931. *Cyclitols. Part XI.*[1] *The Constitution of Liriodendritol.*

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Liriodendritol (from *Liriodendron tulipifera* L.) is shown to be (1*S*)-1,4-di-*O*-methylmyoinositol.

Liriodendritol is the only inositol ether known to occur in Nature whose constitution has not yet been determined. Plouvier, who isolated [2] it from *Liriodendron tulipifera* L., proved that it is a dimethyl ether of myoinositol. It is now shown that liriodendritol is (1*S*)-1,4-di-*O*-methylmyoinositol [3] (I). As in all other naturally occurring inositol ethers, the methoxy-groups in liriodendritol are equatorial.

Partial demethylation of liriodendritol, by short heating with hydriodic acid,[4] gave (−)-bornesitol [(1*S*)-1-*O*-methylmyoinositol [5]] (II) in good yield, thereby establishing the position of one methyl group. A second monomethyl ether could not, however, be isolated.

Liriodendritol reacts rapidly with one mol. of periodate, but after this stage further oxidation is slow. The consumption reaches two mol. after several hours, and titration then shows that approximately one mol. of acid has been formed. Some of this acid is present as an ester, titratable only after hydrolysis. The behaviour of liriodendritol on periodate oxidation appeared similar to that of dambonitol [4] and it was at first concluded that the methoxy-groups were *meta* to each other. (Hence the erroneous 1,5-di-*O*-methylmyoinositol structure for liriodendritol in *Adv. Carbohydrate Chem.*, 1959, **14**, 172 and 197.) The consumption of periodate, however, continues over a long period and is not yet complete after 9 days when 4·8 mol. have reacted; there is also a slow increase in the amount of free and " bound " acid formed (see Table).

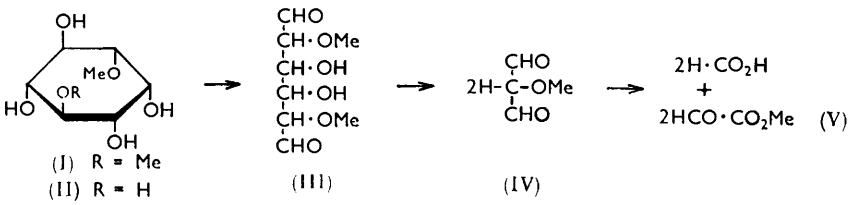
This behaviour is in accord with the annexed sequence, expected [6] for a *para*-di-*O*-methylinositol. The initially formed dialdehyde (III) probably exists mostly in (non-oxidisable) cyclic hemiacetal forms and hence its further oxidation is slow. By analogy with its *O*-benzyl derivative,[7] *O*-methyltartronaldehyde (IV) would be expected to be oxidised to formic acid and methyl glyoxylate; attempts to isolate the dialdehyde (IV) were unsuccessful but its presence was indicated by the decolorisation of iodine in sodium hydrogen carbonate solution, a characteristic reaction of reductones.[8] Methyl glyoxylate

[1] Part X, Angyal and Tate, *J.*, 1961, 4122.
[2] Plouvier, *Compt. rend.*, 1955, **241**, 765.
[3] Nomenclature according to Angyal and Gilham, *J.*, 1957, 3691.
[4] Angyal, Gilham, and Macdonald, *J.*, 1957, 1417.
[5] Bien and Ginsburg, *J.*, 1958, 3189; Anderson and Post, Abs. Papers Amer. Chem. Soc., 1958, **134**, 13D.
[6] Angyal and Klavins, *Austral. J. Chem.*, 1961, in the press.
[7] Schwarz and MacDougall, *J.*, 1956, 3065.
[8] Euler and Eistert, " Reduktone and Reduktonate," Ferdinand Enke, Stuttgart, 1957, p. 7.

Periodate oxidation of liriodendritol (L) and of (±)-1,4-di-*O*-methylmyoinositol (R).

Time	Periodate (mol.)		Free acid (mol.)		Total acid (mol.)		Time	Periodate (mol.)		Free acid (mol.)		Total acid (mol.)	
(hr.)	L	R	L	R	L	R	(hr.)	L	R	L	R	L	R
0·33	1·40	1·40	—	—	—	—	49	3·65	3·59	1·20	1·17	1·87	1·85
7	2·05	1·99	0·46	0·46	0·67	0·62	120	4·36	4·33	1·53	1·55	2·48	2·36
24	2·83	2·80	0·72	0·72	0·88	0·90	168	—	4·54	—	1·63	—	2·77
							216	—	4·81	—	—	—	—

(V) was obtained as its phenylhydrazone; its isolation proves the constitution of liriodendritol because it could not have been formed from an *ortho*- or a *meta*-dimethyl ether.



The bound acid found by titration is not a formate ester (the " bound formate " often obtained in the periodate oxidations of reducing sugars [9]) but methyl glyoxylate. Part of the titration for free acid is due to *O*-methyltartronaldehyde which, like other substituted malonaldehydes, can be titrated as a monobasic acid to the phenolphthalein end-point.

To confirm the 1,4-dimethyl structure of liriodendritol, the corresponding racemate was synthesised by methylation of 1,2:4,5-di-*O*-cyclohexylidenemyoinositol,[10] followed by hydrolysis of the ketal groups. The resulting dimethyl compound had the same R_F value in several solvent systems, and showed the same behaviour with periodate (Table), as liriodendritol; the tetra-acetates of the two compounds had identical infrared spectra in chloroform solution.

It was pointed out previously [4] that in Nature each inositol methyl ether is accompanied by its parent inositol; dambonitol, a dimethyl ether, is also accompanied by bornesitol, the corresponding monomethyl ether. Liriodendritol is no exception: chromatographic evidence indicates that *L. tulipifera* contains small amounts of myoinositol and 1- and 4-*O*-methylmyoinositol, as well as liriodendritol.

[*Added, September 4th*, 1961.] Liriodendritol itself has been synthesised from (−)-bornesitol. Treatment [11] of the latter with acetone diethyl ketal gave 2,3:5,6-di-*O*-isopropylidenebornesitol [5] (in addition to the 2,3:4,5-derivative) which was converted by methylation and subsequent removal of the isopropylidene groups into a dimethyl ether, identical with natural liriodendritol.

Experimental

Liriodendritol (1·25 g.), m. p. 223°, was isolated from dried autumn leaves of *L. tulipifera* (445 g.) as described by Plouvier.[2] The ethanolic mother liquors were concentrated and examined by paper chromatography in butan-1-ol–pyridine–water (6 : 4 : 3): glucose (R_G 1·0), liriodendritol (0·52), 4-*O*-methylmyoinositol (0·31), 1-*O*-methylmyoinositol (0·19), and myoinositol (0·06) were identified. The amount of the monomethyl ethers was insufficient to allow their separation and the determination of their optical activity.

Partial Demethylation.—Liriodendritol (0·36 g.) was heated on a steam bath with concentrated hydriodic acid (0·72 ml.) for 5 min. The acid was removed in a desiccator over sodium hydroxide, and the residue was dissolved in water and extracted with chloroform to remove the iodine. The concentrated solution was then placed on a cellulose powder column and was eluted with 1 : 4 water–acetone. Fractions 1—13 (127 mg.) contained liriodendritol, and fractions 37—50 mainly myoinositol. Fractions 14—36 were evaporated and the residue

[9] Bobbitt, *Adv. Carbohydrate Chem.*, 1956, **11**, 35.
[10] Angyal, Tate, and Gero, *J.*, 1961, 4116.
[11] Angyal and Hoskinson, unpublished work.

was dissolved in hot ethanol: (−)-bornesitol (61 mg.) crystallised. After two recrystallisations it had m. p. 200°, $[\alpha]_D^{18}$ −25° (*c* 2 in H_2O) (lit.,[2,4] m. p. 203—204°, $[\alpha]_D^{20}$ −32°). The penta-acetate, obtained in 76% yield, had m. p. 140°, $[\alpha]_D^{20}$ −14° (*c* 2 in $CHCl_3$) (lit., m. p. 142°, $[\alpha]_D^{20}$ −11°).

(±)-1,4-*Di*-O-*methylmyoinositol*.—Methyl iodide (65 ml.), and then silver oxide (65 g.), were added in small portions with shaking to a solution of 1,2:4,5-di-*O*-cyclohexylidenemyoinositol (10 g.) in *NN*-dimethylformamide (400 ml.) at <25°. After 3 days' shaking at 28°, more silver oxide (35 g.) was added to the mixture, and shaking was continued for another day. The solids were separated by centrifugation and washed with dimethylformamide and with chloroform. After addition of water (500 ml.) and potassium cyanide (5 g.) the combined supernatant liquid and washings were extracted four times with chloroform. The extracts were shaken with water, dried (Na_2SO_4), and evaporated; the residue was heated on a steam bath for 15 min. with 90% acetic acid (200 ml.). After evaporation, the residue was dissolved in hot ethanol from which (±)-1,4-*di*-O-*methylmyoinositol* (4·5 g., 74%), m. p. 195°, crystallised. Three recrystallisations raised the m. p. to 203° (Found: C, 46·1; H, 7·5. $C_8H_{16}O_6$ requires C, 46·15; H, 7·75%).

Acetylation with acetic anhydride and sulphuric acid gave a 70% yield of the *tetra-acetate*, m. p. 155—156° after two crystallisations from ethanol–water (Found: C, 51·1; H, 6·35. $C_{16}H_{24}O_{10}$ requires C, 51·1; H, 6·4%). The infrared spectrum of this compound, taken on a 5% solution in $CHCl_3$ with a Perkin-Elmer model 12C instrument and a rock-salt prism, was found identical with that of tetra-*O*-acetyl-liriodendritol (m. p. 139°). Absorption bands were found at the following frequencies: 868w, 889w, 905w, 943s, 955m, 980m, 998m, 1034s, 1068s, 1086s, 1107s, 1145s cm.$^{-1}$.

Periodate Oxidations.—Each dimethyl ether (41·6 mg., 0·2 millimole) was dissolved in 0·03M-sodium metaperiodate (50 ml., 1·5 millimoles) and kept in the dark. Aliquot parts (5 ml.) were analysed at intervals. For the determination of periodate, M-sodium carbonate (2 ml.), 10% potassium iodide solution (1 ml.), and 0·025N-sodium arsenite (15 ml.) were added to one part and, after 15 min., the solution was titrated with 0·025N-iodine. For the estimation of free acid, ethylene glycol (20 drops) was added to an aliquot part and, after 1 hr., the solution was titrated with 0·01N-sodium hydroxide (Methyl Red). Excess of 0·01N-sodium hydroxide (2—6 ml.) was then added; after the lapse of 1 hr., the solution was titrated with 0·01N-hydrochloric acid (Methyl Red) to determine the "bound" acid. The results are shown in the Table.

To show the presence of a reductone in the mixture, it was treated with ethylene glycol, followed after 10 min. by sodium hydrogen carbonate: the resulting solution decolorised 0·01N-iodine but no sharp end point was obtained. Reductone was detected after only 20 min. of oxidation.

Isolation of Methyl Glyoxylate Phenylhydrazone.—A solution of 1,4-di-*O*-methylmyoinositol (1 g.) and sodium metaperiodate (7·5 g.) in water (170 ml.) was set aside for a week in the dark. Periodate and iodate were destroyed by sulphur dioxide, and the solution was concentrated *in vacuo* to 100 ml., neutralised with sodium hydrogen carbonate, and filtered. To the filtrate a solution of phenylhydrazine hydrochloride (2 g.) and sodium acetate (3 g.) in water (50 ml.) was added; the resulting precipitate (0·38 g., 22%) gave yellow-brown crystals, having m. p. 136° after two recrystallisations from benzene–light petroleum. They did not depress the m. p. (135°) of methyl glyoxylate phenylhydrazone, prepared by the periodate oxidation of methyl tartrate.

[*Added, September* 4th, 1961.] *Liriodendritol*.—A mixture of (1*S*)-2,3:5,6-di-*O*-isopropylidene-1-*O*-methylmyoinositol[5,11] (17 mg.), *NN*-dimethylformamide (0·3 ml.), methyl iodide (1 ml.), and silver oxide (75 mg.) was shaken at 20° for 15 hr. The solids were separated and washed with dimethylformamide and chloroform. The filtrate was shaken with 5% potassium cyanide solution, and the organic layer was washed with water and evaporated. The residual solid was heated with a few drops of N-hydrochloric acid on the steam bath for 10 min.; the solution was evaporated and the residue dissolved in hot ethanol. On cooling, crystals (9 mg., 70%) were deposited which were identified with liriodendritol by appearance (triangular plates), m. p. 224—225°, and mixed m. p.

One of us (V. B.) is indebted to the Nuffield Foundation for a research grant.

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