609. *Sucrose Derivatives. Part I. Reaction of Sucrose with Enol Ethers.*

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Novel acetals, including one copolymer, have been produced by the acid-catalysed reaction of vinyl ethers and cyclic enol ethers with sucrose in dimethylformamide. Oxydiethylidene derivatives have been obtained by condensation with divinyl ethers.

In a search for new derivatives of sucrose the possibility of using the mild reaction (i) of vinyl ethers with hydroxyl groups[1] as a general reaction for the production of sucrose acetals was investigated.

$$\mathrm{RO{\cdot}CH{:}CH_2 + R'OH \longrightarrow RO{\cdot}CHMe{\cdot}OR'} \tag{i}$$

Only traces of acid are required to catalyse such reactions and it was envisaged that the acid-labile glycosidic linkage in sucrose would be strengthened and protected from proton attack by the screen of substituents introduced. This reaction was also attractive economically because of the availability of vinyl ethers from alcohols and acetylene,[2] and certain cyclic enol ethers by dimerisation of acraldehyde.

Conditions for such reactions with sucrose were determined by using 2,3-dihydropyran. This, and other enol ethers are not solvents for sucrose, but the addition of dimethylformamide produced homogeneous solutions in which reactions readily occurred at room temperature after the addition of one drop of mineral acid. In the presence of eight or

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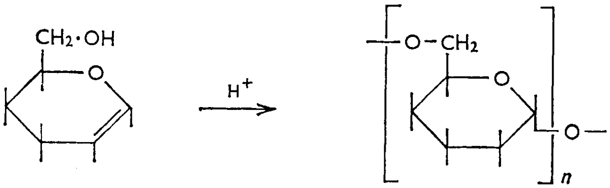
[1] Woods and Krumer, *J. Amer. Chem. Soc.*, 1947, **69**, 2246; Sehostavoski and Gerschtein, *J. Gen. Chem. U.S.S.R.*, 1946, **16**, 937.

[2] Reppe, "Neue Entwicklungen auf dem Gebiete der Chemie des Acetylens und Kohlenoxyds," Springer Verlag, Berlin, 1949.

more equivalents of enol ether, no acid hydrolysis of sucrose could be detected chromatographically and no unchanged sucrose remained after 20 hr. However, in the presence of 2·5 mol. of 2,3-dihydropyran, some unchanged sucrose was recovered, and glucose and fructose were detected in the reaction mixture. A mixture of at least three acetals was produced in this reaction.

Compounds corresponding approximately to the sucrose hepta-acetals were obtained on reaction with an excess of 2,3-dihydropyran and 3,4-dihydro-2*H*-pyran-2-carboxaldehyde, and a compound corresponding to the hexa-acetal with isobutyl vinyl ether. Complete or nearly complete substitution was obtained with the smaller ethers, ethyl and 2-chloroethyl vinyl ether. Such a high degree of substitution is particularly gratifying in view of the resistance[3] of sucrose to complete methylation. Evidence that the acetal obtained by reaction of sucrose and 2,3-dihydropyran was indeed a sucrose acetal and not that of a glucose and fructose mixture includes (1) the molecular weight of the hepta-acetal, (2) the production of sucrose only on alkaline hydrolysis, and (3) comparison with the corresponding tetra-acetals of glucose and fructose. Alkaline hydrolysis of sucrose acetals derived from ethyl and isobutyl vinyl ether also gave sucrose. Acetaldehyde was detected among the acid hydrolysis products of those sucrose acetals formed with vinyl ethers.



The general reaction (i) was extended in several ways. An enol ether which also carried a hydroxyl substituent, *e.g.*, 3,4-dihydro-2-hydroxymethyl-2*H*-pyran, was found to polymerise by itself or co-polymerise with sucrose. The non-dialysable polymer obtained resembled a polysaccharide in having the pyranose ring structure and interglycosidic linkages but differed in that it exhibited lipophilic character due to the methylene groups in the ring.

Alternatively, a divinyl ether can be utilised. Reaction of methyl 4,6-*O*-ethylidene-α-D-glucopyranoside with divinyl ether gave the 2,3-oxydiethylidene derivative. This compound has been reported by Appel *et al.*[4] as formed from paraldehyde and methyl α-D-glucoside. Among the acetals obtained by reaction of sucrose with divinyl ether was one which probably contained three oxydiethylidene groups per two moles of sucrose. Such compounds are very unstable and decomposed to yield sucrose.

EXPERIMENTAL

Paper Chromatography.—Chromatograms were run on Whatman No. 1 paper irrigated with butanol–ethanol–water (4 : 1 : 5) and sprayed with silver nitrate,[5] naphtharesorcinol,[6] or 2,4-dinitrophenylhydrazine.[7]

2,3-Dihydropyran Determination.—Aliquot portions (0—0·02 ml.) of dihydropyran were each treated with iodine solution [25 ml.; iodine (6·3892 g.) and potassium iodide (19·8205 g.) in water (1 l.)], and the residual iodine titrated against sodium thiosulphate solution (24·6441 g./l.) with " Thyodene " starch indicator. The linear relation between the volume of dihydropyran and the equivalent volume of thiosulphate was used to demonstrate that no reaction occurred after 20 hr. at 17° either when sucrose (1·47 g.) was suspended in dihydropyran (4·56 g.)

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[3] Haworth, *J.*, 1915, **107**, 8.

[4] Appel, Haworth, Cox, and Llewellyn, *J.*, 1938, 793.

[5] Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444.

[6] Forsyth, *Nature*, 1948, **161**, 239.

[7] Block, Durrum, and Zweig, " A Manual of Paper Chromatography," Academic Press, New York, 1955, p. 344.

or when sucrose (0·48 g.) was dissolved in a dihydropyran (1·8 g.)–dimethylformamide (8·2 g.) mixture. However, reaction occurred on treatment of sucrose (4·3 g.) with 2,3-dihydropyran (13·2 g.) in dimethylformamide (50 g.) at 20° for 18 hr. in the presence of concentrated hydrochloric acid (0·02 ml.).

Determination of Sucrose Content.—The sucrose acetal (0·2 g.) was hydrolysed by 1 : 1 aqueous-ethanolic N-hydrochloric acid (30 ml.) at 65° for 90 min. and after neutralisation with 2N-sodium hydroxide the solution was continuously extracted with ether for 20 hr. The aqueous layer was separated, any trace of ether removed under reduced pressure, and the solution made up to 250 ml. A known weight of sucrose was hydrolysed simultaneously and treated in the same manner. The total sugar content of both solutions was determined with calibrated Shaffer–Hartmann copper reagent [8] and that in the sucrose hydrolysate used as a blank. Chromatographic analysis of the acid hydrolysates of the sucrose acetals all revealed glucose and fructose. Sucrose acetals derived from vinyl ethers yielded acetaldehyde (detected with 4-hydroxybiphenyl) in their hydrolysates.

Preparation of Tetrahydropyran-2-yl Derivatives.—Sucrose (9·8 g., 28·6 millimoles) was dissolved in a warm mixture of 2,3-dihydropyran (31·9 g., 380 millimoles) and dimethylformamide (105 g.), and concentrated hydrochloric acid (0·03 ml.) was added to the stirred ice-cooled solution. Thereafter the mixture was left at ambient temperature for 20 hr., neutralised with silver carbonate, filtered, and poured into water (400 ml.). The thick white oil which separated was purified by successive reprecipitation by pouring dimethylformamide and ethanol solutions into water. The white powder obtained by drying the precipitate *in vacuo* over P_2O_5 was readily soluble in ether, the lower aliphatic alcohols, pyridine, benzene, and toluene. The *product* (16·7 g., 64% calc. for hepta-acetal), $[\alpha]_D^{21\cdot5}$ $+34°$ (*c* 1·6 in ethanol), had a sucrose content corresponding to a combination with 6·5 mol. of dihydropyran (Found: C, 60·3; H, 8·3. The hepta-acetal $C_{47}H_{78}O_{18}$ requires C, 60·7; H, 8·4%). Its molecular weight (Barger's method [9]) was 904; the hepta-acetal requires *M* 930. Hydrolysis of the acetal with 1 : 1 aqueous-ethanolic N-sodium hydroxide at 100° for 5 hr. followed by neutralisation with Amberlite IR-120 (H^+) yielded sucrose (detected chromatographically).

Products were isolated, after reaction, from mixtures of (i) fructose (2·23 g.), 2,3-dihydropyran (11 g.), dimethylformamide (30 g.), and concentrated hydrochloric acid (0·02 ml.) and (ii) glucose (2·7 g.), 2,3-dihydropyran (11·1 g.), dimethylformamide (21 g.) and concentrated hydrochloric acid (0·02 ml.). The *fructose acetal* (2·1 g., 33% calc. for tetra-acetal), $[\alpha]_D^{21\cdot5}$ $+13°$ (*c* 1·6 in ethanol), was a hard clear glass and had a sugar content corresponding to combination with 3·9 mol. of dihydropyran (Found: C, 60·9; H, 8·6. The tetra-acetal $C_{26}H_{44}O_{10}$ requires C, 60·5; H, 8·5%). The *glucose acetal* was a white meringue-like solid (3·54 g., 46%), $[\alpha]_D^{21\cdot5}$ $+35°$ (*c* 0·9 in ethanol), and had a sugar content corresponding to combination with 3·8 mol. of dihydropyran (Found: C, 59·9; H, 8·5%).

Preparation of 6-C-*Formyltetrahydropyran-2-yl Derivative of Sucrose.*—Sucrose (6·1 g.) was left at 20° for 20 hr. with 3,4-dihydro-2*H*-pyran-2-carboxaldehyde (14·7 g.) in dimethylformamide (65 g.) containing concentrated hydrochloric acid (0·02 ml.). A stream of dry nitrogen was passed throughout the reaction period to prevent oxidation. After neutralisation with silver carbonate, the filtrate was concentrated and the residual gum partitioned between chloroform and water to remove unchanged sucrose. The solid obtained on removal of the chloroform was dissolved in acetone and poured into water. The resulting thick oil was centrifuged off and dried to a solid (1·95 g., 12·2%) *in vacuo* over P_2O_5 (Found: C, 51·7; H, 6·8. The hepta-acetal heptahydrate $C_{54}H_{92}O_{32}$ requires C, 51·8; H, 7·3%). The sugar content corresponded to 7·4 moles of combined residues per mole of sucrose. The infrared spectrum (Nujol) of this *product* showed peaks at 1730 (C=O) and 1650 cm.$^{-1}$ (hydrate), both of which were absent from the spectra of the acetals described above.

Polymerisation of 3,4-*Dihydro-2-hydroxymethyl-*2H-*pyran.*—A solution of 2-hydroxymethyl-3,4-dihydro-2*H*-pyran (4·8 g.) in dimethylformamide (18 g.) containing concentrated hydrochloric acid (0·02 ml.) was left at 20° for 18 hr. and then poured into water. The polymer precipitated was recovered as a white powder (3·2 g., 65%). At least 97% of the polymer was retained in the Visking tubing when its ethanolic solution was dialysed against frequent changes of ethanol for 4 days. No unsaturation of the enol-ether type [10] was detected in the polymer

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[8] Shaffer and Hartmann, *J. Biol. Chem.*, 1920, **45**, 365.

[9] Barger, *J.*, 1904, **85**, 286.

[10] Siggin and Edoberg, *Ind. Eng. Chem. Analyt.*, 1947, **20**, 762.

[Found: C, 63·05; H, 9·0. $(C_6H_{10}O_2)_n$ requires C, 63·2; H, 8·8%]. Hydrolysis of the polymer (0·5 g.) with 1 : 1 aqueous-ethanolic N-hydrochloric acid for 1 hr. at 60—70° yielded only one chromatographically detectable product. This product reacted with silver nitrate,[5] had the same mobility as tetrahydro-6-hydroxymethylpyran-2-ol, and was further characterised as its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 121—122°.

Copolymerisation of Sucrose and 3,4-*Dihydro*-2-*hydroxymethyl*-2H-*pyran*.—Dihydrohydroxymethylpyran (8·7 g.) was added to a cooled (0°) solution of sucrose (2·9 g.) in dimethylformamide (30 g.) containing (0·02 ml.) of concentrated hydrochloric acid. After 18 hr. at 17° the mixture was diluted with dimethylformamide (30 g.) and poured into water to precipitate the polymer (1·1 g., 11%). The polymer could be recovered quantitatively after dialysis of its ethanolic solution in Visking tubing against frequent changes of ethanol during 4 days. No enol-ether unsaturation [10] was detected in the polymer. Its sucrose content corresponded to combination of one mole of sucrose with 19·8 moles of enol ether (Found: C, 59·2; H, 8·7. A sucrose acetal *polymer* having a sucrose : tetrahydro-6-hydroxymethylpyran-2-yl ratio of 1 : 20 requires C, 60·4; H, 8·5%).

Reaction of Sucrose with Vinyl Ethers.—Ethyl vinyl ether (17·8 g.) was added to a solution of sucrose (7·6 g.) in dimethylformamide (80 g.) which was cooled in ice before the addition of concentrated hydrochloric acid (0·02 ml.). After 18 hr. at 17°, the mixture was poured into water and the whole centrifuged. The viscous bottom layer was dissolved in ethanol, poured into water, extracted with ether, and dried ($MgSO_4$). Removal of the solvent gave the product (13·7 g., 71% calc. for a hepta-acetal), $[\alpha]_D^{20}$ +37° (*c* 1·5 in methanol), which did not distil below 160°/0·3 mm. Its sugar content corresponded to a sucrose : 1-ethoxyethyl ratio of 1 : 7·25 [Found: C, 58·3; H, 9·5. Octa-*O*-(1-ethoxyethyl)sucrose $C_{44}H_{86}O_{19}$ requires C, 57·5; H, 9·4%]. Alkaline hydrolysis of the *acetal* yielded sucrose.

Acetals were also isolated from the following reactions: (*a*) 2-Chloroethyl vinyl ether, and (*b*) isobutyl vinyl ether; these were performed in essentially the same manner. Neither product distilled below 160°/0·5 mm. The 1-O-(2-*chloroethoxyethyl)sucrose acetal* (yield 33%) had $n_D^{17\cdot5}$ 1·4892 and $[\alpha]_D^{20\cdot5}$ +8·5° (*c* 0·8 in methanol). Its sugar content corresponded to a sucrose : 2-chloroethoxyethyl ratio of 1 : 7·65 [Found: C, 44·1; H, 6·0. Octa-*O*-1-(2-chloroethoxyethyl)sucrose acetal $C_{44}H_{78}O_{19}Cl_8$ requires C, 44·1; H, 6·5%]. The 1-*isobutoxyethylsucrose acetal* (yield 55·5%) had $n_D^{17\cdot5}$ 1·4510, $[\alpha]_D^{20\cdot5}$ +30·2° (*c* 0·9 in methanol) (Found: C, 60·8; H, 9·7. The hexa-acetal $C_{48}H_{94}O_{17}$ requires C, 61·2; H, 9·55%).

Methyl 4,6-O-*Ethylidene*-2,3-*oxydiethylidene*-α-D-*glucopyranoside*.—Methyl 4,6-*O*-ethylidene-α-D-glucopyranoside (0·52 g.; m. p. 78°) was treated with divinyl ether (4 g.) in carbon tetrachloride (18 g.) containing a trace of concentrated hydrochloric acid at 2° for 18 hr. The filtrate obtained after neutralisation with silver carbonate was concentrated, the residual syrup dissolved in water, and the insoluble material recrystallised from ethanol to yield the product (0·093 g.), having an infrared spectrum identical with that of an authentic specimen,[4] m. p. and mixed m. p. 185—187°.

Reaction of Sucrose with Divinyl Ether.—Sucrose (15·8 g.) was treated at 0° for 18 hr. with divinyl ether (35 g.) in dimethylformamide (142 g.) containing concentrated hydrochloric acid (0·01 ml.). After neutralisation as above the filtrate was concentrated *in vacuo* to a syrup (17·6 g.). Chromatography revealed components with R_{sucrose} 0—0·5, 1·0, 1·5, 4—5, and 6. Some sucrose gradually crystallised and the syrup (9 g.) remaining was decanted. Fractionation of a portion (1·7 g.) of this syrup on a cellulose column eluted with a butanol–ethanol–water (4 : 1 : 5) mixture yielded, *inter al.*, a homogeneous preparation (0·25 g.) of the component of R_{sucrose} 0·5. Hydrolysis with N-hydrochloric acid at 60—65° for 1 hr. and determination of the sugar content of the neutralised solution showed a 78% sucrose content in agreement with a compound containing three oxydiethylidene groups per two sucrose molecules. The acetal readily decomposed on storage to yield sucrose (identified chromatographically).

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