

391. Ethylidene Derivatives of Sorbitol.

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Two substances, both claimed to be triethylidene D-sorbitol, have previously been reported by Appel (*J.*, 1935, 425) and by Sullivan (*J. Amer. Chem. Soc.*, 1945, 67, 837). That of Appel is now shown to be triethylidene D-mannitol, whilst the true triethylidene D-sorbitol is the compound reported by Sullivan. A monoethylidene hexitol, isolated from crude triethylidene D-sorbitol syrup by hydrolysis, is shown to be a true sorbitol derivative and is in fact 2 : 4-ethylidene D-sorbitol. Confirmation is obtained of the structures of 1 : 3-2 : 4-diethylidene D-sorbitol and of 1 : 3-2 : 4-5 : 6-triethylidene D-sorbitol.

THE first systematic study of the ethylidene derivatives of sorbitol was reported by Appel (*loc. cit.*) who, after treating D-sorbitol with paraldehyde and hydrochloric acid, isolated triethylidene D-sorbitol as a syrup, and thence by hydrolysis diethylidene D-sorbitol. It was claimed that a small proportion of the triethylidene compound could be obtained crystalline, m. p. 174—176°, but that crystallisation was wasteful and unnecessary if the syrup was subsequently to be hydrolysed to the diethylidene derivative. More recently Sullivan (*loc. cit.*) prepared triethylidene D-sorbitol, having m. p. 96—97°, in 18% yield; he pointed out that this substance was different from that of Appel and considered that the two substances were possibly *cis-trans* or other isomers. In order to elucidate this interesting problem we have prepared from

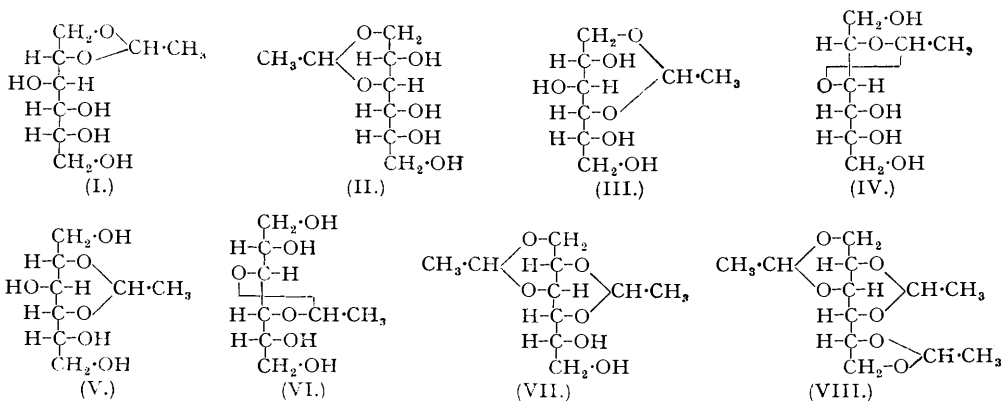
D-sorbitol by Appel's method "triethylidene sorbitol syrup" and have isolated from it both of the "triethylidene sorbitols" mentioned above. Crystallisation of the syrup from alcohol or water very readily gave a small yield (*ca.* 7%) of Appel's derivative, whilst Sullivan's compound could be isolated only after the residual syrup had been fractionally distilled. Even then this lower-melting isomer was difficult to crystallise.

It was noticed that the melting point of Appel's "triethylidene D-sorbitol" agreed closely with that reported by Meunier (*Compt. rend.*, 1889, 108, 408) for triethylidene D-mannitol, which has now been prepared in good yield from D-mannitol. The melting points and specific rotations of the two compounds have been found to be identical and no depression of m.p. was observed on admixture. In addition, Appel's "triethylidene D-sorbitol" has been converted by hydrolysis and subsequent acetylation into crystalline D-mannitol hexa-acetate, isolated in 81% yield. Clearly, the "triethylidene D-sorbitol" reported by Appel is actually triethylidene D-mannitol, arising probably from mannitol present as an impurity in the commercial sorbitol.

Therefore it seemed probable that the isomeric triethylidene hexitol reported by Sullivan was a true sorbitol derivative, but no additional evidence could be found to support this contention since Sullivan, like Appel, conducted his subsequent experiments on the crude syrup. However, we have now prepared the true triethylidene D-sorbitol of Sullivan from diethylidene D-sorbitol, which, as is shown below, is amply proved to be a sorbitol derivative. Furthermore, this triacetal was converted by hydrolysis and subsequent acetylation into crystalline D-sorbitol hexa-acetate, which was recovered in 70% of the theoretical yield.

The structure of diethylidene D-sorbitol has been examined by several workers, all of whom have employed Appel's (*loc. cit.*) original method of preparation, namely, hydrolysis of the syrupy "triethylidene D-sorbitol" with aqueous acetic acid. The presence of two free hydroxyl groups in this product has been demonstrated by the isolation of a ditoluene-*p*-sulphonate (Wiggins, *J.*, 1946, 388; Sullivan, *loc. cit.*), a dibenzoate (Sullivan, *loc. cit.*), a dimethyl ether (Bourne and Wiggins, *J.*, 1944, 517), and a *diacetate*. Since one molecule of diethylidene D-sorbitol utilizes one atom of oxygen when oxidized with lead tetra-acetate in acetic acid solution (Bourne and Wiggins, *loc. cit.*), the two free hydroxyl groups are present as a glycol grouping, which is ruptured in this process to give a diethylidene derivative of L-xylose (Appel, *loc. cit.*). Moreover, Vargha and Puskas (*Ber.*, 1943, 76, 859) effected the conversion of diethylidene D-sorbitol into D-sorbitol hexa-acetate. These facts clearly prove that the diethylidene compound is truly a derivative of D-sorbitol in which the hydroxyl groups on C₅ and C₆ are not involved in acetal linkages.

Only one communication (Gätzi and Reichstein, *Helv. Chim. Acta*, 1938, 21, 86) throws any light on the finer structure of diethylidene D-sorbitol. These authors oxidised it with potassium permanganate in slightly alkaline solution and obtained diethylidene L-xylonic acid and monoethylidene L-threonic acid. The latter substance was shown to have its ethylidene residues attached to C₂ and C₄ of the threonic acid molecule, from which fact Gätzi and Reichstein deduced that the acetal groupings in diethylidene sorbitol were in the 1 : 3- and 2 : 4-positions. We have now confirmed this deduction by a different and more certain method.



Syrupy "triethylidene D-sorbitol" was hydrolysed with 50% aqueous acetic acid to Appel's diethylidene D-sorbitol, m. p. 212—213°. The addition of ether to the alcoholic mother-liquors from this crystallisation gave a *monoethylidene hexitol*, which was also prepared by hydrolysis of

the crystalline diethylidene D-sorbitol itself and was thus shown to be a true derivative D-sorbitol. This conclusion was supported by the isolation in good yield of D-sorbitol hexa-acetate from the monoacetal by hydrolysis and subsequent acetylation. Direct acetylation of the monoethylidene D-sorbitol in pyridine solution gave the characteristic *tetra-acetate*.

Since the monoethylidene D-sorbitol was derived from diethylidene D-sorbitol, in which the hydroxyl groups on C₅ and C₆ are not engaged in acetal formation, it can have one of the structures (I)—(VI). However, when treated with lead tetra-acetate in acetic acid solution it utilized only one atom of oxygen per molecule, a fact which eliminated all these structures except (V). Therefore monoethylidene D-sorbitol is the 2 : 4-derivative and it follows that diethylidene D-sorbitol (VII) has 1 : 3- and 2 : 4-acetal groupings, whilst in triethylidene D-sorbitol (VIII) the acetaldehyde residues may be allocated to the 1 : 3-, 2 : 4-, and 5 : 6-positions.

EXPERIMENTAL.

Ethylidenation of Sorbitol.—When commercial D-sorbitol was shaken with paraldehyde and 40% hydrochloric acid according to Appel's method (*loc. cit.*), the so-called "triethylidene sorbitol syrup" was obtained in 51% yield. A variation of this procedure in which 48% hydrobromic acid was employed in the following way gave somewhat higher yields of condensation products. Sorbitol (50 g.) was shaken overnight with paraldehyde (150 c.c.) and 48% hydrobromic acid (20 c.c.). Chloroform (200 c.c.) and water (50 c.c.) were then added, the mixture shaken, and the chloroform extract separated and washed with dilute sodium hydrogen carbonate and with water. After being dried (MgSO₄), the extract was evaporated to a syrup (45.4 g.). This was diluted with 50% aqueous alcohol (200 c.c.) and the mixture allowed to stand overnight. Feathery needles separated (3.1 g., 7% of the weight of crude syrup), m. p. 172—174°, $[\alpha]_D^{20} = 72.7^\circ$ in chloroform (*c*, 0.8). This was identical with triethylidene mannitol (see below). A m. p. of these crystals in admixture with authentic triethylidene mannitol showed no depression. Appel (*loc. cit.*) isolated crystals from the crude triethylidene sorbitol syrup and quoted m. p. 174—176° (no $[\alpha]_D$ given). This is clearly identical with the product described here, although Appel described it as triethylidene sorbitol. The mother-liquors, after the separation of the feathery needles of triethylidene mannitol, were concentrated to a syrup which distilled almost completely at 102—108°/0.15 mm. The distillate crystallised on cooling and, recrystallised from ether-ligroin, formed short feathery needles of triethylidene sorbitol (12.4 g.), m. p. 92—95, $[\alpha]_D^{20} = 20.2^\circ$ in water (*c*, 4.52). Sullivan (*loc. cit.*) obtained a triethylidene sorbitol (18% from sorbitol) in white needles, m. p. 96—97°, $[\alpha]_D^{22} = 21.6$ in water (*c*, 5) (Found : C, 55.6; H, 7.6. Calc. for C₁₂H₂₀O₆ : C, 55.4; H, 7.7%).

Triethylidene Mannitol from Mannitol.—Mannitol (20 g.) was shaken overnight with paraldehyde (75 c.c.) and 48% hydrobromic acid (10 c.c.). A crystalline precipitate separated. Chloroform was added until this dissolved. The solution was then washed with water, sodium hydrogen carbonate, and again with water. The extract was dried (MgSO₄), filtered, and evaporated to dryness. The residue (26.3 g.) completely crystallised, and when recrystallised from alcohol, the triethylidene mannitol formed feathery needles; yield 19.5 g., m. p. 172°, $[\alpha]_D^{20} = 72.3^\circ$ in chloroform (*c*, 0.8) (Found : C, 55.7; H, 8.0. Calc. for C₁₂H₂₀O₆ : C, 55.4; H, 7.7%). Meunier (*loc. cit.*) prepared triethylidene mannitol by shaking mannitol with paraldehyde and sulphuric acid and described it as forming silky needles of m. p. 174° (rapid heating).

Mannitol Hexa-acetate from Triethylidene Mannitol.—Triethylidene mannitol (0.535 g.), which had been isolated from "triethylidene sorbitol syrup", was hydrolysed with N-hydrochloric acid (3 c.c.) at 100° for 2 hours. The solvent was removed under reduced pressure, and the syrup dried in a vacuum. Thereafter it was boiled for 40 minutes with acetic anhydride (6 c.c.) and fused sodium acetate (1.5 g.). When cold, the mixture was stirred into ice-water, and the ester extracted with chloroform. The chloroform solution was dried (MgSO₄) and evaporated. The product (0.72 g.), recrystallised from aqueous alcohol, had m. p. 124.5—125.5°, alone or in admixture with authentic mannitol hexa-acetate. The m. p. was depressed in admixture with sorbitol hexa-acetate.

D-Sorbitol Hexa-acetate from 1 : 3-2 : 4-5 : 6-Triethylidene D-Sorbitol.—Triethylidene sorbitol (0.5 g.) was boiled for 2 hours with 5N-hydrochloric acid (25 c.c.). The solution was evaporated to dryness under reduced pressure, and the residue acetylated by boiling with acetic anhydride (15 c.c.) and fused sodium acetate (1 g.) for 20 mins. Thereafter the mixture was cooled and poured into ice-water, neutralized with sodium hydrogen carbonate and exhaustively extracted with chloroform. The extract was dried (MgSO₄) and evaporated to dryness. The residue, recrystallised from alcohol in prisms, had m. p. 100—101° alone or in admixture with an authentic specimen of hexa-acetyl sorbitol; yield 0.58 g., 70%.

Hydrolysis of "Triethylidene Sorbitol Syrup."—"Triethylidene D-sorbitol syrup" (108 g.) was hydrolysed with hot aqueous acetic acid according to Appel (*loc. cit.*). The solvent was removed under reduced pressure at 70°, leaving a syrup which was then stirred with alcohol (20 c.c.) and ether (200 c.c.). A white solid (28.1 g.) was precipitated; m. p. 190°. The mother-liquors were evaporated to a syrup, from which white needles of triethylidene D-mannitol (2 g.), m. p. 171°, separated on the addition of water (180 c.c.). The solid (m. p. 190°) was rapidly washed with a small volume of chloroform to remove any triethylidene derivative and twice recrystallised from the minimum volume of ethyl alcohol. The product was 1 : 3-2 : 4-diethylidene D-sorbitol (14.5 g.), m. p. 212—213°, $[\alpha]_D^{15} = 10.9^\circ$ in water (*c*, 5.5). Appel (*loc. cit.*) recorded m. p. 212—214°, $[\alpha]_D^{17} = 11.1^\circ$ in water (*c*, 2.3) for this compound.

The addition of excess of ether to the alcoholic mother-liquors gave a precipitate which, after being twice recrystallised from alcohol-ether, formed white needles (0.73 g.), $[\alpha]_D^{21} = 4.6^\circ$ in water (*c*, 2.2), m. p. 146°, depressed in admixture with 1 : 3-2 : 4-diethylidene D-sorbitol or triethylidene D-mannitol (Found : C, 46.4; H, 7.8. C₁₂H₁₆O₆ requires C, 46.1; H, 7.8%). This compound was 2 : 4-ethylidene D-sorbitol, and was prepared in larger quantity by the same method for further examination.

Acetylation of 1:3-2:4-Diethylidene D-Sorbitol.—Diethylidene sorbitol (0.252 g.) was dissolved in dry pyridine (2.5 c.c.), and acetic anhydride (0.30 c.c.) added. After being kept at room temperature for 24 hours, the mixture was poured into ice-water (30 c.c.). The precipitated 5:6-diacetyl 1:3-2:4-diethylidene D-sorbitol, recrystallised from aqueous alcohol, showed m. p. 153—154° and $[\alpha]_D^{25} + 2.8^\circ$ in chloroform (c, 1.1); yield 0.131 g. (Found: C, 52.9; H, 6.9. $C_{14}H_{22}O_8$ requires C, 52.8; H, 7.0%).

1:3-2:4-5:6-Triethylidene D-Sorbitol from 1:3-2:4-Diethylidene D-Sorbitol.—1:3-2:4-Diethylidene D-sorbitol (1.93 g.) was heated under reflux with chloroform (25 c.c.), paraldehyde (10 c.c.), and concentrated hydrochloric acid (5 c.c.) for 5 minutes and then kept at room temperature for 24 hours. The product was extracted with chloroform (100 c.c.). The extract was washed with water (20 c.c.), dried ($MgSO_4$), and evaporated to a syrup which crystallised on cooling. Recrystallised several times from light petroleum (b. p. 60—80°) in white needles, 1:3-2:4-5:6-triethylidene D-sorbitol showed m. p. 94—95°.

2:4-Monoethylidene D-Sorbitol from 1:3-2:4-Diethylidene D-Sorbitol.—Diethylidene sorbitol (2.08 g.) was heated under reflux on a boiling water-bath with 50% acetic acid (by vol.) (20 c.c.) for 2.5 hours. The solution was evaporated under reduced pressure at 40° to a viscous syrup, which was redissolved in chloroform (30 c.c.). The solution was passed under gravity through a column (1 cm. diameter by 37 cm.) of activated alumina which had already been saturated with chloroform. The column was then washed with the following solvents, the surface of the liquid always being maintained level with the top of the alumina: (a) Chloroform (25 c.c.); evaporation of the eluate revealed the presence of only a trace of brown syrup. (b) Chloroform-alcohol (1:1 by vol., 20 c.c.); the eluate was evaporated, leaving a white solid which, after crystallisation from alcohol, gave a product having m. p. 209—212° (slightly impure diethylidene sorbitol). (c) Chloroform-alcohol (1:1 by vol., 20 c.c.); the syrup isolated from the eluate by evaporation was twice recrystallised from acetone containing a few drops of alcohol, and the white needles obtained (0.061 g.) had m. p. 144—146.5°, not depressed in admixture with the 2:4-monoethylidene sorbitol obtained as above. (d) Alcohol (25 c.c.); treatment of the eluate as in (c) yielded 2:4-monoethylidene sorbitol (0.146 g.), m. p. 146—148°. (e) Alcohol (100 c.c.); this extracted a white solid (0.020 g.), m. p. 50—55°.

From the combined acetone mother-liquors of (c) and (d) a further amount (0.044 g.) of 2:4-monoethylidene sorbitol was isolated.

D-Sorbitol Hexa-acetate from 2:4-Monoethylidene D-Sorbitol.—2:4-Monoethylidene D-sorbitol (0.195 g.) was hydrolysed by heating at 100° for 1 hour with N-hydrochloric acid (2.5 c.c.). The solvent was removed, and the residue dried in a vacuum. It was acetylated by boiling for 45 minutes with fused sodium acetate (0.5 g.) and acetic anhydride (2.0 c.c.). The cold mixture was stirred with ice-water (25 c.c.). Recrystallisation of the precipitate from aqueous alcohol yielded a product (0.126 g.), m. p. 99.5—100.5°, alone or in admixture with authentic sorbitol hexa-acetate; in contrast, the m. p. was markedly depressed by admixture with mannitol hexa-acetate. A second crop (0.209 g.) of sorbitol hexa-acetate (m. p. 98—100.5°) was recovered from the aqueous filtrate by extraction with chloroform, evaporation, and recrystallisation from aqueous alcohol.

Acetylation of 2:4-Monoethylidene D-Sorbitol.—2:4-Monoethylidene D-sorbitol (0.070 g.) was dissolved in dry pyridine (1.5 c.c.), and acetic anhydride (0.30 c.c.) added. The mixture was kept at room temperature for 48 hours. Thereafter it was cooled, poured into ice-water (25 c.c.), and exhaustively extracted with chloroform. The extract was washed with dilute sulphuric acid, dilute sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and evaporated to a syrup, which crystallised on cooling. After being recrystallised twice from aqueous alcohol, tetra-acetyl 2:4-monoethylidene D-sorbitol was isolated in white needles (0.095 g.), m. p. 117—118° (Found: C, 51.4; H, 6.3; Ac, 46.7. $C_{18}H_{24}O_{10}$ requires C, 51.1; H, 6.4; Ac, 45.7%).

Oxidation of Di- and Mono-ethylidene Sorbitol and Triethylidene Mannitol with Lead Tetra-acetate.—The method of Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667) being used, the following values were calculated for the number of g.-atoms of oxygen taken up by 1 g.-mol. of the compound used. The same solution of lead tetra-acetate was employed in each case and 0.0005 mol. of each substance was used: (a) 1:3-2:4-Diethylidene D-sorbitol: 0.14 (8 mins.); 0.55 (60 mins.); 0.76 (120 mins.); 0.87 (180 mins.); 0.95 (290 mins.). (b) 2:4-Monoethylidene D-sorbitol: 0.14 (8 mins.); 0.54 (60 mins.); 0.76 (120 mins.); 0.87 (180 mins.); 0.95 (290 mins.). (c) Triethylidene D-mannitol: 0.00 (8—290 mins.).

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