The Allyl Group for Protection in Carbohydrate Chemistry. Part 21.[1] (±)-1,2:5,6- and (±)-1,2:3,4-Di-*O*-isopropylidene-*myo*-inositol. The Unusual Behaviour of Crystals of (±)-3,4-Di-*O*-acetyl-1,2,5,6-tetra-*O*-benzyl-*myo*-inositol on Heating and Cooling: a 'Thermosalient Solid'

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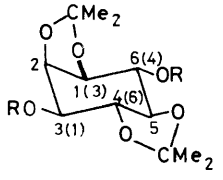
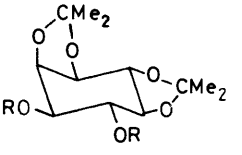
Racemic 1,2-*O*-isopropylidene-*myo*-inositol was converted into a mixture of 1,2:5,6-, 1,2:3,4-, and 1,2:4,5-di-*O*-isopropylidene-*myo*-inositols which were resolved by g.l.c. The 1,2:4,5- and 1,2:5,6-isomers were isolated from the mixture as benzoate derivatives. Allylation of the mixed isomers allowed the separation of all three allyl ethers by column chromatography and these were converted into the corresponding di-*O*-allyl-*myo*-inositols. 1,4-Di-*O*-allyl-*myo*-inositol was converted into 1,4-di-*O*-allyl-5,6-*O*-isopropylidene-*myo*-inositol on kinetic acetonation. Removal of the allyl groups from 5,6-di-*O*-allyl-1,2:3,4-di-*O*-isopropylidene-*myo*-inositol gave pure 1,2:3,4-di-*O*-isopropylidene-*myo*-inositol which gave the known 1,2,3,4-tetra-*O*-benzyl-*myo*-inositol. Crystals of the diacetate of 1,2,5,6-tetra-*O*-benzyl-*myo*-inositol showed interesting 'jumping' behaviour on heating and cooling.

In our recorded[2] preparation of (±)-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**1**) (which we are using extensively[1,3,4] as a starting material for the synthesis of intermediates for the preparation of biologically interesting inositol phosphates) it was possible to separate it from the other two thermodynamic isomers (**5**) and (**9**) also formed in the reaction, (*a*) because, unlike the others, it is a non-vicinal diol and is thus more readily eluted from alumina columns or (*b*) because of the very low solubility of its benzoate (**2**) in organic solvents. We have now prepared the other two isomers from the mixture. All three isomers and their acetates and the benzoates (**6**) and (**10**) migrated together on t.l.c. (silica) but the trimethylsilyl ethers separated on g.l.c. and the allyl ethers separated on t.l.c.

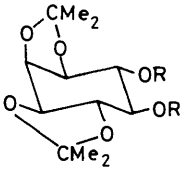
Racemic 1,2-*O*-isopropylidene-*myo*-inositol[2] was converted into the mixture of di-*O*-isopropylidene derivatives as described[2] and this was converted into the mixture of benzoates.



(**1**) R = H
(**2**) R = Bz
(**3**) R = $CH_2CH{=}CH_2$
(**4**) R = Ac



(**5**) R = H
(**6**) R = Bz
(**7**) R = $CH_2CH{=}CH_2$
(**8**) R = Ac

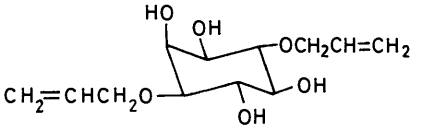


(**9**) R = H
(**10**) R = Bz
(**11**) R = $CH_2CH{=}CH_2$
(**12**) R = Ac
(**13**) R = CH=CHMe

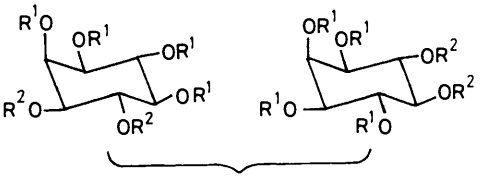
After the highly crystalline benzoate (**2**)[2] had been removed from the mixture, the soluble benzoates were fractionally crystallised to give the benzoate (**6**) which on basic hydrolysis gave (**5**) and this in turn gave the crystalline acetate (**8**). It was not possible to obtain a pure sample of the benzoate (**10**) from the mother liquors and therefore a pure sample of (**9**) was obtained as described below from the allyl ether (**11**).

In order to distinguish chemically between the two isomers (**5**) and (**9**), they were converted into the corresponding tetra-*O*-benzyl ethers (**17**) and (**21**), *via* the allyl ethers (**7**) and (**11**). 1,2,3,4,-Tetra-*O*-benzyl-*myo*-inositol (**21**) had been prepared previously[4] from 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-*myo*-inositol by way of 5,6-di-*O*-allyl-1,4-di-*O*-benzyl-*myo*-inositol.

T.l.c. resolved all three di-*O*-allyl derivatives (**3**),[4] (**7**), and (**11**) and their mobilities on t.l.c. were in the reverse order of those of the corresponding trimethylsilyl ethers on g.l.c. Silica gel chromatography gave pure samples of all three di-*O*-allyl derivatives from the mixture and the individual hydrolysis of the isopropylidene groups from these gave the crystalline tetraols (**14**), (**15**), and (**19**) respectively. For the preparation of pure (**9**), the allyl groups were removed from (**11**) by isomerisation to the prop-1-enyl ether (**13**) using tristriphenylphosphine-rhodium(I) chloride[5] and subsequent removal of the prop-1-enyl groups



(**14**)



(**15**) R^1 = H, R^2 = $CH_2CH{=}CH_2$ (**19**)
(**16**) R^1 = CH_2Ph, R^2 = $CH_2CH{=}CH_2$ (**20**)
(**17**) R^1 = CH_2Ph, R^2 = H (**21**)
(**18**) R^1 = CH_2Ph, R^2 = Ac (**22**).

with mercury(II) chloride in the presence of mercury(II) oxide.[6] Compound (**9**) gave a crystalline acetate (**12**).

Benzylation of the tetraols (**15**) and (**19**) gave the tetra-*O*-benzyl ethers (**16**) and (**20**) and the allyl groups were removed from these by the action of potassium t-butoxide in dimethyl sulphoxide[7] or palladium-on-charcoal[8] to give the diols (**17**) and (**21**) which were converted into the acetates (**18**) and (**22**) respectively. Compounds (**21**) and (**22**) were identical with the materials described[4] previously, thus establishing that the most soluble isomer of the di-*O*-isopropylidene-*myo*-inositols, which had intermediate mobility in both g.l.c. (as the trimethylsilyl ether) and on t.l.c. (as the diallyl ether), was 1,2:3,4-di-*O*-isopropylidene-*myo*-inositol (**9**).

The acetate (**18**) of 1,2,5,6-tetra-*O*-benzyl-*myo*-inositol showed interesting behaviour when heated and cooled. It melted sharply at 106—108 °C but prior to this at *ca.* 70 °C the crystals were observed to 'jump' in the m.p. tube and this was initially assumed to be due to the presence of solvent of crystallisation. However, crystals that had been warmed to 80 °C and allowed to cool, exhibited further 'jumping' at *ca.* 40 °C. This behaviour could be observed many times on taking the same sample of the crystals through this warming and cooling cycle. Preliminary observations of the crystals in polarised light suggest 'that they may be in the form of a bundle of parallel fibres or leaves ... with crystallographically non-identical faces in contact ... and that a composite crystal of this sort may act in the same way as a bimetallic strip at different temperatures'.[9] Some interesting mobile behaviour of crystals of 1,4-dimethoxy-2,5-di-t-butylbenzene[10] and of methyl *p*-nitrobenzoate[11] has been observed but does not appear to be related to the above phenomenon.

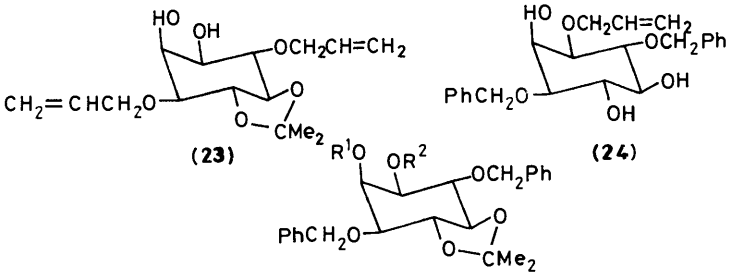
We have shown previously[1] that kinetic acetonation of racemic 1,4-di-*O*-benzyl-*myo*-inositol gives predominantly 1,4-di-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol and we describe here the preparation of the corresponding 1,4-di-*O*-allyl-5,6-*O*-isopropylidene-*myo*-inositol (**23**) in a similar way from 1,4-di-*O*-allyl-*myo*-inositol (**14**). We have also shown previously[12] that ethers of 1,2-*O*-isopropylidene-*myo*-inositol are converted into ethers of benzene-1,2,4-triol on treatment with potassium t-butoxide in dimethyl sulphoxide and it was of interest to see if the isopropylidene group at other positions in the inositol molecule would lead to an aromatisation reaction under these conditions. The allyl ether (**24**) was previously[1] found to be a useful intermediate in the preparation of 1,2,4-tri-*O*-benzyl-*myo*-inositol (required for the synthesis of inositol 1,4,5-trisphosphate) and an improved procedure for the preparation of (**24**) by removal of the tin derivatives before crystallisation or column chromatography is described. Compound (**24**) was converted into the isopropylidene derivatives (**25**) and (**26**) and treatment of (**26**) with potassium t-butoxide in dimethyl sulphoxide at 50 °C for long periods gave the prop-1-enyl ether (**27**) without evidence of further significant changes. The behaviour of the benzyl ethers of the isomeric di-*O*-isopropylidene-*myo*-inositols (**1**), (**5**), and (**9**) with potassium t-butoxide in dimethyl sulphoxide is under investigation.

Experimental

All the inositol derivatives described are racemic. T.l.c. was carried out on microscope slides coated with silica gel G and products were visualised by spraying the plates with 50% sulphuric acid and heating. G.l.c. was performed on a Perkin Elmer Sigma 3B Dual FID chromatograph. Light petroleum had b.p. 40—60 °C unless otherwise stated.

*G.l.c. of the Di-*O*-isopropylidene-*myo*-inositols.*—The mixture of di-*O*-isopropylidene derivatives was prepared from 1,2-*O*-isopropylidene-*myo*-inositol as described[2] and was purified by chromatography on silica gel eluting with ethyl acetate. G.l.c. of the trimethylsilyl ethers, on SE 30 with a column temperature of 175 °C gave retention times of 4, 4.5 and 5.25 min with a relative abundance of 2:1:2 respectively. Under the same conditions the trimethylsilyl ether of 1,2-*O*-isopropylidene-*myo*-inositol had R_t 8.5 min and the trimethylsilyl ether of pure 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol[2] (**1**) had R_t 4 min.

3,4-*Di*-O-*benzoyl*-1,2:5,6-*di*-O-*isopropylidene*-myo-*inositol* (**6**).—The mixture of di-*O*-isopropylidene derivatives prepared as described above was treated with benzoyl chloride in pyridine in the usual way and the benzoate (**2**)[2] which separated from the solution was filtered off and purified as described.[2] The soluble benzoates were isolated in the usual way and triturated with boiling light petroleum (b.p. 60—80 °C). The insoluble material was recrystallised from methanol (10 ml g^{-1}) to give the *benzoate* (**6**), m.p. 197—200 °C (Found: 66.75; H, 6.2. $C_{26}H_{28}O_8$ requires C, 66.65; H, 6.0%). The light petroleum-soluble benzoate was hydrolysed with base, and g.l.c. of the trimethylsilyl ether showed that the product was predominantly the isomer of R_t 4.5 min but still containing some of the R_t 5.25 min isomer.



(**25**) R^1 = H, R^2 = $CH_2CH=CH_2$
(**26**) R^1 = CH_2Ph, R^2 = $CH_2CH=CH_2$
(**27**) R^1 = CH_2Ph, R^2 = CH=CH-Me
(**28**) R^1 = CH_2Ph, R^2 = H

1,2:5,6-*Di*-O-*isopropylidene*-myo-*inositol* (**5**).—The benzoate (**6**) was hydrolysed with sodium hydroxide in methanol. An excess of solid carbon dioxide was then added and the solvent was evaporated. The product was extracted from the residue with dichloromethane and recrystallisation from ethyl acetate

gave the *isopropylidene derivative* (**5**), m.p. 172—175 °C (Found: C, 55.5; H, 7.9. $C_{12}H_{20}O_6$ requires C, 55.4; H, 7.75%). G.l.c. of the trimethylsilyl ether showed an elution time of 5.25 min together with trace contamination by 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**1**) (R_t 4 min). The di-*O*-isopropylidene derivative (**5**) gave an *acetate* (**8**), m.p. 165—168 °C (Found: C, 55.9; H, 7.1. $C_{16}H_{24}O_8$ requires C, 55.8; H, 7.0%).

1,2:3,4-*Di*-O-*isopropylidene*-myo-*inositol* (**9**).—The crude product obtained by hydrolysis of the light-petroleum-soluble benzoates (see above) was allylated with an excess of sodium hydride and allyl bromide in *N,N*-dimethylformamide in the usual way. T.l.c. [ether–light petroleum (1:1)] showed a major product (R_F 0.75) and a minor product (R_F 0.85) together with a trace product (R_F 0.65). The di-*O*-allyl ether (**3**)[2] had R_F 0.65 and the allyl ether (**7**) prepared from 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol (**5**) had R_F 0.85. Chromatography of the crude product on silica gel [ether–light petroleum (1:2)] gave a pure fraction of the major compound (R_F 0.75). This fraction (600 mg), tristriphenylphosphinerhodium(I) chloride (250 mg) and 1,4-diazabicyclo[2.2.2]octane (100 mg) were heated under reflux in ethanol–water (9:1; 30 ml) for 6 h after which time t.l.c. (as above) showed almost complete conversion of the starting material (R_F 0.75) into a product (R_F 0.8). The mixture was filtered through Celite and the solvents were evaporated and the crude product was chromatographed on silica gel [ether–light petroleum (1:1)] to give the crude diprop-1-enyl ether (**13**) (600 mg) which showed an intense vinyl ether peak in the i.r. spectrum at 1 670 cm^{-1}. The vinyl ethers were hydrolysed[6] with mercury(II) chloride–mercury(II) oxide in acetone–water (9:1). The excess of mercury(II) oxide was removed by filtration through Celite and the solvents were evaporated. An excess of saturated aqueous potassium iodide was added to the residue and the aqueous layer was extracted ten times with an equal volume of chloroform. The chloroform extract was dried (K_2CO_3) and evaporated, and the product (400 mg) was chromatographed on silica gel (ethyl acetate) to give 1,2:3,4-*di*-O-*isopropylidene*-myo-*inositol* (**9**) (300 mg), m.p. 150—152 °C [from light petroleum–ethyl acetate (10:1); trimethylsilyl ether R_t 4.5 min) (Found: C, 55.7; H, 8.0. $C_{12}H_{20}O_6$ requires C, 55.4; H, 7.75%), which gave the *acetate* (**12**) m.p. 140—142 °C (from ethanol) (Found: C, 55.9; H, 7.2. $C_{16}H_{24}O_8$ requires C, 55.8; H, 7.0%).

4,5-*Di*-O-*allyl*-myo-*inositol* (**19**).—The di-*O*-allyl ether (**11**), prepared as described above, was hydrolysed by heating in acetic acid–water (4:1) at reflux for 30 min. The solvents were evaporated, and recrystallisation of the residue from ethanol gave the *tetraol* (**19**), m.p. 137—138 °C (Found: C, 55.0; H, 7.8. $C_{12}H_{20}O_6$ requires C, 55.4; H, 7.75%).

5,6-*Di*-O-*acetyl*-1,2,3,4-*tetra*-O-*benzyl*-myo-*inositol* (**22**).[4]—The tetraol (**19**) was treated with an excess of benzyl bromide and sodium hydride in *N,N*-dimethylformamide, and the product was isolated in the usual way[4] to give the benzyl ether (**20**). The allyl groups were removed with potassium t-butoxide in dimethyl sulphoxide as described previously[4] to give the diol (**21**) (m.p. and mixed m.p. 87—89 °C) which was converted into the acetate (**22**) (m.p. and mixed m.p. 132—134 °C) identical with the materials described previously.[4]

1,4-*Di*-O-*allyl*-myo-*inositol* (**14**).—The di-*O*-allyl ether (**3**)[4] was hydrolysed by heating in acetic acid–water (4:1) at reflux for 30 min. The solvents were then evaporated to give the *tetraol* (**14**), m.p. 137—139 °C (from ethanol) (Found: C, 55.1; H, 7.8. $C_{12}H_{20}O_6$ requires C, 55.4; H, 7.75%).

1,6-*Di*-O-*allyl*-myo-*inositol* (**15**).—The di-*O*-isopropylidene derivative (**5**) was converted into the allyl ether (**7**) in the usual way and this was hydrolysed with acetic acid [as described above for the preparation of the isomer (**14**)] to give the *tetraol* (**15**) m.p. 142—144 °C (from ethanol) (Found: C, 55.1; H, 7.9. $C_{12}H_{20}O_6$ requires C, 55.4; H, 7.75%).

1,2,5,6-*Tetra*-O-*benzyl*-myo-*inositol* (**17**) *and* 3,4-*Di*-O-*acetyl*-1,2,5,6-*tetra*-O-*benzyl*-myo-*inositol* (**18**): *Thermosalient Crystals*.—The tetraol (**15**) was converted into the benzyl ether (**16**) in the usual way and the allyl groups were removed with Pd–C as described previously[4] for the isomer (**20**). Recrystallisation of the product from ethanol gave the *diol* (**17**) m.p. 169—170 °C (Found: C, 75.6; H, 6.8. $C_{34}H_{36}O_6$ requires C, 75.5; H, 6.7%). This in turn gave an *acetate* (**18**), m.p. 106—108 °C (from light petroleum 60—80 °C) (Found: C, 73.1; H, 6.6. $C_{38}H_{40}O_8$ requires C, 73.1; H, 6.45%). When heated to 70 °C on a watch glass or in a melting point tube these crystals were seen to 'jump' and when cooled to 40 °C they 'jumped' again. This behaviour could be observed repeatedly on heating and cooling.

1,4-*Di*-O-*allyl*-5,6-O-*isopropylidene*-myo-*inositol* (**23**).—1,4-Di-*O*-allyl-*myo*-inositol (**14**) (3.7 g) was stirred with dry *N,N*-dimethylformamide (15 ml) at 20 °C until it dissolved. 2,2-Dimethoxypropane (2 ml) and toluene-*p*-sulphonic acid (50 mg) were added and the mixture was kept at 20 °C for 10 min. Saturated aqueous sodium hydrogen carbonate (0.5 ml) was added and most of the solvents were evaporated off. The residue was diluted with water (10 ml) and extracted with ether (4 × 50 ml), and the combined extracts were dried (K_2CO_3) and evaporated. T.l.c. (eluting with ether) of the crude product (1.9 g) showed a minor product (R_F 0.95), a major product (R_F 0.6), and a minor product (R_F 0.5). These were separated by chromatography on silica gel [ether–light petroleum (2:1 and 3:1)]. The product of R_F 0.95 (250 mg, m.p. 85—86 °C) was identical with 3,6-di-*O*-allyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol[4] and the product of R_F 0.5 (390 mg, m.p. 134—136 °C) was identical with 1,4-di-*O*-allyl-2,3-*O*-isopropylidene-*myo*-inositol.[4] The major product (R_F 0.6; 1.25 g, 29%) was the *isopropylidene derivative* (**23**), m.p. 108—110 °C (Found: C, 59.9; H, 8.3. $C_{15}H_{24}O_6$ requires C, 60.0; H, 8.1%).

1-O-*Allyl*-3,6-*di*-O-*benzyl*-myo-*inositol*[1] (**24**).—This was prepared as described previously[1] by reaction of allyl bromide with the dibutylstannylene derivative of 1,4-di-*O*-benzyl-*myo*-inositol in the presence of tetrabutylammonium iodide in toluene under reflux. The solution was cooled and most of the toluene was evaporated off. The residue, taken up in ether, was washed with dilute hydrochloric acid and saturated aqueous potassium chloride and was then stirred with saturated aqueous sodium hydrogen carbonate for 30 min. The brown precipitated tin derivatives produced were removed by filtration through Celite, and the filtrate was dried (K_2CO_3) and evaporated. The product (m.p. 107—108 °C), identical with the material described previously,[1] could be obtained in 50% yield by crystallisation of the crude product from ethyl acetate–light petroleum. Further material was obtained from the mother liquors by silica gel chromatography as described.[1]

2,3,6-*Tri*-O-*benzyl*-4,5-O-*isopropylidene*-1-O-(*prop*-1-*enyl*)-myo-*inositol* (**27**).—1-*O*-Allyl-3,6-di-*O*-benzyl-*myo*-inositol (**24**) was converted into 1-*O*-allyl-3,6-di-*O*-benzyl-4,5-*O*-isopropylidene-*myo*-inositol[1] (**25**) by reaction with 2,2-dimethoxypropane and toluene-*p*-sulphonic acid in acetone and this was converted into 1-*O*-allyl-2,3,6-tri-*O*-benzyl-4,5-*O*-isopropylidene-*myo*-inositol (**26**) as described.[1] Chromatography of the crude product on silica gel [eluting with ether–light petroleum (1:2)] gave the pure *allyl ether* (**26**), m.p. 82—84 °C (from light

petroleum) (Found: C, 74.5; H, 7.4. $C_{33}H_{38}O_6$ requires C, 74.7; H, 7.2%). The allyl ether (**26**) (1 g) was treated with potassium t-butoxide (500 mg) in dry dimethyl sulphoxide (8 ml) at 50 °C for 2 h, the solution was cooled and diluted with water, and the product was extracted with ether. Crystallisation of the concentrated extract from light petroleum (b.p. 60—80 °C) gave the *prop*-1-*enyl ether* (**27**) (800 mg) m.p. 115—116 °C (Found: C, 74.8; H, 7.3. $C_{33}H_{38}O_6$ requires C, 74.7; H, 7.2%). The prop-1-enyl ether was treated with mercury(II) chloride and mercury(II) oxide in aqueous acetone and the product was isolated in the usual way[6] to give 1,2,4-tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol (**28**) identical with the material described previously.[4]

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