·6°, for the monohydrate of 3-*O*-toluene-*p*-sulphonyl-D-glucose.

Oxygen-free 0·04N-lime-water (700 ml.) was added during 8 hr. to a stirred, oxygen-free solution of 3-*O*-toluene-*p*-sulphonyl-D-glucose (4·79 g.) in water (50 ml.) at room temperature and stirring was continued overnight. The solution was then de-ionised by passage through successive columns of Amberlite resins IR-120(H) and IR-4B and evaporated to a colourless syrup (1·95 g.) which was shown by paper chromatography (solvent " c ") to consist mainly of 2-deoxy-D-ribose (R_F 0·47), a small amount of 3-*O*-toluene-*p*-sulphonyl-D-glucose (R_F 0·76), and a trace of an unidentified compound (R_F 0·18). The syrup was transferred in 10% aqueous solution to a carbon–Celite column (45 × 5 cm.) and eluted under pressure of 2 m. with aqueous ethanol. Increasing the concentration of ethanol by a linear gradient (cf. ref. 21) from 0 to 5% yielded chromatographically pure 2-deoxy-D-ribose as a syrup which crystallised rapidly (1·44 g., 76%) and when recrystallised several times from propan-2-ol had m. p. and mixed m. p. 90—92°. Further increase of the ethanol concentration in the eluant from 5 to 20% yielded unchanged 3-*O*-toluene-*p*-sulphonyl-D-glucose (0·21 g., 4%), m. p. and mixed m. p. 74—76°.

(*b*) A solution of 3-*O*-methanesulphonyl-D-glucose [22] (4·20 g.) in oxygen-free water (50 ml.) was stirred at room temperature while oxygen-free 0·04N-lime-water (820 ml.) was added during 1½ hr. After being stirred at room temperature for a further 30 min. the solution was de-ionised and evaporated as in the preceding experiments, to yield a colourless syrup (2·15 g.) shown by paper chromatography (solvent " d ") to consist mainly of 2-deoxy-D-ribose (R_F 0·43), with 3-*O*-methanesulphonyl-D-glucose (R_F 0·31) and a trace of the unidentified compound (R_F 0·20 in " d ", R_F 0·18 in " c ") observed in the preceding experiment. Chromatography of the syrup under the conditions described above yielded 2-deoxy-D-ribose (1·41 g., 65%), m. p. 89—91° after recrystallisation from propan-2-ol. Unchanged 3-*O*-methanesulphonyl-D-glucose (0·43 g., 10%), m. p. and mixed m. p. 133—134°, was also obtained from the column at 5—20% ethanol concentration.

[20] Freudenberg and Ivers, *Ber.*, 1922, **55**, 929.

[21] Lindberg and Wickberg, *Acta Chem. Scand.*, 1954, **8**, 569.

[22] Helferich, Dressler, and Griebel, *J. prakt. Chem.*, 1939, **153**, 285.

Rate of Acid Formation.—Solutions of 3-*O*-toluene-*p*-sulphonyl- (0·167 g.) and 3-*O*-methanesulphonyl-D-glucose (0·129 g.) in oxygen-free 0·040N-lime-water (50 ml.) were kept at 25° while formation of acid was measured by back-titration as described earlier.[1] Results were:

3-O-*Toluene*-p-*sulphonyl*-D-*glucose.*

Time (hr.)	0·1	0·35	2·0	4·0	6·0	72	420
Acid (equiv./mole)	1·58	1·59	1·70	1·71	1·72	1·83	2·08

3-O-*Methanesulphonyl*-D-*glucose.*

Time (hr.)	0·1	0·2	0·5	1·0	3·0	5·0
Acid (equiv./mole)	1·86	1·89	1·91	1·94	1·96	2·00

A solution of 3-*O*-toluene-*p*-sulphonyl-D-glucose (0·167 g.) in oxygen-free 2·03N-sodium hydroxide (50 ml.) was kept at 25°. At intervals aliquot parts (5 ml.) were passed through a column of Amberlite resin IR-120(H) (5 g.), and the eluate and washings titrated to phenolphthalein with 0·025N-sodium hydroxide. Formation of acid was observed as 1·13 (0·25 hr.); 1·30 (0·75 hr.); 1·35 (2·0 hr.); 1·40 (7·0 hr.); 1·69 (25 hr.); 1·75 (127 hr.); 1·93 (222 hr.) equivs. per mole.

We thank Mr. J. Shaw for extensive assistance in the experimental work. This work forms part of the programme of fundamental research undertaken by the Council of the British Rayon Research Association.

THE BRITISH RAYON RESEARCH ASSOCIATION, HEALD GREEN LABORATORIES,
WYTHENSHAWE, MANCHESTER, 22.
[*Received, March 4th,* 1957.]