1282. *Cyclitols. Part XXI.*[1] *Benzyl Ethers of Myoinositol. Aromatisation of a Tosyl Derivative of Myoinositol*

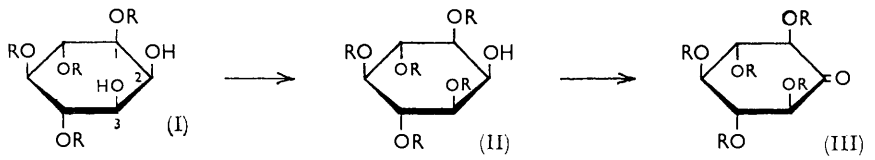
By S. J. Angyal and M. E. Tate

Tetra-, penta-, and hexa-benzyl ethers of myoinositol have been synthesized. 1,4,5,6-Tetra-*O*-benzyl-3-*O*-tosylmyoinositol is converted by potassium hydroxide into 2,4-dibenzyloxyphenol. The configuration at the benzylidene carbon atom in derivatives of 1,2-*O*-benzylidenemyoinositol has been determined by n.m.r. spectroscopy.

Partially substituted derivatives of myoinositol are required as intermediates for the synthesis of inositol glycosides and phosphates. The acetates are unsuitable because of the ready migration of the acetyl groups;[2] substituents resistant to the action of acids and alkalis are desirable. The benzyl ethers appear to be the derivatives of choice because they can be prepared in good yield, are crystalline, and are readily cleaved by hydrogenolysis. In this Paper we describe the preparation of several benzyl ethers of myoinositol, and the unexpected aromatisation of a benzylated tosylinositol.

The key compound in this work is 1,4,5,6-tetra-*O*-benzylmyoinositol (I), readily prepared by benzylation of 1,2-*O*-cyclohexylidenemyoinositol,[1,3] followed by acid hydrolysis of the acetal group. This compound has an equatorial (at C-3) and an axial (at C-2) hydroxyl group, and it was found, as in the case of the corresponding tetra-acetate,[4] that some reagents substitute it selectively on the equatorial oxygen atom while others show no such selectivity.

Benzylation of the tetrabenzyl compound (I) with excess benzyl chloride gave hexabenzylmyoinositol; however, by employing one equivalent of the reagent, a 63% yield of 1,3,4,5,6-penta-*O*-benzylmyoinositol (II) was obtained. The axially substituted isomer, 1,2,4,5,6-penta-*O*-benzylmyoinositol, was isolated in approximately 1% yield. The structure of the major product (II) was established by oxidation with chromium trioxide



to the inosose derivative (III), followed by reduction and removal of the benzyl groups; a mixture of myo- and scyllo-inositols was obtained. It is worth noting that in this case reduction of the keto-group results predominantly in the formation of an axial hydroxyl group; the proportion of myo- to scyllo-inositol was 88 : 12 when the reduction was carried out by lithium aluminium hydride, and 80 : 20 when the Meerwein–Ponndorf method was used. The predominance of the axial product is in contrast to the exclusively equatorial product reported[5] for the reduction of penta-*O*-acetylscylloinosose with lithium aluminium hydride, and to the nearly equal proportion of the two inositols obtained in the reduction of the inosose itself by sodium borohydride.[6]

1,3,4,5,6-Penta-*O*-benzylmyoinositol (II) was converted into its acetate, benzoate, and tetrahydropyranyl ether. Methylation, followed by hydrogenolysis, gave an unequivocal synthesis in good yield of 2-*O*-methylmyoinositol, a compound previously obtained only

[1] Part XX, S. J. Angyal, G. C. Irving, V. D. Rutherford, and M. E. Tate, *J.*, 1965, 6662.
[2] S. J. Angyal and G. J. H. Melrose, *J.*, 1965, 6494.
[3] S. J. Angyal, M. E. Tate, and S. D. Gero, *J.*, 1961, 4116.
[4] S. J. Angyal and S. D. Gero, *J.*, 1965, 5255.
[5] N. Z. Stanacev and M. Kates, *J. Org. Chem.*, 1961, **26**, 912.
[6] D. Reymond, *Helv. Chim. Acta*, 1957, **40**, 492.

as a minor product in the methylation of myoinositol.[7] On the other hand, methylation of the tetrabenzyl ether (I) with one equivalent of methyl iodide affords predominantly the equatorially substituted 3-*O*-methyl derivative. Hydrogenolysis and acetylation of the crude methylation mixture, followed by gas-chromatographic analysis, indicated the following ratios: 3-methyl ether 79·5, 2-methyl ether 0·7, 2,3-dimethyl ether 13, unmethylated compound 6·6%. The crystalline 1,4,5,6-tetra-*O*-benzyl-3-*O*-methylmyoinositol was isolated in 64% yield and was hydrogenolysed to give (±)-1-*O*-methylmyoinositol (bornesitol),[7] the optically active forms of which occur in Nature. Complete methylation of the tetrabenzyl compound, followed by hydrogenolysis, gave the known [7,8] 1,2-di-*O*-methylmyoinositol.

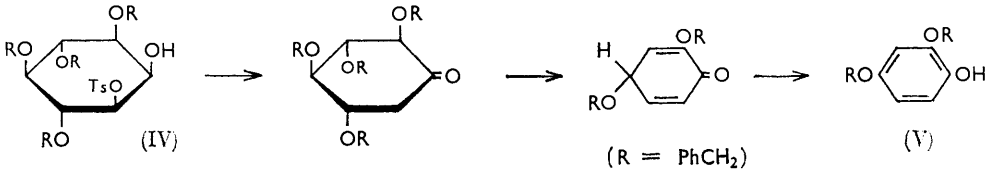
1,2,4,5,6-Penta-*O*-benzylmyoinositol would be a very useful synthetic intermediate and, since it was produced in such low yield by the direct benzylation of the tetrabenzyl ether, other methods for its synthesis were sought. A blocking group was required which could be selectively introduced on to the equatorial oxygen atom at C-3 and would withstand the strongly alkaline conditions required for benzylation of the other hydroxyl group. Previous experience [4] indicated that formation of a tetrahydropyranyl ether occurs unselectively on both axial and equatorial oxygen atoms. The reaction with benzyloxymethyl chloride in the presence of potassium hydroxide, formally analogous to that with benzyl chloride, appeared more promising; benzyloxymethyl ethers can readily be cleaved by acid hydrolysis or by hydrogenolysis.[9] However, this reagent also proved to be unselective; gas chromatography, after methylation, hydrogenolysis, and acetylation, indicated that the reaction mixture consisted of 33% of 1-benzyloxymethyl ether, 21·5% of the 2-ether, 39·5% of the diether, and 6% of unreacted starting material. The two monobenzyloxymethyl ethers were separated by thin-layer chromatography but were not further investigated.

Apparently the reactions which show preference towards the equatorial hydroxyl group in derivatives of myoinositol are those which involve an intermediate or a transition state, reversibly formed, in which the carbon atom forming the new bond with the oxygen atom is attached to more atoms than it is in the final product. Such reactions are esterifications (acetylation, tosylation) and S_N2 type substitutions (methylation, benzylation). On the other hand, dihydropyran in the presence of acids, and benzyloxymethyl chloride in the presence of bases,[10] apparently form carbonium ions, and the subsequent rapid reactions of the bond-deficient carbon atoms are not sensitive to steric hindrance.

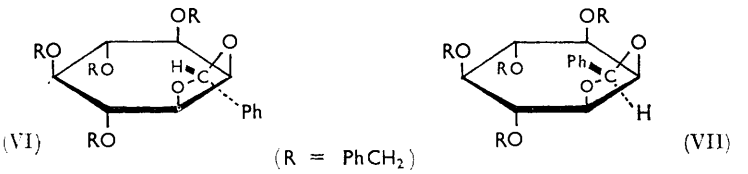
Yet another approach was then explored; tosylation of the tetrabenzyl compound in the 3-position, followed by benzylation on O-2 and removal of the tosyl group by sodium amalgam.[11] Introduction of the tosyl group proved indeed specific, and 1,4,5,6-tetra-*O*-benzyl-3-*O*-tosylmyoinositol (IV) was readily obtained; but an attempt to benzylate this compound with benzyl chloride and potassium hydroxide led to the unexpected loss of the tosyl group. Further investigation showed that potassium hydroxide alone smoothly converted 1,4,5,6-tetra-*O*-benzyl-3-*O*-tosylmyoinositol in benzene solution into a phenolic substance which was identified on the basis of its n.m.r. spectrum as a dibenzyl ether of 1,2,4-trihydroxybenzene. The spectrum (in deuteriochloroform) showed four benzylic protons, one proton exchangeable by deuterium, no aliphatic protons, and three aromatic protons as a doublet (J=8·5), a doublet (J=2·7), and a pair of doublets (J=2·7 and 8·5 c./sec.). These protons represent an ABC system and, since the coupling constant between *o*-hydrogen atoms is 7—10, between *m*-hydrogens 2—3, and between *p*-hydrogens 0—1 c./sec.,[12] the three protons on the benzene ring must be in 1,2,4-relationship.

[7] S. J. Angyal, P. T. Gilham, and C. G. Macdonald, *J.*, 1957, 1417.
[8] M. L. Wolfrom and L. M. Pande, Abstracts of Papers, *Amer. Chem. Soc.*, 1962, **142**, 7D.
[9] M. R. Salmon and G. Powell, *J. Amer. Chem. Soc.*, 1939, **61**, 3507.
[10] C. L. Graham and F. J. McQuillin, *J.*, 1963, 4634.
[11] S. J. Angyal, P. T. Gilham, and G. J. H. Melrose, *J.*, 1965, 5252.
[12] L. M. Jackson, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1959, p. 85.

This unexpected aromatisation is reminiscent of the easy conversion [13] of penta-acylinososes by bases into derivatives of 1,2,3,5-tetrahydroxybenzene. The reaction is regarded [14] as occurring by two successive β-eliminations leading to an unsaturated ketone; the first intermediate, an αβ-unsaturated ketone, has been isolated.[5] In the present case the same mechanism can be postulated to occur after initial elimination of toluenesulphonic acid, as shown in formulæ (IV)—(V). If this mechanism is correct, the product of aromatisation must be 2,4-dibenzyloxyphenol (V). This deduction was confirmed by methylation of the phenolic compound to give a dibenzyloxyanisole which was hydrogenolysed to yield 2,4-dihydroxyanisole, characterised as its diacetate [15] and di-*p*-nitrobenzoate.[16]



Condensation of 1,4,5,6-tetra-*O*-benzylmyoinositol with benzaldehyde gave two products, (VI) and (VII), which were separable by thin-layer chromatography. Formation of two diastereoisomers in the condensation of benzaldehyde with asymmetrical diols has been observed [17] in several instances but only recently have configurations been assigned to the isomers. Baggett *et al.*[17] found that the signal in the n.m.r. spectrum of the *endo*-benzylidene proton of one diastereoisomer is at lower field (by about 0·3 p.p.m.) than that of the *exo*-proton of the other diastereoisomer. Our crude reaction mixture



showed two signals of nearly equal intensity for benzylidene protons at δ 5·84 and 6·14 p.p.m. (in deuteriochloroform). One of the isomers crystallised; this is the *endo*-H compound (VI) because it showed a signal at 6·14 p.p.m. The other diastereoisomer has not been obtained crystalline.

It appeared of interest to determine the configuration of the previously prepared 1,2-*O*-benzylidenemyoinositol.[18] This compound was now prepared in a different way, by the condensation of 1,4,5,6-tetra-*O*-acetylmyoinositol with benzaldehyde. Again two diastereoisomers were obtained; the less soluble isomer was purified by crystallisation and was shown to be identical with the compound previously reported.[18] Its n.m.r. spectrum showed a signal at δ 6·30 p.p.m., indicative of an *endo*-H configuration. This configuration was proven by benzylating the compound, the resulting tetrabenzyl ether being identical with the derivative (VI) obtained from tetra-*O*-benzylmyoinositol.

Experimental

Melting points are corrected. All the asymmetric compounds described are racemates. All reactions were followed by thin-layer chromatography [19] on microscope slides coated with

[13] T. Posternak, *Helv. Chim. Acta*, 1936, **19**, 1333; 1941, **24**, 1045.
[14] H. S. Isbell, *Ann. Rev. Biochem.*, 1943, **12**, 213.
[15] C. W. Moore, *J.*, 1911, **99**, 1045.
[16] K. R. Hargraves, A. McGookin, and A. Robertson, *J. Appl. Chem.*, 1958, **8**, 273.
[17] N. Baggett, K. W. Buck, A. B. Foster, M. H. Randall, and J. M. Webber, *Proc. Chem. Soc.*, 1964, 118; *J.*, 1965, 3401.
[18] S. J. Angyal and R. M. Hoskinson, *J.*, 1963, 2043.
[19] M. E. Tate and C. T. Bishop, *Canad. J. Chem.*, 1963, **41**, 1801.

Silica Gel G using the method of Peifer;[20] benzyl derivatives were detected by exposure to iodine vapour, acetates as their ferric hydroxamates.[21] All evaporations were carried out under reduced pressure, unless otherwise stated. Light petroleum had a boiling range of 60—80°.

1,4,5,6-*Tetra*-O-*benzyl*-2,3-O-*cyclohexylidenemyoinositol*. — **1,2-*O*-Cyclohexylidenemyoinositol**[1,3] (17·5 g.) was vigorously stirred with powdered potassium hydroxide (105 g.) and benzyl chloride (175 ml.) on a steam-bath for 19 hr. The mixture was steam-distilled (to remove benzyl chloride) and was then extracted with benzene (3 × 100 ml.); the extract was washed with water (100 ml.), dried ($MgSO_4$), and evaporated to dryness. The residue, after dissolution in boiling methanol (400 ml.), deposited the *tetrabenzyl ether* (32·0 g., 74%) as prisms, m. p. 80—84°; recrystallisation raised the m. p. to 85—87° (Found: C, 77·3; H, 7·1. $C_{40}H_{44}O_6$ requires C, 77·4; H, 7·1%).

1,4,5,6-*Tetra*-O-*benzylmyoinositol* (I).—The foregoing monoketal (7·74 g.) was heated on a steam-bath with glacial acetic acid (160 ml.) and water (40 ml.) for 2·5 hr. The mixture was evaporated, methanol was added to the residue and again evaporated. The crystalline residue was crystallised from methanol (25 ml.), to give needles (5·72 g., 84%), m. p. 114—115°; after another crystallisation from methanol or benzene, the *tetra*-O-*benzylmyoinositol* melted at 115° (Found: C, 75·5; H, 6·8. $C_{34}H_{36}O_6$ requires C, 75·55; H, 6·7%). Occasionally a second allotropic modification, m. p. 127°, crystallised from the crude reaction mixture.

Hexa-O-*benzylmyoinositol*.—Tetra-*O*-benzylmyoinositol (2·0 g.) was vigorously stirred with powdered potassium hydroxide (6·0 g.) and benzyl chloride (10 ml.) on a steam-bath for 1 hr. After cooling and addition of water (10 ml.), the reaction mixture was steam-distilled. The residue was extracted with chloroform (3 × 20 ml.); the extract was washed with water (20 ml.), dried ($MgSO_4$), and evaporated. The resulting syrup was dissolved in boiling methanol and left to crystallise at 5°. The crude product (2·22 g., 82%) was recrystallised from methanol (75 ml.), to give the *hexabenzyl ether* (1·84 g.) which on heating passes through a transition at 96—98° from rods to needles, m. p. 109—110° (Found: C, 79·95; H, 6·7. $C_{48}H_{48}O_6$ requires C, 79·95; H, 6·7%).

Penta-O-*benzylmyoinositols*.—A solution of tetrabenzylmyoinositol (5·4 g.) in benzene (100 ml.), a mixture (1 : 9 v/v; 13·5 ml.) of benzyl chloride and benzene, and powdered potassium hydroxide (29 g.) were stirred under anhydrous conditions on a steam-bath for 1·5 hr. To the cooled mixture water (100 ml.) was added and, after complete dissolution, the benzene layer was separated and the aqueous layer was extracted with benzene (3 × 15 ml.). The combined benzene extracts were dried (K_2CO_3), and evaporated. The remaining brown syrup (5·8 g.) was dissolved in boiling light petroleum (1 l.) which was filtered and concentrated to 250 ml.; by next day colourless needles (3·97 g., 63%), m. p. 124—127°, separated out. Recrystallisation from methanol gave **1,3,4,5,6-*penta*-O-*benzylmyoinositol*** (II) (3·3 g., 52%) as needles, m. p. 128—129° (Found: C, 78·05; H, 6·9. $C_{41}H_{42}O_6$ requires C, 78·05; H, 6·7%).

The petroleum mother liquors were evaporated under reduced pressure, and the residue, after being dissolved in boiling methanol (30 ml.), deposited needles (0·79 g., 11%) of hexabenzylmyoinositol, m. p. 109—111° (after transition at 95—98°). The mother-liquors were evaporated to a syrup (0·78 g.) which was chromatographed on a column (15 × 2 cm.) of alumina packed in anhydrous benzene. The column was irrigated with benzene (200 ml.; fractions 1—14), benzene–chloroform (9 : 1) (200 ml.; fractions 15—30), and finally benzene–chloroform (8 : 2) (260 ml.; fractions 31—52); each fraction was examined by thin-layer chromatography. Crystalline material was obtained from fractions 3 and 4 (hexabenzylmyoinositol, 317 mg., 4%), 35—40 (crude 1,2,4,5,6-penta-*O*-benzylmyoinositol, 73 mg., 1%; m. p. 86—92°), and 43—47 (crude 1,3,4,5,6-penta-*O*-benzylmyoinositol, 72 mg., 1%; m. p. 124—127°). The contents of fraction 35—40 were recrystallised from light petroleum and twice from methanol, to give needles of **1,2,4,5,6-*penta*-O-*benzylmyoinositol*** (38 mg.), m. p. 94—95° (Found: C, 77·65; H, 6·8. $C_{41}H_{42}O_6$ requires C, 78·05; H, 6·7%).

Penta-O-*benzylscylloinososе* (III).—1,3,4,5,6-Penta-*O*-benzylmyoinositol (0·63 g.), dissolved in acetic acid (10 ml.), was added to a hot solution of chromium trioxide (0·35 g.) in acetic acid (70 ml.); the mixture was heated on a steam-bath for 40 min. and then evaporated. An aqueous solution of potassium carbonate (10%; 30 ml.) was added, and the mixture was extracted with benzene (5 × 30 ml.). The benzene extracts were dried and concentrated, and the solid

[20] J. J. Peifer, *Mikrochim. Acta*, 1962, 529.
[21] M. E. Tate and C. T. Bishop, *Canad. J. Chem.*, 1962, **40**, 1043.

residue was crystallised from ethyl acetate, to yield needles of the *inosose* (0·31 g., 49%), m. p. 158—161°. Recrystallisation raised the m. p. to 163—164° (Found: C, 78·2; H, 6·35. $C_{41}H_{40}O_6$ requires C, 78·3; H, 6·4%). The infrared spectrum showed carbonyl absorption at 1725 cm.$^{-1}$.

Reduction of the inosose (10 mg.) with lithium aluminium hydride (20 mg.) in ether (20 ml.), followed by hydrogenolysis of the benzyl groups with 10% palladium chloride on carbon in glacial acetic acid, gave a mixture which on paper chromatography (phenol–water, 8 : 2) showed two spots corresponding to myo- and scyllo-inositol. Gas chromatography [22] of the acetylated mixture gave peak areas of 88 : 12 for myo- and scyllo-inositol, respectively.

Reduction of the inosose (10 mg.) by aluminium isopropoxide (1 g.) in benzene (10 ml.) and propan-2-ol (10 ml.) for 24 hr., followed by hydrogenolysis with 10% palladium chloride on carbon in glacial acetic acid, gave a mixture of inositols. Gas chromatography indicated a proportion of myo- to scyllo-inositol of 8 : 2.

Derivatives of 1,3,4,5,6-*Penta*-O-*benzylmyoinositol*.—Acetylation with acetic anhydride and pyridine gave 2-O-*acetyl*-1,3,4,5,6-*penta*-O-*benzylmyoinositol* (82%), m. p. 110—111° (from methanol). Recrystallisation did not raise the m. p. (Found: C, 76·85; H, 6·65. $C_{43}H_{44}O_7$ requires C, 76·75; H, 6·6%).

Benzoylation with benzoyl chloride in pyridine gave the 2-*benzoate* (77%), m. p. 120—121° (from methanol). Recrystallisation did not raise the m. p. (Found: C, 78·2; H, 6·3. $C_{49}H_{49}O_7$ requires C, 78·45; H, 6·6%).

To a solution of 1,3,4,5,6-penta-*O*-benzylmyoinositol (132 mg.), in a mixture of chloroform (2·5 ml.) and 2,3-dihydropyran (0·5 ml.), a solution of toluene-*p*-sulphonic acid (10 mg.) in chloroform (1 ml.) was added. After 45 min., the mixture was washed with potassium carbonate solution (10%) and water, and was dried (K_2CO_3), and evaporated. The residue crystallised on trituration with methanol; the crystals (92 mg., 60%), m. p. 121—123°, were recrystallised from methanol, to give needles of 1,3,4,5,6-*penta*-O-*benzyl*-2-O-(2-*tetrahydropyranyl*)*myoinositol*, m. p. 123·5° (Found: C, 76·8; H, 6·8. $C_{46}H_{50}O_7$ requires C, 77·3; H, 7·05%).

A sample of the tetrahydropyranyl ether was hydrogenolysed in a mixture of dioxan and methanol with a palladium hydroxide catalyst; the resulting compound, crystallised from ethanol, melted at 208—209° and did not depress the m. p. of 2-*O*-(2-tetrahydropyranyl)-myoinositol (prepared by catalytic deacetylation of its penta-acetate [4]).

1,4,5,6-*Tetra*-O-*benzyl*-2,3-*di*-O-*methylmyoinositol*.—A solution of 1,4,5,6-tetra-*O*-benzylmyoinositol (0·54 g.) in benzene (10 ml.) was heated on a steam-bath with powdered potassium hydroxide (3·9 g.). After 30 min., dimethyl sulphate (1·0 ml.) was added, and heating continued for another 30 min. Water (25 ml.) was added to the cold mixture, and the benzene layer was separated, dried (K_2CO_3), and evaporated. The residue was dissolved in boiling light petroleum (12 ml.) from which prisms of the *dimethyl ether* (0·38 g., 67%), m. p. 101—103°, crystallised. After recrystallisation the m. p. was 101·5—102·5° (Found: C, 75·9; H, 7·0. $C_{36}H_{40}O_6$ requires C, 76·05; H, 7·1%).

1,2-*Di*-O-*methylmyoinositol*.—The preceding compound (285 mg.) was hydrogenolysed in glacial acetic acid (12 ml.) in the presence of 10% palladium chloride on carbon (0·3 g.). Hydrogen uptake was complete in 30 min.; the catalyst was centrifuged off and washed with acetic acid (2 × 5 ml.), and the supernatant liquor was evaporated. The residual solid was crystallised from ethanol, to give plates of 1,2-di-*O*-methylmyoinositol (76 mg., 73%), m. p. 158°. Recrystallisation from ethanol raised the m. p. to 158—159° (lit.,[8] 161—162°) (Found: C, 46·15; H, 7·5. Calc. for $C_8H_{16}O_6$: C, 46·15; H, 7·7%). Professor M. L. Wolfrom kindly informed us that the *X*-ray diffraction pattern of our compound was identical with that prepared in his laboratory by a different method.

Acetylation with pyridine and acetic anhydride gave the *tetra-acetate* which sublimed at 140°/0·7 mm. as prisms, m. p. 146—148° (Found: C, 51·5; H, 6·4. $C_{16}H_{24}O_{10}$ requires C, 51·05; H, 6·45%).

1,3,4,5,6-*Penta*-O-*benzyl*-2-O-*methylmyoinositol*.—1,3,4,5,6-Penta-*O*-benzylmyoinositol (631 mg.) was methylated as described for the tetrabenzyl ether above. Crystallisation from methanol gave needles of the *methyl ether* (569 mg., 88%), m. p. 114—115° (Found: C, 78·3; H, 7·0. $C_{42}H_{44}O_6$ requires C, 78·25; H, 6·9%).

Hydrogenolysis of the compound (283 mg.) in glacial acetic acid (15 ml.) with 10% palladium

[22] Z. S. Krzeminski and S. J. Angyal, *J.*, 1962, 3251.

chloride on carbon (280 mg.) gave 2-*O*-methylmyoinositol (52 mg. 60%), m. p. 211—212° (from methanol) (lit.,[7] 212°) (Found: C, 43·25; H, 7·0. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·25%). The penta-acetate crystallised from methanol as needles, m. p. 231—232° (lit.,[7] 235—236°).

1,4,5,6-*Tetra*-O-*benzyl*-3-O-*methylmyoinositol*.—A mixture of tetra-*O*-benzylmyoinositol (1·08 g.), benzene (40 ml.), methyl iodide (0·14 ml.), and powdered potassium hydroxide (13 g.) was stirred on a steam-bath for 2 hr. Water (40 ml.) was added to the cold mixture, the organic layer was separated, and the aqueous layer was extracted with benzene (3 × 20 ml.). The benzene extracts were dried (K_2CO_3) and evaporated; the solid residue, on crystallisation from light petroleum, gave needles of the *methyl ether* (0·76 g., 64%), m. p. 107—108°. To remove traces of the starting material, a sample was chromatographed on Silica Gel G; it then melted at 109—110° (Found: C, 76·15; H, 6·95. $C_{35}H_{38}O_6$ requires C, 75·8; H, 6·9%).

Hydrogenolysis of the compound (1·11 g.) in glacial acetic acid (20 ml.) with 10% palladium chloride on carbon (1·14 g.) gave 1-*O*-methylmyoinositol (0·30 g., 77%), m. p. 200—201° (from methanol) (Found: C, 43·0; H, 7·15. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·25%). The m. p. was not depressed by admixture with an authentic sample.[7] The penta-acetate melted, along or on admixture with an authentic sample, at 152·5—153·5° (Found: C, 50·2; H, 5·7. Calc. for $C_{17}H_{24}O_{11}$: C, 50·5; H, 6·0%).

Benzyloxymethyl Ethers.—(*a*) A solution of 1,4,5,6-tetra-*O*-benzylmyoinositol (541 mg.) in benzene (10 ml.), a mixture of benzyloxymethyl chloride and benzene (1 : 9 v/v; 1·6 ml.), and powdered potassium hydroxide (5 g.) were heated together on a steam-bath for 4 hr. Dimethyl sulphate (1·1 ml.) was then added and the mixture heated with stirring for 1 hr. After the addition of water (15 ml.) and further heating for 30 min., the benzene layer was separated, washed with water (2 × 10 ml.), dried (K_2CO_3), and evaporated. A portion of the syrupy residue was hydrogenolysed as described above, acetylated with acetic anhydride and pyridine, and examined by gas chromatography;[22] the acetates of 1,2-di-*O*-methylmyoinositol (R_{myo} 0·50; 6·3%), 1-*O*-methylmyoinositol (R_{myo} 0·59; 21·5%), 2-*O*-methylmyoinositol (R_{myo} 0·87; 32·8%), and myoinositol (R_{myo} 1·00; 39·4%) were found.

(*b*) In another experiment, carried out without the addition of dimethyl sulphate, two fractions, m. p. 83—85° and 90—97°, were separated laboriously by fractional crystallization from light petroleum. Thin-layer chromatography (in light petroleum–methanol, 95 : 5) showed that both fractions were essentially monobenzyloxymethyl ethers of tetrabenzylmyoinositol. Benzylation of the isomer, m. p. 83—85°, gave a benzyloxymethyl pentabenzyl derivative, m. p. 98—102°; hydrolysis of this product with boiling 80% acetic acid for 2 hr. yielded 1,3,4,5,6-penta-*O*-benzylmyoinositol, m. p. 126—128°, mixed m. p. 125—127°. The compound of m. p. 83—85° is therefore 2-*O*-benzyloxymethyl-1,4,5,6-tetra-*O*-benzylmyoinositol. A similar reaction sequence with the other sample, m. p. 90—97°, gave no crystalline material, but thin-layer chromatography confirmed that the product was mainly 1,2,4,5,6-penta-*O*-benzylmyoinositol; the material, m. p. 90—97°, is therefore impure 3-*O*-benzyloxymethyl-1,4,5,6-tetra-*O*-benzylmyoinositol.

1,4,5,6-*Tetra*-O-*benzyl*-3-O-*tosylmyoinositol* (IV).—After standing overnight, a mixture of 1,4,5,6-tetra-*O*-benzylmyoinositol (0·54 g.), toluene-*p*-sulphonyl chloride (0·22 g.), and dry pyridine (1 ml.) was poured on to ice. The pale yellow oil which separated was washed with water by decantation and was triturated with methanol (10 ml.) whereupon it solidified. Crystallisation from methanol gave long needles of the *tosyl ester* (0·39 g., 57%), m. p. 115—117°; recrystallisation did not alter the m. p. (Found: C, 70·65; H, 6·05. $C_{41}H_{42}O_8S$ requires C, 70·85; H, 6·1%). In other experiments, the use of 2 mol. of toluene-*p*-sulphonyl chloride gave a 75% yield of the monotosyl derivative and no detectable amount of the diester (cf. the difficulty in preparing a ditosyl derivative from 1,4,5,6-tetra-*O*-acetylmyoinositol [11]).

2,4-*Dibenzyloxyphenol* (V).—The preceding compound (0·65 g.) was dissolved in benzene (6 ml.) and was stirred at 50° with powdered potassium hydroxide (1·5 g.); the mixture became viscous and an exothermic reaction occurred. After 10 min., when the viscosity decreased, water (20 ml.) and glacial acetic acid (1·6 ml.) were added, and the organic layer was separated, washed with water (2 × 20 ml.), dried (Na_2SO_4), and evaporated. The residue was crystallised from light petroleum, to give plates of 2,4-*dibenzyloxyphenol* (0·21 g., 71%), m. p. 93—94°, $\lambda_{max.}$ 290 mμ ($E^{1\%}_{1\,cm.}$ 112; 95% ethanol), $\lambda_{max.}$ 307 mμ ($E^{1\%}_{1\,cm.}$ 141; 95% ethanol at pH 9—10) (Found: C, 78·6; H, 5·75. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9%). N.m.r. data (in $CDCl_3$): δ 4·92 and 4·96 singlets (CH_2), 5·40 singlet (OH), 6·48 pair of doublets, J = 2·7 and 8·5 (H-5), 6·65 doublet, J = 2·7 (H-3), 6·86 doublet, J = 8·5 (H-6), and 7·35 p.p.m., singlet (Ph).

2,4-*Dibenzyloxyanisole*.—The dibenzyloxyphenol (153 mg.) was heated in benzene (5 ml.) with methyl iodide (1 ml.) and powdered potassium hydroxide (0·5 g.) on a steam-bath for 45 min. Water (25 ml.) was added, and the benzene layer was separated, washed with water (2 × 25 ml.), dried (K_2CO_3), and evaporated. The crystalline residue on dissolution in light petroleum gave needles of 2,4-*dibenzyloxyanisole* (114 mg., 71%), m. p. 88—89° (Found: C, 79·05; H, 6·4. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·3%). The same compound was obtained in 82% overall yield from 1,4,5,6-tetra-*O*-benzyl-3-*O*-tosylmyoinositol by the addition of methyl iodide to the reaction mixture after the first exothermic reaction with potassium hydroxide had subsided.

Hydrogenolysis of 2,4-*Dibenzyloxyanisole*.—The compound (200 mg.) was hydrogenated in glacial acetic acid (16 ml.) in the presence of 10% palladium chloride on carbon (217 mg.). When starting material could no longer be observed by thin-layer chromatography the catalyst was removed by centrifugation and the supernatant was concentrated to a colourless syrup. Since the 2,4-dihydroxyanisole could not be induced to crystallise it was acetylated with acetic anhydride (2·5 ml.) and pyridine (1·5 ml.) on the steam-bath for 1 hr. After evaporation the residue crystallised and was recrystallised from methanol to give needles of 2,4-diacetoxyanisole (69 mg., 50%), m. p. 62—63° (lit.,[15] 62—64°) (Found: C, 58·75; H, 5·4. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%). The m. p. was not depressed on admixture with an authentic sample, m. p. 62—63°, prepared by Dakin oxidation from isovanillin; the ultraviolet and infrared spectra of the two samples were indistinguishable.

Another sample of the syrupy dihydroxyanisole was converted into its di-*p*-nitrobenzoate, m. p. 164—165° (Found: C, 58·0; H, 3·35; N, 6·75. Calc. for $C_{21}H_{14}N_2O_9$: C, 57·55; H, 3·2; N, 6·4%). Since this m. p. is considerably higher than the one reported [16] (155—156°), an authentic sample was prepared as follows. 2,4-Dihydroxyanisole (148 mg.) (kindly presented to use by Dr. D. G. Crosby, University of California, Davis) and *p*-nitrobenzoyl chloride (400 mg.) in pyridine (5 ml.) were heated on the steam-bath for 1 hr., then the mixture was poured into water. Two crystallisations of the resulting precipitate from ethanol gave the yellow di-*p*-nitrobenzoate, m. p. 163·5—164·5°, mixed m. p. 163·5—164·5°.

1,4,5,6-*Tetra*-O-*benzyl*-2,3-O-*benzylidenemyoinositol*.—1,4,5,6-Tetra-*O*-benzylmyoinositol (1·0 g.), benzaldehyde (2·5 ml.), toluene-*p*-sulphonic acid (50 mg.), and benzene (20 ml.) were heated to reflux under a Dean and Stark separator for 1·5 hr. Thin-layer chromatography indicated the presence of two compounds. Potassium carbonate solution (10%; 10 ml.) was added, and the mixture steam-distilled. The oily residue was extracted with benzene (3 × 30 ml.), and the extracts were washed, dried (K_2CO_3), and evaporated; the residue (1·0 g.) was crystallised from methanol. The product (0·55 g., 48%), m. p. 83—84·5°, corresponded to the faster moving component on thin-layer chromatography. Recrystallisation gave needles of the *benzylidene compound* (VI), m. p. 84—85° (Found: C, 78·2; H, 6·4. $C_{41}H_{40}O_6$ requires C, 78·3; H, 6·4%).

1,4,5,6-*Tetra*-O-*acetyl*-2,3-O-*benzylidenemyoinositol*.—1,4,5,6-Tetra-*O*-acetylmyoinositol [3] (1·0 g.) was treated with benzaldehyde as described above. After steam-distillation, the residue (0·69 g.) solidified. It was filtered and crystallised from ethanol, to give needles (0·34 g., 27%), m. p. 147—150°. Several crystallisations were required to raise the m. p. to 156—158°; it was not depressed by admixture with a sample prepared by Angyal and Hoskinson [18] (Found: C, 57·95; H, 5·55. Calc. for $C_{21}H_{24}O_{10}$: C, 57·8; H, 5·55%). Benzylation of this product in the usual way gave the tetrabenzyl ether (VI), m. p. and mixed m. p. 84—85°.

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