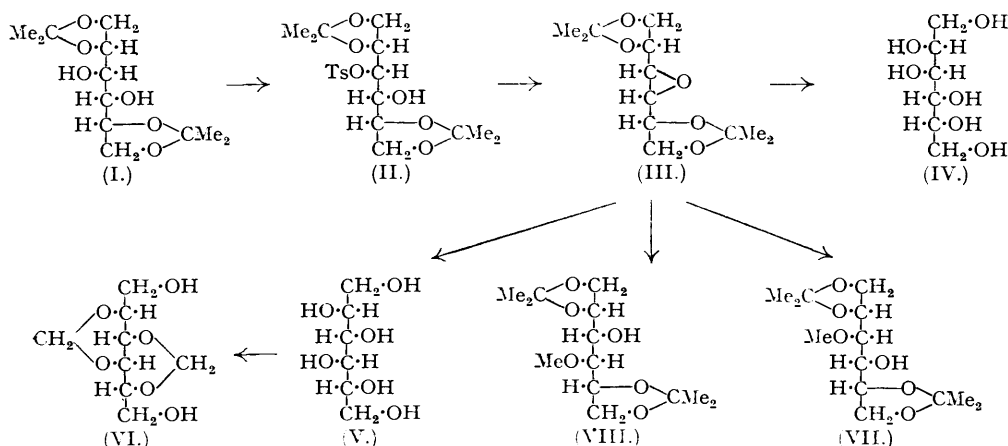


114. 1 : 2-5 : 6-Diisopropylidene 3 : 4-Anhydro-D-talitol.

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The preparation of 1 : 2-5 : 6-diisopropylidene 3 : 4-anhydro-D-talitol from 3-tosyl 1 : 2-5 : 6-diisopropylidene mannitol is described. This anhydro-compound is the first non-terminal hexitol derivative of the ethylene oxide type to be obtained. Although the anhydro-ring is more stable than when it is attached to a terminal carbon atom, it is broken by acid hydrolysis, to give a mixture of D-mannitol and D-iditol, and also by treatment with alkoxides under vigorous conditions.

DERIVATIVES of only three anhydro-hexitols of the ethylene oxide type have hitherto been described, *viz.*, 1-tosyl 2 : 4-benzylidene and 1 : 3-2 : 4-diethylidene 5 : 6-anhydrosorbitol (Vargha, *Ber.*, 1935, **68**, 1377; Vargha and Puskás, *Ber.*, 1943, **76**, 859; Sullivan, *J. Amer. Chem. Soc.*, 1945, **67**, 837; Wiggins, *J.*, 1946, 388); 1 : 2-3 : 4-diisopropylidene 5 : 6-anhydromannitol (Wiggins, *loc. cit.*); and 3 : 4-isopropylidene and 3 : 4-ethylidene 1 : 2-5 : 6-dianhydromannitol (Wiggins, *J.*, 1946, 384). In all these, the oxide rings engage terminal carbon atoms and are readily opened either by acid hydrolysis or by treatment with alkoxides or organic bases; the ring fission occurs usually between the oxygen atom and the terminal carbon atom, so that no change of configuration results. For example, 3 : 4-isopropylidene 1 : 2-5 : 6-dianhydromannitol on acid hydrolysis gives only mannitol, and with sodium methoxide only 1 : 6-dimethyl 3 : 4-isopropylidene mannitol is obtained. The sole exception to this generalisation is provided by 1-tosyl 2 : 4-benzylidene 5 : 6-anhydrosorbitol, which on acid hydrolysis gives 1-tosyl 2 : 5-anhydro-L-iditol by Walden inversion at C₅ (Vargha and Puskás, *loc. cit.*).



In connection with the synthesis of polyhydroxy-dithiols, the 5 : 6-anhydro-derivatives of mannitol and of sorbitol have been used for the preparation of the 6-allyl ethers, by effecting ring fission with sodium allyl oxide in allyl alcohol (Bladon and Owen, Part VI, *J.*, 1950, 591). As part of a possible route for the synthesis of non-terminal allyl ethers of polyhydric alcohols, a non-terminal epoxide was required, and, since anhydro-compounds of the ethylene oxide type are most conveniently prepared from tosyl compounds (cf. Peat, "Advances in Carbohydrate Chemistry," **2**, 37), attempts were made to form the monotosyl derivative (II) of 1 : 2-5 : 6-diisopropylidene mannitol (I). When this compound was treated with 1 mole of toluene-*p*-sulphonyl chloride in pyridine, a syrup was obtained from which 3 : 4-ditosyl 1 : 2-5 : 6-diisopropylidene mannitol (Brigl and Grüner, *Ber.*, 1934, **67**, 1969) could be separated by crystallisation from methanol, and from which, on one occasion, crystalline 3-tosyl 1 : 2-5 : 6-diisopropylidene mannitol (II) was also obtained. Subsequent attempts to isolate this mono-derivative from the reaction mixture were unsuccessful, but such isolation proved to be unnecessary, since treatment of the crude reaction product, in chloroform, with cold methanolic sodium methoxide gave an oil, from which the ditosyl compound (unaffected by this treatment) was precipitated by light petroleum; distillation of the material soluble in this solvent then gave crystalline 1 : 2-5 : 6-diisopropylidene 3 : 4-anhydro-D-talitol (III).

The configuration allocated to this compound is in conformity with the knowledge that, in the formation of an epoxide from a tosyl compound, a Walden inversion occurs on the carbon

atom carrying the sulphonyloxy-group; it was also confirmed by the following observations. Acid hydrolysis of the epoxide resulted in fission of the ring and loss of the isopropylidene residues, and gave a mixture of hexitols from which mannitol (IV) was isolated by crystallisation. The material in the mother-liquors, on treatment with formaldehyde and concentrated hydrochloric acid, gave a dimethylene hexitol, the properties of which agreed with those given by Hann and Hudson (*J. Amer. Chem. Soc.*, 1945, **67**, 602) for 2 : 4-3 : 5-dimethylene L-iditol, except that the optical rotation was of opposite sign. Accordingly, the product is formulated as 2 : 4-3 : 5-dimethylene D-iditol (VI), formed from D-iditol (V) resulting from the hydrolysis of the anhydro-compound. Acetylation of (VI) gave 1 : 6-diacetyl 2 : 4-3 : 5-dimethylene D-iditol which likewise had properties, differing only in the sign of rotation, similar to those recorded by Hann and Hudson (*loc. cit.*) for the enantiomorph. The production of both D-mannitol and D-iditol from the anhydro-compound can be explained only by assigning to it the D-talitol configuration; ring-opening thus occurs in two directions, leading (with inversion on $C_{(3)}$) to the mannitol configuration and (with inversion on $C_{(4)}$) to the iditol configuration.

1 : 2-5 : 6-Diisopropylidene 3 : 4-anhydro-D-talitol, the first non-terminal epoxide in the hexitol series, was noticeably more resistant than terminal epoxides to attack by alkoxides, being recovered largely unchanged after being heated under reflux with 0.2N-methanolic sodium methoxide, conditions under which terminal epoxides are readily opened (Vargha and Puskás, *loc. cit.*). With 3.5N-methanolic sodium methoxide at 100°, however, it gave a mixture of 3-methyl 1 : 2-5 : 6-diisopropylidene D-mannitol (VII) and (probably) 3(or 4)-methyl 1 : 2-5 : 6-diisopropylidene D-iditol (VIII), from which, by acid hydrolysis, 3-methyl mannitol was obtained, identical with the compound prepared by Haskins, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1943, **65**, 70) by reduction of 3-methyl mannose. It was not possible to isolate the 3-methyl iditol which presumably was also present.

Similarly, on being heated with sodium allyl oxide in allyl alcohol at 100°, the epoxide gave a mixture of 3-allyl 1 : 2-5 : 6-diisopropylidene D-mannitol and (probably) 3-allyl 1 : 2-5 : 6-diisopropylidene D-iditol. Acid hydrolysis then gave a mixture of allyl hexitols from which 3-allyl D-mannitol was isolated, identical with the material obtained by direct allylation of 1 : 2-5 : 6-diisopropylidene mannitol (Bladon and Owen, *loc. cit.*).

EXPERIMENTAL.

3-Tosyl 1 : 2-5 : 6-Diisopropylidene Mannitol.—A solution of 1 : 2-5 : 6-diisopropylidene mannitol (52.4 g., 0.2 mol.) (Baer, *J. Amer. Chem. Soc.*, 1945, **67**, 338) in dry pyridine (200 c.c.) was stirred vigorously and cooled during the addition of a solution of toluene-*p*-sulphonyl chloride (40 g., 0.21 mol.) in dry pyridine (100 c.c.) during 2½ hours, the temperature being kept below 2°. After the mixture had remained for 20 hours at room temperature, the greater part of the pyridine was removed by distillation under reduced pressure. The syrupy residue was taken up in chloroform (250 c.c.) and treated with crushed ice (300 g.). The chloroform layer was separated and the aqueous solution was extracted twice more with chloroform. The extracts were washed with water, dilute sulphuric acid, and finally with sodium hydrogen carbonate solution, and then dried (Na_2SO_4). The solvent was removed by distillation, leaving a syrup (66.1 g.) which was, in general, used without further treatment for the next stage. In one experiment, however, a portion (4.5 g.) of this crude monotosyl derivative was crystallised from methanol; the first crop of solid consisted of 3 : 4-ditosyl 1 : 2-5 : 6-diisopropylidene mannitol, m. p. and mixed m. p. 118—119°. Treatment of the methanolic mother-liquors with water gave a solid (2.6 g.), m. p. 75—90°; this was dissolved in ethyl acetate, and the solution was dried (Na_2SO_4), concentrated to small volume, and treated with light petroleum (b. p. 60—80°) to give a solid, m. p. 98—100°. Further recrystallisation from ethyl acetate—light petroleum (b. p. 60—80°) gave 3-tosyl 1 : 2-5 : 6-diisopropylidene mannitol, m. p. 100°, $[\alpha]_D^{19} -27^\circ$ (c, 0.9 in chloroform) (Found: C, 54.6; H, 6.6. $\text{C}_{19}\text{H}_{28}\text{O}_5\text{S}$ requires C, 54.8; H, 6.8%). Attempts to isolate this compound on other occasions were unsuccessful; furthermore, the analytically pure material decomposed after a few weeks to a viscid mass, which was acidic and contained free acetone.

1 : 2-5 : 6-Diisopropylidene 3 : 4-Anhydro-D-talitol.—To a solution of the crude 3-tosyl diisopropylidene mannitol syrup (60 g.) in chloroform (240 c.c.), cooled in ice, was added a solution of sodium (3.5 g.) in dry methanol (150 c.c.), with shaking and cooling. The sodium toluene-*p*-sulphonate first separated as a gel, which later crystallised. The mixture was left overnight at 0° and was then treated with water (500 c.c.). The chloroform layer was separated, and the aqueous portion was extracted thrice with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated to a syrup (37.6 g.), which was dissolved in boiling light petroleum (b. p. 60—80°; 100 c.c.); the solid which separated on cooling was collected and extracted twice more with light petroleum. The insoluble material (15 g.) was recrystallised from methanol (100 c.c.) and gave long needles of 3 : 4-ditosyl 1 : 2-5 : 6-diisopropylidene mannitol (8.5 g.), m. p. 118°, $[\alpha]_D^{19} +7.8^\circ$ (c, 2.5 in chloroform) (Found: C, 54.8; H, 5.9. Calc. for $\text{C}_{22}\text{H}_{34}\text{O}_{10}\text{S}_2$: C, 54.7; H, 6.0%). Brigl and Grüner (*Ber.*, 1934, **67**, 1969) give m. p. 120—121°, $[\alpha]_D +9.3^\circ$ (in chloroform).

Evaporation of the petroleum solution under reduced pressure gave a crystalline residue (25 g.) which was distilled at 80—140° (air-bath)/0.0001 mm.; the distillate (20.7 g.) solidified in the form of large plates, m. p. 49—53°. Recrystallisation from aqueous methanol gave large granular crystals of

1 : 2-5 : 6-diisopropylidene 3 : 4-anhydro-D-talitol, m. p. 54—56°, $[\alpha]_D^{25}$ -16.2° (*c*, 1.5 in chloroform) (Found : C, 59.3; H, 8.1. $C_{12}H_{20}O_6$ requires C, 59.0; H, 8.3%). The overall yield of the anhydro-compound from diisopropylidene mannitol was 43%.

Acid Hydrolysis of 1 : 2-5 : 6-Diisopropylidene 3 : 4-Anhydro-D-talitol.—The compound (4.9 g.) was heated on the steam-bath with 0.9N-sulphuric acid (5 c.c.) for 2½ hours, the liberated acetone being allowed to escape. The cooled solution was then extracted once with ether, to remove a trace of oily impurity, and treated with a slight excess of barium hydroxide solution, the excess then being neutralised with carbon dioxide. The precipitate was removed on the centrifuge and washed twice with a little water. Evaporation of the aqueous solution under reduced pressure then gave a syrup, which was evaporated several times with ethanol and then dissolved in ethanol (45 c.c.) and water (4 c.c.). This solution was filtered and concentrated to small bulk; successive treatments with small quantities of ethyl acetate then gave three crops of mannitol, m. p. 163—166°, 160—161°, and 161—163°, respectively, undepressed on admixture with authentic mannitol of m. p. 166° (iditol has m. p. 73—74°). The total yield was 1.83 g. Evaporation of the mother-liquors gave a syrup (2.0 g.), which contained iditol (see below).

2 : 4-3 : 5-Dimethylene D-Iditol.—The syrup (2.0 g.) was heated on the steam-bath with 40% aqueous formaldehyde solution (5 c.c.) and concentrated hydrochloric acid (5 c.c.) for 6 hours, and then left overnight at room temperature. The solution was filtered and evaporated on the steam-bath to a syrup, which was dissolved in a little water and again evaporated to yield a solid residue. This was dissolved in boiling water (10 c.c.), and the solution was filtered; on cooling, a crystalline solid separated, m. p. 262—265° (0.52 g.), and on further recrystallisation from water and from aqueous methanol (with charcoal) small plates of 2 : 4-3 : 5-dimethylene D-iditol were obtained, having m. p. 262—265° (decomp.), $[\alpha]_D^{25}$ -38.5° (*c*, 0.3 in water) (Found : C, 46.25; H, 6.6. $C_8H_{14}O_6$ requires C, 46.6; H, 6.8%). Hann and Hudson (*loc. cit.*), for the L-form, recorded m. p. 260—262° (decomp.), $[\alpha]_D^{20}$ +39.2° in water.

The mother-liquors from the above crystallisations were re-treated with formaldehyde and hydrochloric acid, and gave a further small quantity of dimethylene D-iditol.

1 : 6-Diacetyl 2 : 4-3 : 5-Dimethylene D-Iditol.—2 : 4-3 : 5-Dimethylene D-iditol (0.2 g.) was dissolved in a mixture of acetic acid (0.6 c.c.) and acetic anhydride (1.4 c.c.). Concentrated sulphuric acid (0.05 c.c.) was added, and after a few minutes the reaction mixture was poured into water. The precipitated solid was recrystallised first from ethanol and finally from water, and gave needles (0.1 g.) of the diacetyl derivative, m. p. 220—221°, $[\alpha]_D^{20}$ +4.8° (*c*, 0.9 in chloroform) (Found : C, 49.7; H, 6.1. $C_{12}H_{18}O_8$ requires C, 49.65; H, 6.25%). Hann and Hudson (*loc. cit.*), for the L-enantiomorph, give m. p. 219—220°, $[\alpha]_D^{20}$ -3.9° in chloroform.

Reaction of 1 : 2-5 : 6-Diisopropylidene 3 : 4-Anhydro-D-talitol with Sodium Methoxide.—Heating of the anhydro-compound with 0.2N-methanolic sodium methoxide under reflux for periods up to 15 hours resulted in no significant change in optical rotation, and the material was recovered almost quantitatively from the solution. With 2N-methanolic sodium methoxide in a sealed tube at 100°, a change in $[\alpha]_D$ from -23.2° (initial) to +5.1° (6 hours) was observed.

The anhydro-compound (5 g.) was therefore dissolved in 3.5N-methanolic sodium methoxide (35 c.c.); and the solution was heated in a small autoclave at 100—105° for 20 hours. The cooled product was diluted with water, neutralised with carbon dioxide, and concentrated under reduced pressure to remove most of the methanol. The aqueous solution was then extracted with ether (5 × 50 c.c.), the extracts were dried (Na_2SO_4), and the solvent was evaporated. Distillation of the residual syrup (5.0 g.) gave a colourless liquid, probably a mixture of 3-methyl 1 : 2-5 : 6-diisopropylidene D-mannitol and 3-methyl 1 : 2-5 : 6-diisopropylidene D-iditol, b. p. 96°/0.003 mm., n_D^{19} 1.4530, $[\alpha]_D^{21}$ +6.8° (*c*, 4 in chloroform) (Found : C, 56.5; H, 8.6. Calc. for $C_{13}H_{24}O_6$: C, 56.5; H, 8.8%). A diisopropylidene compound of uncertain structure from 3-methyl mannitol, prepared by Haskins, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1943, 65, 70), had m. p. 57—58°, $[\alpha]_D^{20}$ +9.0° (in alcohol).

3-Methyl Mannitol.—The above mixture was hydrolysed by being heated with 0.45N-sulphuric acid (10 c.c.) for 7 hours, the acetone being removed from the liquid by the passage of a slow stream of nitrogen. The solution was extracted once with ether, to remove oily impurities, and it was then heated to ca. 80° and treated with a slight excess of barium hydroxide solution, the excess then being removed with carbon dioxide. The precipitate was filtered off, and the filtrate was evaporated under reduced pressure to a syrup, which was dried by evaporation several times with ethanol. It was then dissolved in hot ethanol (20 c.c.) and filtered from a small amount of insoluble matter. Evaporation then gave a syrup (2.7 g.; calc. yield of methyl hexitol, 2.8 g.) which on treatment with ethanol-ethyl acetate gave a precipitate of 3-methyl mannitol monohydrate (1.25 g., 45%), m. p. 85—86°. Haskins, Hann, and Hudson (*loc. cit.*) give m. p. 86—87°. Crystallisation from dry ethanol gave the anhydrous 3-methyl mannitol, m. p. 132—133°, $[\alpha]_D^{20}$ +16.5° (*c*, 2 in water). Haskins *et al.* (*ibid.*) give m. p. 133—134°, $[\alpha]_D^{20}$ +16.7° (*c*, 2 in water).

Evaporation of the mother-liquors from the initial precipitation of 3-methyl mannitol gave a syrup (1.4 g.) which could not be induced to crystallise, and presumably contained 3-methyl iditol.

3-Allyl D-Mannitol.—When 3 : 4-anhydro-D-talitol was heated with 0.1N-sodium allyl oxide in allyl alcohol for 5½ hours under reflux, the greater part of the material was recovered unchanged. A solution of the anhydro-compound (6.1 g.) in dry allyl alcohol (50 c.c.) containing sodium (5 g.; *i.e.*, a 4N-solution) was heated under an air reflux condenser for 17 hours, during which time the solution became more concentrated owing to loss of solvent. The syrupy product was treated with water (100 c.c.) and steam-distilled to remove allyl alcohol. The alkali was neutralised with carbon dioxide, and the solution was extracted with ether (4 × 60 c.c.). The dried (Na_2SO_4) extracts were then evaporated and the residual oil was distilled to give a mixture (7.0 g., 94%) of 3-allyl 1 : 2-5 : 6-diisopropylidene D-mannitol and 3-allyl 1 : 2-5 : 6-diisopropylidene D-iditol, b. p. 94—97°/0.001 mm., n_D^{20} 1.4634, $[\alpha]_D^{22}$ +4.1° (*c*, 2 in chloroform) (Found : C, 59.85; H, 8.4. Calc. for $C_{15}H_{26}O_6$: C, 59.6; H, 8.7%). This mixture was hydrolysed in a similar way to that used for the corresponding methyl compounds and gave 3-allyl D-mannitol (1.6 g., 30%), m. p. and mixed m. p. 117—118°, $[\alpha]_D^{25}$ +17.7° (*c*, 1 in water) (cf. Bladon and

Owen, J., 1950, 591). Evaporation of the mother-liquors gave a syrup (1.75 g.) from which no crystalline material could be obtained.

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