

264. *Anhydrides of Polyhydric Alcohols. Part XV. The Reactions of Sodium Iodide and Lithium Chloride with Dimethanesulphonyl and Ditoluene-*p*-sulphonyl Derivatives of the 1 : 4-3 : 6-Dianhydrides of D-Mannitol, D-Sorbitol, and L-Iditol.*

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The reactivity of the sulphonyl groups in methanesulphonyl and toluene-*p*-sulphonyl derivatives of the dianhydrides of the epimeric series D-mannitol, D-sorbitol, and L-iditol has been shown to be related to the stereochemistry of the hexitols. In the case of mannitol derivatives both groups are replaced by iodine on treatment with sodium iodide or by chlorine on treatment with lithium chloride. In the case of the corresponding sorbitol derivatives, which differ from the mannitol compounds only by the configuration at C₍₂₎, only one sulphonic acid residue is replaced by either iodine or chlorine. When analogous derivatives of dianhydro-L-iditol, in which the configurations of C₍₂₎ and C₍₅₎ are reversed with respect to mannitol, are treated similarly no reaction occurs in either case.

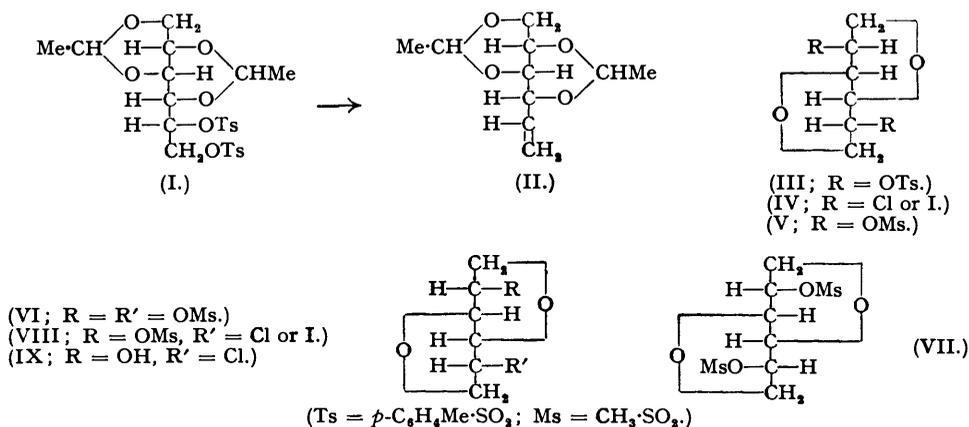
The ease of reaction of the three dianhydrides with thionyl chloride shows a similar gradation. 1 : 4-3 : 6-Dianhydromannitol is readily converted into the 2 : 5-dichloro-derivative (Wiggins, *J.*, 1945, 4); 1 : 4-3 : 6-dianhydro-sorbitol gives, with considerable difficulty, a monochloro-derivative (Overend, Montgomery, and Wiggins, *J.*, 1948, 2201). It has not been possible to isolate chlorine-containing derivatives from 1 : 4-3 : 6-dianhydro-L-iditol.

TREATMENT of toluene-*p*-sulphonic esters of carbohydrates with sodium iodide in acetone, leading to replacement of the sulphonyloxy-groups by iodine, constitutes a well-known method of distinguishing between primary and secondary hydroxyl groups (Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366). In general a toluene-*p*-sulphonyloxy-group attached to CH₂ reacts readily at 100—105°, being replaced by iodine with simultaneous formation of sodium toluene-*p*-sulphonate, while such a group attached to >CH• does not react. Methanesulphonyl derivatives behave similarly (Foster, Overend, Stacey, and Wiggins, *J.*, 1949, 2542). The degree to which replacement occurs varies with different compounds, being influenced by neighbouring groups in the molecule.

Exceptions to Oldham and Rutherford's rule have however been reported. Thus when vicinal primary and secondary toluene-*p*-sulphonyloxy-groups are present, both are removed; two equivalents of sodium toluene-*p*-sulphonate are produced but, instead of a di-iodo-derivative, an unsaturated compound results. Thus 1 : 3-2 : 4-diethylidene 5 : 6-ditoluene-*p*-sulphonyl sorbitol (I) gives 1 : 3-2 : 4-diethylidene 5 : 6-sorbitoleen (II) (Bladon and Owen, *J.*, 1950, 598). Similarly, all the toluene-*p*-sulphonyloxy-residues in glycerol tritoluene-*p*-sulphonate are removed by sodium iodide treatment (Levene and Mehlretter, *Enzymologia*, 1937, **4**, ii, 232), and erythritol tetratoluene-*p*-sulphonate behaves in the same way, furnishing butadiene (Tipson and Cretcher, *J. Org. Chem.*, 1943, **8**, 95).

Notable among the exceptions to this replacement rule is the case of 2 : 5-ditoluene-*p*-sulphonyl 1 : 4-3 : 6-dianhydromannitol (III), in which both sulphonyl groups are quantitatively replaced by iodine with the formation of the di-iodo-compound (IV; R = I) when the sodium iodide treatment is carried out under quite mild conditions, despite the fact that both sulphonyloxy-residues are known with certainty to be secondary (Hockett *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 930). It has now been found that the reaction (III) → (IV) is only one case of a more general peculiarity of sulphonyl derivatives of 1 : 4-3 : 6-dianhydrohexitols. 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-dianhydromannitol (V) reacted readily with sodium iodide in acetone to give the same 2 : 5-di-iodo-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol (IV; R = I) as is obtained from the corresponding toluene-*p*-sulphonyl derivative (III). Dimethanesulphonyl dianhydrosorbitol (VI) also underwent reaction with sodium iodide, but in this case only one methanesulphonyl group was replaced, giving a methanesulphonyl monoiodo-1 : 4-3 : 6-dianhydrodeoxysorbitol in 27% yield; this compound is probably (VIII; R' = I). 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-dianhydro-L-iditol (VII) was, however, almost completely

unaffected by sodium iodide treatment : the yield of sodium methanesulphonate was only 4.1%, and a 90% recovery of the dimethanesulphonate was obtained.



Clarke and Owen (*J.*, 1949, 315) have shown that the monomethanesulphonyl and monotoluene-*p*-sulphonyl derivatives of *cyclohexane*-1 : 2-diol readily react with sodium iodide in acetone and also with lithium chloride in alcohol; in the latter case the sulphonyloxy-group is replaced by chlorine. This suggested that the action of lithium chloride on dimethanesulphonyl dianhydrohexitols might be studied, and it has been found that reaction does take place, although rather more drastic conditions, namely, heating at 150° for 48 hours, are necessary to effect it. The chlorine-exchange reaction with the three isomeric dimethanesulphonyl compounds follows exactly the same course as iodine-exchange. 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-dianhydromannitol (V) yielded 2 : 5-dichloro-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol (IV; R = Cl), identical with that prepared by Wiggins (*J.*, 1945, 4) by direct chlorination of dianhydromannitol. Dimethanesulphonyl dianhydrosorbitol (VI) gave under the same conditions a methanesulphonyl monochlorodianhydrodeoxysorbitol (VIII; R' = Cl). Hydrolysis of this with sodium hydroxide led to the formation of the monochlorodianhydrodeoxysorbitol reported by Overend, Montgomery, and Wiggins (*J.*, 1948, 2201) as a product of the action of thionyl chloride on 1 : 4-3 : 6-dianhydrosorbitol. From these facts it is certain that the monochloro-compound must be either 2- or 5-chloro-1 : 4-3 : 6-dianhydro-2(5)-deoxysorbitol; it is not possible as yet to decide definitely which of these alternatives is correct, but there is no reason to dispute the argument put forward by Overend, Montgomery, and Wiggins that it is probably the 5-chloro-compound (IX).

In an attempt to replace both methanesulphonyloxy-residues in dimethanesulphonyl 1 : 4-3 : 6-dianhydrosorbitol by chlorine, the compound was heated with lithium chloride in alcohol-acetone at a higher temperature. The liquid product which was obtained in small yield was free from sulphur, but ultimate analysis indicated that it contained only one chlorine atom; in addition it was found to be unsaturated. It is tentatively formulated as a monochlorodianhydrodeoxysorbitoleen.

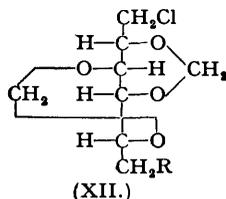
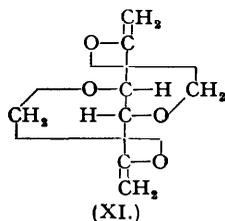
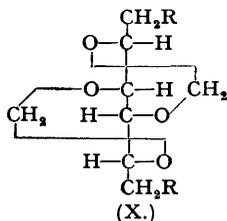
The action of lithium chloride on ditoluene-*p*-sulphonyl dianhydrosorbitol under the normal conditions was found, as expected, to give the toluene-*p*-sulphonyl derivative of the monochlorodianhydrodeoxyhexitol of Overend, Montgomery, and Wiggins, but in lower yield than that in which the corresponding methanesulphonyl compound was obtained.

Interaction of 2 : 5-dimethanesulphonyl 1 : 4-3 : 6-dianhydro-*L*-iditol (VII) and lithium chloride did not lead to any definite results. After treatment at 150° the starting material was recovered in high yield, no other product being isolated; at 180° only a black tar was obtained.

Thus, a considerable difference exists between the 1 : 4-3 : 6-dianhydro-derivatives of mannitol, sorbitol, and iditol regarding the reactivity of substituent sulphonyl groups at positions 2 and 5. The observed behaviour is closely paralleled by the results of the earlier attempts to introduce chlorine atoms directly into the dianhydrohexitol molecule by the action of thionyl chloride in pyridine. The dimethanesulphonate of the mannitol dianhydride reacts readily with replacement of both sulphonyloxy-groups by halogen, while the action of thionyl chloride on the dianhydride easily affords the same 2 : 5-dichloro-derivative. With dianhydro-

sorbitol, on the other hand, only one sulphonyloxy-group is replaced by halogen, and the action of thionyl chloride directly on the dianhydride results in the formation of a monochloro-derivative. In the case of dianhydritol, the dimethanesulphonate does not react smoothly with sodium iodide or lithium chloride and it has now been found impossible to obtain chloro-derivatives from the dianhydride by thionyl chloride under the conditions which are successful in the case of dianhydromannitol.

It is not possible, from the evidence at present available, to explain this behaviour. Other experimental results have suggested that whereas in 1 : 4-3 : 6-dianhydromannitol both anhydro-rings are equally stable, in the sorbitol isomeride one ring (the 1 : 4) is rather more stable than the other; these facts bear some similarity to the observed variations in reactivity of the anhydrides in substitution reactions, but no theoretical basis for a connection between these effects is as yet apparent. Of allied interest are some observations on the reactivity of halogen



substituents attached to the terminal carbon atoms of various derivatives of mannitol and sorbitol. 2 : 4-3 : 5-Dimethylene 1 : 6-dichloro-1 : 6-dideoxymannitol (X; R = Cl) is known to react readily with sodium or with alcoholic potash to yield "2 : 4-3 : 5-dimethylene 1 : 6-dideoxy-1 : 2-5 : 6-mannitoldiene" (XI) (Micheel, *Annalen*, 1932, **496**, 77; Haworth, Heath, and Wiggins, *J.*, 1944, 155) and with sodium iodide in acetone to give 2 : 4-3 : 5-dimethylene 1 : 6-di-iodo-1 : 6-dideoxymannitol (X; R = I) (Micheel, *loc. cit.*). The reaction of 2 : 4-3 : 5-dimethylene 1 : 6-dichloro-1 : 6-dideoxysorbitol (XII; R = Cl) (Haworth and Wiggins, *J.*, 1944, 58) with sodium was found to involve only one of the terminal carbon atoms, affording probably 2 : 4-3 : 5-dimethylene 1-chloro-1 : 6-dideoxy-5 : 6-sorbitoleen (XIII); a similar effect accompanied the reaction of the same dichloro-compound with sodium iodide, leading to the replacement of only one chlorine atom by iodine with the probable formation of 2 : 4-3 : 5-dimethylene 1-chloro-6-iodo-1 : 6-dideoxysorbitol (XII; R = I).

The structures assigned above to the two sorbitol derivatives are supported by work of Ness, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1944, **66**, 1901) on the action of sodium iodide in acetone on 2 : 4-3 : 5-dimethylene 1 : 6-ditoluene-*p*-sulphonyl sorbitol. These authors supplied conclusive evidence that the product of this reaction was 2 : 4-3 : 5-dimethylene 1-toluene-*p*-sulphonyl 6-iodo-6-deoxysorbitol, which demonstrates that it is C₍₁₎, which is unreactive in this case; it is reasonable to suppose that the same effect obtains with the chloro-derivatives discussed above. From purely theoretical considerations the same conclusion may be reached; the only difference between the mannitol and the sorbitol molecule lies in the configuration at C₍₂₎, and therefore it is probable that this end of the molecule is responsible for the difference in chemical behaviour of analogous mannitol and sorbitol derivatives. By extending this argument to L-iditol derivatives, in which the configuration of both C₍₂₎ and C₍₅₎ are reversed with respect to mannitol, it might be expected that both ends of the iditol chain would be unreactive in the circumstances under discussion and this appears in fact to be the case.

The replacement of methanesulphonyloxy-, toluene-*p*-sulphonyloxy-, or hydroxyl groups in dianhydrohexitol derivatives by iodine or chlorine atoms may of course lead to Walden inversion. We have assumed at this stage of the research, that no such inversion takes place and have named the compounds obtained according to the parent hexitol. We wish to make it clear, however, that the question whether or not configurational changes occur is not yet settled.

EXPERIMENTAL.

Action of Sodium Iodide on 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-Dianhydromannitol.—The dimethanesulphonate (10 g.) (Montgomery and Wiggins, *J.*, 1948, 2204) was heated in dry acetone with sodium iodide (30 g.) at 110° for 18 hours. The precipitate of sodium methanesulphonate was removed by filtration and the filtrate evaporated to dryness. The residue was extracted with a mixture of chloroform and water, and the chloroform layer separated, washed with dilute sodium thiosulphate solution and with water, dried (MgSO₄), and evaporated. Recrystallisation of the residue (7.5 g.) from alcohol gave 2 : 5-di-iodo-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol, m. p. 61—63°, [α]_D¹⁹ +107.9° (c, 1.97 in chloroform)

(Found : C, 19.8; H, 2.2. Calc. for $C_6H_8O_3I_2$: C, 19.7; H, 2.2%). Some difficulty was experienced in obtaining a product of well-defined m. p. Hockett *et al.* (*loc. cit.*) give m. p. 61—62°; Brigl and Grüner (*Ber.*, 1934, 67, 1582) give m. p. 69—70°, $[\alpha]_D^{20} + 101.4^\circ$.

Action of Sodium Iodide on 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-Dianhydrosorbitol.—The dimethanesulphonate (20 g.) (Bashford and Wiggins, *J.*, 1948, 299) was heated in dry acetone with sodium iodide (30 g.) at 125° for 12 hours. After removal of the sodium methanesulphonate the solution was evaporated to dryness and the product isolated as described above. *Methanesulphonyl monoiodo-1 : 4-3 : 6-dianhydrodeoxyorsorbitol* was obtained and, recrystallised from hot water, formed fine needles (6 g., 25%), m. p. 104—105°, $[\alpha]_D^{20} + 74.2^\circ$ (*c.*, 2.42 in chloroform) (Found : C, 25.4; H, 3.4. $C_7H_{11}O_5I_2$ requires C, 25.1; H, 3.3%).

Action of Sodium Iodide on 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-Dianhydro-L-iditol.—Dimethanesulphonyl dianhydroiditol (0.5 g.) (Wiggins, *J.*, 1947, 1403) was heated with sodium iodide (0.75 g.) in dry acetone (15 c.c.) at 110—120° for 8 hours. The solution was filtered hot to prevent crystallisation of the unchanged ester; the yield of sodium methanesulphonate was 0.016 g. (4.1%). On evaporation the filtrate gave the unchanged starting material (0.45 g., 90% recovery).

Action of Lithium Chloride on 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-Dianhydromannitol.—The dimethanesulphonyl compound (0.85 g.) was heated with anhydrous lithium chloride (0.55 g.), absolute alcohol (10 c.c.), and dry acetone (10 c.c.) at 150° for 48 hours. The solution was evaporated to dryness and extracted with water; the insoluble residue, recrystallised from alcohol, furnished long needles of 2 : 5-dichloro-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol (0.25 g., 49%), m. p. 63—64°, $[\alpha]_D^{20} + 99.0^\circ$ (*c.*, 0.62 in chloroform). The m. p. was not depressed on admixture with an authentic specimen prepared by Wiggins's method (*loc. cit.*).

Action of Lithium Chloride on 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-Dianhydrosorbitol.—(i) Dimethanesulphonyl dianhydrosorbitol (0.85 g.) was treated with lithium chloride in alcohol-acetone as in the preceding experiment. The product, isolated as before, recrystallised from alcohol in long stout needles (0.45 g., 66%), m. p. 115—116°, $[\alpha]_D^{20} + 71.6^\circ$ (*c.*, 0.53 in chloroform). It was *methanesulphonyl monochloro-1 : 4-3 : 6-dianhydrodeoxyorsorbitol* (Found : C, 35.1; H, 4.4; Cl, 15.7; S, 14.1. $C_7H_{11}O_4ClS$ requires C, 34.6; H, 4.5; Cl, 14.7; S, 13.2%). The m. p. was undepressed on admixture with the methanesulphonyl derivative prepared from the monochlorodianhydrodeoxyorsorbitol, m. p. 63—64°, described by Overend, Montgomery, and Wiggins (*loc. cit.*).

(ii) Dimethanesulphonyl dianhydrosorbitol (5.0 g.) was heated with anhydrous lithium chloride (3.2 g.), absolute alcohol (60 c.c.), and dry acetone (30 c.c.) in an autoclave at 180—190° for 48 hours. The solution was evaporated to dryness and the residue extracted with a mixture of chloroform and water. The chloroform layer was washed with water, dried ($MgSO_4$), and evaporated to a black syrup (3.0 g.). Distillation of the latter under reduced pressure gave a mobile liquid (0.4 g.), b. p. (bath-temp.) 145—150°/15 mm., $n_D^{20} 1.5009$, $[\alpha]_D^{20} + 53.3^\circ$ (*c.*, 1.26 in chloroform). This was almost colourless when first collected but rapidly darkened on exposure to the air. It contained chlorine but no sulphur; it immediately decolorised a solution of bromine in carbon tetrachloride. The compound is tentatively described as a monochlorodianhydrodeoxyorsorbitoleen (Found : Cl, 26.0. Calc. for $C_6H_7O_2Cl$: Cl, 24.2%).

Hydrolysis of Methanesulphonyl Monochloro-1 : 4-3 : 6-dianhydrodeoxyorsorbitol.—The methanesulphonyl compound (0.12 g.), obtained by the lithium chloride reaction above, was heated with alcohol (5 c.c.) and 5% sodium hydroxide solution (15 c.c.) on the boiling water-bath for 1 hour. The solution was then neutralised with acetic acid and evaporated to dryness under reduced pressure and the residue extracted several times with boiling chloroform. The combined extracts were dried ($MgSO_4$) and on evaporation afforded a crystalline residue; recrystallisation of this from ether-light petroleum gave a monochlorodianhydrodeoxyhexitol in long needles, m. p. 63—65° alone or on admixture with the compound described by Overend, Montgomery, and Wiggins.

Action of Lithium Chloride on 2 : 5-Ditoluene-p-sulphonyl 1 : 4-3 : 6-Dianhydrosorbitol.—The ditoluene-*p*-sulphonyl compound (0.75 g.) was heated with anhydrous lithium chloride (0.3 g.), absolute alcohol (10 c.c.), and dry acetone (10 c.c.) at 150° for 48 hours. The solution was evaporated to dryness and the residue extracted with a mixture of chloroform and water. The chloroform extract was washed with water, dried ($MgSO_4$), and evaporated to a syrup (0.5 g.) which partly crystallised on being kept. Recrystallisation of the solid portion (0.12 g., 23%) from aqueous alcohol gave toluene-*p*-sulphonyl monochlorodianhydrodeoxyorsorbitol in stout needles, m. p. 94—95° alone or on admixture with the compound prepared by Overend, Montgomery, and Wiggins (*loc. cit.*).

Action of Lithium Chloride on 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-Dianhydro-L-iditol.—(i) The dimethanesulphonyl compound (0.5 g.) was heated with anhydrous lithium chloride (0.35 g.), absolute alcohol (10 c.c.), and dry acetone (10 c.c.) at 150° for 48 hours. The product, isolated in the same way as in the preceding experiments, was unchanged starting material (0.3 g., 60% recovery).

(ii) The dimethanesulphonyl compound (0.85 g.) was heated with anhydrous lithium chloride (0.55 g.), absolute alcohol (20 c.c.), and dry acetone (15 c.c.) in an autoclave at 180° for 48 hours. Treatment of the resulting solution in the usual way yielded only a black tar (0.16 g.) which showed no tendency to crystallise.

Treatment of 1 : 4-3 : 6-Dianhydro-L-iditol with Thionyl Chloride.—Dianhydro-L-iditol (2.25 g.) was dissolved in dry pyridine (5 c.c.), and thionyl chloride (2.2 c.c.) carefully added at 0°. The mixture was heated in an oil-bath to 95—100°, whereupon a vigorous reaction occurred; after the temperature had been kept at 100° for 2 hours, the mixture was cooled, poured into ice-water, and set aside overnight. The resulting suspension was extracted several times with chloroform, and the combined extracts were washed successively with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was negligible.

Action of Sodium on 2:4-3:5-Dimethylene 1:6-Dichloro-1:6-dideoxysorbitol.—The dichloro-compound (1 g.) (Haworth and Wiggins, *J.*, 1944, 58) was heated to its m. p., and clean sodium (0.2 g.) added in portions. The mixture was heated at 120° until it had become almost solid owing to the separation of sodium chloride, then diluted with dry toluene and refluxed for 2 hours. The toluene solution was decanted and the residue extracted several times further with boiling toluene. The combined extracts on evaporation yielded a syrup (0.8 g.) which crystallised on trituration with ether; recrystallisation from the same solvent gave the product as clusters of crystals, m. p. 96–97°, $[\alpha]_D^{25} +149.5^\circ$ (*c.* 2.02 in chloroform). It decolorised alkaline potassium permanganate and a solution of bromine in chloroform. It was probably 2:4-3:5-dimethylene 1-chloro-1:6-dideoxy-5:6-sorbitoleen (Found: C, 46.5; H, 5.5; Cl, 17.0. $C_8H_{11}O_4Cl$ requires C, 46.5; H, 5.3; Cl, 17.2%). The syrupy residues were combined and re-treated with sodium (0.2 g.) as above. In this way a further quantity of crystalline material, m. p. 96–97°, was obtained. The total yield was 0.42 g. (50%).

Action of Sodium Iodide on 2:4-3:5-Dimethylene 1:6-Dichloro-1:6-dideoxysorbitol.—The dichloro-compound (0.5 g.) was dissolved together with dry sodium iodide (2 g.) in dry acetone (20 c.c.) and heated at 110° for 48 hours. Thereafter the solution was evaporated to dryness, the residue extracted with chloroform, and the extract washed successively with sodium thiosulphate solution and water. Evaporation of the solvent gave a solid residue which, recrystallised from alcohol, formed stout needles, m. p. 126–128°, $[\alpha]_D^{25} +19.2^\circ$ (*c.* 2.28 in chloroform). The substance contained both chlorine and iodine and was probably 2:4-3:5-dimethylene 1-chloro-6-iodo-1:6-dideoxysorbitol (Found: C, 28.5; H, 3.5 $C_8H_{12}O_4ClI$ requires C, 28.7; H, 3.6%).

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