HAWORTH MEMORIAL LECTURE*

The Sweeter Side of Chemistry

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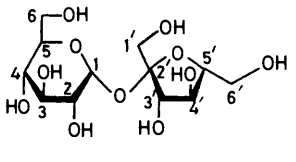
Sir Walter Norman Haworth's researches played an important role in the determination of the molecular structure of sucrose [1] and he was fully aware of its potential 'as a source of new industrial materials and intermediates'. After World War 2, he organized a research programme at the University of Birmingham on 'The Utilisation of Sucrose',[2] under Dr. Leslie F. Wiggins and supported by the Colonial Products Research Council, with a view to finding a market for surplus sugar. Their efforts were concentrated upon degradation products, such as furfural and its derivatives, and it is noteworthy that the review written by Wiggins in 1947 cites only a few genuine sucrose derivatives, mostly octa-substituted, owing to the difficult experimental problems in handling sucrose. Studies were hampered by the multiplicity of hydroxy-groups on sucrose and its sensitivity to acid, coupled with its limited solubility in organic solvents and the lack of suitable protective groups, since standard procedures usually failed. The energy crisis of the 1970s focussed attention on the economic potential of sucrose as an ubiquitous feed stock for chemical and microbiological exploitation, consequently chemical studies have taken on an added importance.

Sucrose (1) is a non-reducing disaccharide with eight hydroxy-groups, arranged in the crystal with a conformation [3] in which the α-D-glucopyranosyl unit is $^4C_1$ whilst the β-D-fructofuranoside unit is $_3T^4$ (2), and the two units are bridged by two intramolecular hydrogen bonds (3) from O-6′ to O-5 and O-1 to O-2. The unprimed and primed numbers are used to indicate the carbons, and associated oxygen atoms, in the glucosyl and fructoside units respectively. In solution the overall conformation is similar to that found in the crystal, particularly around the inter-glycosidic linkage (3), as revealed by ^{1}H- and ^{13}C-n.m.r. spectra.[4] The original chemical synthesis of natural D-sucrose (1) by Lemieux and Huber [5] in 1953 was preceded by its enzymic synthesis in 1944,[6] and followed in 1978 by a synthesis [7] of

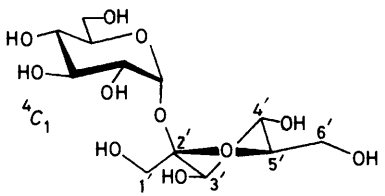
* Delivered at the Spring Meeting of the Royal Society of Chemistry Carbohydrate Group on 1st April 1985 at the University of Bristol.

[1] I. Levi and C. B. Purves, *Adv. Carbohydr. Chem.*, 1942, **4**, 1.
[2] L. F. Wiggins, *Adv. Carbohydr. Chem.*, 1949, **4**, 293.
[3] M. R. Jenner, in 'Developments in Food Carbohydrate', ed. C. K. Lee, Applied Science Publishers Ltd., England, 1980, Vol. 2, p. 91.
[4] K. Bock and R. U. Lemieux, *Carbohydr. Res.*, 1982, **100**, 63.
[5] R. U. Lemieux and G. Huber, *J. Am. Chem. Soc.*, 1953, **75**, 4118.
[6] W. Z. Hassid and M. Doudoroff, *Adv. Carbohydr. Chem.*, 1950, **5**, 29.
[7] Queen's University, 1979, Canada Patent 1 556 007.

L-sucrose (4) which was also sweet but not metabolized. Hence L-sucrose is a potential non-nutritive sweetener provided that it can be made economically. Combinations of either L-fructose and D-glucose, or D-fructose and L-glucose, termed D,L-sucrose and L,D-sucrose respectively, are also sweet and neither absorbed nor metabolized, hence they are calorie-free (non-nutritive).[8] The direct use of the monosaccharides L-glucose or L-fructose for sweetening purposes is complicated by their absorption and consequent circulation in the blood stream for long periods. The 1-thio analogue of sucrose[9] proved to be a competitive inhibitor of yeast invertase, an enzyme that hydrolyses sucrose.



(1)



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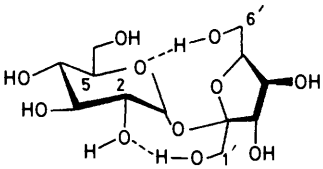
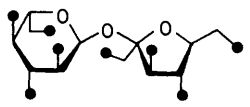


(3)



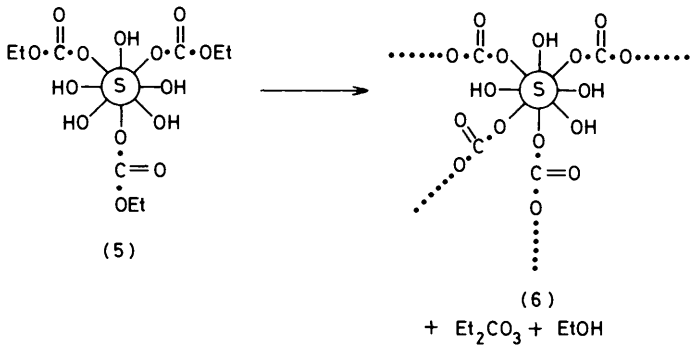
(4)

α-L-glucopyranosyl-
β-L-fructofuranoside (● = OH)
(L-sucrose)

Attempts were made to insert a covalent intramolecular bridge across the two hexose units of sucrose, as for example methylene or carbonate, with a view to retaining the combination after hydrolysis of the hemiacetal linkage to give a di-reducing disaccharide. As might have been anticipated, reactions of sucrose with phosgene–pyridine, ethylene dichloroformate–sodium hydroxide, and diphenyl carbonate–sodium hydrogen carbonate led to intermolecular bridges with the direct formation of polymers—the poly(sucrose carbonates).[10] Treatment of sucrose with ethyl chloroformate–aqueous alkali, a procedure introduced by Allpress and Haworth[11] for monosaccharides, yielded an approximately tri-substituted *O*-ethoxycarbonyl sucrose (5), which on heating *in vacuo* polymerized,

[8] A. I. Bakal, 1984, U.S. Patent 4 459 316.
[9] J. Defaye, H. Driguez, S. Poncet, R. Chambert, and M.-F. Petit-Glatron, *Carbohydr. Res.*, 1984, **130**, 299.
[10] R. S. Theobald, *J. Chem. Soc.*, 1961, 5359, 5365, 5370; L. Hough, J. E. Priddle, and R. S. Theobald, *Adv. Carbohydr. Chem.*, 1960, **15**, 91.
[11] C. F. Allpress and W. N. Haworth, *J. Chem. Soc.*, 1924, **125**, 1223.

with the elimination of diethyl carbonate and ethanol, to form thermosetting resins by the formation of a network of inter-linked carbonate bridges (6). The acid-



sensitive glucosidic linkage of sucrose was considerably stabilized by the presence of *O*-alkoxycarbonyl groups, even a small number, and penta- and octa-*O*-ethoxycarbonyl sucroses were not significantly hydrolysed by N-HCl. In exploiting the subtle differences in the reactivity of the eight hydroxy-groups of sucrose to produce partially substituted derivatives, it was recognized that whilst a large number of isomers are theoretically possible (Table 1) the preferential reactivity of

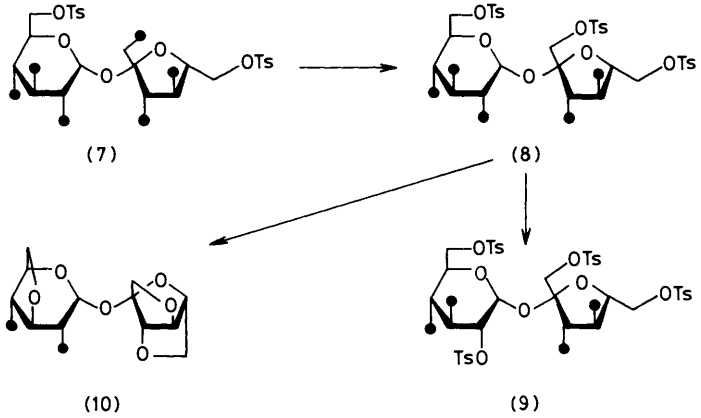
Table 1 *Number of isomers of sucrose derivatives*

Mono	8	Penta	56
Di	28	Hexa	28
Tri	56	Hepta	8
Tetra	70	Octa	1

the primary hydroxy-groups could simplify these apparently complex reactions. Thus etherification of sucrose with trityl chloride in pyridine [3,12] afforded the 6,1′,6′-tri-*O*-tritylate and 6,6′-di-*O*-tritylate as major products with the 6,1′- and 1′,6′-di-*O*-tritylates as minor products, indicating that the 1′-OH is less reactive than the other primary 6- and 6′-hydroxy-groups, presumably due to its neopentyl character. A similar order of reactivity was observed on trimolar-tosylation of sucrose in pyridine, yielding after chromatography a crystalline 6,6′-di-*O*-tosylate (7),[13,14] a mixed tri-*O*-tosylate [13,15,16] and a little of the 2,6,1′,6′-tetra-*O*-tosylate (9).[17] Detailed studies revealed that the 'tri'-fraction contained predominantly the 6,1′,6′-tri-*O*-tosylate (8), but containing some 2,6,6′-tri-*O*-tosylate,[16] thereby suggesting

[12] R. Khan, *Pure Appl. Chem.*, 1984, **56**, 833.
[13] R. U. Lemieux and J. P. Barrette, *Can. J. Chem.*, 1960, **38**, 656.
[14] C. H. Bolton, L. Hough, and R. Khan, *Carbohydr. Res.*, 1972, **21**, 133.
[15] P. D. Bragg and J. K. N. Jones, *Can. J. Chem.*, 1959, **37**, 575.
[16] D. H. Ball, F. H. Bissett, and R. C. Chalk, *Carbohydr. Res.*, 1977, **55**, 149.
[17] J. M. Ballard, L. Hough, S. P. Phadnis, and A. C. Richardson, *Carbohydr. Res.*, 1980, **83**, 138.

the order of reactivity as HO-6, HO-6′ > HO-1′ > HO-2. In accord with studies in the monosaccharide field, sodium methoxide converted the 6,6′-di-*O*-tosylate (7) into 3,6:3′,6′-dianhydro-sucrose by participation of the 3- and 3′-hydroxy-groups in the intra-bimolecular substitution of the 6- and 6′-sulphonyloxy substituents. Likewise, the 6,1′,6′-tri-*O*-tosylate (8) afforded the 3,6:1′,4′:3′,6′-trianhydride (10),[16,18,19] and not, as suggested on previous evidence,[13] the 3,6:2,1′:3′,6′-trianhydride.

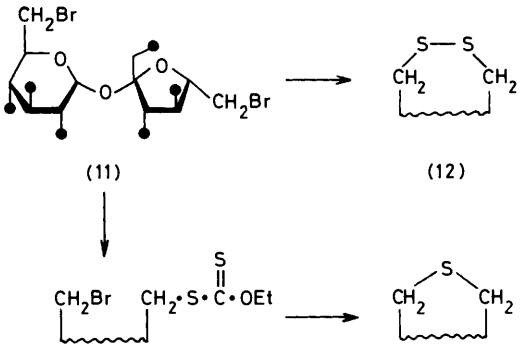


(7) (8) (10) (9)

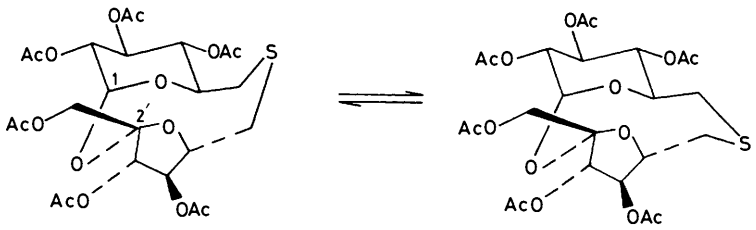
The availability of these primary sulphonate esters enabled the selective synthesis by nucleophilic substitution reactions of a range of mono-, di-, and tri-substituted derivatives of sucrose including azido-,[20] amino,[20–22] halogeno-,[23] thio-, deoxy-, and unsaturated derivatives.[14,24] Greater selectivity during sulphonation was noted using the more bulky 2,4,6-trimethylbenzene (mesitylene or 'trimsyl') sulphonyl chloride[25,26] and 2,4,6-tri-isopropylbenzene ('tripsyl') sulphonyl chloride,[27] which had the additional advantage that they gave the 6,1′,6′-tri-*O*-sulphonate esters directly, without recourse to chromatography, and in >50% yield. Later studies showed that chloro- and bromo-derivatives could be utilized as alternative substrates to the sulphonate esters, often with advantage because of their ready availability.[28] Thus, selective bromination of sucrose with carbon tetrabromide–triphenylphosphine in pyridine gives in >90% yield the 6,6′-dibromide (11), which can be used in the form of its hexa-acetate for a series of displacement reactions, in particular to achieve an original objective of bridging the

[18] R. Khan, *Carbohydr. Res.*, 1972, **22**, 441.
[19] N. W. Isaacs, C. H. L. Kennard, G. W. O'Donnell, and G. N. Richards, *Chem. Commun.*, 1970, 260.
[20] L. Hough and K. S. Mufti, *Carbohyd. Res.*, 1973, **29**, 291.
[21] R. Khan, K. S. Mufti, and M. R. Jenner, *Carbohydr. Res.*, 1973, **30**, 183.
[22] T. Suami, T. Ikeda, S. Nishiyama, and R. Adachi, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1953.
[23] L. Hough, in 'Sucrochemistry', ed. J. L. Hickson, A.C.S. Symposium Series No. 41, 1977, p. 9.
[24] R. Khan and M. R. Jenner, *Carbohydr. Res.*, 1976, **48**, 306.
[25] S. E. Creasey and R. D. Guthrie, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1373.
[26] L. Hough, S. P. Phadnis, and E. Tarelli, *Carbohydr. Res.*, 1975, **44**, C12.
[27] R. G. Almquist and E. J. Reist, *J. Carbohydr., Nucleosides, Nucleotides*, 1976, **3**, 261; *Carbohydr. Res.*, 1976, **46**, 33.
[28] R. Khan, C. L. Bhardwaj, K. S. Mufti, and M. R. Jenner, *Carbohydr. Res.*, 1980, **78**, 185.

6,6′-positions.[29] When thiourea reacted with the 6,6′-dibromide (11) it gave the 6,6′-dithiouronium salts, which on treatment with sodium metabisulphite were transformed into the 6,6′-disulphide (12) containing an 11-membered ring. Likewise, the 6,6′-dibromide (11) reacted with potassium *O*-ethyl dithiocarbonate to give the 6,6′-sulphide (14),[29] and not the expected 6,6′-bis(dithiocarbonate): the cyclization probably proceeds *via* the mono-bromo mono-(dithiocarbonate) (13). The 10-membered ring in the crystalline 6,6′-sulphide (14) was shown by *X*-ray



analysis[30] to have a boat:chair:chair conformation (14a) with the sulphur *exo* to the ring-oxygen (attached to C-1 and C-2′). In solution, ^{1}H-n.m.r. spectra of the 6,6′-sulphide (14a) were consistent with conformational equilibration with a boat:chair:chair conformation (14b) due to the movement of the sulphur atom from *exo*- to *endo*-positions.[29]

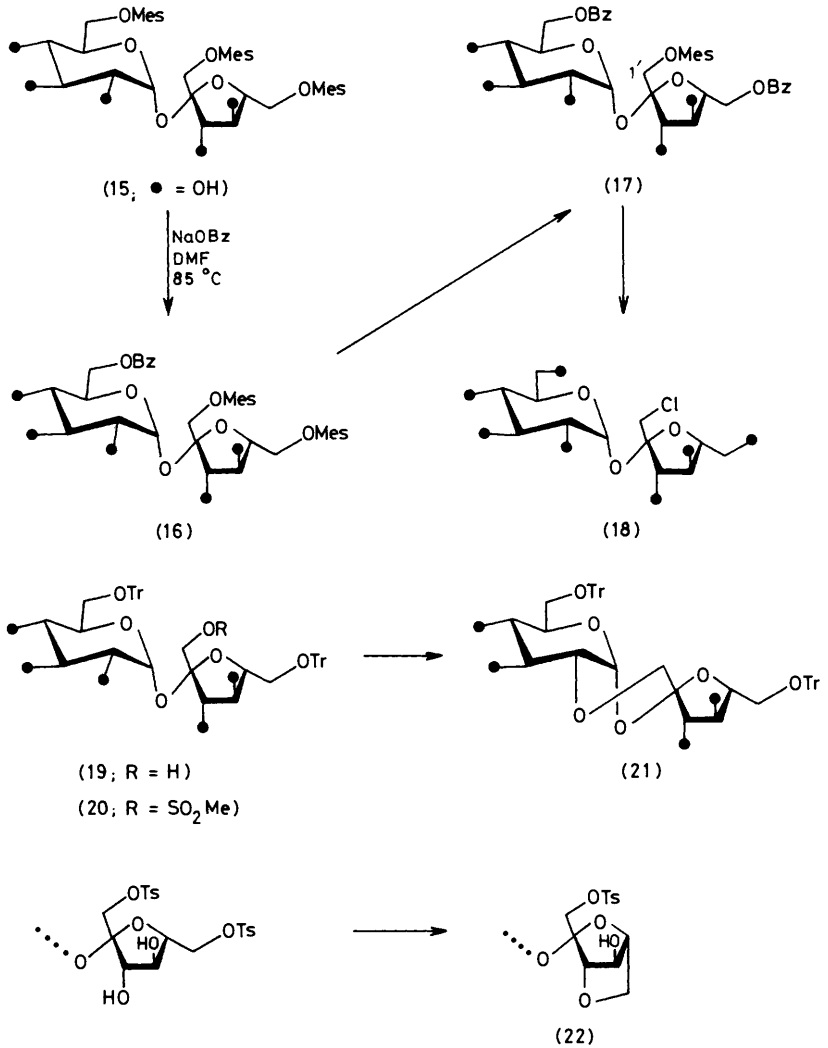


(14a) (14b)

An entry into the 1′,6′- and 1′-derivatives of sucrose was gained from a careful study[31] of the nucleophilic substitution of the sulphonyloxy substituents in the

[29] L. V. Sincharoenkul, Ph.D. Thesis, University of London, 1981.
[30] M. G. B. Drew, University of Reading, unpublished results.
[31] M. R. Gurjar, Ph.D. Thesis, University of London, 1980.

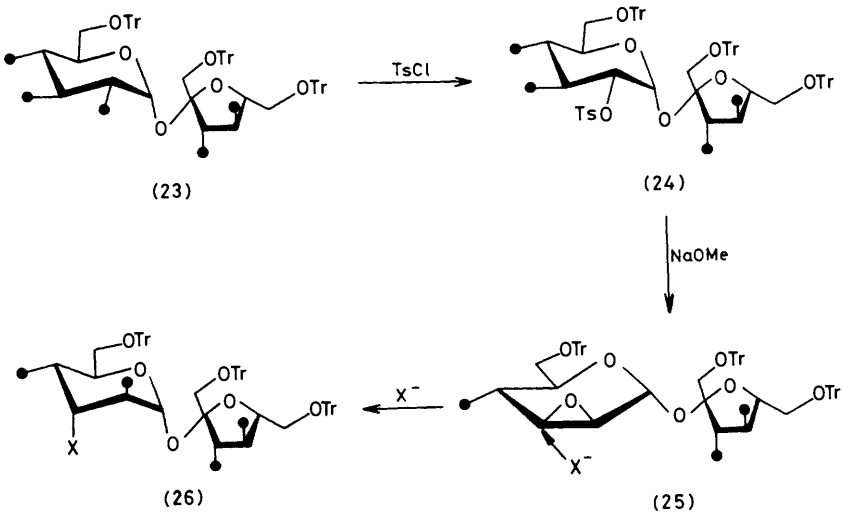
6,1′,6-tri-*O*-trimsylate (15), which with sodium benzoate progressed from the initial 6-*O*-benzoate (16) to the 6,6′-di-*O*-benzoate (17). Replacement of the trimsyloxy substituents in (16) and (17) by a variety of nucleophiles then gave 1′,6′-and 1′-derivatives of sucrose. Using this approach, Guthrie and Watters[32] synthesized 1′-chloro-1′-deoxy-sucrose (18), which was not hydrolysed by the enzyme invertase, a fructofuranosidase, and was more stable to acidic hydrolysis, the rate of hydrolysis being 10 times slower than that of sucrose. An alternate route to the 1′-derivatives is



[32] R. D. Guthrie and J. J. Watters, *Aust. J. Chem.*, 1980, **33**, 2487.

via the 6,6′-di-trityl ether (19), which by selective reaction affords the 1′-sulphonate ester (20). Unlike the 6,1′,6′-tri-*O*-tosylate (8), the 1′-tosylate (20) was transformed, somewhat surprisingly, into the 2,1′-anhydride (21),[33] the ring system being of the strainless *cis*-decalin type. After de-tritylation this bridged derivative of sucrose was tasteless, suggesting the involvement of the 2-and/or 1′-positions in the sweetness template. The difference in the cyclization of the 1′,6′-disulphonate (8) has been attributed to the prior formation of the 3′,6′-anhydro ring (22) from the latter which brings the 4′-OH and the 1′-sulphonate into close proximity, thereby giving the 1′,4′-anhydro ring (10) in preference to the 2,1′-anhydride (21).

The isolation of the 2,6,1′,6′-tetratosylate (9) suggested that if the primary hydroxy-groups are protected, as in the 6,1′,6′-tritrityl ether (23), the 2-OH would then be preferentially esterified, as confirmed by the isolation of the 2-tosylate (24).[31] As anticipated, the 2,3-anhydro-D-*manno*-derivative (25) was obtained by the action of sodium methoxide upon the 2-tosylate (24) and subsequent ring-opening occurred exclusively at the 3-position to give after de-tritylation D-*allo*-sucrose, a non-sweet compound, and its 3-derivatives (26). Modifications at

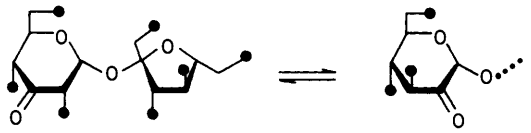


HO-2 and HO-3 can also be achieved by oxidation using both biochemical and chemical oxidants; thus 3-ketosucrose (27)[34] was isolated from the culture medium of *Agrobacterium tumefaciens* and subsequent reduction with sodium borohydride gave D-*allo*-sucrose (28) and sucrose in the ratio 12:1. D-*allo*-Sucrose (28) was more readily obtained by oxidation of sucrose with dimethyl sulphoxide–acetic anhydride, then reduction *in situ* followed by fractionation on a Dowex 50 × 8

[33] A. K. B. Chiu, M. K. Gurjar, L. Hough, L. V. Sincharoenkul, and A. C. Richardson, *Carbohydr. Res.*, 1982, **100**, 247.

[34] L. Hough and E. O'Brien, *Carbohydr. Res.*, 1980, **984**, 95.

(Ca^{2+}) resin which complexes with the axial–equatorial–axial triol at C-2, C-3, and C-4. 2-Ketosucrose (29)[35] arises from the enolization of 3-ketosucrose (27) and reduction of both keto-derivatives with sodium borodeuteride afforded, after chromatographic separation, [2-^{2}H]sucrose and [3-^{2}H]sucrose respectively, thereby enabling the C-2 and C-3 signals of the ^{13}C-n.m.r. spectrum of sucrose[36] to be confirmed.



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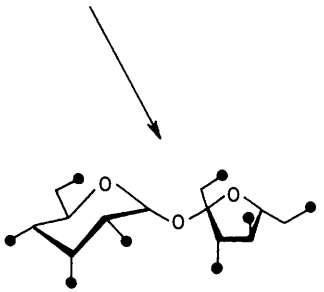
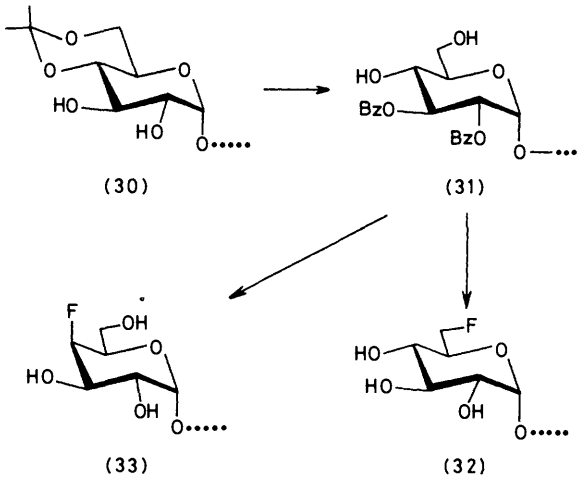


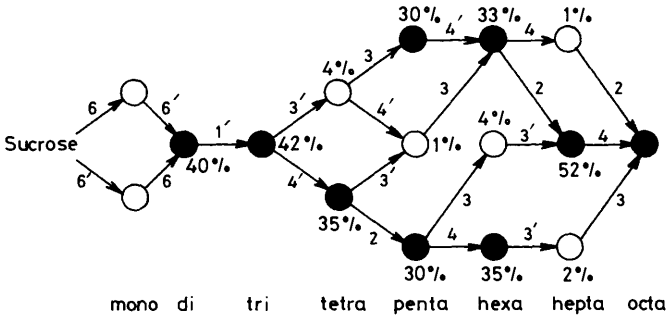
(28)

Modifications at C-4 of sucrose were achieved *via* the elusive 4,6-acetal derivatives, *e.g.* (30), which were first prepared in 1974 by Khan,[37] despite many previous attempts. Reaction of sucrose with 2,2-dimethoxypropane in *N,N*-dimethyl formamide (DMF) with tosic acid as catalyst, gave 2,1′:4,6-di-*O*-isopropylidene sucrose (55%), another bridged derivative, and the 4,6-*O*-isopropylidene derivative (30).[38] The latter (30) was obtained in higher yield (65%) using methyl isoprenyl ether (2-methoxypropene) from which 2,3,1′,3′,4′,6′-hexa-*O*-benzyl-sucrose (31) was obtained and thence its 4,6-dimesylate.[39] Selective displacements of this 4,6-sulphonate ester with fluoride anion (from tetrabutylammonium fluoride), in interplay with benzoate anion, then afforded 6-deoxy-6-fluorosucrose (32), 6 deoxy-6-fluoro- and 4-deoxy-4-fluoro-*galacto*-sucrose (33), and 4,6-dideoxy-4,6-difluoro-sucrose and -galacto-sucrose.[40] Pivaloylation of sucrose[41] is a novel and potentially valuable route to specifically blocked esters

[35] L. Hough and E. O'Brien, *Carbohydr. Res.*, 1981, **92**, 314.
[36] L. Hough, S. P. Phadnis, E. Tarelli, and R. Price, *Carbohydr. Res.*, 1976, **47**, 151.
[37] R. Khan, *Carbohydr. Res.*, 1974, **32**, 375.
[38] R. Khan and R. S. Mufti, *Carbohydr. Res.*, 1975, **43**, 247.
[39] L. Hough, A. K. M. S. Kabir, and A. C. Richardson, *Carbohydr. Res.*, 1984, **125**, 247.
[40] L. Hough, A. K. M. S. Kabir, and A. C. Richardson, *Carbohydr. Res.*, 1984, **131**, 335.
[41] L. Hough, M. S. Chowdhary, and A. C. Richardson, *J. Chem. Soc., Chem. Commun.*, 1978, 664.

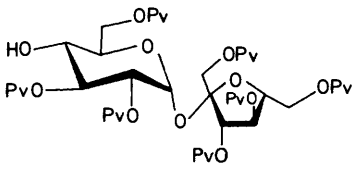
(Scheme 1) using pivaloyl chloride (2,2-dimethylpropanoyl chloride), a reagent that was originally exploited for the synthesis of 5′-esters of nucleosides. Thus a heptapivalate (34) with only one hydroxy-group free at C-4 was isolated directly in 45% yield and then converted into *galacto*-sucrose (35), its 4-chloro derivative (36), and 4-ketosucrose (37).[41–43] The lack of sweetness in *galacto*-sucrose (35) is of considerable interest since it implicates the 4-position in the sweetness template.[44] The hexapivalates with free hydroxy-groups at C-3 and C-3′, and at C-3 and C-4′ are of value since they provide an entry to modifications in the fructofuranose ring, for example *via* the 3′,4′-epoxides. In an alternative approach, selective de-esterification of sucrose octa-acetate on an alumina column yields a hepta-acetate





Scheme

[42] A. K. B. Chiu, Ph.D. Thesis, University of London, 1983.
[43] R. Khan, *Carbohyd. Res.*, 1972, **25**, 232.
[44] M. J. Lindley, G. G. Birch, and R. Khan, *J. Sci. Food. Agric.*, 1976, **216**, 480.



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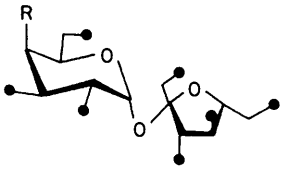
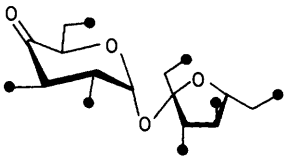


(35; R = OH)

(36; R = Cl)

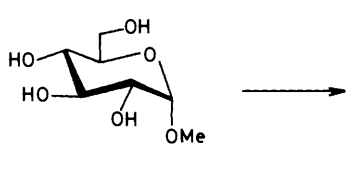


(37)

in 9% yield, in which the 6′-hydroxy-group is free, thus making the 6′-chloride and 6′-deoxy derivative available.[45]

The direct replacement of hydroxy-groups by chloride, *via* their chlorosulphate intermediates, was first observed by Helferich in 1921,[46] and extended by Jones *et al.*[47,48] forty years later, for example by the characterization of the product from methyl α-D-glucopyranoside (38) as methyl 4,6-dichloro-4,6-dideoxy-2,3-sulpho-α-D-galactopyranoside (39) wherein the reaction was characterized by inversion of chirality at C-4 (*gluco* ⟶ *galacto*). Residual chlorosulphate groups in the reaction products are readily removed by treatment of sodium iodide in methanol. Application of this multi-centred reaction to sucrose was expected to give the same pattern of derivatization in the D-glucopyranosyl ring of sucrose, together with the introduction of new substituents in the fructofuranoside ring. Initial experiments confirmed these generalizations and gave rise to a complex mixture of products[49] from which three derivatives were isolated, differing only in the furanose ring which was observed to contain a 3′,4′-epoxide (40), a 3′-ene (41), or a 1′,4′,6′-trichloride (42).[50] The reaction can be controlled to avoid cyclic sulphate formation by reaction at low temperatures, adjusting the ratio of sulphuryl chloride to pyridine and dilution of the reaction with chloroform. The reaction of sulphuryl chloride with sucrose was observed to give the 6′-chloride [43%; (43)] and then proceed progressively *via* the 6,6′-dichloride [29%; (44)][50] to the 4,6,6′-trichloro- [50%;

[45] J. M. Ballard, L. Hough, and A. C. Richardson, *Carbohydr. Res.*, 1974, **34**, 184.
[46] B. Helferich, *Ber.*, 1921, **54**, 1082.
[47] J. K. N. Jones, M. B. Perry, and J. C. Turner, *Can. J. Chem.*, 1960, **38**, 1122.
[48] A. G. Cottrell, E. Buncel, and J. K. N. Jones, *Can. J. Chem.*, 1959, **37**, 1412.
[49] P. D. Bragg, J. K. N. Jones, and J. C. Turner, *Can. J. Chem.*, 1959, **37**, 1412.
[50] J. M. Ballard, L. Hough, A. C. Richardson, and P. H. Fairclough, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1524.



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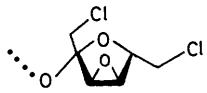

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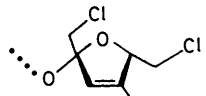

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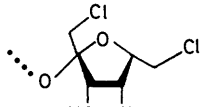
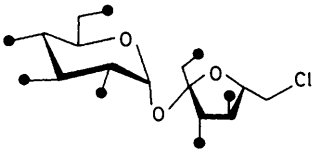


(42)

(45)][51,52] and 4,6,1′,6′-tetrachloro-[40%; (46)][53] derivatives of *galacto*-sucrose, suggesting a sequence of stereoselective reactions where the order of reactivity HO-6′ > HO-6 > HO-4 > ,HO-1′,HO-4′. It is noteworthy that the 4-OH reacts more readily than the hindered but primary 1′-OH. The 6,6′-dichloride (44) can be more conveniently prepared in higher yield (>70%) by reaction of sucrose with triphenylphosphine and carbon tetrachloride in pyridine.[54] Under more forcing



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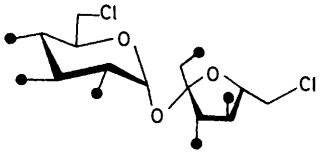

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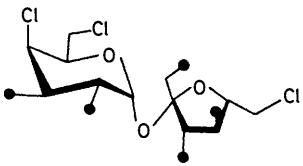

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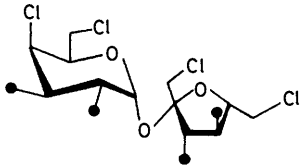
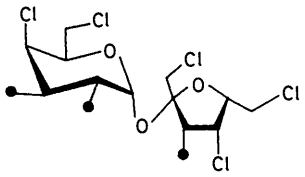


(46)

[51] L. Hough, S. P. Phadnis, and E. Tarelli, *Carbohydr. Res.*, 1975, **44**, 37.
[52] H. Parolis, *Carbohydr. Res.*, 1976, **48**, 132.
[53] C. K. Lee and M. R. Jenner, unpublished results.
[54] A. K. M. Anisuzzaman and R. L. Whistler, *Carbohydr. Res.*, 1980, **78**, 185; 1978, **61**, 511.

conditions, sulphuryl chloride reacts with sucrose to give the 4,6,1′,4′,6′-pentachloride (47) which on treatment with base is transformed, in common with other chloro-sucroses, into an anhydro derivative, in this case a 3,6;3′,6′; 2,1′-trianhydro derivative (48).[55] The 6,1′,6′-trichloride (49) was synthesized from the



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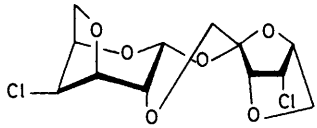

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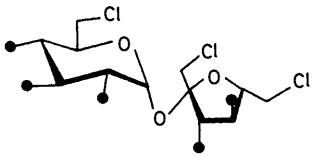

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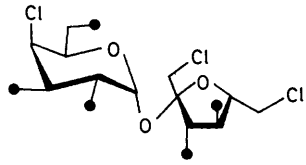


(50)

6,1 ,6 -trimesitylene sulphonate (15) by substitution with lithium chloride and as anticipated it reacted with sulphuryl chloride to give the 4,6,1′,6′-tetrachloride of *galacto*-sucrose [(46) 'serendipitose'].[56] Serendipity then played a part when Phadnis[56] tasted this compound for the reasons that *galacto*-sucrose (35) was not sweet whereas 4,6,4′,6′-tetrachloro-4,6,4′,6′-tetradeoxy-*galacto*-trehalose was as

Table 2 *Relative sweetness of chloro-sucroses*[3,62]

Sugar	*Relative Sweetness*
Sucrose	1
1′-Chloro-1′-deoxysucrose (18)	20
4-Chloro-4-deoxy-*galacto*-sucrose (36)	5
6-Chloro-6-deoxysucrose	bitter
6′-Chloro-6′-deoxysucrose (43)	20
4,1′-Dichloro-4,1′-dideoxy-*galacto*-sucrose	120
1′,6′-Dichloro-1′,6′-dideoxysucrose	76
6,6′-Dichloro-6,6′-dideoxysucrose (44)	not sweet
4,1′,6′-Trichloro-4,1′,6′-trideoxy-*galacto*-sucrose (50)	650
4,6,1′,6′-Tetrachloro-4,6,1′,6′-tetradeoxy-*galacto*-sucrose (46)	200
4,1′,4′,6′-Tetrachloro-4,1′,4′,6′-tetradeoxy-*galacto*-sucrose[71] (59)	2 200

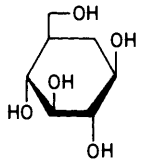
[55] S. P. Phadnis, unpublished results.
[56] L. Hough and S. P. Phadnis, *Nature* (*London*), 1976, **263**, 800.

bitter as quinine,[57] and a sample of (46) required for 'testing' was misinterpreted as 'tasting'. Against all predictions, the tetrachloride (46) proved to be several hundred times sweeter than sucrose[56] (Table 2). Clearly the 4-position of sucrose plays an important role in the enhancement of its sweetness,[3] coupled with the increased lipophilicity of the molecule. This behaviour was difficult to predict since there was no precedent in carbohydrate chemistry. Indeed, modification usually results in a loss of sweetness,[58] as in sucrose mono-acetate,[59] or even bitterness as in the benzoates,[60,61] and sucrose octa-acetate, a natural bitter principle of *Clematis japonica*, is a well known denaturant.

A large number of chloro derivatives, ranging from mono- to penta-chloro substituents, were then synthesized from sucrose in order to investigate the structure–activity relationships.[62,63] The 4,1 ,6 -trichloro-4,1 ,6 -trideoxy-*galacto*-sucrose (50) emerged as the sweetest compound at this stage (Table 2). This trichloride (50) is synthesized[64] from the penta-acetate of the 6,1 ,6 -tri-*O*-trityl ether (23) which on de-tritylation undergoes a 4 ⟶ 6 acetyl migration *via* the 4,6-orthoacetate to yield the 2,3,6,3′,4′-penta-acetate. Clearly chloro substituents at C-4, C-1 , or C-6′ induce extra sweetness in *galacto*-sucrose, whereas substitution is disadvantageous at C-6, and a combination of two of the favourable substituents is synergistic and raises the sweetness by an order of magnitude, whilst the combination of all three gives intense sweetness, 600 × sucrose (Table 2).[62,63] The replacement of the 1′-OH by chloride appears to be a key factor in the intensification phenomena. The 4,1′,6′-trichloride (50) and 4,6,1′6′-tetrachloride (46) are resistant to hydrolysis by α-galactosidase and β-fructofuranosidase ('invertase') and more resistant to acid hydrolysis than sucrose.[3,56,63] The favourable properties of the trichloride (50), especially its low toxicity, have singled it out for development as a high intensity sweetener that is non-nutritive, non-cariogenic, and safe for human use.

Our interest in sweetness had been aroused, so we examined the sweetness property of sucrose in terms of its structure and that of related compounds. Methyl α-D-glucopyranoside (38) is only 1/10th as sweet as sucrose whilst methyl β-D-fructofuranoside is tasteless, hence it was logical to suggest that hydroxy-groups on both the fructose and glucose components of sucrose act in harmony to initiate the sweet response.[62] The ring oxygens can be discounted since *pseudo*-glucose (51)[65] and *pseudo*-fructose[66] are equisweet with glucose and fructose respectively. Sweetness is induced by a wide variety of chemical structures (Table 3) but

[57] G. G. Birch, *Olfaction and Taste VI*, 1977, 27.
[58] G. G. Birch and C. K. Lee, *J. Food. Sci.*, 1976, **41**, 1403.
[59] O. K. Konenko and I. L. Kestenbaum, *J. Appl. Chem.*, 1961, **11**, 7.
[60] D. M. Clode, N. A. Laurie, D. McHale, and J. B. Sheridan, *Carbohydr. Res.*, 1985, **139**, 147, 161.
[61] D. M. Clode, D. McHale, J. B. Sheridan, G. G. Birch, and E. B. Rathbone, *Carbohydr. Res.*, 1985, **139**, 141.
[62] L. Hough and R. Khan, *Trends Biochem. Sci.*, 1978, **3**, 61.
[63] L. Hough, S. P. Phadnis, R. Khan, and M. R. Jenner, 1979, British Patents 1 543 167; 1 543 168.
[64] P. H. Fairclough, L. Hough, and A. C. Richardson, *Carbohydr. Res.*, 1975, **40**, 285.
[65] T. Suami, S. Ogawa, and T. Toyokuni, *Chem. Lett.* (*Japan*), 1983, 611.
[66] T. Suami, S. Ogawa, M. Takata, K. Yasuda, A. Suga, K. Takei, and Y. Uematsu, *Chem. Lett.* (*Japan*), 1985.



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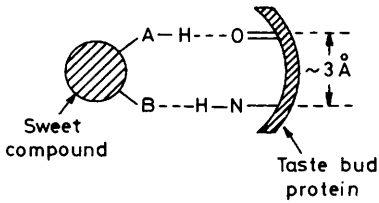

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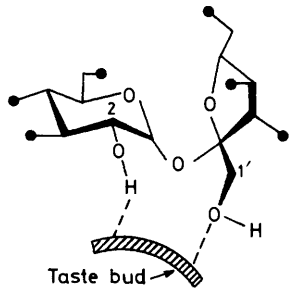


(53)

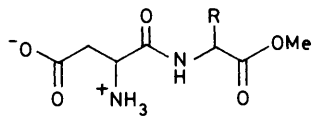
Shallenberger and Acree[67] noted a common feature of two electronegative atoms, A and B, separated by 2.5—4.0Å, with an hydrogen atom covalently linked to A, thus giving an AH,B system (52). They postulated an interaction of the AH,B system with a similar system (–NH–CO–) on the proteinaceous, cell membrane receptor of the tongue. Application of this theory to sucrose, coupled with the behaviour of the chloro-sucroses led to the suggestion that the AH,B is situated at the 2-OH and the oxygen of the 1′-OH respectively (53), and the latter can be replaced by a chloro group with intensification of the sweet response.[62] The AH,B theory was clearly inadequate since many organic compounds with this requirement were not sweet. In 1976, Kier[68] extended the theory from a study of a series sweet 1-alkoxy-2-amino-4-nitrobenzenes by introducing the concept of a binding site X, that is hydrophobic (lipophilic) in nature and located 3.5 A and A and 5.5 A from B to give an AH,B,X triangle. Two such triangles were recognized in the sweet 4,1 ,6 -trichloride (50), involving lipophilic groups on the upper face of the molecule at the axial C-4 and C-6′ respectively, which bind the molecule to the receptor [(54) and (55)]. The adverse effect of the 6-chloro group could be due[62] to its competition for the dispersive locking site on the receptor resulting in a misfit of the AH,B at C-2,C-1 . It is significant that the immunoassay for the sweet protein thaumatin ('Talin') also reponds to other high intensity sweeteners, including the chloro-sucroses, and a direct relationship was observed between the immunoassay

[67] R. S. Shallenberger and T. E. Acree, *Nature* (*London*), 1976, **216**, 480.
[68] L. B. Kier, *J. Pharm. Sci.*, 1976, **61**, 1394.

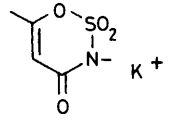
and the sweetness response, thereby suggesting a common glucophore.[69] The AH,B,X tripartite theory will undoubtedly be further refined, taking into account a trio of physical parameters, lipophilicity, electron distribution, and molecular conformation in exploring the structure–activity relationships in conjunction with the associated neuro-physiological mechanisms.

Table 3 *Relative sweetness of organic substances (sucrose = 1)*

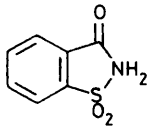
Cyclamate (sodium cyclohexylsulphamate)	30—80
Glycyrrhizin	50
L-Aspartyl-L-phenylalanine methyl ester (Aspartame)	100—200
Acesulfam-K	150
6-Chlorosaccharin	100—350
Sodium saccharin	200—700
Stevioside	300
4,1′,6′-trichloro-*galacto*-sucrose (50)	650
Neohesperidin dihydrochalcone	2 000
1-n-Propoxy-2-amino-4-nitrobenzene	4 000
Thaumatin (Talin) (Al^{3+})	3—4 000
D-Tryptophan	35
6-Chloro-D-tryptophan	1 000
Fenchyl derivative of aspartame (methyl fenchyl L-aspartylaminomalonate)	25 000



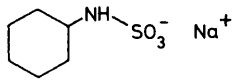
ASPARTAME (R = CH_2Ph)



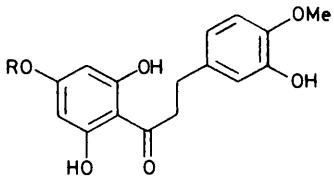
ACESULFAM-K



SACCHARIN

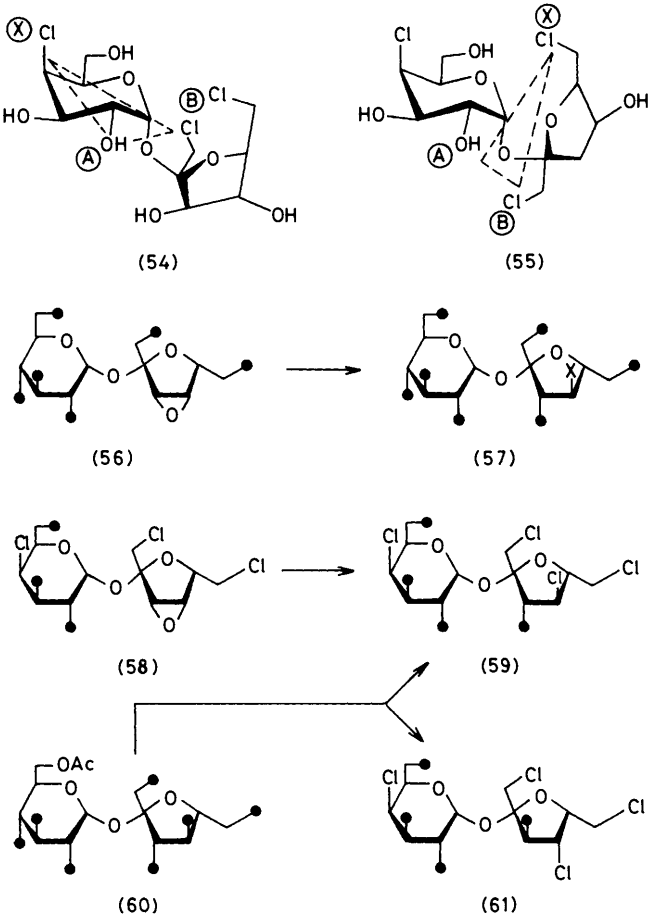


CYCLAMATE



NEOHESPERIDIN DIHYDROCHALCONE

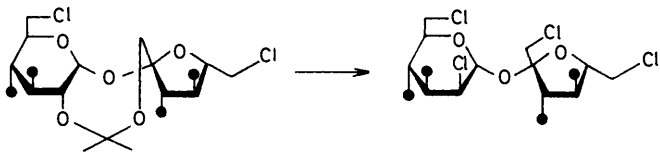
Derivatization at C-3′ and C-4′ of sucrose has led to an interesting group of compounds. Guthrie *et al.*[70] synthesized the 3′,4′-*lyxo*-epoxide (56) directly from sucrose in 42% yield by the agency of triphenylphosphine–diethylazodicarboxylate and incorporating acetic acid to prevent 3,6- and 1′,4′-anhydro formation. When the primary positions were protected, as in the 6,1′,6′-tri-*O*-tritylate (23) and the 4,6;2,1′-*O*-isopropylidene derivative, the corresponding 3′,4′-*lyxo*-epoxides were obtained in >80% yield.[12] Ring-opening of these epoxides with various nucleophiles occurred exclusively at the 4′-position (57), thus reverting back to the fructofuranose configuration.[12] When the 3′,4′-*lyxo*-epoxide (58) derived from 4,1′,6′-trichloro-4,1′,6′-trideoxy-*galacto*-sucrose (50), was opened with lithium chloride in DMF, it gave the 4,1′,4′,6′-tetrachloride (59), which on tasting proved to



[69] C. A. M. Hough and J. A. Edwardson, *Nature* (*London*), 1978, **271**, 381.
[70] R. D. Guthrie, I. D. Jenkins, S. Thang, and R. Yamaski, *Carbohydr. Res.*, 1980, **85**, C5; 1983, **121**, 109.

2200 times sweeter than sucrose (Table 2), the introduction of a 4′-chloro group having quadrupled the sweetness of its precursor (50).[71] The 4,1′,4′,6′-tetrachloride (59) was also isolated[71] as a minor component from the reaction of sucrose 6-acetate (60) with sulphuryl chloride, the major component being the *sorbo*-isomer (61), and they probably arise from the opening of the corresponding 3′,4′-*lyxo*- and *ribo*-epoxides. Another tetrachloride, namely the 2,6,1′,6′-tetrachloro-2,6,1′,6-tetradeoxy-*manno*-sucrose (63) was synthesized[72] from the 6,6′-dichloro-2,1′-isopropylidene derivative (62), and it proved to be as bitter as quinine, thus supporting the view that an equatorial 2-OH is essential for sweetness.

The fructofuranose ring of sucrose can be expanded to a pyranoside by selective oxidation with lead tetra-acetate[73] to give the dialdehyde (64) which can then be cyclized by condensation with nitromethane to give the 4′-nitro-4′-deoxy-β-D-glucoheptulopyranoside (65), and thence to 4′-amino and 4′-acetamido derivatives,[74,75] Extension of these reactions to the tetra-aldehyde (66), produced by oxidation of sucrose with periodate, gave the 3-nitro-3-deoxy-α-D-glucopyranosyl 4 -nitro-4′-deoxy-β-D-heptulopyranoside (67) as the major product.[75]



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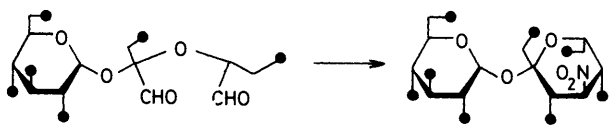

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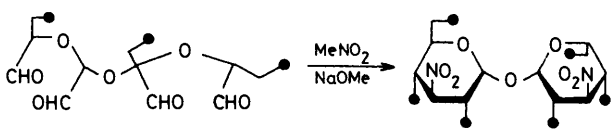

(66) (67)

[71] C. K. Lee, 1982, U.K. Patent 2 088 855A.
[72] R. A. Khan and M. R. Jenner, 1980, U.K. Patent 2 037 561A.
[73] A. K. Mitra and A. S. Perlin, *Can. J. Chem.*, 1959, **37**, 2047.
[74] H. H. Baer and A. Ahammed, *Can. J. Chem.*, 1966, **44**, 2893.
[75] L. Hough, K. J. Hale, and A. C. Richardson, unpublished results.

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