AN ISOPROPYLIDENE DERIVATIVE OF THE BISULPHITE ADDUCT OF D-GLUCOSE

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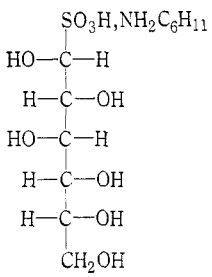
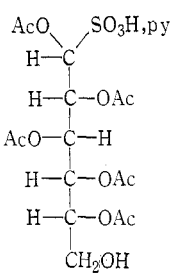
[Manuscript received March 27, 1969]

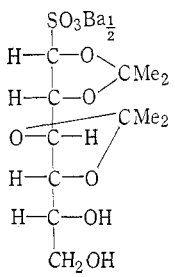
Evidence for the existence of bisulphite adducts† of glucose was first described in 1904;[1] crystalline examples were isolated in 1953 [2] and in 1959;[3] and recently chemical derivatives were prepared for the first time and the acyclic structure assigned to the adducts was demonstrated conclusively. Thus, acetylation of the adduct (I) of glucose and cyclohexylamine bisulphite gave[4] the water-soluble acetate of the sulphonic acid (II).



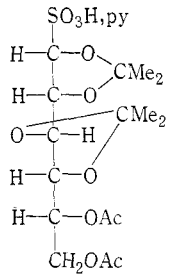
(I)



(II)



(III)



(IV)

When Braverman[2] reported the isolation of the crystalline adduct of glucose and sodium bisulphite, he also claimed the preparation of a mono-condensation product of acetone with the adduct. However, in contrast to the usual procedure for the preparation of isopropylidene derivatives of sugars Braverman *added* water to this reaction mixture. Our attempts to repeat this aspect of Braverman's work have been unsuccessful: the adduct itself is partly hydrolysed in acetone–water mixtures and it seems likely that Braverman isolated a mixture of the sodium bisulphite adducts of both glucose and acetone.

However, when the cyclohexylamine salt of the adduct (I) was stirred at 25° in dry acetone containing concentrated sulphuric acid, complete solution occurred in about 1 hr. After 3–4 hr the reaction mixture was neutralized with ammonium carbonate and worked up as described below to yield the crystalline di-*O*-isopropylidene derivative (III).

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† I am indebted to a referee who pointed out that Wachtel (*Öst. Zuckerzeitschr.*, 1877, 340) obtained the sodium bisulphite adduct of glucose by warming the reagents together under pressure.

[1] Kerp, W., *Arb. K. GesundhAmt.*, 1904, **21**, 236.

[2] Braverman, J. B. S., *J. Sci. Fd Agric.*, 1953, **4**, 540.

[3] Ingles, D. L., *Aust. J. Chem.*, 1959, **12**, 97 and 275.

[4] Ingles, D. L., *Chemy Ind.*, 1969, 50.

That the two hydroxyl groups at C 5 and C 6 were free was shown by periodate oxidation. One mole of the compound consumed 1 mole of periodate and liberated 1 mole of formaldehyde. A crystalline diacetate (IV) was also obtained by applying the acetylation procedure used previously.[4] When (III) was treated with barium hydroxide, no sulphite was liberated even at 100°. Thus the hydroxyl group at C 1 must be involved in an acetal link since the latter is stable to alkali. This behaviour contrasts with that of (II) since even cold barium hydroxide hydrolysed the acetate ester group at C 1 of (II), liberating sulphite.

It is not certain, however, that the 1,2 : 3,4 diacetal linkages shown in (III) are correct. Other arrangements, e.g. 1,3 : 2,4 etc., are possible but are considered less likely since acetone usually condenses to form a five- rather than a six-membered ring under these conditions.[5]

The configurations at C 1 in (II), (III), and (IV) are not known and remain to be elucidated.

Under the acid conditions of the Monier-Williams method[6] for the estimation of sulphur dioxide, both (II) and (III) released sulphur dioxide quantitatively within 60 and 18 min respectively, at 100°. This result indicates that the acetal linkage in (III) was more readily ruptured by acid than the acetate link at C 1 of (II), leading in both cases eventually to the hydroxy sulphonic acids which are unstable. Conversely, as already discussed, (III) was stable to alkali whereas (II) was readily hydrolysed.

The derivatives (II) and (III) appear to have valuable potential as food additives in cases where sulphur dioxide is used to enhance the stability and storage life of a particular food. Both compounds release sulphur dioxide at rates which will vary with the pH and perhaps other conditions in a food. The adducts have not been tested for toxicity but all the breakdown products are relatively non-toxic. Thus, for example, the sodium salt of (II) is hydrolysed to glucose, acetic acid, and sodium bisulphite whereas (III) yielded glucose, acetone, and sodium bisulphite. The possibility can thus be envisaged of a controlled rate of release of sulphur dioxide in a food during the whole of its storage life by the use of these or similar derivatives.

Experimental

Melting points are uncorrected. Microanalyses were from the Australian Microanalytical Service, Melbourne.

Reaction of Glucose with Cyclohexylammonium Bisulphite

The present procedure constitutes an improvement over that reported earlier.[3] D-Glucose (28 g), dissolved in water (30 ml), was treated at 25° with a solution of cyclohexylamine bisulphite formed from cyclohexylamine (15 ml) in water (20 ml). The reaction mixture was concentrated to a syrup under vacuum when ethanol (500 ml) was added and the mixture stored at 0°. After 16 hr the crystalline product, cyclohexylammonium (1*R*)-D-dulcitol-1-sulphonate (I) (37·5 g), m.p. 116–117°, was filtered off and dried. The product had the properties reported earlier, but the melting point was higher and the yield was improved from 25 to 67%.

[5] Pigman, W., (Ed.), "The Carbohydrates." p. 237. (Academic Press: New York 1957.)
[6] Monier-Williams, G. W., *Rep. publ. Hlth med. Subj., Lond.*, 1927, No. 43.

Formation of the Isopropylidene Derivative (III)

The adduct (I) (20 g) was suspended in dry acetone (200 ml) containing concentrated sulphuric acid (5 ml) and stirred for 3–4 hr. The reaction mixture was then treated with excess ammonium carbonate. Inorganic salts were filtered off and washed with acetone (100 ml). The filtrate was then concentrated under vacuum to a syrup which was dissolved in water. This aqueous solution was passed through a column containing Zeo Karb 225 cation resin (H^+ form), 100 g, and the acid effluent was neutralized immediately with barium carbonate. After filtration to remove insoluble barium salts, the filtrate was concentrated to a syrup which crystallized upon the addition of ethanol. The product, barium (1*R* or *S*)-1,2-3,4-di-*O*-isopropylidene-D-dulcitol-1-sulphonate (III) (9·0 g), m.p. > 300°, $[\alpha]_D^{25}$ +44·6° (*c*. 1·0 in water), was filtered off and dried. Recrystallization was effected from water–ethanol mixture (Found: C, 35·0; H, 5·2; S, 7·8. Calc. for $(C_{12}H_{21}O_9S)_2Ba$: C, 35·2; H, 5·1; S, 7·8%). ν_{max} (KBr disk) 3500 (OH), 1375 (=CMe_2), 1200, 1030 cm^{-1} (SO_3H). The compound gave no precipitate with barium chloride nor with barium hydroxide at 25° or 100°.

Periodate Oxidation of (III)

The barium salt (III) was converted into its crystalline sodium salt by passing an aqueous solution over Zeo Karb 225 (Na^+ form). Concentration of the effluent gave the sodium salt which was used in the standard periodate oxidation procedure.[7] The sodium salt consumed 1 mole of periodate per mole and liberated 1 mole of formaldehyde (estimated by the dimedone method of Reeves[8]). The dimedone derivative was identical with the product from formaldehyde (m.p., mixed m.p., and infrared spectra).

Acetylation of (III)

The barium salt (III) (8 g) was dissolved in water and the solution passed through a column of Zeo Karb 225 (H^+ form) (100 g). The acid effluent was neutralized with cyclohexylamine and then concentrated under vacuum to a syrup. The dry syrup was then dissolved in pyridine–acetic anhydride mixture (50 : 25) and kept 3 hr at 25°. After concentration under vacuum to remove excess pyridine and acetic anhydride, the residual syrup was dissolved in ether (100 ml). The crystalline product, pyridinium (1*R* or *S*)-5,6-di-*O*-acetyl-1,2-3,4-di-*O*-isopropylidene-D-dulcitol-1-sulphonate (IV) (8 g), formed rapidly and was filtered off. Recrystallization was effected from ethyl acetate, m.p. 158°; $[\alpha]_D^{25}$ 48·7° (*c*, 1·0 in ethanol); ν_{max} (KBr disk) 1740 (OAc), 1370 (=CMe_2), 1200, 1030 cm^{-1} (SO_3H) (Found: C, 49·6; H, 6·1; N, 2·8; O, 34·8; S, 6·1. Calc for $C_{21}H_{31}NO_{11}S$: C, 50·0; H, 6·1; N, 2·8; O, 34·9; S, 6·3%).

Estimation of Sulphur Dioxide

The standard method of Monier-Williams[6] was modified slightly. Solutions of the derivatives (II) and (III) (0·5 g) in hydrochloric acid (500 ml; 0·1M) were distilled into 0·1 M sodium hydroxide (50 ml), and sulphur dioxide was estimated in an aliquot (5 ml) of this solution by titration with 0·1M iodine. All aliquots were acidified with excess acetic acid before titration. The acetate (II) and the acetal (III) gave quantitative yields of sulphur dioxide in 60 and 20 min, respectively.

[7] Whistler, R. L., and Wolfrom, M. L., (Eds.), "Methods in Carbohydrate Chemistry." Vol. 1, p. 435. (Academic Press: New York 1962.)

[8] Reeves, R. E., *J. Am. chem. Soc.*, 1941, **63**, 1476.