69. *Cyclitols. Part VIII.* Elimination of Vicinal Sulphonyloxy-groups by Iodide Ion.*

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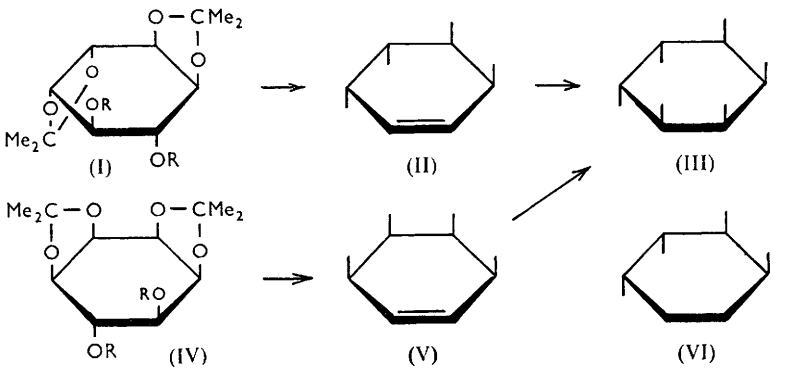
Two *cyclo*hex-5-ene-1 : 2 : 3 : 4-tetrols (II) and (V) were prepared by elimination of two secondary sulphonyloxy-groups by iodide ion from suitably substituted inositols. The *p*-nitrobenzenesulphonyloxy-group is more readily eliminated than the toluene-*p*-sulphonyloxy-group.

In an attempt to synthesise *cis*inositol, the all-*cis*-*cyclo*hex-5-ene-1 : 2 : 3 : 4-tetrol (V) was prepared; it was hoped that its *cis*-hydroxylation would yield some *cis*inositol. However, addition occurred from the unhindered side and *allo*inositol (III) was the only product; *cis*inositol was subsequently obtained by a different route.[1] Preparation of the unsaturated tetrol, and of a diastereomer, is now described.

a: R = *p*-$C_6H_4Me{\cdot}SO_2$
b: R + *p*-$NO_2{\cdot}C_6H_4{\cdot}SO_2$
c: R = $Me{\cdot}SO_2$.



The preparations involved elimination of two vicinal sulphonyloxy-groups by iodide ion, which has several times been used in the carbohydrate field [2] but is there applicable only to compounds in which one of the sulphonyloxy-groups is primary. There is one case [3] of the formation of iodine and sodium toluene-*p*-sulphonate from a sugar derivative containing two secondary toluene-*p*-sulphonyl groups, but there no other product could be isolated. Elimination of secondary sulphonyloxy-groups is possible, however, from some other type of compounds, such as steroids [4] and αβ-diacyloxy-carboxylic acids.[5]

The readily available di-*O*-*iso*propylidene derivative (Ia) of 3 : 4-di-*O*-tosyl-(−)-inositol [6] † was used for the first experiments. Both toluene-*p*-sulphonyloxy-groups,

* Part VII, *J.*, 1957, 3691.

† For the pair of optically active inositols, (+)- and (−)- take the place of prefixes. In this paper these symbols, placed *immediately* before "inositol," denote the configurational series and not necessarily the sign of rotation of the complete compound. [N.B. This practice must not be generalised, as it is contrary to I.U.P.A.C. rules (see *J.*, 1951, 3522). Ed.] The modified (*R*)(*S*) nomenclature [7] is used in the experimental section.

[1] Angyal and McHugh, *J.*, 1957, 3682.
[2] For a summary, see Tipson, *Adv. Carbohydrate Chem.*, 1953, **8**, 201.
[3] Owen and Bladon, *J.*, 1950, 598.
[4] Slates and Wendler, *Chem. and Ind.*, 1955, 168; *J. Amer. Chem. Soc.*, 1956, **78**, 3749.
[5] Linstead, Owen, and Webb, *J.*, 1953, 1220.
[6] Angyal and Matheson, *J. Amer. Chem. Soc.*, 1955, **77**, 4343.

although secondary, reacted smoothly with sodium iodide in acetone; reaction was nearly complete in 24 hours at 100° or in 2 hours at 140° and gave (+)-*cyclo*hex-5-ene-1 : 2/3 : 4-tetrol (II) as its di*iso*propylidene derivative. Hydrolysis gave the free tetrol. Di-*O*-tosyl-(—)-inositol itself also reacted with sodium iodide but its tetra-acetate did not, even at 140°, probably owing to steric hindrance. These and other runs are summarised in the Table.

However, the di-*O-iso*propylidene derivative (IVa) of 5 : 6-di-*O*-tosyl*epi*inositol [7] did not react with sodium iodide at 100° and even at 140° the reaction required long heating, with consequent destruction of the unsaturated tetrol (V) presumably formed. The di-*O-iso*propylidene derivative (Ib) of 3 : 4-di-*O*-*p*-nitrobenzenesulphonyl-(—)-inositol underwent elimination faster than the toluene-*p*-sulphonyl analogue, in accord with a suggestion by Tipson.[8] The di-*O-iso*propylidene derivative (IVb) of 5 : 6-di-*O*-*p*-nitrobenzenesulphonyl*epi*inositol was sufficiently reactive at 100° to allow the preparation of the di-*O-iso*propylidene derivative of the all-*cis-cyclo*hex-5-ene-1 : 2 : 3 : 4-tetrol (V). Even the tetra-acetate of the dinitrobenzenesulphonyl compound reacted in boiling acetic anhydride with sodium iodide, giving the tetra-acetate of (V). The free tetrol (V) itself, however, could not be obtained crystalline.

The di-*O-iso*propylidene derivative (Ic) of 3 : 4-di-*O*-methanesulphonyl-(—)-inositol, prepared in the hope that the smaller sulphonyloxy-groups would prove more reactive, showed surprisingly low reactivity with sodium iodide (see Table).

The mechanism of the elimination, which is not clearly understood despite some recent discussion,[3,9] is at present under investigation.

Hydroxylation of the 1 : 2/3 : 4-tetrol (II) by silver chlorate in the presence of osmium tetroxide [10] gave *allo*inositol (III),[11] providing a new synthesis of this rare inositol. The *cis*tetrol (V) also gave *allo*inositol by this reaction, but the other possible product, *cis*-inositol, was not detected by paper chromatography.

Reaction of disulphonyl compounds with sodium iodide. (0·5 g. of compound and 1·5 g. of sodium iodide in 10 ml. of acetone.)

Compound	Temp.	Time (hr.)	Yield (%) of sodium sulphonate
3 : 4-Di-*O*-tosyl-(—)-inositol	100°	20	85
3 : 4-Di-*O*-*p*-nitrobenzenesulphonyl-(—)-inositol	100	10	100
Tetra-*O*-acetyl-3 : 4-di-*O*-tosyl-(—)-inositol *	140	13	0
Di-*O-iso*propylidene derivative of:			
3 : 4-di-*O*-tosyl-(—)-isositol (Ia)	100	23	99
	140	2	81
3 : 4-di-*O*-*p*-nitrobenzenesulphonyl-(—)-inositol (Ib)	100	13	93
3 : 4-di-*O*-methanesulphonyl-(—)-inositol (Ic)	100	20	9
5 : 6-di-*O*-tosyl*epi*inositol (IVa)	100	20	0
	140	10	95
5 : 6-di-*O*-*p*-nitrobenzenesulphonyl*epi*inositol (IVb)	100	20	69

* 0·3 g. of sodium iodide.

Hydrogenation of the tetrol (II) gave (+)-*cyclo*hexane-1 : 2/3 : 4-tetrol (VI), $[\alpha]_D^{26}$ +72° (in H_2O). Posternak and Friedli [10] prepared the racemic form of this compound by the hydroxylation of (±)-*cis-cyclo*hex-3-ene-1 : 2-diol and resolved it by the action of *Acetobacter suboxydans* which dehydrogenated only one enantiomorph. The unattacked stereoisomer, the configuration of which was not known to the Swiss workers, had a rotation of −74° and was therefore the enantiomer of our compound, the action of *A. suboxydans* being in agreement with the rules proposed by Magasanik, Franzl, and Chargaff.[12]

In an attempt to prepare cyclitols by cyclisation, Micheel [13] treated what he believed

[7] Angyal and Gilham, *J.*, 1957, 3691.
[8] Ref. 2, p. 211.
[9] Foster and Overend, *J.*, 1951, 3452; Newth, *J.*, 1956, 471.
[10] Posternak and Friedli, *Helv. Chim. Acta*, 1953, **36**, 251.
[11] Dangschat and Fischer, *Naturwiss.*, 1939, **27**, 756.
[12] Magasanik, Franzl, and Chargaff, *J. Amer. Chem. Soc.*, 1952, **74**, 2618
[13] Michael, *Annalen*, 1932, **496**, 96.

to be 1 : 6-dideoxy-1 : 6-di-iodo-2 : 3-4 : 5-dimethylene-D-mannitol with "molecular" silver at 165—170° and obtained, after hydrolysis of the methylene groups, a compound to which he ascribed structure (VI). The properties of his compound are different, however, from those of ours or of its enantiomorph, indeed from those of any *cyclo*hexane-1 : 2 : 3 : 4-tetrol, all of which are now known.[14] It is also clear now[15] that Micheel's starting material had the methylene groups in the 2 : 4-3 : 5-positions (not 2 : 3-4 : 5) which would make cyclisation to a six-membered ring sterically impossible without inversion or rearrangement. The structure and configuration of Micheel's compound are therefore unknown.

Experimental

M. p.s are corrected. Analyses are by Dr. E. Challen and Mr. D. G. Weeden.

(1R)-1 : 2 : 5 : 6-*Tetra*-O-*acetyl*-3 : 4-*di*-O-*tosylinositol*.—(1*R*)-3 : 4-Di-*O*-tosylinositol[6] (0·5 g.) was heated for 1 hr. at 100° with pyridine (4 ml.) and acetic anhydride (4 ml.). After being poured into water, the *product* (0·9 g.) was crystallised from aqueous ethanol, forming needles, m. p. 138—139°, or from ethanol forming plates, m. p. 158°, $[\alpha]_D^{17}$ +17·4° (*c* 1·3 in $CHCl_3$) (Found: C, 51·15; H, 4·9; S, 9·8. $C_{28}H_{32}O_{14}S_2$ requires C, 51·2; H, 4·9; S, 9·7%).

(1R)-1 : 2-5 : 6-*Di*-O-iso*propylidene*-3 : 4-*di*-O-p-*nitrobenzenesulphonylinositol* (Ib).—A solution of (1*R*)-di-*O*-*iso*propylideneinositol[16] (1·0 g.) and *p*-nitrobenzenesulphonyl chloride (3·4 g.) in anhydrous pyridine (10 ml.) was set aside at room temperature for 3 days, then diluted with water. The gum was separated, washed with water, and crystallised from ethanol. Recrystallisation from that solvent gave the *sulphonyl derivative* as plates (2·2 g., 90%), m. p. 171—172°, $[\alpha]_D^{17}$ −62° (*c* 1·0 in $CHCl_3$) (Found: C, 45·55; H, 4·05. $C_{24}H_{26}O_{14}N_2S_2$ requires C, 45·7; H, 4·15%).

The *iso*propylidene groups were removed from the compound (0·71 g.) by 80% aqueous acetic acid (25 ml.) at 100° in 3 hr. Evaporation gave crystals of (1*R*)-3 : 4-di-*O*-*p*-nitrobenzenesulphonylinositol which decomposed above 170°.

(1R)-1 : 2-5 : 6-*Di*-O-iso*propylidene*-3 : 4-*di*-O-*methanesulphonylinositol* (Ic).—(1*R*)-Di-*O*-*iso*propylideneinositol (1·0 g.) and methanesulphonyl chloride (1·76 g.) in anhydrous pyridine (10 ml.) were set aside at room temperature for 16 hr. Water was then added and the precipitate (1·50 g.) recrystallised from ethyl acetate, to give plates of the *dimethanesulphonyl derivative* (1·38 g., 87%), m. p. 260°, $[\alpha]_D^{17}$ −120° (*c* 1·0 in $CHCl_3$) (Found: C, 40·35; H, 5·8. $C_{14}H_{24}O_{10}S_2$ requires C, 40·25; H, 5·7%).

(+)-cyclo*Hex*-5-*ene*-1 : 2/3 : 4-*tetrol* (II).—(1*R*)-1 : 2-5 : 6-Di-*O*-*iso*propylidene-3 : 4-di-*O*-tosylinositol[6] (10 g.) and anhydrous sodium iodide (15 g.) in anhydrous acetone (100 ml.) were heated at 100° for 23 hr. The precipitated sodium toluene-*p*-sulphonate (6·78 g., 99·5%) was separated and washed with acetone. The filtrate was added to light petroleum (b. p. 40—60°) (500 ml.), and the precipitate of iodine and sodium iodide was filtered off. The filtrate was evaporated to a syrup which did not crystallise and was hydrolysed by 50% aqueous acetic acid (40 ml.) for 3 hr. at 100°. The solution was then evaporated to dryness and the residue extracted with cold water (2 × 10 ml.); evaporation of the extracts gave the crude *tetrol* (1·57 g.). After recrystallisation from methanol it was obtained as plates (0·81 g., 32%), m. p. 193°, $[\alpha]_D^{28}$ +332° (*c* 1·9 in H_2O) (Found: C, 49·15; H, 6·8. $C_6H_{10}O_4$ requires C, 49·3; H, 6·9%).

With pyridine and acetic anhydride it gave a gum from which the tetrol was recovered by hydrolysis.

1 : 2-3 : 4-*Di*-O-iso*propylidene*cyclo*hex*-5-*ene*-1 : 2/3 : 4-*tetrol*.—(1*R*)-Di-*O*-*iso*propylidenedi-*p*-nitrobenzenesulphonylinositol (0·63 g.) and anhydrous sodium iodide (1·50 g.) in anhydrous acetone (10 ml.) were heated in a sealed tube at 100° for 13 hr. The precipitated sodium *p*-nitrobenzenesulphonate (0·42 g., 93%) was separated; the filtrate was poured into chloroform, and the chloroform solution washed with sodium thiosulphate solution, dried (Na_2SO_4), and evaporated to dryness. The oily residue was extracted with light petroleum and the extract evaporated to dryness. The residue (0·19 g.) was sublimed twice at *ca.* 60°/1·5 mm., to give

[14] Posternak and Reymond, *Helv. Chim. Acta*, 1955, **38**, 195.
[15] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 170.
[16] Angyal and Macdonald, *J.*, 1952, 686.

plates (0·12 g., 52%) of the *compound*, m. p. 60—61° (Found: C, 63·65; H, 7·95. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%).

This product (90 mg.) was hydrolysed by 20% aqueous acetic acid (10 ml.) at 100° in 2 hr. Evaporation gave *cyclo*hex-5-ene-1 : 2/3 : 4-tetrol (60 mg.), m. p. 190°.

Hydroxylation of (+)-cyclo*Hex-5-ene*-1 : 2/3 : 4-*tetrol*.—The unsaturated tetrol (147 mg.) and silver chlorate (64 mg.) were dissolved in water (9 ml.) and 1% osmium tetroxide solution (1 ml.) was added. After being kept for 3 days in the dark, the solution was filtered from the precipitated silver chloride and evaporated to dryness. The residue was sublimed at 0·1 mm., to give *allo*inositol (65 mg., 36%), m. p. 310—320° (decomp.). Dangschat and Fischer [11] record m. p. 270—275°.

The inositol (35 mg.) was heated with acetic anhydride (1 ml.) and pyridine (1 ml.) for 3 hr. at 100°. The mixture was evaporated *in vacuo* and the residue recrystallised from aqueous ethanol, to give *allo*inositol hexa-acetate (75 mg.) as needles, m. p. 143—144° (Found: C, 50·05; H, 5·7. Calc. for $C_{18}H_{24}O_{12}$: C, 50·0; H, 5·6%). The m. p. of authentic *allo*inositol hexa-acetate [7] was not depressed.

(+)-cyclo*Hexane*-1 : 2/3 : 4-*tetrol* (VI).—(+)-*cyclo*Hex-5-ene-1 : 2/3 : 4-tetrol (0·215 g.) in water (10 ml.) was hydrogenated in the presence of 10% palladium–carbon (0·1 g.); after the uptake of 1 mol. of hydrogen, the solution was filtered and evaporated, and the residue (0·20 g.) crystallised from methanol, to give the *tetrol* (0·135 g.) as prisms, m. p. 215°, $[\alpha]_D^{26}$ +72° (*c* 1·14 in H_2O) (Found: C, 48·9; H, 8·2. $C_6H_{12}O_4$ requires C, 48·65; H, 8·15%). For the enantiomorph Posternak and Friedli [10] give m. p. 218°, $[\alpha]_D^{23}$ −73·7° (*c* 11·4 in H_2O).

(±)-1 : 2-3 : 4-*Di*-O-iso*propylidene*epi*inositol*.—The following method is shorter than the previous procedure.[16] *epi*Inositol (10 g.) and anhydrous zinc chloride (50 g.) in acetone (300 ml.) were heated under reflux for 40 hr. After the mixture had cooled, a solution of potassium carbonate (60 g.) in water (50 ml.) was added with good stirring. The precipitated salts were filtered off and washed with acetone (2 × 50 ml.); the filtrate was dried (K_2CO_3) and evaporated. The residual oil was diluted with light petroleum, and the crude crystalline product (4·5 g.) was recrystallised from ethyl acetate, to give the di-*O*-*iso*propylidene derivative (3·66 g., 25%), m. p. 180—181°. By acid hydrolysis of the mother-liquors, about 30% of the *epi*inositol was recovered; acetylation of the mixed zinc and potassium salts with acetic anhydride and zinc chloride gave another 30% of *epi*inositol as the hexa-acetate.

(±)-1 : 2-3 : 4-*Di*-O-iso*propylidene*-5 : 6-*di*-O-p-*nitrobenzenesulphonyl*epi*inositol* (IVb).—The preceding compound (1·00 g.) and *p*-nitrobenzenesulphonyl chloride (2·13 g., 2·5 mol.) in anhydrous pyridine (10 ml.) were set aside at room temperature for one week. The mixture was then diluted with water, and the crude product, which solidified, recrystallised from ethanol, to give the *disulphonyl derivative* (1·92 g., 80%) as plates, m. p. 145° (Found: C, 45·8; H, 4·3%).

(±)-1 : 2 : 3 : 4-*Tetra*-O-*acetyl*-5 : 6-*di*-O-p-*nitrobenzenesulphonyl*epi*inositol*.—The preceding compound was heated in acetic acid (10 ml.) and water (10 ml.) at 100° for 2 hr. to remove the *iso*propylidene groups. The solution was then evaporated *in vacuo* and the crystalline residue heated with acetic anhydride (10 ml.) and pyridine (10 ml.) at 100° for 1 hr. The cooled solution was poured into water: the precipitate solidified and was collected. Recrystallisation from ethanol gave the *tetra-acetate* (2·0 g., 88%) as cubes, m. p. 190° (Found: C, 43·4; H, 3·6. $C_{26}H_{26}O_{18}N_2S_2$ requires C, 43·45; H, 3·65%).

all-cis-1 : 2-3 : 4-*Di*-O-iso*propylidene*cyclo*hex*-5-*ene*-1 : 2 : 3 : 4-*tetrol*.—Di-*O*-*iso*propylidene-di-*p*-nitrobenzenesulphonyl*epi*inositol (0·63 g.) and anhydrous sodium iodide (3·0 g.) in anhydrous acetone (20 ml.) were heated in a sealed tube at 100° for 20 hr. The precipitated sodium salt (0·31 g., 69%) was separated and chloroform was added to the filtrate. The solution was washed with sodium thiosulphate solution, dried (Na_2SO_4), and evaporated. The residual oil (0·33 g.) was extracted with light petroleum (2 × 20 ml.) which left some starting material (0·16 g.) undissolved. The extracts were evaporated and the crude product (104 mg.) was sublimed at 60°/0·2 mm. to give the *tetrol* (60 mg., 26%), m. p. 67—68° (Found: C, 61·8; H, 7·65. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%).

all-cis-1 : 2 : 3 : 4-*Tetra*-O-*acetyl*cyclo*hex*-5-*ene*-1 : 2 : 3 : 4-*tetrol*.—Tetra-*O*-acetyl-di-*O*-*p*-nitrobenzenesulphonyl*epi*inositol (1·0 g.) and anhydrous sodium iodide (2·0 g.) in acetic anhydride (20 ml.) were heated under reflux for 20 hr., then poured into water and, when the acetic anhydride had been hydrolysed, the solution was extracted with chloroform. The chloroform layer was washed with sodium thiosulphate solution, sodium carbonate solution, and water.

The solvent was dried (Na_2SO_4) and evaporated, and the residue was sublimed at *ca.* 100°/0·1 mm. The sublimate crystallised from light petroleum to give prisms of the *tetra-acetate* (184 mg., 42%), m. p. 102—104° (Found: C, 53·6; H, 5·75. $C_{14}H_{18}O_8$ requires C, 53·5; H, 5·7%).

Deacetylation of the tetra-acetate with sodium methoxide, or hydrolysis of the di-*O-iso*-propylidene derivative with aqueous acetic acid, gave the all-*cis-cyclo*hexenetetrol (V) as an oil which was reconverted by acetylation into the tetra-acetate, m. p. 103°.

On hydrogenation the tetrol or its tetra-acetate each absorbed a mol. of hydrogen but the resulting saturated derivatives did not crystallise.

Hydroxylation of all-cis-cyclo*Hex*-5-*ene*-1 : 2 : 3 : 4-*tetrol* (V).—The tetrol (80 mg.) and silver chlorate (35 mg.) were dissolved in water (4 ml.) and, after the addition of 1% osmium tetroxide solution (1 ml.), were kept in the dark for 24 hr. A paper chromatogram [17] (4 : 1 acetone–water) showed the presence of *allo*inositol, but not of *cis*inositol.

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[17] Angyal, McHugh, and Gilham, *J.*, 1957, 1432.