152. *New Ethylidene Compounds of α- and β-Methylglucosides.*

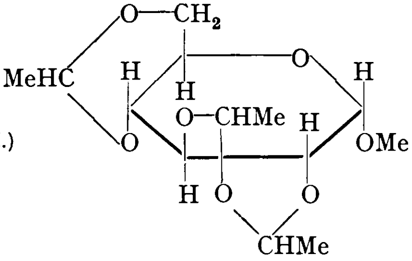
By Herbert Appel, W. N. Haworth, and (in part) E. G. Cox and F. J. Llewellyn.

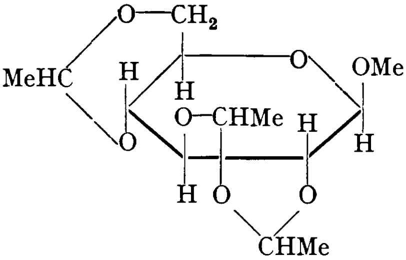
α- and β-Methylglucosides give, on treatment with paraldehyde and concentrated sulphuric acid, triethylidene compounds, which are shown to be 2 : 3-*oxidodiethylidene* 4 : 6-*ethylidene*-α- and -β-*methylglucosides.* A 2 : 3-*oxidodiethylidene* 4 : 6-*benzylidene* α-*methylglucoside* has also been prepared. The monoethylidene α-methylglucoside obtained by Hibbert and Hill (*J. Amer. Chem. Soc.*, 1923, **45**, 3115) is found to be 4 : 6-ethylidene α-methylglucoside. *X*-Ray data for these compounds are recorded, and the bearing of the results on the question of the conformation of the pyranose ring discussed.

It has long been known that α- and β-methylglucosides combine with benzaldehyde to form 4 : 6-benzylidene compounds; more recently, furfural (Bredereck, *Ber.*, 1935, **68**, 777, 2299) and acetaldehyde have been shown to react in the same manner as benzaldehyde. Hibbert and Hill (*J. Amer. Chem. Soc.*, 1923, **45**, 3115; cf. Hill, *ibid.*, 1928, **50**, 2729) obtained 4 : 6-ethylidene α-methylglucoside by the action of acetylene on a solution of α-methylglucoside in glycol containing mercuric sulphate and sulphuric acid; the structural formula was assigned only by analogy with the benzylidene compounds. The structure of 4 : 6-ethylidene β-methylglucoside was later proved by Helferich and Appel (*Ber.*, 1931, **64**, 1841), who prepared it by shaking β-methylglucoside with paraldehyde and a trace of concentrated sulphuric acid.

The method of Helferich and Appel leads, however, under suitable conditions to ethylidene derivatives of α- and β-methylglucosides of a hitherto unknown type. The experimental evidence shows that the new substances are 2 : 3-*oxidodiethylidene* 4 : 6-*ethylidene*-α- (I) and -β-*methylglucosides* (II). The percentages of carbon and hydrogen in

(I.)





(II.)

a diethylidene methylglucoside are very close to those in an oxidodiethylidene ethylidene methylglucoside, but accurate determination of the molecular weight of the oxidodiethylidene ethylidene α-methylglucoside by the *X*-ray method (E. G. C. and F. J. L.) and also the acetaldehyde determinations leave no doubt about the empirical formulæ of the new substances.

In order to decide on the structure of the new compounds it was necessary to establish the constitution of the monoethylidene α-methylglucoside of Hibbert and Hill (*loc. cit.*). This was done by the method which Helferich and Appel (*loc. cit.*) used to prove the structure of 4 : 6-ethylidene β-methylglucoside. The compound was methylated with methyl iodide and silver oxide, and the resulting syrup treated with benzaldehyde and zinc chloride. 4 : 6-Benzylidene 2 : 3-dimethyl α-methylglucoside was obtained and the assumption of Hibbert and Hill was therefore correct. Attention may be drawn to the fact that the melting point of 4 : 6-ethylidene α-methylglucoside (77°) is about 100° lower than the melting points of all corresponding compounds. When oxidodiethylidene ethylidene-α (or β)-methylglucoside is boiled for a few minutes with ether containing a few drops of bromine, 4 : 6-ethylidene-α (or β)-methylglucoside is formed (the probable reason for the hydrolysis is the small amount of hydrogen bromide present). This reaction affords evidence that two molecules of acetaldehyde are involved in a link between the atoms C_2 and C_3 of the glucose chain. It also shows the great lability of the new ring system towards acids.

It was further possible to obtain 2 : 3-oxidodiethylidene 4 : 6-benzylidene α-methylglucoside from 4 : 6-benzylidene α-methylglucoside by treatment with paraldehyde and concentrated sulphuric acid. This substance and 2 : 3-oxidodiethylidene 4 : 6-ethylidene α-methylglucoside have molecular rotations of 23,400° and 24,200° respectively, suggesting that the two substances agree not only in structure but also in configuration.

It is to be expected that the new type of oxidodiethylidene ring may also be formed with other compounds having two hydroxyl groups at a suitable distance. Such substances may be *trans-cyclo*hexane-1 : 2-diol and *cis-cyclo*hexane-1 : 3-diol; it is intended to test this hypothesis.

EXPERIMENTAL.

2 : 3-*Oxidodiethylidene* 4 : 6-*Ethylidene* α-*Methylglucoside*.—α-Methylglucoside (1·0 g.) was shaken for several hours with a mixture of paraldehyde (10 c.c.) and concentrated sulphuric acid (2 drops). Chloroform was then added, and the clear solution was treated with solid potassium carbonate for a few minutes and filtered. The solvent was removed under diminished pressure, and the residue recrystallised from alcohol or ligroin. Yield, 0·8 g.; m. p. 182·5—183·5°, $[\alpha]_D^{20^\circ}$ +83·5° in chloroform [Found : C, 53·9; H, 7·85; *M*, by *X*-ray method (see p. 796), 288 ± 5; *M*, cryoscopic in benzene, 266. (All the molecular weights determined by the cryoscopic method in benzene were found to be somewhat low, but tetra-acetyl β-methylglucoside also gave in a test experiment a molecular weight of 339 instead of the calculated 362.) 2 : 3-*Oxidodiethylidene* 4 : 6-*ethylidene* α-*methylglucoside*, $C_{13}H_{22}O_7$, requires C, 53·8; H, 7·6%; *M*, 290. Calc. for a diethylidene methylglucoside, $C_{11}H_{18}O_6$: C, 53·6; H, 7·4%; *M*, 246].

2 : 3-*Oxidodiethylidene* 4 : 6-*Ethylidene* β-*Methylglucoside*.—β-Methylglucoside (1·0 g.) was shaken with a mixture of paraldehyde (10 c.c.) and concentrated sulphuric acid (1 drop) for 6

days (the time is probably unnecessarily long; 2 days should suffice). The reaction mixture was worked up as described above. The *product*, recrystallised from alcohol, had m. p. 208—209° and $[\alpha]_D^{21°}$ −57·8° in chloroform (Found : C, 53·7; H, 7·6%; *M*, in benzene, 260).

Acetaldehyde determinations. A weighed amount of the compound was boiled for 15—20 minutes with 2% sulphuric acid. The acetaldehyde was distilled into ice-cooled water and determined in the solution by means of dimedone (Vörlander, *J. pr. Chem.*, 1929, **77**, 321). Oxidodiethylidene ethylidene-α- and -β-methylglucoside gave 41·8 and 42·2% respectively of acetaldehyde (Calc., 45·5%. Calc. for a diethylidene methylglucoside, 35·8%).

2 : 3-*Oxidodiethylidene* 4 : 6-*Benzylidene α-Methylglucoside*.—4 : 6-Benzylidene α-methylglucoside (m. p. 165°; 3·6 g.) was shaken with a mixture of paraldehyde (37 c.c.) and concentrated sulphuric acid (4 drops). After 8 minutes the clear solution was diluted with benzene, washed at once with sodium carbonate solution and water, and dried with calcium chloride. The solvent was removed under diminished pressure. The residue was dissolved in methyl alcohol, and water added until no further crystalline material separated. The crystals (0·55 g.) were filtered off from the solution (A) and recrystallised several times from alcohol; m. p. 192—193°; $[\alpha]_D^{20·5°}$ +66·4° in chloroform (Found : C, 61·5; H, 6·9; OMe, 9·2; *M*, in benzene, 333. 2 : 3-*Oxidodiethylidene* 4 : 6-*benzylidene α-methylglucoside*, $C_{18}H_{24}O_7$, requires C, 61·3; H, 6·9; OMe, 8·8%; *M*, 352·2. Calc. for a monoethylidene benzylidene methylglucoside, $C_{16}H_{20}O_6$: C, 62·3; H, 6·5; OMe, 10·1%; *M*, 308·2). The solution (A) contained oxidodiethylidene α-methylglucoside.

4 : 6-*Ethylidene α-Methylglucoside*.—(a) Conditions are described here which permit the preparation of a certain amount of this compound from α-methylglucoside directly by the paraldehyde method. The hydrolysis of oxidodiethylidene ethylidene α-methylglucoside [see (b)] is, however, more satisfactory.

α-Methylglucoside (1·0 g.) was shaken with a mixture of paraldehyde (10 c.c.) and concentrated sulphuric acid (1 drop) for 1 hour. Chloroform was added and the mixture, which contained undissolved material, was treated with solid potassium carbonate, filtered, and the solvent removed in a vacuum. The residue was dissolved in slightly alkaline water, leaving a residue (0·2 g.) of oxidodiethylidene ethylidene α-methylglucoside. The aqueous solution was evaporated to dryness, and the product extracted with hot ether. The ethereal solution contained 4 : 6-ethylidene α-methylglucoside (about 0·1 g.), which was recrystallised by careful addition of light petroleum to a solution in carbon tetrachloride; m. p. 77°, $[\alpha]_D^{20°}$ +109·1° in water (Hibbert and Hill, *loc. cit.*, give m. p. 77°, but do not record the rotation) (Found : C, 48·7; H, 7·6. Calc. for $C_9H_{16}O_6$: C, 49·1; H, 7·3%).

(b) 2 : 3-Oxidodiethylidene 4 : 6-ethylidene α-methylglucoside (1·5 g.) was boiled in ether (100 c.c.) containing a few drops of bromine until the compound had dissolved. The boiling was then continued for a further 3 minutes. An aqueous solution of sodium thiosulphate was added and, when the bromine colour had disappeared, the solution was made alkaline. The ether was evaporated, and 0·4 g. of unchanged starting material removed by filtration. The clear aqueous solution was taken down to dryness, and the residue extracted with hot carbon tetrachloride. After removal of the carbon tetrachloride a syrup (0·95 g.) was obtained which readily crystallised on seeding with 4 : 6-ethylidene α-methylglucoside; m. p., after two recrystallisations from carbon tetrachloride, 76—77°.

4 : 6-*Ethylidene β-Methylglucoside*.—2 : 3-Oxidodiethylidene 4 : 6-ethylidene β-methylglucoside (0·5 g.) was boiled for about 10 minutes with ether (30 c.c.) containing a few drops of bromine. The product, which began to separate before complete solution had occurred, was filtered off and washed with ether. Yield, 0·3 g.; m. p., after one recrystallisation from acetone, 183—185°; $[\alpha]_D^{19°}$ −76·9° in water [Helferich and Appel, *loc. cit.*, found after about ten recrystallisations m. p. 189—190° (corr.) and $[\alpha]_D$ −79·1°; but a specimen of m. p. 182—183° showed the same rotation and gave correct analytical values (cf. Helferich and Masamune, *Ber.*, 1931, **64**, 1260)].

4 : 6-*Benzylidene* 2 : 3-*Dimethyl α-Methylglucoside from* 4 : 6-*Ethylidene α-Methylglucoside*.—4 : 6-Ethylidene α-methylglucoside (2·0 g.) was dissolved in acetone (8 c.c.), methyl iodide (15 c.c.) added, and the solution boiled on the water-bath for 6 hours. Silver oxide (12 g.) was introduced during this time in three portions; acetone was then added, and the filtered solution evaporated to dryness. The syrup (2·05 g.) was mixed with freshly distilled benzaldehyde (16 c.c.), and zinc chloride (2·5 g.) dissolved with shaking. After 48 hours, the solution was stirred with an aqueous solution of sodium bisulphite until the benzaldehyde had dissolved. The solution was extracted with ether, and the extract washed with sodium bisulphite solution, dilute alkali, and water, and dried with calcium chloride. Removal of the ether left 0·8 g. of

crystalline material, which after recrystallisation from light petroleum showed m. p. 120—121°, not depressed by an authentic specimen (m. p. 120—121·5°); $[\alpha]_D^{25°}$ +96·2° in chloroform (Mathers and Robertson, J., 1933, 698, give m. p. 121—122° and $[\alpha]_D$ +94·6°).

Crystallographic Section.

By E. G. Cox and F. J. Llewellyn.

X-Ray studies of carbohydrates (see, *e.g.*, Cox, Goodwin, and Wagstaff, J., 1935, 1495) suggest that the conformation of the pyranose ring in glucose and its derivatives is not, as is frequently assumed, of the Sachse *trans*-type, and the formation of the compounds described in this paper supports this view. Since a five-membered acetal ring must normally be flat, the ease of formation of such rings between adjacent *cis*-hydroxyl groups in pyranose sugars is difficult to reconcile with a Sachse *trans*-ring, because with such a conformation adjacent C—OH bonds cannot be coplanar. If, in spite of this, the idea of the Sachse *trans*-ring is adhered to, then on account of the symmetrical nature of this ring and the consequent equality of distances between *cis*- and *trans*-pairs of hydroxyl groups, it must be admitted that five-membered ring formation can occur with equal facility whether *trans*- or *cis*-hydroxyl groups are involved. The exceptional seven-membered ring embracing the *trans* O_2 and O_3 atoms in the compounds now described is in marked contrast with the usual five-membered ring involving *cis*-oxygen atoms, and is in agreement with the view that the pyranose ring in glucose is not of the Sachse *trans*-form.

The length of the *c*-axis for the two oxidodiethylidene ethylidene methylglucosides is almost the same as for 4 : 6-ethylidene α-methylglucoside and for the 4 : 6-benzylidene derivatives (Cox *et al.*, *loc. cit.*); this indicates that the form of the ring is not greatly changed by the addenda in the 2 : 3-position. When a model is made, it is seen that the seven-membered ring is readily formed without strain and lies in approximately the same plane as the remainder of the molecule. It is interesting to note that comparison of the birefringence and cell-dimensions of the four compounds now examined suggests that the molecules of the β-compounds are " flatter " than those of the α-forms. This lends further support to the views previously expressed (Cox *et al.*, *loc. cit.*) regarding the relative configuration of α- and β-derivatives of glucose.

Experimental.

The *X*-ray data were obtained by means of single crystal rotation and oscillation photographs, using copper K_α radiation. Refractive indices are for sodium light.

4 : 6-*Ethylidene* β-*Methylglucoside.*—The crystals of this substance are monoclinic sphenoidal combinations of *a*{100}, *c*{001}, *R*{10$\bar{1}$}, *m*{1$\bar{1}$0}, and *p*{011}, elongated parallel to [*b*], sometimes tabular on *a* and sometimes on *R*. The dimensions of the unit cell (which contains two molecules) are $a = 8·58$, $b = 9·56$, and $c = 6·48$ A., with $\beta = 112° 54'$. The space group is $P2_1$ and the calculated density is 1·40 g./c.c. (obs., 1·40). The refractive indices are $\alpha = 1·50$ [perp. to *a*(100)], $\beta = 1·52$, and $\gamma = 1·56$ (parallel to [*b*]). A positive obtuse bisectrix interference figure is visible through *a*(100). The optical results are consistent with the molecules being oriented with their planes approximately parallel to *a*(100), in which case their " thickness " would be *a*/2, *i.e.*, 4·3 A.

4 : 6-*Ethylidene* α-*Methylglucoside.*—Only very small, acicular crystals of this compound could be obtained; they showed straight extinction with negative elongation. By taking a rotation photograph of a bundle of approximately parallel crystals, the unit cell dimension in the needle direction was found to be 4·8 A.

2 : 3-*Oxidodiethylidene* 4 : 6-*Ethylidene* β-*Methylglucoside.*—This substance occurs as minute needles similar to those of the preceding compound, with straight extinction and negative elongation, but having higher birefringence. The length of the needle axis was found to be 4·7 A.

2 : 3-*Oxidodiethylidene* 4 : 6-*Ethylidene* α-*Methylglucoside.*—The crystals of this substance are monoclinic combinations of *a*{100} and *b*{010} elongated parallel to [*c*] and terminated by *m*{011}. [A crop of crystals having a slightly low m. p. (178—179·5°), however, were found to be of pronounced sphenoidal habit, tabular on *a*, with *b'*{0$\bar{1}$0} and *n*{021}. The same type of crystal was sometimes obtained by recrystallisation from carbon tetrachloride.] The unit

cell dimensions are $a = 9{\cdot}78$, $b = 15{\cdot}47$, and $c = 4{\cdot}74$ A., with $\beta = 99° 24'$, and the space-group is $P2_1$. The density (by flotation) is 1·340 g./c.c., so that with two molecules in the unit cell the molecular weight is 288 ± 5 (calc., 290·2). The crystals are optically negative with refractive indices $\alpha = 1{\cdot}502$ inclined at 3° to [c] in the obtuse angle β, $\beta = 1{\cdot}539$ (parallel to [b]), and $\gamma = 1{\cdot}542$. An obtuse bisectrix interference figure is visible through a(100).

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