481. *The* iso*Propylidene Derivatives of Hexahydric Alcohols. Part III.** iso*Propylidene Derivatives of* L-*Iditol.*

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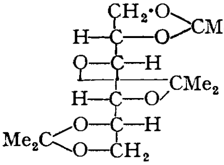
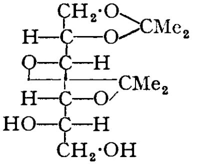
Treatment of L-iditol with acetone and concentrated sulphuric acid is shown to give the 1 : 2-3 : 4-5 : 6-tri*iso*propylidene derivative. Graded acidic hydrolysis of this compound yields 1 : 2-3 : 4-di*iso*propylidene L-iditol, 3 : 4-*iso*propylidene L-iditol, and L-iditol. Proofs of the structures of these three ketals are given and some of their derivatives are described.

Although there is now available a considerable amount of information concerning the structures of the products which result from the condensation of aldehydes and ketones with polyhydric alcohols, little is known of the acetals and ketals of iditol. Indeed the only direct condensation between iditol and a carbonyl compound which has been studied in detail is that involving formaldehyde; Hann and Hudson (*J. Amer. Chem. Soc.*, 1944, **66**, 1909; 1945, **67**, 602) found that, when a mixture of L-iditol, 37% formaldehyde solution, and concentrated hydrochloric acid was evaporated at 25°, the principal product was 2 : 4-3 : 5-dimethylene L-iditol, which appeared to be identical with the methylene derivative of L-iditol prepared by Lobry de Bruyn and van Ekenstein (*Rec. Trav. chim.*, 1900, **19**, 1, 178). Early references were made to a di- and a tri-benzylidene iditol (last reference was : Bertrand, *Ann. Chim. Phys.*, 1907, [viii], **10**, 450), but no structures were assigned to these compounds and, in view of the work of Hann and Hudson in the methylene series, there is some doubt whether a tribenzylidene iditol could, in fact, be prepared (cf. Barker and Bourne, *J.*, 1952, 905). The only *iso*propylidene derivative of iditol recorded is 3(or 4)-methyl 1 : 2-5 : 6-di*iso*propylidene D-iditol, which Bladon and Owen (*J.*, 1950, 604) believed they had obtained, together with 3-methyl 1 : 2-5 : 6-di*iso*propylidene D-mannitol, by treatment of 1 : 2-5 : 6-di*iso*propylidene 3 : 4-anhydro-D-talitol with sodium methoxide. We now report the synthesis of 1 : 2-3 : 4-5 : 6-tri*iso*propylidene L-iditol (I), and thence, by partial hydrolysis, of 1 : 2-3 : 4-di*iso*propylidene and 3 : 4-*iso*propylidene L-iditol (II and III).


(I)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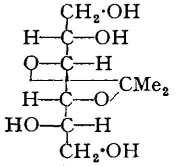
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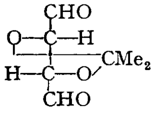
(IV)

The sample of L-iditol employed had been prepared from L-sorbose by the method of Jones and Wiggins (*J.*, 1944, 363), which involved hydrogenation in the presence of Raney nickel and separation of the resulting L-iditol and sorbitol by fractional crystallisation of their acetates. When L-iditol was shaken with dry acetone and concentrated sulphuric acid, a highly crystalline tri*iso*propylidene derivative was obtained. Partial hydrolysis of the triketal with hydrochloric acid in aqueous ethyl alcohol and fractionation of the products yielded unchanged starting material, a syrupy di*iso*propylidene hexitol, a crystalline mono*iso*propylidene hexitol, and L-iditol. Confirmation that all three *iso*propylidene compounds were derivatives of L-iditol was obtained when they were converted, by hydrolysis and subsequent acetylation, into L-iditol hexa-acetate.

Treatment of the mono*iso*propylidene L-iditol with sodium metaperiodate solution resulted in the rapid consumption of 2·0 mols. of oxidising agent and in the production of 1·9 mols. of formaldehyde, which was isolated as its crystalline dimedone derivative; these facts proved that the acetone residue spanned positions 3 and 4 of the hexitol molecule (III). In conformity with this conclusion, the major fragment of the oxidative cleavage

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* Part II, *J.*, 1952, 1408.

was shown to be probably *iso*propylidene D-*threo*dihydroxysuccindialdehyde (IV) by its conversion, with toluene-ω-thiol and fuming hydrochloric acid, into the known crystalline bis(dibenzyl mercaptal) of D-*threo*dihydroxysuccindialdehyde. The assignment of the ketal group of the mono*iso*propylidene L-iditol to the 3 : 4-position was in agreement with two other facts, namely, (*a*) that the compound readily gave a ditrityl ether (isolated as its crystalline diacetate) (cf. Helferich, *Adv. Carbohydrate Chem.*, 1948, **3**, 79), and (*b*) that its tetratoluene-*p*-sulphonate afforded 3·9 mols. of sodium toluene-*p*-sulphonate, together with iodine, when heated with sodium iodide in acetone at 100° for 5 hours.

In the case of the di*iso*propylidene L-iditol, too, it was possible to define the positions of the free hydroxyl groups by studying its oxidation with periodate, for the consumption of 1·0 mol. of the oxidising agent was accompanied by the production of formaldehyde, which was isolated after distillation in steam as its dimedone derivative (0·7 mol.). Thus positions 5 and 6 were not engaged by the acetone residues. (N.B. In the case of iditol it is not necessary to distinguish between the 1 : 2- and 5 : 6-positions.) The second product of the oxidation, di*iso*propylidene *aldehydo*-L-xylose, will be discussed in a later communication. As confirmatory evidence that the di*iso*propylidene L-iditol carried a terminal α-glycol group, it was shown that it gave a trityl ether under mild conditions, and that its crystalline ditoluene-*p*-sulphonate yielded 2·0 mols. of sodium toluene-*p*-sulphonate, together with iodine, when treated with sodium iodide in acetone at 100° for 6 hours.

There were still three possible arrangements (*viz.*, 1 : 2-3 : 4, 1 : 3-2 : 4, and 1 : 4-2 : 3) of the ketal groups in the di*iso*propylidene L-iditol which would have been in keeping with all of the above experimental facts, but two of these possibilities were eliminated when 3 : 4-*iso*propylidene L-iditol was obtained after acidic hydrolysis of the compound. Hence the acetone residues were located on the 1 : 2- and 3 : 4-positions, so that the parent tri*iso*propylidene L-iditol, from which both the mono- and di-ketals were derived initially, must have possessed the 1 : 2-3 : 4-5 : 6-structure. Iditol is similar therefore to mannitol and sorbitol inasmuch as they all afford 1 : 2-3 : 4-5 : 6-tri*iso*propylidene derivatives (cf. Wiggins, *J.*, 1946, 13; Bourne, McSweeney, Stacey, and Wiggins, *ibid.*, 1952, 1408); in each case, too, the α-rings are less stable during acidic hydrolysis than the αT-rings (for a definition of these symbols see Barker and Bourne, *loc. cit.*).

EXPERIMENTAL

L-Iditol Hexa-acetate from L-Sorbose.—L-Iditol hexa-acetate, prepared from L-sorbose by hydrogenation, acetylation, and fractional crystallisation, as described by Jones and Wiggins (*loc. cit.*), had m. p. 122°, $[\alpha]_D^{23}$ −25·9° (*c*, 1·4 in chloroform). Recorded constants are m. p. 121·5°, $[\alpha]_D^{18}$ −25·7° (in chloroform) (Bertrand, *Bull. Soc. chim.*, 1905, **33**, 166), m. p. 119·5—120·5°, $[\alpha]_D^{19}$ −26·1° (in chloroform) (Meyer and Reichstein, *Helv. Chim. Acta*, 1946, **29**, 152), and m. p. 122°, $[\alpha]_D^{15}$ −24·8° (in chloroform) (Jones and Wiggins, *loc. cit.*).

L-Iditol.—A suspension of L-iditol hexa-acetate (28 g.) in absolute methyl alcohol (150 c.c.), containing sodium methoxide (0·10 g.), was kept at room temperature for 20 hours, before being concentrated under diminished pressure to a syrup (11·6 g.), which partly crystallised *in vacuo*, and was used without further purification for the following experiments.

L-Iditol Hexabenzoate.—A solution of L-iditol (0·50 g.) and benzoyl chloride (2·10 c.c.) in dry pyridine (4 c.c.) was kept at 20° for 20 hours, poured into ice-water, and extracted with chloroform. The extracts were washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and concentrated to a syrup, which crystallised when triturated with alcohol. After two more crystallisations, *L-iditol hexabenzoate* (0·50 g.), m. p. 142—143°, $[\alpha]_D^{19}$ +48·5° (*c*, 1·8 in chloroform), was obtained as colourless prisms (Found : C, 71·2; H, 4·5. $C_{48}H_{38}O_{12}$ requires C, 71·5; H, 4·7%).

1 : 2-3 : 4-5 : 6-*Tri*iso*propylidene L-Iditol.*—L-Iditol (38 g.) was shaken with dry acetone (500 c.c.) and concentrated sulphuric acid (3·8 c.c.) until dissolution was complete (*ca.* 36 hours). The solution was neutralised with aqueous ammonia (*d* 0·880) and filtered. The combined filtrate and acetone washings (70 c.c.) were concentrated, in the presence of sodium carbonate, to a syrup, which was transferred in alcohol solution into excess of ice-water. The precipitate, recrystallised from aqueous acetone, gave 1 : 2-3 : 4-5 : 6-*tri*iso*propylidene L-iditol* (32 g.), m. p. 57—58°, $[\alpha]_D^{16}$ +5·8° (*c*, 5·5 in chloroform), $[\alpha]_D^{18}$ +12·2° (*c*, 3·3 in absolute ethanol) (Found : C, 59·5; H, 8·6. $C_{15}H_{26}O_6$ requires C, 59·6; H, 8·7%).

L-Iditol Hexa-acetate from 1 : 2-3 : 4-5 : 6-*Trï*iso*propylidene* *L-Iditol*.—A solution of the tri*iso*propylidene derivative (0·80 g.) in 2N-hydrochloric acid (6 c.c.) was kept at 100° for 2 hours and then evaporated at 12 mm., to give a syrup (0·47 g.), which was acetylated in the usual way with acetic anhydride (3 c.c.) and fused sodium acetate (0·5 g.). The product, recrystallised from aqueous ethyl alcohol, gave L-iditol hexa-acetate (0·59 g.), m. p. and mixed m. p. 119—120°.

Graded Hydrolysis of 1 : 2-3 : 4-5 : 6-*Trï*iso*propylidene* *L-Iditol*.—A solution of 1 : 2-3 : 4-5 : 6-tri*ïso*propylidene L-iditol (20·1 g.) in a mixture of absolute ethyl alcohol (396 c.c.) and 10N-hydrochloric acid (4 c.c.) was kept at room temperature for 70 minutes, cooled to 0°, neutralised with lead carbonate, and filtered. The filtrate and alcoholic washings were evaporated at 12 mm. to a syrup (17·9 g.), which was transferred in a small volume of alcohol into ice-water (250 c.c.), containing a trace of ammonia. The precipitate (3 g.), collected by filtration, had m. p. 57° alone or on admixture with 1 : 2-3 : 4-5 : 6-tri*ïso*propylidene L-iditol; a second crop of this material was obtained when the solution was concentrated. Complete evaporation of the filtrate left a syrup, which was extracted with dry acetone; acetylation of the insoluble residue with fused sodium acetate–acetic anhydride afforded L-iditol hexa-acetate (1·0 g.). The syrup obtained when the acetone solution was concentrated was extracted with warm benzene (3 × 40 c.c.), leaving an insoluble syrup (A; 5·1 g.); evaporation of the extracts gave another syrup (B; 8·5 g.).

Syrup (A), crystallised several times from dry acetone, yielded 3 : 4-iso*propylidene* *L-iditol* (0·73 g.), m. p. 90—91° (depressed on admixture with 3 : 4-*iso*propylidene sorbitol), $[\alpha]_D^{20}$ + 41·7° (*c*, 3·5 in methyl alcohol) (Found : C, 48·9; H, 8·4. $C_9H_{18}O_6$ requires C, 48·6; H, 8·2%).

Fractional distillation of syrup (B) gave 1 : 2-3 : 4-*di*iso*propylidene* *L-iditol* (6·0 g.), b. p. 136—140° (bath-temp.)/0·005 mm., $[\alpha]_D^{19}$ + 23·8° (*c*, 2·9 in ethyl alcohol) (Found : C, 54·8; H, 8·5. $C_{12}H_{22}O_6$ requires C, 54·9; H, 8·5%).

L-Iditol Hexa-acetate from 1 : 2-3 : 4-*Di*iso*propylidene* *L-Iditol and* 3 : 4-iso*Propylidene* *L-Iditol*.—The mono- and di-*iso*propylidene derivatives (0·30 g.), when hydrolysed and then acetylated, as described above, gave L-iditol hexa-acetate (0·25 g. and 0·30 g., respectively), m. p. 121° alone or on admixture with an authentic specimen.

2 : 5-*Diacetyl* 3 : 4-iso*Propylidene* 1 : 6-*Ditrityl* *L-Iditol*.—A solution of 3 : 4-*iso*propylidene L-iditol (0·33 g.) and triphenylmethyl chloride (0·83 g.) in pyridine (3 c.c.) was kept at 25° for 20 hours before acetic anhydride (0·40 c.c.) was added. After a further 24 hours, the solution was poured into water, and the precipitate was collected by filtration. Several crystallisations from ethyl alcohol gave 2 : 5-*diacetyl* 3 : 4-iso*propylidene* 1 : 6-*ditrityl* *L-iditol* (1·05 g.), m. p. 196—200°, $[\alpha]_D^{19}$ + 11·7° (*c*, 2·7 in pyridine) (Found : C, 77·2; H, 6·2. $C_{51}H_{50}O_8$ requires C, 77·5; H, 6·4%).

3 : 4-iso*Propylidene* 1 : 2 : 5 : 6-*Tetratoluene*-p-*sulphonyl* *L-Iditol*.—A solution of 3 : 4-*iso*propylidene L-iditol (0·30 g.) and toluene-*p*-sulphonyl chloride (1·55 g.) in pyridine (3 c.c.) was kept at 25° for 20 hours, poured into ice-water, and extracted with chloroform. The extracts were washed with 0·5N-sulphuric acid at 0°, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), filtered, and evaporated, to give 3 : 4-iso*propylidene* 1 : 2 : 5 : 6-*tetratoluene*-p-*sulphonyl* *L-iditol* as a glass (1·05 g.), $[\alpha]_D^{21}$ +10·0° (*c*, 4·0 in chloroform) (Found : C, 53·1; H, 5·3; S, 15·0. $C_{37}H_{42}O_{14}S_4$ requires C, 53·0; H, 5·0; S, 15·3%).

Treatment of 3 : 4-iso*Propylidene* 1 : 2 : 5 : 6-*Tetratoluene*-p-*sulphonyl* *L-Iditol with Sodium Iodide*.—The toluene-*p*-sulphonate (0·16 g.) was heated with sodium iodide (0·17 g.) in dry acetone (10 c.c.) at 100° for 5 hours, during which an iodine colour developed. The precipitated sodium toluene-*p*-sulphonate was collected, washed with a small volume of dry acetone, and dried at 110°; it corresponded to an exchange of 3·86 toluene-*p*-sulphonyloxy-groups per molecule of the iditol derivative.

Periodate Oxidation of 3 : 4-iso*Propylidene* *L-Iditol*.—(a) *Amount of periodate consumed.* An aqueous solution of 3 : 4-*iso*propylidene L-iditol (0·032 g.) was mixed with 0·30M-sodium metaperiodate (10 c.c.) and then diluted to 50 c.c. The iditol derivative was omitted from a similar control solution. Portions (2 c.c.) of the reaction mixture and of the control solution were withdrawn at intervals; each portion was mixed immediately with a solution of sodium hydrogen carbonate (0·50 g.) and potassium iodide (1·0 g.) in water (50 c.c.), and the iodine liberated was titrated against sodium arsenite solution (cf. Jackson, *Org. Reactions*, 1944, **2**, 341). The number of moles of periodate consumed per mole of 3 : 4-*iso*propylidene L-iditol was : 1·85 (1·5 minutes), 1·96 (2·5 minutes), 2·02 (4·5 minutes), and 2·12 (61 minutes).

(b) *Determination of formaldehyde produced.* 3 : 4-*iso*Propylidene L-iditol (0·028 g.) was oxidised with periodate, and the formaldehyde produced was isolated as its dimedone derivative

(m. p. 188°), as described by Reeves (*J. Amer. Chem. Soc.*, 1941, **63**, 1476). The yield of the dimedone compound corresponded to the production of 1·91 moles of formaldehyde per mole of 3 : 4-*iso*propylidene L-iditol.

(c) *Isolation of* D-threo*dihydroxysuccindialdehyde bis*(*dibenzyl mercaptal*). A solution of 3 : 4-*iso*propylidene L-iditol (0·50 g.) and sodium metaperiodate (1·10 g.) in water (10 c.c.) was kept at room temperature for 20 hours, saturated with sodium chloride, and evaporated at 40°/12 mm. in the presence of sodium hydrogen carbonate (0·25 g.). The residue was extracted with chloroform; the extracts were dried ($MgSO_4$), filtered, and evaporated, leaving a glass (0·25 g.). Part (0·10 g.) of the product was shaken with toluene-ω-thiol (0·20 c.c.) and fuming hydrochloric acid (1 c.c.) for 4 hours before the mixture was diluted with water and extracted with chloroform. The extracts were washed with dilute sodium hydroxide solution and then with water, dried ($MgSO_4$), filtered, and evaporated to a syrup, which crystallised from ethyl alcohol in silky needles, $[\alpha]_D^{16}$ +70·0° (*c*, 1·2 in pyridine), m. p. 101° alone or on admixture with a specimen of D-*threo*dihydroxysuccindialdehyde bis(dibenzyl mercaptal) prepared from 3 : 4-*cyclo*hexylidene D-mannitol by a similar process (Bourne and Corbett, unpublished).

1 : 2-3 : 4-*Di*iso*propylidene* 5 : 6-*Ditoluene*-p-*sulphonyl* L-*Iditol*.—A solution of 1 : 2-3 : 4-di*iso*propylidene L-iditol (0·40 g.) and toluene-*p*-sulphonyl chloride (0·70 g.) in pyridine (2 c.c.) was kept at 30° for 2 days, poured into ice-water, and extracted with chloroform. The extracts were washed successively with 0·1N-sulphuric acid at 0°, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), filtered, and evaporated to a syrup, which crystallised from methyl alcohol. Two recrystallisations from aqueous methyl alcohol gave colourless needles (0·33 g.) of 1 : 2-3 : 4-*di*iso*propylidene* 5 : 6-*ditoluene*-p-*sulphonyl* L-*iditol*, m. p. 113—114°, $[\alpha]_D^{21}$ +11·5° (*c*, 2·8 in pyridine) (Found: C, 55·0; H, 6·2; S, 11·0. $C_{26}H_{34}O_{10}S_2$ requires C, 54·7; H, 6·0; S, 11·2%).

Treatment of 1 : 2-3 : 4-*Di*iso*propylidene* 5 : 6-*Ditoluene*-p-*sulphonyl* L-*Iditol with Sodium Iodide*.—The ditoluene-*p*-sulphonate (0·12 g.) was heated for 6 hours at 100° with sodium iodide (0·13 g.) in dry acetone (5 c.c.), iodine being liberated. The precipitated sodium toluene-*p*-sulphonate was collected by filtration, washed with acetone, and dried at 110°; it represented an exchange of 2·00 toluene-*p*-sulphonyloxy-groups per molecule of the di*iso*propylidene compound.

5-*Acetyl* 1 : 2-3 : 4-*Di*iso*propylidene* 6-*Trityl* L-*Iditol*.—A solution of 1 : 2-3 : 4-di*iso*propylidene L-iditol (0·33 g.) and triphenylmethyl chloride (0·35 g.) in pyridine (2 c.c.) was kept at room temperature for 24 hours before acetic anhydride (0·26 c.c.) was added. After a further 20 hours, the solution was poured into ice-water, and the precipitate was collected 2 days later. It was purified by precipitation (as a gel) from methanol with a few drops of water, and was hardened with water. A repetition of the purification procedure gave 5-*acetyl* 1 : 2-3 : 4-*di*iso*propylidene* 6-*trityl* L-*iditol* (0·20 g.) as an amorphous solid, which, after being dried over phosphoric anhydride, had m. p. 117—120°, $[\alpha]_D^{18}$ +7·9° (*c*, 3·3 in pyridine) (Found : C, 72·2; H, 6·8. $C_{33}H_{38}O_7$ requires C, 72·5; H, 7·0%).

Periodate Oxidation of 1 : 2-3 : 4-*Di*iso*propylidene* L-*Iditol*.—(a) *Amount of periodate consumed.* 1 : 2-3 : 4-Di*iso*propylidene L-iditol (0·058 g.) was oxidised with sodium metaperiodate, and the excess of the oxidising agent was determined, at intervals, by titration with sodium arsenite, as described above. The number of mols. of periodate consumed was : 0·74 (1 minute), 0·88 (2 minutes), 0·94 (3·3 minutes), 0·98 (4·5 minutes), and 0·98 (24 minutes).

(b) *Determination of formaldehyde.* The di*iso*propylidene compound (0·029 g.) was oxidised with periodate and an attempt was made to isolate the resulting formaldehyde as its dimedone derivative, following the procedure recommended by Reeves (*loc. cit.*). The product, which corresponded in weight to the production of 1·69 mols. of formaldehyde, had m. p. 174—184° and was probably a mixture of the dimedone derivatives of formaldehyde and 2 : 3-4 : 5-di*iso*propylidene *aldehydo*-L-xylose.

In a second experiment, an aqueous solution (2 c.c.) of 1 : 2-3 : 4-di*iso*propylidene L-iditol (0·064 g.) was mixed with 0·2M-sodium periodate (5 c.c.) and kept at room temperature for 2 hours before being steam-distilled at 8 cm. The dimedone derivative prepared from the distillate corresponded in weight to the production of 0·72 mol. of formaldehyde, and had m. p. 188° alone or on admixture with an authentic specimen of the dimedone derivative of formaldehyde.

3 : 4-iso*Propylidene* L-*Iditol from* 1 : 2-3 : 4-*Di*iso*propylidene* L-*Iditol*.—A solution of 1 : 2-3 : 4-di*iso*propylidene L-iditol (1·03 g.) in a mixture of ethyl alcohol (18 c.c.) and N-hydrochloric acid (2 c.c.) was kept at room temperature for 82 minutes, cooled to 0°, neutralised with lead carbonate, and centrifuged. The combined supernatant liquid and ethyl alcohol washings were evaporated at 12 mm. to a syrup (0·94 g.), which was extracted with dry acetone. The extracts were evaporated to a syrup, which was then extracted with warm benzene. The insoluble

portion was crystallised twice from dry acetone, to give **3** : 4-*iso*propylidene L-iditol (0·20 g.), m. p. 90° alone or on admixture with the specimen mentioned above.

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