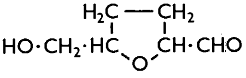
160. *The Iodine-catalysed Conversion of Sucrose into 5-Hydroxymethylfurfuraldehyde.*

By T. G. Bonner, E. J. Bourne, and M. Ruszkiewicz.

Sucrose in dry dimethylformamide containing small amounts of iodine is converted at 100° in comparatively high yield into 5-hydroxymethylfurfuraldehyde (I). The degradation is confined to the fructose unit, and the glucose portion appears to remain unaffected. In the absence of iodine, formation of the aldehyde is negligible.

A mechanism for the reaction is proposed, based on the function of iodine as a catalyst in the dehydration of hydroxy-compounds.

The conversion of pentoses into furfuraldehyde and of hexoses into 5-hydroxymethylfurfuraldehyde (I) by loss of three moles of water per mole of the carbohydrate is normally regarded as an acid-catalysed process.[1] While concentrated mineral acid is used preparatively for the treatment of pentoses, heating with 0·3% oxalic acid at 120° is sufficient to convert either fructose or sucrose into the aldehyde.[2] An investigation [3] of the optimum conditions for the reaction of sucrose established that the formation of the aldehyde originated entirely in the fructose portion of the molecule, the glucose being recovered quantitatively; the maximum yield of aldehyde was 54% (based on the fructose content only). A slightly lower yield (22%, based on the sucrose used) was later obtained,[4] together with humin material, by heating sucrose under pressure in an atmosphere of hydrogen between 130° and 170°, where almost complete fission of the sucrose was found to precede formation of the aldehyde; although no acid was added in this treatment, a pH of 2—3 developed during the heating; this was attributed to the formation of acetol and was regarded as an essential step in the degradation of the fructose.



(I)

Attempts to utilise glucose also as a source of 5-hydroxymethylfurfuraldehyde have been carried out by pre-treatment with potassium or calcium hydroxide followed by heating with oxalic acid,[3] by heating an aqueous solution with and without hydrochloric acid,[5] by reaction with glycine compounds,[6] and by the action of heat on aqueous solutions for several hours.[7,8] The yield from this source is considerably less than from fructose.

During an investigation of iodine-catalysed condensation of sucrose with carbonyl and other compounds in dimethylformamide, a fast-moving product was found on the chromatograms which by comparison of R_F values in different solvents and by its ultraviolet absorption indicated the presence of 5-hydroxymethylfurfuraldehyde. Further investigation established that a high yield of this was obtained by heating sucrose alone with catalytic quantities of iodine in dry dimethylformamide for 1 hr. Sufficient pure

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[1] Newth, *Adv. Carb. Chem.*, 1951, **6**, 83.
[2] Kiermayer, *Chem. Ztg.*, 1895, **19**, 1003.
[3] Haworth and Jones, *J.*, 1944, 667.
[4] Montgomery and Wiggins, *J. Soc. Chem. Ind.*, 1947, **66**, 31.
[5] Wolfrom, Schuetz and Cavalieri, *J. Amer. Chem. Soc.*, 1948, **70**, 514.
[6] *Idem, ibid.*, 1949, **71**, 3518.
[7] Scallet and Gardner, *J. Amer. Chem. Soc.*, 1945, **67**, 1934.
[8] Estigneev and Nikiforova, *Doklady Akad. Nauk, S.S.S.R.*, 1950, **73**, 523.

material was separated by paper chromatography to afford its semicarbazone and 2,4-dinitrophenylhydrazone of correct melting points and oxidation with silver oxide gave 5-hydroxymethylfuroic acid. The yield from sucrose by this method was substantially higher than by previous methods and as in the sucrose–oxalic reaction the product appeared to originate solely from the fructose part of the molecule.

EXPERIMENTAL

Materials.—Dimethylformamide was dried over magnesium sulphate and distilled before use. Sucrose and iodine were the AnalaR and resublimed grade respectively.

Identification of 5-*Hydroxymethylfurfuraldehyde* (I).—Sucrose (14 g.) was heated, with stirring, with dimethyl formamide (50 ml.) and a small crystal of iodine on a boiling-water bath, moisture being excluded. Samples were examined at intervals by paper chromatography with butanol–ethanol–water (4 : 1 : 5 v/v) as solvent. After 30 min. only a trace of unchanged sucrose remained, the main constituents being glucose (R_F 0·18), fructose (R_F 0·16), and 5-hydroxymethylfurfuraldehyde (R_F 0·75). The last spot gave a positive reaction with sprays of *p*-anisidine hydrochloride, urea phosphate, urea hydrochloride, anthrone–phosphoric acid, and diphenylamine–aniline–phosphoric acid, most of which are recognised as reagents for hexoses by virtue of their ability to convert the latter into furfuraldehyde derivatives.[1] After a further hour at 100°, sucrose and fructose had disappeared, only glucose and the aldehyde remaining, with traces of three substances with R_F values intermediate between those of fructose and the aldehyde, and a little oligosaccharide. Heating for a further 3 hr. produced no further change in the pattern of the chromatograms or increase in the amounts of the products. During the experiment, the iodine colour rapidly faded and additional iodine was introduced when the solution appeared colourless. In the absence of iodine, sucrose remained unchanged in dimethylformamide at 100° for 1·5 hr. The need for anhydrous conditions was shown when after an aqueous solution had been heated for 2 hr. at 100°, no sucrose remained, the main products being fructose and glucose together with a little oligosaccharide and a trace of aldehyde; further heating did not modify this result.

The aldehyde was identified by comparison with specimens provided by Drs. O. Theander and H. A. Bouveng, and by Dr. J. D. Garber. The same R_F values were found with the following solvents: butanol–ethanol–water (4 : 1 : 5 v/v); propanol–ethyl acetate–water (7 : 1 : 2, v/v); butanol–acetic acid–water (4 : 1 : 5, v/v); ethyl acetate–acetic acid–water (9 : 2 : 2 v/v); and butanol–benzene–pyridine–water (5 : 1 : 3 : 2, v/v), and the behaviour on electrophoresis in borate [9] buffer was similar. The samples gave identical positive reactions on chromatograms with the spray reagents noted above and with silver nitrate–sodium hydroxide, α-naphthol–phosphoric acid and phloroglucinol–trichloroacetic acid. Identical reactions were also obtained with the orcinol–trichloroacetic acid and 2,4-dinitrophenylhydrazine–hydrochloric acid reagents used [10] in the detection of 5-hydroxymethylfurfuraldehyde.

Sufficient material for the preparation of derivatives was obtained by heating sucrose (20 g.) in dimethylformamide (20 ml.) with iodine for 1·5 hr. with stirring. After cooling, water (20 ml.) was added and the solution extracted with ether (3 × 200 ml.). The concentrated ether extract was chromatographed on thick paper (Whatman No. 3) with butanol–ethanol–water; the appropriate section of the paper was pulped and extracted with ether (Soxhlet). This gave the aldehyde which was converted into the semicarbazone,[11,12] m. p. 194—195° (Found: C, 46·2; H, 5·2; N, 23·2. Calc. for $C_7H_9O_3N_3$: C, 45·9; H, 4·9; N, 23·0%), 5-hydroxymethylfuroic acid (by silver oxide in dilute aqueous sodium hydroxide [12]), m. p. 165—166° (Found: C, 50·7; H, 4·2. Calc. for $C_6H_6O_4$: C, 50·7; H, 4·3%), and the 2,4-dinitrophenylhydrazone,[13] m. p. 200—201° (Found: C, 47·1; H, 3·5; N, 18·0. Calc. for $C_{12}H_{10}O_6N_4$: C, 47·1; H, 3·3; N, 18·3%). In the last case the mother-liquor yielded a second crystalline specimen, m. p. 215° (Found: C, 47·1; H, 3·7; N, 18·2%), behaviour previously attributed to geometrical isomerism.[7,13]

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[9] Assarsson and Theander, *Acta Chem. Scand.* 1958, **12**, 1319.

[10] Potter and Patton, *J. Dairy Sci.*, 1956, **39**, 978.

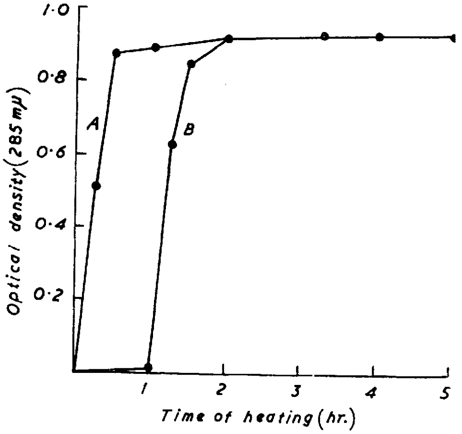
[11] Patton, *ibid.*, 1950, **33**, 324.

[12] Reichstein, *Helv. Chim. Acta*, 1926, **9**, 1066.

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

In comparative experiments sucrose (4 g.) and fructose (2 g.) were separately dissolved in dimethylformamide (25 ml.) containing catalytic quantities of iodine. On prolonged shaking at room temperature, chemical change became apparent only after two days, the sucrose solution showing the presence of glucose and fructose and of two faster-moving constituents with R_F values intermediate between those of fructose and the aldehyde; the last two constituents were also present in the fructose solution. The glucose solution showed no observable change. There was no evidence for the aldehyde in any of the solutions but further examination of the two fast-moving constituents in the sucrose and fructose solutions may help to establish its precursors. After a further 4 days at room temperature the similar degradation of sucrose and fructose had proceeded further, and in both cases oligosaccharides were also present. Glucose continued to show no change.

Quantitative Determination by Ultraviolet Absorption Spectra.—Paper chromatograms of the sucrose–iodine solutions in dimethylformamide indicated a high yield of aldehyde after 1 hr. at 100°. An attempt was made to determine the yield by mixing the final solution with powdered cellulose, applying the dry mixture to a cellulose column, eluting this with butanol–ethanol–water, analysing the separate 50 ml. fractions by means of anthrone [14] or by the absorption [5] at 285 mμ, and then pooling the appropriate fractions and evaporating them to dryness. This procedure was not satisfactory because of loss of product by " tailing " on the column during elution and by volatilisation during concentration of the eluates. Since the aldehyde can be determined *in situ* [7,15] the conditions for the optimum yield were readily obtained by heating sucrose (1 g.) in dry dimethylformamide (37 ml.), with a crystal of iodine, removing 1 ml. of the mixture at various times, diluting it to 1 l. with water, and measuring the optical density at 285 mμ with a Hilger Uvispek spectrophotometer. The small amounts of iodine and dimethylformamide present had a negligible absorption at this wavelength. The yield of aldehyde after 1 hr. at 100°, calculated from a value of $\varepsilon = 16{,}500$ [5] at 285 mμ, was 71% (based on the fructose portion) and this did not increase on continued heating, as indicated in the Figure.



A, Iodine added at zero time. B, Iodine added after 1 *hour's heating.*

DISCUSSION

The mechanism of elimination of three molecules of water from a pentose or hexose to form the furan ring has not yet been clearly established. Haworth and Jones [3] suggested a sequence for the dehydration of fructose starting with the furanose structure (II) from which the loss of the first molecule of water gives the intermediate (III). They noted that a similar intermediate could in theory be obtained from glucose (IV) *via* the 1,2-enediol tautomer (V).

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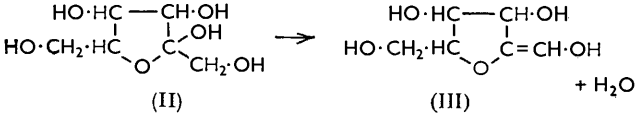
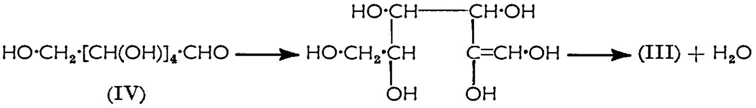
[14] Mowery, *Analyt. Chem.*, 1957, **29**, 1451.

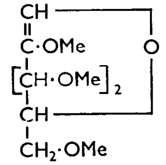
[15] Turner, Rebers, Barrick, and Cotton, *ibid.*, 1954, **26**, 898; O'Neill, *J. Amer. Chem. Soc.*, 1955, **77**, 2837.

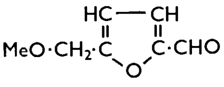
Haworth *et al.*[16] had similarly interpreted the conversion of tetramethylfructofuranose (by dilute hydrochloric acid at 80° or warm acetic anhydride and sodium acetate) into 5-methoxymethylfurfuraldehyde (VII) with elimination of three mols. of methanol. This aldehyde was later[17] obtained by the action of acid on tetramethyl-1,2-glucoseen (VI), this reaction providing the only intermediate which has been isolated in reactions of this type, although the facts adduced to assign to the intermediate the structure of a 3,4-unsaturated osone were not decisive.


(II) (III)

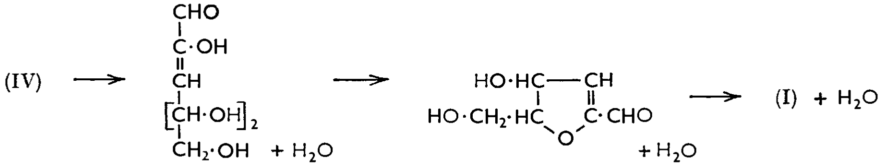

(IV) (V)

Later studies[5,8] on the ultraviolet absorption of acid solutions of glucose undergoing conversion into the aldehyde by heat revealed the development of strong absorption at 228 mμ before that of absorption at 285 mμ due to the aldehyde. As αβ-unsaturated aldehydes absorb strongly at 230 mμ, the initial appearance of the band at 228 mμ was attributed to the elimination of a molecule of water at $C_{(2)}$ and $C_{(3)}$ in glucose reacting in its open-chain form; an intermediate (VIII) resulted which is structurally suitable for elimination of two further molecules of water through (IX) to the aldehyde (I).


(VI)


(VII)

In the present work the existence of an intermediate (VIII) in the reaction could not be tested because of the strong absorption of dimethylformamide at 228 mμ.[18] However, for degradation of fructose or sucrose the dehydration is unlikely to involve this compound since the furan ring is already present. A more likely intermediate is (III) since it is the enolic form of chitose, which is readily converted into 5-hydroxymethylfurfuraldehyde by hot 0·3% aqueous oxalic acid.[19]


(VIII) (IX)

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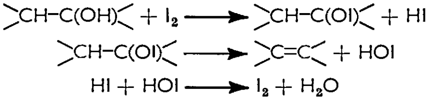
[16] Haworth, Hirst, and Nicholson, *J.*, 1927, 1513.

[17] Wolfrom, Wallace, and Metcalf, *J. Amer. Chem. Soc.*, 1942, **64**, 265.

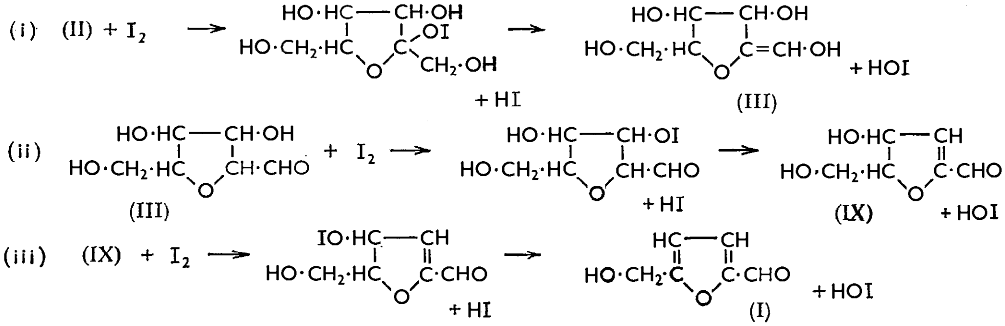
[18] Hunt and Simpson, *ibid.*, 1953, **75**, 4540.

[19] Ekenstein and Blanksma, *Ber.*, 1910, **43**, 2355.

The formation of an intermediate (III) from fructose and its successive dehydration to compounds (IX) and (I) by iodine can be readily envisaged in terms of the interpretation of catalysis by iodine suggested by Hibbert.[20] The familiar dehydration of hydroxy-compounds by iodine was represented:



For stepwise dehydration of fructose a scheme such as (i)—(iii) would apply.



In each pair of steps (i), (ii), and (iii), one molecule each of hydrogen iodide and hypoiodous acid are eliminated which by interaction can regenerate the catalyst with loss of a molecule of water. The sequence outlined follows naturally from the fact that the order of reactivity of iodine with hydroxyl groups is tertiary > secondary > primary [20] and that once compound (III) is formed, the introduction of an olefinic bond between $C_{(2)}$ and $C_{(3)}$ will be assisted by the α-aldehyde group. A similar recurrent formation of iodine from hydrogen iodide and alkyl iodide intermediates has been proposed in the iodine-catalysed decomposition of acetaldehyde at high temperatures.[21]

It is evident that the same catalyst could achieve this sequence of reactions with glucose under conditions of appreciable isomerisation to the open-chain form, provided that the latter readily undergoes iodine-catalysed dehydration to the intermediate (VIII). However, it is possible that a sequence of dehydration steps such as (i)—(iii) can be initiated only at a tertiary carbon atom in a pre-formed furanoside structure.

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[20] Hibbert, *J. Amer. Chem. Soc.*, 1915, **37**, 1748.
[21] Rollefson and Faull, *ibid.*, 1937, **59**, 625.