199. *The Replacement of Secondary Tosyloxy-groups by Iodine in Polyhydroxy-compounds.*

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The replacement of secondary tosyloxy-groups by iodine in open-chain polyhydroxy-derivatives has been studied. It has been found that reaction occurs under conditions comparable with those necessary to replace many primary toxyloxy-groups. The ease of the reaction is dependent on steric factors and is greatly diminished when the tosyl group is attached to a carbon atom which is a member of a ring.

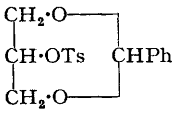
IT is generally accepted that secondary tosyloxy-groups in polyhydroxy-compounds (carbohydrates) are not replaced by iodine when the compounds are heated with sodium iodide in acetone under certain standard conditions, while primary tosyloxy-groups react readily. Oldham and Rutherford, who first formulated this rule (*J. Amer. Chem. Soc.*, 1932, **54**, 366), have found that in aldohexoses only the tosyloxy-group attached to the terminal carbon atom was exchanged on 2 hours' heating at 100°, and that this exchange was quantitative. Other authors have extended this work to aldopentoses (Levene and Raymond, *J. Biol. Chem.*, 1933, **102**, 317), ketoses (Gardner and Lee, *J. Org. Chem.*, 1947, **12**, 733), and polyhydric alcohols (Hann, Ness, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 73), reaching the same conclusion. There are many examples in the work of Hudson and his co-workers of replacement of primary, but none of secondary, groups. Thus 1 : 3-4 : 6-dimethylene 2 : 5-ditosyl dulcitol and the corresponding dibenzylidene derivative were unchanged after being heated with sodium iodide in acetic anhydride (*ibid.*, 1942, **64**, 986). A 1 : 3-4 : 6- or 1 : 3-5 : 6-dimethylene ditosyl D-mannitol, heated in acetone at 100° or in acetic anhydride at 140°, did not react (*idem, ibid.*, 1943, **65**, 67). 1 : 3-4 : 6-Dimethylene 2 : 5-ditosyl D-talitol was unchanged after being heated for 48 hours at 80° in acetonylacetone (*idem, ibid.*, 1947, **69**, 624). These considerations, however, apply only to isolated tosyl groups; it is well-known that a secondary tosyl group adjacent to a primary tosyl group is reactive (*e.g.*, Bladon and Owen, *J.*, 1950, 598; Tipson and Cretcher, *J. Org. Chem.*, 1943, **8**, 95).

Subsequent work has shown that to replace some primary tosyloxy-groups more vigorous conditions are required than those specified by Oldham and Rutherford (*loc. cit.*). Foster, Overend, Stacey, and Wiggins (*J.*, 1949, 2542) found that some derivatives of 6-tosyl galactose needed much longer heating. Seeback, Sorkin, and Reichstein (*Helv. Chim. Acta*, 1945, **28**, 934) report that methyl 2 : 3-4 : 5-dibenzylidene 6-tosyl D-idonate did not react with sodium iodide on being heated for 5 hours at 100°. The reaction is particularly slow with ketoses in which the tosyl group is adjacent to the glycosidic carbon atom (Gardner and Lee, *loc. cit.*); in one case, that of 2 : 3-4 : 5-di*iso*propylidene 1-tosyl fructose, no reaction occurred on heating at 130° for 3 days (Müller and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 263; Levene and Tipson, *J. Biol. Chem.*, 1937, **120**, 607).

Secondary tosyloxy-groups are, as a rule, unreactive even under these more vigorous conditions; but several exceptions have been reported. Oldham and Rutherford (*loc. cit.*) have already given warning that prolonged heating may cause gradual exchange of secondary groups. Failure of an attempt to determine quantitatively the primary and secondary tosyloxy-groups in cellulose by the iodine exchange reaction (Malm, Tanghe, and Laird, *J. Amer. Chem. Soc.*, 1948, **70**, 2740) was traced to the slow reaction of the secondary groups. In 2 : 5-ditosyl 1 : 4-3 : 6-dianhydro-D-mannitol both tosyloxy-groups were replaced on 3 hours' heating at 120° (Hockett, Fletcher, Sheffield, Goepp, and Soltzberg, *J. Amer. Chem. Soc.*, 1946, **68**, 930) and in the corresponding D-sorbitol derivative one tosyloxy-group was exchanged under similar conditions (*idem, ibid.*, p. 927). Helferich and Gnüchtel (*Ber.*, 1938, **71**, 712) found that 1 : 2 : 3 : 6-tetra-acetyl 4-methanesulphonyl β-D-glucose, after 70 hours at 135°, gave the calculated amount of sodium methanesulphonate, and the iodo-compound could be isolated in good yield. Helferich assumed that methanesulphonyl groups react faster than tosyl groups; but this explanation was rendered invalid by the work of Foster *et al.* (*loc. cit.*) who found methanesulphonyl not more but rather somewhat less reactive. Curiously, the reaction of sodium iodide with 1 : 2 : 3 : 6-tetra-acetyl 4-tosyl D-glucose, the tosyl analogue of Helferich's methanesulphonyl compound, has not yet been reported.

In spite of these exceptions, the reaction with sodium iodide is still widely used as a diagnostic aid in locating tosyl groups (*e.g.*, Foster, Overend, and Stacey, *J.*, 1951, 976, 982; Foster and Overend, *J.*, 1951, 1132). Nevertheless, it is known that secondary tosyloxy-groups attached to simple hydroxy-compounds react readily; *e.g.*, 1-propyl-*n*-butyl toluene-*p*-sulphonate is converted into the iodide at room temperature (Tipson, Clapp, and Cretcher, *J. Org. Chem.*, 1947, **12**, 133). It occurred to us that most of the unreactive secondary tosyloxy-groups were attached to carbon atoms which were members of a ring (either a pyranose or furanose, or an acetal ring); primary tosyloxy-groups, naturally, could not be thus located. In order to see whether this difference is an important factor we tested a number of compounds containing secondary tosyloxy-groups which were not attached to rings.

As the simplest case of a secondary tosyloxy-group attached to a polyhydric alcohol, the synthesis of glycerol 2-toluene-*p*-sulphonate was undertaken. 5-Hydroxy-2-phenyl-1 : 3-dioxan was treated with toluene-*p*-sulphonyl chloride, and the resulting ring-compound (I) was found to react so readily with sodium iodide that it was not thought necessary to try the unsubstituted glycerol 2-toluene-*p*-sulphonate. A number of hexitols partly esterified with toluene-*p*-sulphonic acid (II—VIII) were then prepared, varying in configuration and in substituents; they were heated with sodium iodide in acetone, and the precipitated sodium toluene-*p*-sulphonate was collected and weighed. The results are given in the Table.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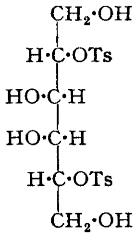
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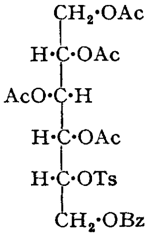
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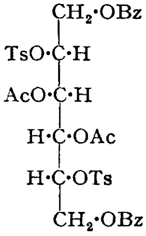
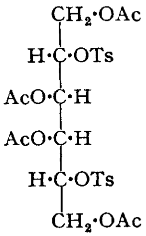

(IV)

(Ts = p-$C_6H_4Me\cdot SO_2$–).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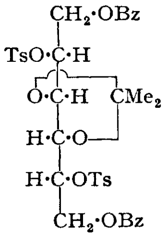
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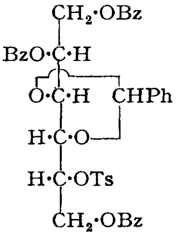
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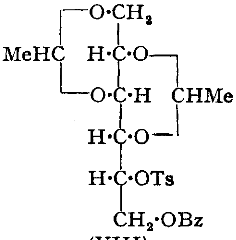
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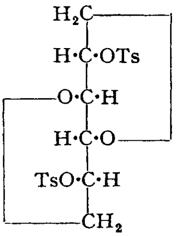
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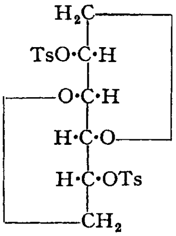
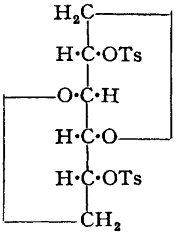

(X)


(XI)

Replacement of tosyloxy-groups in hexitols

Compound	Yield (%) of sodium toluene-*p*-sulphonate *		
	(1)	(2)	(3)
(I)	>100%	—	—
(II) §	88	—	—
(III)	57	—	—
(IV) §	45	>100%	—
(V) §	0	57	>100%
(VI) §	11	54	—
(VII)	9	—	95
(VIII)	0	82	100
(IX)	0	0	33

* Conditions : (1) 2 hours at 100—103°; (2) 3 hours at 115—120°; (3) 4 hours at 135—140°.
§ Yield calc. on replacement of both tosyloxy-groups.

It is evident from these results that some secondary tosyloxy-groups in hexitols are replaced by iodine under conditions such that primary tosyloxy-groups are not readily replaced in some hexitol and hexose derivatives. Thus 2 : 4-3 : 5-dimethylene 1 : 6-ditosyl iditol gave only a 10% yield on 2 hours' heating at 100° (Hann and Hudson, *J. Amer. Chem. Soc.*, 1945, **67**, 602); and 3 : 4-*iso*propylidene 2 : 6-ditosyl methyl-D-galactoside gave a 17·9% yield of sodium toluene-*p*-sulphonate after 5 hours at 115—125° (Foster *et al.*, *loc. cit.*). In contrast to this, 2 : 5-ditosyl dulcitol (II), as shown in the Table, gave a high yield in 2 hours at 100°.

It is apparent that factors other than the primary or secondary nature of the tosyloxy-group have a profound influence on the reaction rate. Of these factors the following—which are all steric—can be mentioned :

(1) The nature of adjacent groups. The reactivity of a secondary tosyloxy-group in hexitols diminishes in the following order : tosyl next to free hydroxyl, tosyl next to an ester group, tosyl next to an acetal ring (compare II and V, III and VIII). The reactivity of primary tosyloxy-groups is similarly affected (cf. Foster *et al.*, *loc. cit.*).

(2) Configurational differences exert an effect (compare III, IV, and V) which is not understood.

(3) The most important retarding factor is the attachment of the tosyloxy-group to a carbon atom which is in a ring, particularly in a six-membered ring. This is the same effect that causes *cyclo*pentyl halides to react slower, and *cyclo*hexyl halides even more slowly, than aliphatic halogen compounds. (For a discussion and references see Brown, Fletcher, and Johannesen, *J. Amer. Chem. Soc.*, 1951, **73**, 212, with whose conclusions, however, we do not concur.) A simple example, in the case of tosyl groups, is the comparison between 1-*n*-propyl-*n*-butyl toluene-*p*-sulphonate—which gave a 24% yield of sodium toluene-*p*-sulphonate on being kept for 2 hours with a solution of sodium iodide in acetone—and *cyclo*hexyl toluene-*p*-sulphonate which gave only a 3% yield under the same conditions (Tipson, Clapp, and Cretcher, *loc. cit.*). In a six-membered ring with few substituents the reaction will still be sufficiently fast at 100° : toluene-*p*-sulphonates of the *cyclo*hexanediols react (Clarke and Owen, *J.*, 1949, 315; 1950, 2103; Owen and Robins, *J.*, 1949, 320). In 2-phenyl-5-toluene-*p*-sulphonyloxy-1 : 3-dioxan (I), which reacts readily, the tosyl group is in a six-membered ring with only one other substituent. In 2 : 5-ditosyl 1 : 4-3 : 6-dianhydro-D-mannitol each tosyl group is in a five-membered ring and, though adjacent to another ring, is still moderately reactive. In 1 : 3-4 : 6-dimethylene 2 : 5-ditosyl dulcitol, however, the tosyl groups are in six-membered rings and adjacent to another ring; they show little reactivity. Finally, when a six-membered ring is heavily substituted, as in the sugar pyranosides, the reaction becomes very difficult. Nevertheless, under vigorous conditions, it is possible to exchange a tosyloxy-group even in an inositol (unpublished result). When, further, the tosyl group is in a ring to which other rings are fused, as in acetals of sugar pyranosides, the reaction becomes too slow to be carried out under practical conditions.

A comparison of the three epimeric 2 : 5-ditosyl 1 : 4-3 : 6-dianhydro-hexitols shows in a particularly striking manner that steric factors prevent the exchange of certain tosyloxy-groups. As mentioned earlier, both tosyloxy-groups are readily exchanged in 2 : 5-ditosyl 1 : 4-3 : 6-dianhydro-D-mannitol (X) but only one reacts in the corresponding D-sorbitol compound (XI) (Hockett *et al.*, *loc. cit.*). 2 : 5-Ditosyl 1 : 4-3 : 6-dianhydro-L-iditol (IX) has now been tested and both tosyloxy-groups have been found to be quite unreactive. After this work was finished, a paper by Wiggins and Wood (*J.*, 1951, 1180) described a more extensive comparison of these hexitol dianhydrides. They have studied the reaction of the dianhydro-hexitols with thionyl chloride and the reaction of their dimethanesulphonates with sodium iodide and with lithium chloride. The ease of reaction in all cases shows the same gradation : two methanesulphonyl or hydroxyl groups are exchanged in the mannitol derivative, only one in the sorbitol derivative, and, under the same conditions, no reaction occurs with the compounds derived from iditol.

An explanation of these facts is suggested by a study of molecular models. The three anhydrides differ only in the configuration of $C_{(2)}$ and $C_{(5)}$. They all contain two fused five-membered rings inclined to each other, forming a V-shaped molecule. Since all the above reactions involve attack on the molecule by a negative ion and removal of a group as a negative ion, they probably occur by the S_N2 mechanism, *i.e.*, an approach of the entering atom to the face of the carbon opposite to the group to be displaced. If that face is on the inside of the V, the attack is sterically hindered.

In ditosyl dianhydroiditol both tosyl groups are on the outside of the V; an inspection of Fischer–Hirschfelder atomic models shows that any approach to the opposite sides of the carbons, on the inside of the V, is obstructed. In ditosyl dianhydromannitol the two tosyl groups are attached to the inside of the V and attacking groups can approach without steric impediment. In dianhydrosorbitol, $C_{(2)}$ has the configuration of the iditol, and $C_{(5)}$ that of the mannitol derivative; the reaction is therefore hindered at $C_{(2)}$ but not at $C_{(5)}$.

It is clear from these results that any evidence on the position of tosyl groups, derived from the iodine exchange reaction, should be treated with suspicion unless the comparison is made between primary and secondary tosyl compounds of otherwise similar structural features.

It was not the purpose of this work to isolate the iodine compounds resulting from the exchange reaction. In a few cases, however, the mixture was worked up to give syrups which failed to crystallise and could not be distilled *in vacuo* without decomposition. They contained iodine but less than the required amount.

The reactivity of tosyloxy-groups in open-chain polyhydric alcohols suggests that secondary iodo-derivatives of reducing sugars might be prepared by this reaction if the sugars were in the open-chain form, *e.g.*, as mercaptals. Work is in progress to test this possibility.

EXPERIMENTAL

(M. p.s are corrected. Microanalyses by Mrs. E. Bielski, of this Department, and by Dr. W. Zimmermann, Commonwealth Scientific and Industrial Research Organisation, Melbourne.)

2-*Phenyl*-5-*toluene*-p-*sulphonyloxy*-1 : 3-*dioxan* (1 : 3-*Benezylidene* 2-*Tosyl Glycerol*) (I).—1 : 3-Benzylidene glycerol (6·5 g.) (Hill, Whelen, and Hibbert, *J. Amer. Chem. Soc.*, 1928, **50**, 2235) was dissolved in dry pyridine (10 ml.) and toluene-*p*-sulphonyl chloride (8 g.) was added. After 12 hours the solution was poured into water, and the precipitated solid was filtered off and recrystallised from methanol, to give the *toluene*-p-*sulphonate* (7·5 g., 62%), m. p. 125° (Found : C, 61·1; H, 5·5; S, 9·3, 9·1. $C_{17}H_{18}O_5S$ requires C, 61·1; H, 5·4; S, 9·6%).

6-*Benzoyl* 1 : 3-2 : 4-*Diethylidene* 5-*Tosyl* D-*Sorbitol* (VIII).—6-Benzoyl 1 : 3-2 : 4-diethylidene D-sorbitol (10 g.) (Sullivan, *J. Amer. Chem. Soc.*, 1945, **67**, 837) was dissolved in dry pyridine (150 ml.), toluene-*p*-sulphonyl chloride (7 g.) added, and the mixture set aside for 3 days. The solution was then poured into water (1 l.). The precipitated solid was filtered off, dried, and recrystallised from light petroleum (1500 ml.), to give 6-*benzoyl* 1 : 3-2 : 4-*diethylidene* 5-*tosyl* D-*sorbitol* as fine needles (9·9 g., 68%), m. p. 121°, $[\alpha]_D^{23}$ + 5·5° (*c*, 8·1 in chloroform) (Found : C, 58·6; H, 5·9; S, 6·5. $C_{24}H_{28}O_9S$ requires C, 58·5; H, 5·7; S, 6·5%).

1 : 6-Dibenzoyl 3 : 4-*iso*propylidene 2 : 5-ditosyl D-mannitol (VI) and 3 : 4-diacetyl 1 : 6-dibenzoyl 2 : 5-ditosyl D-mannitol (IV) were prepared by Brigl and Grüner's method (*Ber.*, 1934, **67**, 1969).

1 : 2 : 3 : 4-*Tetra-acetyl* 6-*Benzoyl* 5-*Tosyl* D-*Sorbitol* (III).—1 : 2-3 : 4-Diethylidene 6-benzoyl 5-tosyl D-sorbitol (2 g.) was heated on a steam-bath with a mixture of acetic anhydride (20 ml.), acetic acid (20 ml.), and concentrated sulphuric acid (3 ml.) for 1 hour. The solution was then poured on crushed ice and set aside overnight. The precipitate was collected and recrystallised from a large volume of light petroleum, to give 1 : 2 : 3 : 4-*tetra-acetyl* 6-*benzoyl* 5-*tosyl* D-*sorbitol* (1·1 g., 45%), m. p. 98°, $[\alpha]_D^{23}$ + 21·8° (*c*, 6·85 in ethyl acetate) (Found : C, 55·4; H, 5·4; S, 5·3, 5·5. $C_{28}H_{32}O_{13}S$ requires C, 55·3; H, 5·3; S, 5·3%). The compound slowly deliquesced and gave a solution that smelt strongly of acetic acid.

1 : 2 : 6-*Tribenzoyl* 3 : 4-*Benzylidene* 5-*Tosyl* D-*Mannitol* (VII).—1 : 2 : 6-Tribenzoyl 3 : 4-benzylidene D-mannitol (2·4 g.) (Brigl and Grüner, *Ber.*, 1933, **66**, 931) was dissolved in dry pyridine (10 ml.) and treated with toluene-*p*-sulphonyl chloride (3 g.) at room temperature. After 4 days the mixture was poured into water, and the precipitated solid was recrystallised from methanol, to give 1 : 2 : 6-*tribenzoyl* 3 : 4-*benzylidene* 5-*tosyl* D-*mannitol* (2·3 g., 76%) as long feathery needles, m. p. 117°, $[\alpha]_D^{23}$ +6·0° (*c*, 8·2 in chloroform) (Found : C, 66·8; H, 5·3; S, 4·3. $C_{41}H_{36}O_{11}S$ requires C, 66·8; H, 4·9; S, 4·4%).

1 : 3 : 4 : 6-*Tetra-acetyl* 2 : 5-*Ditosyl Dulcitol* (V).—1 : 3-4 : 6-Dibenzylidene 2 : 5-ditosyl dulcitol (8 g.) (Hann, Haskins, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 132), acetic anhydride (250 ml.), acetic acid (100 ml.), and concentrated sulphuric acid (6 ml.) were heated on a steam-bath until all the solid had been dissolved (1 hour). The solution was allowed to cool and then poured on crushed ice (1500 g.), and the precipitated solid was filtered off. On recrystallisation from a large volume of ethanol, 1 : 3 : 4 : 6-*tetra-acetyl* 2 : 5-*ditosyl dulcitol* was obtained as

needles (6·2 g., 78%), m. p. 169° (Found : C, 51·1; H, 5·3; S, 10·0. $C_{28}H_{34}O_{14}S_2$ requires C, 51·1; H, 5·2; S, 9·7%).

2 : 5-*Ditosyl Dulcitol* (II).—1 : 3 : 4 : 6-Tetra-acetyl 2 : 5-ditosyl dulcitol (2 g.) was suspended in a mixture of methanol (50 ml.) and hydrochloric acid (20 ml.; 15%) and boiled under reflux for 3 hours. The solution was cooled, neutralised with silver carbonate, filtered, saturated with hydrogen sulphide, and filtered again. It was then evaporated to dryness under reduced pressure and the residue recrystallised from a small volume of ethanol, to give 2 : 5-*ditosyl dulcitol* (0·8 g., 34%), m. p. 163° (decomp.) (Found : C, 49·5; H, 4·9; S, 13·5. $C_{20}H_{26}O_{10}S_2$ requires C, 49·0; H, 5·3; S, 13·1%).

To show that the hydrolysis had not affected the tosyl groups, this compound was reacetylated. Ditosyl dulcitol (0·2 g.) and acetic anhydride (1 ml.) in dry pryidine (4 ml.), were set aside for 18 hours, the solution was then poured into water, and the product filtered off and recrystallised from ethanol, to give a substance which melted, alone and in admixture with tetra-acetyl ditosyl dulcitol, at 169°.

2 : 5-*Ditosyl* 1 : 4-3 : 6-*Dianhydro*-L-*iditol* (IX).—This was prepared from 1 : 4-3 : 6-dianhydro-L-iditol by Bashford and Wiggins's method (*J.*, 1950, 373) but was found to have different constants, namely m. p. 106°, $[\alpha]_D^{23}$ +33° (*c*, 2·0 in chloroform) (Found : C, 52·8; H, 4·8; S, 14·0, 14·2. Calc. for $C_{20}H_{22}O_8S_2$: C, 52·8; H, 4·9; S, 14·1%). Bashford and Wiggins report m. p. 90°, $[\alpha]_D$ +38·2° (*c*, 2·0 in chloroform). The dianhydro-iditol was prepared according to Wiggins's directions (*J.*, 1947, 1403), and melted at 60—62°, in agreement with Fletcher and Goepp (*J. Amer. Chem. Soc.*, 1945, **67**, 1042; 1946, **68**, 939); but the hemihydrate described by Wiggins was not obtained. To identify further the dianhydro-compound, it was converted into its dibenzoate, m. p. 109°, $[\alpha]_D^{21}$ +142°, in good agreement with both Fletcher and Goepp's and Wiggins's data.

Conditions of Replacement.—The amount of compound equivalent to 0·2 g. of sodium iodide was heated in a sealed tube with sodium iodide (0·3 g.) and dry acetone (10 ml.) for the requisite time. The tube was then opened, the contents were filtered through a sintered-glass crucible, and the precipitate was washed with acetone (2 ml.) and dried at 100° to constant weight. The crucible was then washed with water, dried, and reweighed. In only one case was there a residue and that was with 1 : 3 : 4 : 6-tetra-acetyl 2 : 5-ditosyl dulcitol (2 hours at 100°). This was the only substance insoluble in cold acetone.

Allowance was made for the solubility of sodium toluene-*p*-sulphonate in acetone (0·0012 g. per ml. at 18°, Foster *et al.*, *loc. cit.*). In those cases where the amount of sodium toluene-*p*-sulphonate is given as >100%, the value was sometimes as high as 108% which indicates the limit of accuracy obtainable with this method.

Attempted Preparation of Iodo-compounds.—Three compounds (IV, V, and VI) were treated in the following manner : The compound (1·0 g.) was heated under reflux for 1 hour with acetic anhydride (10 ml.) and sodium iodide (1·0 g.). The solution was then poured into a sodium hydrogen carbonate solution whereupon a syrup separated. The aqueous layer was decanted and the syrup washed with water until free from chloride. The syrup was then taken up in benzene, and the solution washed with sodium thiosulphate solution and then several times with water. The solvent was dried and evaporated. In each case a syrup was obtained which could not be induced to crystallise and would not distil under reduced pressure. The syrups were dried for 4 hours at 66°/0·5 mm. and analysed (Found, for 3 : 4-diacetyl 1 : 6-dibenzoyl 2 : 5-dideoxy-2 : 5-di-iodohexitol : I, 28·6. $C_{24}H_{24}O_8I_2$ requires I, 36·5%. Found, for 1 : 3 : 4 : 6-tetra-acetyl 2 : 5-dideoxy-2 : 5-di-iodohexitol : I, 32·0. $C_{14}H_{20}O_8I_2$ requires I, 44·5%. Found, for 1 : 6-dibenzoyl 3 : 4-*iso*propylidene 2 : 5-dideoxy-2 : 5-di-iodohexitol : I, 28·4. $C_{23}H_{24}O_6I_2$ requires I, 39·0%).

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