183. *The Conversion of Sucrose into Furan Compounds. Part I. 5-Hydroxymethylfurfuraldehyde and Some Derivatives.*

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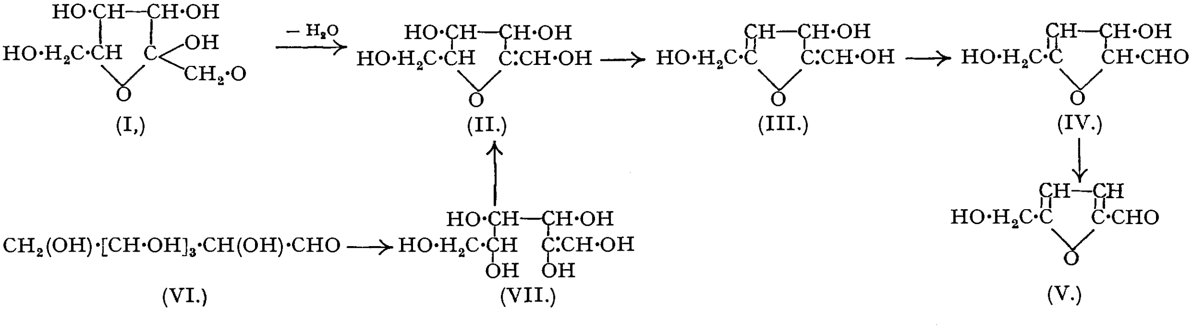
Treatment of sucrose in aqueous solution with 0·25% oxalic acid leads to the formation of 5-hydroxymethylfurfuraldehyde and it has been shown that only the fructose half of the sucrose molecule takes part in this reaction. The conversion of glucose into 5-hydroxymethylfurfuraldehyde has been brought about by the pretreatment of its aqueous solution with alkali and the subsequent treatment with 0·25% oxalic acid. Improvements in the preparation of 5-chloromethylfurfuraldehyde from sucrose and several new 2 : 5-disubstituted derivatives of furan are described.

The preparation and properties of 5-hydroxymethylfurfuraldehyde have been investigated with a view to its providing a source of useful organic intermediate compounds. The conversion of sucrose into 5-hydroxymethylfurfuraldehyde has been described previously (Düll, *Chem. Ztg.*, 1895, 216; Kiermayer, *ibid.*, p. 1003; Middendorp, *Rec. Trav. chim.*, 1919, **38**, 1) and the method used in this investigation was based on the procedure of Kiermayer.

Sucrose was treated with oxalic acid in aqueous solution under pressure under various conditions; the results are in Table II. The maximum yield obtained amounted to 54% of the theoretical (calculated on the amount of fructose present). The product was a brown, mobile oil which could be purified by distillation in a good vacuum, with a small amount of decomposition only, provided that the distillation was carried out in an oxygen-free atmosphere immediately upon isolation of the crude product. The special apparatus described by Middendorp (*loc. cit.*) for the distillation of 5-hydroxymethylfurfuraldehyde was found to offer no advantages. That only the fructose portion of the sucrose molecule reacts with oxalic acid solution under these conditions was demonstrated by the oxidation with nitric acid of the residual solution after the removal of the 5-hydroxymethylfurfuraldehyde. Potassium hydrogen saccharate was obtained in practically the same yield as that obtained in previous experiments from pure glucose (Haworth and Jones, this vol., p. 65). It therefore appears that the reaction between oxalic acid and sucrose under these conditions is such that the fructose half of the sucrose molecule only is utilised, leaving the glucose portion unattacked.

This is explained by the fact that the fructose part of the sucrose molecule is initially in the furanose form and under the acid conditions continues to exist in this form in equilibrium with the pyranose form. Thus by the following scheme (I ⟶ V) fructose (I) in the furanose form can be converted into 5-hydroxymethylfurfuraldehyde (V) :



Moreover it was envisaged that this reaction could take place with glucose (VI) if the latter could be made to react in its enolic form (VII), which by loss of water would give (II) intermediate in the conversion of fructose into hydroxymethylfurfuraldehyde. This being the case, preliminary treatment of glucose with alkali, followed by acid treatment, would provide the required conditions for its conversion into 5-hydroxymethylfurfuraldehyde.

The formation of the enolic form (VII) as a first stage of the treatment of glucose with alkali was first postulated by Lobry de Bruyn and van Eckenstein (*Rec. Trav. chim.*, 1895, **14**, 195) and later by Nef (*Annalen*, 1907, **357**, 295) and the action of alkali on glucose has more recently been studied by Evans (*J. Amer. Chem. Soc.*, 1926, **48**, 2665) and by Wolfrom and Lewis (*ibid.*, 1928, **50**, 842).

Evans and co-workers have investigated the action of potassium hydroxide on aqueous solutions of glucose and have utilised the formic acid ultimately produced as an index of the amount of 1 : 2 ene-diol present in the reaction products. Treatment of aqueous solutions of glucose with potassium hydroxide under various conditions, and subsequent treatment of the neutralised solutions of the reaction products with 0·25% oxalic acid as in the case of sucrose, led to the isolation of 5-hydroxymethylfurfuraldehyde as anticipated. Thus the amount of hydroxymethylfurfuraldehyde isolated from the reaction products after treatment with acid also provided an index of the amount of 1 : 2 ene-diol produced by the initial reaction with alkali. To obtain the maximum yields of hydroxymethylfurfuraldehyde, the treatment of glucose with alkali must be directed towards ensuring the maximum amount of 1 : 2 ene-diol formation. Table I shows the amounts of hydroxymethylfurfuraldehyde isolated from the products of reaction of glucose (100 g.) with potassium hydroxide in water (300 c.c.), followed by treatment with oxalic acid as above described.

TABLE I.

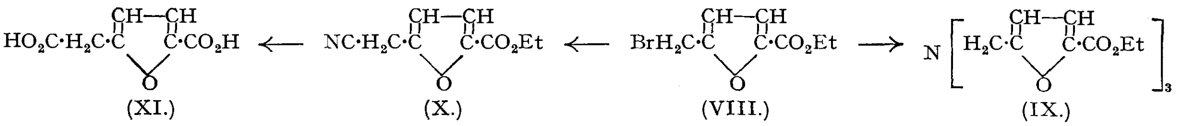
Wt. of KOH, g.	5·0	5·0	2·0	1·0
Time, hrs.	48	24	16	24
Temp. of alkali treatment	50°	50°	50°	50°
Final yield of 5-hydroxymethylfurfuraldehyde, g.	12	10	10	5

Similarly glucose was pretreated with calcium hydroxide solution at 35° for 10 days and after neutralisation with oxalic acid the products were treated with 0·25% oxalic acid as in the case of sucrose itself, and 5-hydroxymethylfurfuraldehyde isolated. The aqueous solution, after the extraction of the latter compound, was again treated with calcium hydroxide, and a further quantity of hydroxymethylfurfuraldehyde obtained. As a result of four such treatments hydroxymethylfurfuraldehyde was obtained from glucose to the extent of 28·5% of the theoretical yield.

The conversion of glucose into 5-hydroxymethylfurfuraldehyde might also be brought about in one stage by the action of suitable buffers. Treatment of glucose with disodium hydrogen phosphate under various conditions gave in one instance 5-hydroxymethylfurfuraldehyde in small yield, but these experiments sufficed to show that no appreciable conversion of glucose into 5-hydroxymethylfurfuraldehyde could be effected in this manner.

Fenton *et al.* (J., 1901, **79**, 808; 1909, **95**, 1334) have described the preparation of 5-chloromethylfurfuraldehyde from keto-hexoses, sucrose, and cellulose by the action of hydrogen chloride in an inert solvent. Optimum conditions for the reaction have been obtained by saturating a suspension in carbon tetrachloride of a concentrated aqueous solution of sucrose with hydrogen chloride. 5-Chloromethylfurfuraldehyde was isolated from the product in 21·3% yield, based on the whole sucrose molecule. It was converted into 5-hydroxymethylfurfuraldehyde in 90% yield by hydrolysis with boiling water by the method of Cooper and Nuttall (J., 1912, **101**, 1075). However, the overall yield of 5-hydroxymethylfurfuraldehyde from sucrose in this way does not compare with that obtained by the direct treatment of sucrose with oxalic acid.

5-Hydroxymethylfurfuraldehyde was oxidised to 5-hydroxymethylfuran-2-carboxylic acid by the method of Reichstein (*Helv. Chim. Acta*, 1926, **9**, 1066) and from it the hitherto undescribed *ethyl* ester has been prepared. The 5-*chloromethyl* and corresponding *bromo*-derivatives of the ester were readily prepared from the hydroxy-derivative by the use of the appropriate halogen acid in dry ether. The halogen is extremely reactive and treatment of *ethyl* 5-*bromomethylfuran*-2-*carboxylate* (VIII) with concentrated aqueous ammonia in the cold gave almost immediately the crystalline tertiary amine, *tri*-(2-*carbethoxy*-5-*furfuryl*)*amine* (IX).



Ethyl 5-*cyanomethylfuran*-2-*carboxylate* (X) was prepared from the bromo-derivative in the usual manner, and on hydrolysis gave the corresponding dibasic acid, *furan*-2-*carboxylic*-5-*acetic acid* (XI).

EXPERIMENTAL.

5-*Hydroxymethylfurfuraldehyde*.—(a) *From the fructose portion of the sucrose molecule.* Sucrose (100 g.) was dissolved in water (300 c.c.), hydrated oxalic acid (0·7 g.) added, and the solution heated to 145° in an autoclave, maintained thereat for 15 minutes and then at 125° for 2¼ hours, cooled to room temperature, and neutralised with calcium carbonate. Basic lead acetate (5 g.) was added, the solution stirred for 1 hour, the precipitate removed by centrifuging, and the clear filtrate extracted (Soxhlet) with ethyl acetate. The extract, dried over anhydrous magnesium sulphate, yielded, after distillation of the solvent, a brown syrup which crystallised slowly at 0°. Yield, 20 g. The material distilled at 110°/0·02 mm. as a light yellow, mobile liquid, crystallising immediately at 0°, m. p. 31·5°, $n_{\mathrm{D}}^{18^\circ}$ 1·5627. It was soluble in alcohol, acetone, ether, and chloroform, very slightly soluble in light petroleum (b. p. 60—80°), and gave a semicarbazone, m. p. 192° (Found: C, 45·9; H, 5·0; N, 23·1. Calc. for $C_7H_9O_3N_3$: C, 45·9; H, 4·9; N, 23·0%). The function of the basic lead acetate in the isolation of 5-hydroxymethylfurfuraldehyde was to remove an impurity, extractable from the aqueous solution with ethyl acetate, the presence of which completely inhibited crystallisation of the aldehyde. The effect of variations in the conditions of preparation of 5-hydroxymethylfurfuraldehyde is shown in Table II.

TABLE II.

Treatment of Sucrose with Oxalic Acid in Aqueous Solution under Various Conditions.

The experiments were performed on 100 g. of sucrose in each case and the yield represents the amount of crystalline product obtained after distillation of the ethyl acetate extraction solvent.

Vol. of solution, c.c.	Wt. of oxalic acid, g.	Time, hrs.	Temp.	Pressure, atms.	Atmosphere.	5-Hydroxymethyl-furfuraldehyde, g.
200	0·6	2·5	135—140°	4·5	Air	12·2
300	,,	,,	130—135	,,	,,	13·0
200	0·7	,,	135—140	,,	,,	12·3
250	,,	2·0	135—140	,,	,,	13·0
,,	,,	2·5	125—130	3·5	,,	11·0
,,	,,	,,	155° for 15 mins., then maintained at 120—125°	3·0	,,	0·0
300	,,	,,	130—135	4·0	,,	13·3
,,	,,	2·0	130—135	,,	,,	15·0
,,	,,	2·5	125—130	3·5	,,	16·0
,,	,,	,,	145° for 15 mins., then maintained at 125°	3·0	,,	20·0
,,	,,	,,	160° for 15 mins., then maintained at 135—140°	4·5	,,	15·0
200	0·8	,,	135—140	,,	,,	11·7
300	,,	,,	115—120	1·5	,,	0·0
,,	,,	,,	135—140	5·5	Nitrogen	14·0
,,	,,	,,	135° for 15 mins., then maintained at 120—125°	3·0	Air	13·0
,,	,,	2·0	130—140	4·5	,,	15·0
,,	,,	2·5	130—135	,,	Nitrogen	12·5
,,	,,	,,	100—105	28·0	,,	1·25
,,	1·26	,,	135—140	4·5	Air	9·0
,,	,,	,,	145—150	6·0	,,	9·0
,,	,,	1·5	155—160	7·5	Nitrogen	8·5
,,	1·4	2·5	145—150	7·0	,,	10·0
,,	,,	,,	135—140	5·5	,,	9·5

(b) *From the glucose portion of the molecule.* (i) *By preliminary treatment of glucose with calcium hydroxide.* Glucose (200 g.) was dissolved in an aqueous solution of calcium hydroxide (600 c.c., saturated at 35°), and xylene (1 c.c.) added. The solution was heated at 35° for 10 days, and aqueous oxalic acid then added until the pH was equal to that of a 0·25% solution of oxalic acid. Calcium oxalate was removed on the centrifuge, and the clear brown solution heated in an autoclave at 130—135° for 3 hours. The solution, after cooling, was neutralised with calcium carbonate and extracted (Soxhlet) with ethyl acetate. 5-Hydroxymethylfurfuraldehyde (18·5 g.) was isolated as previously described.

The residues from the above preparation were concentrated on the boiling water-bath to 300 c.c., and all traces of ethyl acetate removed. Calcium hydroxide was added in amount sufficient to give a saturated solution at 35°, and the solution heated for 10 days at this temperature. 5-Hydroxymethylfurfuraldehyde was isolated as described above. As the result of four such treatments the yield of the aldehyde from 200 g. of glucose was 40 g. (28·5% of the theoretical).

(ii) *By preliminary treatment of glucose with potassium hydroxide.* Quantities of glucose (100 g.) were dissolved in water (300 c.c.), and potassium hydroxide, in amounts indicated by Table I, added. The resultant solutions were heated at 50° for various times as shown, and thereafter in each case brought to pH 7 by addition of dilute hydrochloric acid. An aqueous solution of oxalic acid was then added until the pH was equivalent to that of a 0·25% solution of oxalic acid. The solutions were then heated at 135—140° for 3 hours in an autoclave and subsequently treated for the isolation of 5-hydroxymethylfurfuraldehyde as previously described.

Treatment of Glucose with Disodium Hydrogen Phosphate.—Glucose (25 g.) was dissolved in water (75 c.c.), and disodium hydrogen phosphate (9 g.) added. The solution was heated in a sealed tube at 185° for 3 hours. Black humous material was deposited and the solution was acidic at the end of the reaction. It was treated for the isolation of 5-hydroxymethylfurfuraldehyde as above described. Yield, 0·7 g.

Isolation of Potassium Hydrogen Saccharate from the Glucose Portion of the Sucrose Molecule after Conversion of the Fructose Portion into 5-Hydroxymethylfurfuraldehyde.—The aqueous solution, after the extraction of 5-hydroxymethylfurfuraldehyde (*vide supra*), was concentrated to 250 c.c. Nitric acid (160 c.c., *d* 1·42) was added, and the solution heated on the boiling water-bath; vigorous oxidation took place. The nitric acid was then boiled off as completely as possible with repeated additions of water. The syrupy residue finally obtained was diluted and kept for 12 hours. The solution was filtered, neutralised at 70° with potassium hydroxide solution, rendered faintly alkaline, and cooled to 0° On addition of glacial acetic acid in moderate excess, potassium hydrogen saccharate crystallised. Yield, 30 g. (43·5% of the theoretical), equiv., 252 (calc., 248), $[\alpha]_{\mathrm{D}}^{20^\circ} + 5·1^\circ$ (*c*, 1·0).

Glucose (50 g.) on oxidation under precisely similar conditions gave potassium hydrogen saccharate in a yield of 31 g.

Conversion of Sucrose into 5-Chloromethylfurfuraldehyde.—The conditions used for the optimum yield of product were as follows: Cane sugar (30 g.) was dissolved in water (20 c.c.), and carbon tetrachloride (250 c.c.) added. Hydrogen chloride was passed through the mechanically stirred mixture for 1 hour, the temperature then raised to 40°, and stirring continued for 4 hours. The volume of carbon tetrachloride solution was maintained at 250 c.c. by frequent additions. After standing for 12 hours, the carbon tetrachloride solution was decanted, and the dark syrupy residue re-treated as above described. The carbon tetrachloride solutions were combined, neutralised with sodium bicarbonate, and dried over anhydrous magnesium sulphate. Distillation of the carbon tetrachloride left a dark mobile syrup. It distilled in a vacuum and was obtained as a colourless liquid, crystallising completely at 0°. Yield, 5·4 g. (21·3% of the theoretical), m. p. 37°.

Conversion of 5-Chloromethylfurfuraldehyde into 5-Hydroxymethylfurfuraldehyde.—The method described by Cooper and Nuttall (*vide supra*) was used. The 5-chloromethyl-aldehyde was added to a large excess of boiling water, and the 5-hydroxymethyl-aldehyde extracted with ethyl acetate. Yield, 90% of the theoretical.

Ethyl 5-Hydroxymethylfuran-2-carboxylate.—5-Hydroxymethylfuran-2-carboxylic acid, prepared from 5-hydroxymethylfurfuraldehyde (Reichstein, *loc. cit.*), was refluxed for 7 hours in 1% ethyl-alcoholic hydrogen chloride. The resultant solution was neutralised with lead carbonate, and the residue obtained after distillation of the ethyl alcohol fractionally distilled under reduced pressure. The *ester*, b. p. 120—130° (bath temp.)/0·02 mm., was obtained as a mobile liquid which crystallised completely on standing. Recrystallised from ether–light petroleum, it had m. p. 46° (Found: C, 56·5; H, 5·95; OEt, 27·1. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9; OEt, 26·5%).

5-Hydroxymethylfuran-2-carboxyamide.—This was prepared from the ethyl ester by treatment with ethyl-alcoholic ammonia. The solid product, recrystallised from methyl alcohol–ether, had m. p. 151—152°.

Ethyl 5-Chloromethylfuran-2-carboxylate.—Ethyl 5-hydroxymethylfuran-2-carboxylate (1 g.) was dissolved in carbon tetrachloride (40 c.c.) and refluxed while dry hydrogen chloride was passed in until the solution was saturated. The solution was kept at 0° for 12 hours, neutralised with sodium bicarbonate, and dried over anhydrous magnesium sulphate. Distillation of the carbon tetrachloride left a mobile syrup which partly crystallised. It was triturated with ether–light petroleum, and the insoluble unchanged starting material (0·6 g.) removed by filtration. Distillation of the ether and light petroleum left a mobile liquid (0·4 g.), which was ethyl 5-chloromethylfuran-2-carboxylate, $n_D^{20°}$ 1·5103, b. p. (bath temp.) 115°/0·015 mm.

Ethyl 5-Bromomethylfuran-2-carboxylate.—Ethyl 5-hydroxymethylfuran-2-carboxylate was added to a 50% solution of hydrogen bromide in dry ether and kept at 0° for 2 days. The solution was then neutralised with sodium bicarbonate and dried over anhydrous magnesium sulphate. Distillation of the ether gave ethyl 5-bromomethylfuran-2-carboxylate in 90% of the theoretical yield. It was a mobile, yellow liquid, b. p. (bath temp.) 125°/0·005 mm., $n_D^{18°}$ 1·5414.

Ethyl 5-Cyanomethylfuran-2-carboxylate.—Ethyl 5-bromomethylfuran-2-carboxylate (2 g.) was dissolved in alcohol (2 c.c.) and added gradually to a solution of sodium cyanide (0·5 g.) in water (1 c.c.). The mixture was refluxed on a boiling water-bath for 2 hours and then filtered. Water was added, and the mixture extracted with ether. Distillation of the ether gave a mobile liquid, b. p. 120° (bath temp.)/0·012 mm. The colourless liquid crystallised on standing at 0°, and was recrystallised from ether–light petroleum; yield, 1·4 g., m. p. 42—43°.

Furan-2-carboxylic-5-acetic Acid.—The preceding ester (0·5 g.) was dissolved in ethyl alcohol (1·5 c.c.) and added to sodium hydroxide (0·4 g.) dissolved in water (0·5 c.c.). The whole was boiled under reflux for 24 hours, insoluble material separating after 2 hours' boiling. Alcohol was removed by evaporation, the residue dissolved in the minimum amount of water, and the free acid precipitated by addition of 60% sulphuric acid. The crystalline material was removed by filtration and recrystallised from hot water, forming fine needles, m. p. 217°. Yield, almost quantitative (Found: C, 50·0; H, 3·7. $C_7H_6O_5$ requires C, 49·5; H, 3·5%).

Tri-(2-carbethoxy-5-furfuryl)amine.—Ethyl 5-bromomethylfuran-2-carboxylate (0·5 g.) was added to concentrated aqueous ammonia (20 c.c.) and kept at 40° for 2 days. The solid product was removed by filtration and recrystallised from ether–light petroleum. The product (0·2 g.) was obtained in long, white needles, m. p. 76° [Found: C, 60·9; H, 5·8; N, 3·6; OEt, 28·2. $(C_8H_9O_3)_3N$ requires C, 60·9; H, 5·7; N, 3·0; OEt, 28·5%].

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