Tetrahedron. Vol. 25, pp. 5681 to 5687. Pergamon Press 1969. Printed in Great Britain

SYNTHESIS OF OPTICALLY ACTIVE DERIVATIVES OF *MYO*-INOSITOL

PREPARATION OF 1 L-*MYO*-INOSITOL 1-PHOSPHATE

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(*Received in the UK* 19 *June* 1969; *Accepted for publication* 5 *August* 1969)

Abstract—1 L-1-O-toluene-*p*-sulphonyl-*chiro*-inositol **5** has been prepared by the selective de-O-methylation and de-cyclohexylidenation of 1L-3,4:5,6-di-O-cyclohexylidene-2-O-methyl-1-O-toluene-*p*-sulphonyl-*chiro*-inositol obtained from quebrachitol, 1L-2-O-methyl-*chiro*-inositol. This optically active toluene-*p*-sulphonyl derivative, which is by inversion at C-1, a potential source of optically active *myo*-inositol derivatives, has, after benzoylation, been converted into a mixture of 1D-1,2,4,5,6-penta-O-benzoyl-*myo*-inositol and 1,3,4,5,6-penta-O-benzoyl-*myo*-inositol, which were separated. From the former, after phosphorylation and debenzoylation, 1L-*myo*-inositol 1-phosphate, the product of the enzyme, glucose 6-phosphate-inositol 1-phosphate cyclase, was obtained as the crystalline dicyclohexylamine salt.

INTRODUCTION

Myo-INOSITOL is widely distributed throughout nature in both free and combined forms.[1] Although *myo*-inositol is one of the meso forms of inositol, in the combined form it occurs almost always as an optically active derivative. Hitherto the only method available for the synthesis of these derivatives has been the conversion of one into another.

Of the simple optically active derivatives of *myo*-inositol, perhaps the most important is 1L-*myo*-inositol 1-phosphate, which is the cyclization product of D-glucose 6-phosphate by an enzyme glucose 6-phosphate-inositol 1-phosphate cyclase.[2] Furthermore it appears to be the only primary source of inositol in nature. Recent mechanistic studies on this enzyme[3–6] and related enzymes[2,4,6] have highlighted the need for a convenient synthesis of this substance, previously obtained only enzymically,[5,6] or from galactinol[7] (1-O-α-D-galactosyl-1L-*myo*-insitol).

This paper, therefore, describes the synthesis of 1L-*myo*-inositol 1-phosphate **13** from the readily available quebrachitol, 1L-2-O-methyl-*chiro*-inositol **2** by a method which might be adapted to the synthesis of a large variety of optically active cyclitol derivatives of biological interest.

Throughout the paper the recommended rules of cyclitol nomenclature[8] are used. It should be noted that the compound here described as 1L-*myo*-inositol 1-phosphate was previously known as D-*myo*-inositol 1-phosphate.

Preliminary accounts of some of this work have been published.†

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† Preliminary communications: S. D. Géro, *Tetrahedron Letters* (1966) 591 and D. Mercier and S. D. Géro, *Tetrahedron Letters* (1968) 3459.

RESULTS AND DISCUSSION

In order to synthesize optically active 1L-*myo*-inositol 1-phosphate, we needed a penta-substituted *myo*-inositol **10** in which R is a readily removable substituent and the free OH is located at the 1L-position of the *myo*-inositol molecule. This type of molecule was previously obtained by Ballou and Pizer[7] from galactinol but this material is not a practical source for large scale preparations.

It can be seen that in *chiro*-inositol **1**, the hydroxyls at C-1, C-2 and C-3 are equivalent to those at C-6, C-5 and C-4 respectively, and that inversion at either C-1 or C-6 leads to *myo*-inositol. Due to the symmetry along the axis 1,6:3,4 of *chiro*-inositol, it is not possible, using optically inactive reagents, to selectively modify C-1 without C-6, or *vice-versa*. An assymmetrically substituted form is required. A suitable source of the required derivative seemed possible therefore from the readily available quebrachitol **2** (1L-2-O-methyl-*chiro*-inositol, in which the twofold axis of symmetry of *chiro*-inositol is destroyed by the Me substituent).

To achieve our objective we required: (a) a convenient method for the preparation of a 1L-3,4,5,6-di-O-alkylidene-2-O-methyl-*chiro*-inositol **3** and its 1-O-toluene-*p*-sulphonyl ester **4**; (b) a reagent which would demethylate the methyl ester without cleavage of the sulphonyl ester; (c) a stereospecific inversion of the configuration of the toluene-*p*-sulphonyl at C-1 to OH, after protection of the other OH groups in the molecule.

It has been shown[9,10] that under energetic conditions, even *trans* pairs of OH groups will react with cyclohexanone. Accordingly quebrachitol was heated for 4 hr with cyclohexanone, toluene-*p*-sulphonic acid and benzene with azeotropic removal of water. The expected 1L-3,4,5,6-di-O-cyclohexylidene-*chiro*-inositol **3** was obtained in 55–72% yield. The free OH, which is the correct one for inversion was tosylated under rather vigorous conditions (70% for 3 hr) to give 1L-3,4,5,6-di-O-cyclohexylidene-1-O-toluene-*p*-sulphonyl-*chiro*-inositol **4**.

The use of boron trichloride for dealkylation in the presence of toluene-*p*-sulphonyl groups was suggested by Bonner, *et al.*[11] in 1960. When the toluene-*p*-sulphonyl derivative **4** was treated with 43 moles of BCl_3 at $-60°$, after 15 hr the crude peracetylated product showed complete disappearance of the OMe proton signal, whereas the presence of a toluene-*p*-sulphonyl group was confirmed by the presence of aromatic and Me proton signals. 1L-O-toluene-*p*-sulphonyl-*chiro*-inositol **5** was obtained in 90% yield.

Next we turned our attention to the inversion of the configuration of the toluene-*p*-sulphonyl group at C-1 and its conversion to OH.

The choice of protecting group was governed by the ease of its final removal, the stability of the toluene-*p*-sulphonyl group during its preparation and the possibility of a smooth inversion at C-1 in the next stage. Use of the benzyl ether group was not possible since the strongly alkaline conditions used in its preparation caused displacement of the toluene-*p*-sulphonyl group which is *trans* to the OH at C-6.

The benzoyl group seemed to fulfil these requirements and the 1L-2,3,4,5,6-penta-O-benzoyl-1-O-toluene-*p*-sulphonyl-*chiro*-inositol **6** was prepared by treating 1L-1-O-toluene-*p*-sulphonyl-*chiro*-inositol **5** with benzoyl chloride in anhydrous pyridine.

Attack of an anion on a *trans*-toluene-*p*-sulphonyl benzoate **6** can lead to the products shown in Fig. 1. In order to maximize the formation of the desired hydroxyl-benzoates **7** and **10** (Fig. 1), we needed a substance which would act as a weak núcleo-

phile and allow the formation of the phenoxonium ion intermediate and its subsequent hydroylsis by water. Although the sodium benzoate-DMF reagent of Baker[12] has been successfully[13,14] used for this type of reaction, a better reagent appeared to be the very weakly nucleophilic sodium fluoride-DMF.[13,15]

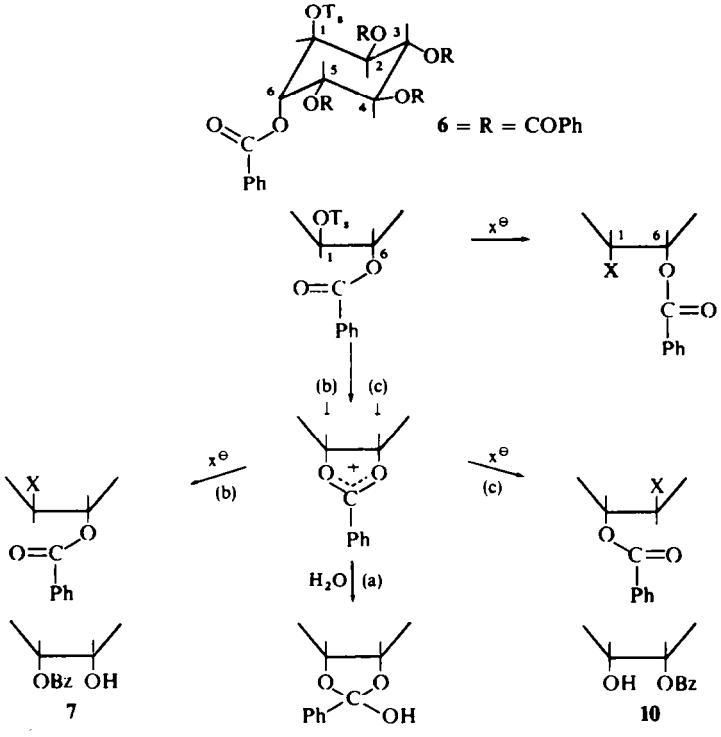


FIG. 1

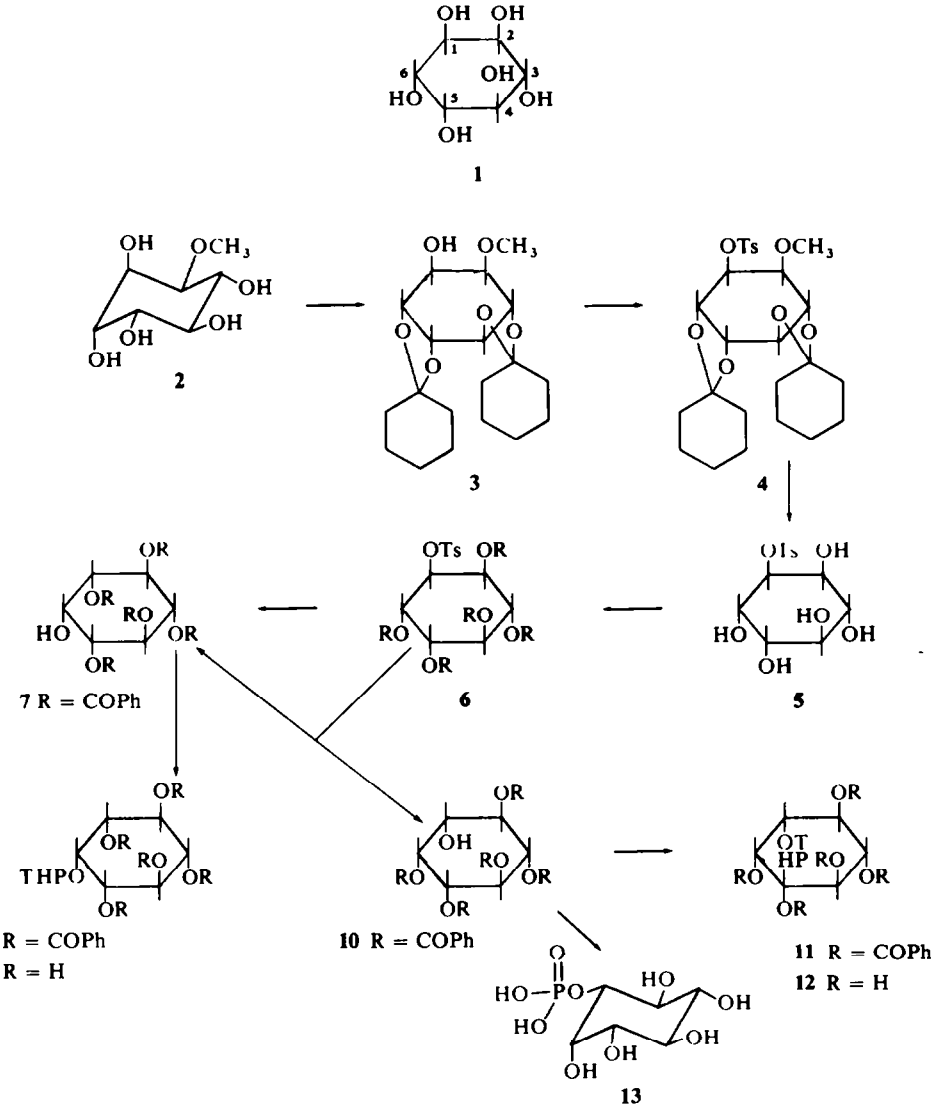
When 1L-penta-O-benzoyl-1-O-toluene-*p*-sulphonyl-*chiro*-inositol **6** was treated with sodium fluoride in DMF at 140° for 3 days after pouring the reaction mixture into water only 1D-1,2,4,5,6-penta-O-benzoyl-*myo*-inositol **10** and 1,3,4,5,6-penta-O-benzoyl-*myo*-inositol **7** were formed, in approximately equal quantities.

The crude reaction mixture of the penta-benzoates **10** and **7** was converted to the pyranyl derivatives using dihydropyran and acidic catalyst. The crystalline mixture of tetrahydropyranyl esters **8** and **11** could be separated on preparative thin layer plates. Debenzoylation of **8** and **11** with methanolic sodium methoxide gave **9** and **12**, which were shown to be identical chromatographically with authentic DL-1-O-pyranyl-*myo*-inositol and 2-O-pyranyl-*myo*-inositol,[16] respectively.

Preparative TLC proved to be the best method of separating the two isomers **10** and **7**, and it was found, as expected, that one, the 1D-1,2,4,5,6-penta-O-benzoyl-*myo*-inositol **10** had an optical rotation, $[\alpha]_D^{22} = -53°$, while the *meso*-1,3,4,5,6-penta-O-benzoyl-*myo*-inositol **7** was without rotation. Both gave *myo*-inositol on catalytic debenzoylation, as shown by paper chromatography.

The synthesis of the optically active 1D-1,2,4,5,6-penta-O-benzoyl-*myo*-inositol **10**

in 34% yield from 1 L-penta-O-benzoyl-1-O-toluene-*p*-sulphonyl-*chiro*-inositol **6** now allowed the facile preparation of 1L-*myo*-inositol-1-phosphate **13** by established procedures, using diphenylphosphochloridate in pyridine, subsequent hydrogenolysis



of the phenyl groups and catalytic removal of the benzoyl groups with sodium methoxide. The product was isolated as the crystalline dicyclohexylamine salt and was chromatographically and optically pure, ($[\alpha]_D^{20} = -4{\cdot}9° \pm 1$, cf. $[\alpha]_D^{25} = -3{\cdot}2°$ and 3·53° for the phosphates prepared from galactinol[7] and enzymically,[5] respectively). The compound was identical, chromatographically and in m.p. to a sample kindly provided by Professor C. E. Ballou.

EXPERIMENTAL

M.ps are corrected. Specific rotations were determined with "Quick" Roussel and Jouan polarimeter. Elemental analysis was performed by the Central Microanalitical Laboratory, C.N.R.S.

Purification of quebrachitol, 1L-2-O-*methyl*-chiro-*inositol*. Crude quebrachitol (100 g) obtained from the Uniroyal Plantation, Baltimore, USA, was dissolved in water (3 l) and norit (45 g) added. The mixture was boiled for 15 min and filtered through a pad of celite on a bacteriological filter. The colourless filtrate was evaporated to 100 ml and EtOH (500 ml) added. The soln was seeded and left several days to crystallize, yield: 65 g, m.p. 193–195°.

1L-1,2:3,4-*di*-O-*cyclohexylidene*-5-O-*methyl*-chiro-*inositol* **3**[10] (1L-3,4:5,6-dicyclohexylidene-2-O-methyl-*chiro*-inositol). Purified quebrachitol (20 g), cyclohexanone (200 ml) and benzene (60 ml) were refluxed with azeotropic distillation and magnetic stirring in a Dean–Stark apparatus, bath temp 150°, until no more water distilled over. The apparatus was cooled slightly and toluene-*p*-sulphonic acid (400 mg) added. There was a rapid initial formation of water and the distillation was continued for 4 hr. The soln was cooled, poured into ice/$NaHCO_3$ aq and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water and dried over Na_2SO_4. The $CHCl_3$ was removed *in vacuo* and finally cyclohexanone and some condensation products were removed at 70°/0·05 mm. To the resulting pale yellow syrup light petroleum (100 ml) was added and the soln left several days at 0° giving **3**, 18 g, 72%, m.p. 117–119°, $[\alpha]_D^{20}$ −19·3° (*c*, 0·775 in $CHCl_3$). Found: C, 64·3, H, 8·3; calc. for $C_{19}H_{30}O_6$: C, 64·4, H, 8·5%. The yield is variable, successive preparations gave 55–72%.

1L-3,4:5,6-*di*-O-*cyclohexylidene*-2-O-*methyl*-1-O-*toluene*-p-*sulphonyl*-chiro-*inositol* **5**. 1L-1,2:3,4-di-O-cyclohexylidene-5-O-methyl-*chiro*-inositol (12 g) was dissolved in pyridine (100 ml) and toluene-*p*-sulphonyl chloride (13·1 g) added at 0° over 45 min. The soln was heated at 70° for 4·5 hr and left at room temp overnight. The soln was poured into ice/5% $NaHCO_3$ aq and extracted with $CHCl_3$ (3 × 70 ml). The $CHCl_3$ soln was washed with 10% $KHSO_4$ aq at 0°, until the washings were acidic and finally with water and 5% $NaHCO_3$ aq. The soln was dried over Na_2SO_4 and evaporated *in vacuo*. 1L-3,4:5,6-di-O-cyclohexylidene 2-O-methyl-1-O-toluene-*p*-sulphonyl-*chiro*-inositol crystallized from EtOH (400 ml) as needles, 14·7 g, 81%, m.p. 128–129°, $[\alpha]_D^{25}$ −12° (*c*, 0·73 in $CHCl_3$). Found: C, 61·1; H, 7·1; S, 6·1. Calc. for $C_{26}H_{36}O_8S$: C, 61·4; H, 7·1; S, 6·3%.

1L-1-O-*toluene*-p-*sulphonyl*-chiro-*inositol* **5**. 1L-3,4:5,6-di-O-cyclohexylidene-2-O-methyl-1-O-toluene-*p*-sulphonyl-*chiro*-inostiol (10 g) was magnetically stirred with BCl_3 (75 g) at 60° in dry apparatus, surmounted by a cold finger, which allowed reflux and closed by a drying tube. After 2 hr at −60°, further BCl_3 (25 g) was added and the temp allowed to rise so that the BCl_3 gently refluxed for 5 hr. The temp was allowed to rise to room temp overnight. The remaining trichloride removed on the water pump and MeOH (100 ml) added, and removed, 4 times. The solid product had a greenish-brown coloration. This was mostly removed by suspending the solid in ice-cold $CHCl_3$ (20 ml) filtering and washing with a little more $CHCl_3$. The 1L-1-O-toluene-*p*-sulphonyl-*chiro*-inositol which contained no O-Me as shown by TLC on silica-gel G using $CHCl_3$–MeOH, 80:20 (R_f = 0·45, c.f. 0·7 for 1L-2-O-methyl-1-O-toluene-*p*-sulphonyl-*chiro*-inositol) was recrystallized from MeOH–$CHCl_3$, 5·1 g, 80%. After one further recrystallization from MeOH, m.p. 172–174°, $[\alpha]_D^{22}$ = −37·7° (*c*, 1·825 in $CHCl_3$). Found: C, 46·8; H, 5·6; S, 9. Calc. for $C_{13}H_{18}O_8S$: C, 46·7; H, 5·4; S, 9·3%.

1L-2,3,4,5,6-*penta*-O-*benzoyl*-1-O-*toluene*-p-*sulphonyl*-chiro-*inositol* **6**. 1L-1-O-toluene-*p*-sulphonyl-*chiro*-inositol (10 g) was dissolved in dry pyridine (250 ml) and benzoyl chloride (70 ml) added dropwise at 0°. The mixture was then left at room temp for 24 hr and poured into ice/5% $NaHCO_3$ aq, extracted with $CHCl_3$, washed with HCl until the washings were acidic, and finally with water. After drying over Na_2SO_4 and taking to dryness *in vacuo*, the oil obtained crystallized from EtOH, 3·5 g, 86%, giving a single spot on TLC on silica gel G, using benzene–EtOAc, 95:5 as solvent, R_f 0·52, m.p. 195–197°, $[\alpha]_D^{25}$ = −41·8° (*c*, 2·46 in $CHCl_3$). Found: C, 67·7; H, 4·4; S, 3·9. Calc. for $C_{48}H_{38}O_{13}S$; C, 67·3; H, 4·4; S, 3·7%.

1D-1,2,4,5,6-*penta*-O-*benzoyl*-myo-*inositol* **10**. 1L-2,3,4,5,6-penta-O-benzoyl-1-O-toluene-*p*-sulphonyl-*chiro*-inositol **6** (5 g) and NaF (5 g) were heated in anhyd DMF (50 ml) at 137° with rapid stirring. After 3 days, TLC on silica gel G (benzene–MeOH 94:6) showed only a trace of the tosylated compound and two other, slower moving, products. The mixture was cooled and poured into ice/water. The solids were a mixture of the required product **10**, the corresponding **7** and a little unchanged starting material, in ascending order of mobility on TLC.

The mixture was partially dissolved in boiling alcohol and the hot soln filtered off from the undissolved solid which was mainly *myo*-inositol 1,3,4,5,6-penta-O-benzoate (0·9 g). On cooling in the refrigerator, the mother liquors gave a mixture of solids rich in 1D-1,2,4,5,6-penta-O-benzoyl-*myo*-inositol (2 g) and on

evaporation *in vacuo* and recrystallization a further crop (0·4 g) was obtained which was almost pure 1D-1,2,4,5,6-penta-O-benzoyl-*myo*-inositol.

The fractions containing the product, including the final mother liquors, were chromatographed on 1·5 mm thick Merck Kiesel gel PF254 plates, using benzene/MeOH 94:6 as solvent (250 mg per 40 cm plate). The bands containing the product were eluted with EtOAc and crystallized from EtOH to give chromatographically pure 1D-1,2,4,5,6-penta-O-benzoyl-*myo*-inositol, recrystallized again from EtOH, yield: 1·35 g, 34%, m.p. 125–130° (unsharp), $[\alpha]_D^{22} = -53° \pm 3$ (*c*, 1·6 in $CHCl_3$). Found: C, 70·0; H, 4·7; O, 24·9; calc. for $C_{41}H_{32}O_{11}$: C, 70·1; H, 4·6; O, 25·05%.

Myo-*inositol*-1,3,4,5,6-*penta*-O-*benzoate* **7**. The crystalline fractions containing *myo*-inositol 1,3,4,5,6-penta-O-benzoate were chromatographed as described above and the product, the middle band on TLC, crystallized from EtOH, yield: 1·25 g, 32%, m.p. 240–245°, $[\alpha]_D^{22} = 0° \pm 3$.

Both products, **10** and **7**, of the solvolysis of the toluene-*p*-sulphonyl-*chiro*-inositol **6** gave only *myo*-inositol on debenzoylation (paper chromatographic analysis).

1L-O-*diphenylphosphoryl*-myo-*inositol* 2,3,4,5,6-*pentabenzoate*. 1-D-*myo*-inositol 1,2,3,4,5,6-penta-O-benzoate (400 mg) was dissolved in pyridine (5 ml) and diphenylchlorophosphidate (0·5 ml) added. The mixture was left at room temp for 60 hr and poured into ice/water. The product crystallized immediately, was filtered off, or preferably centrifuged down at 3000 g for 10 min, resuspended in 2 ml water and then filtered, washed with water and air-dried overnight. The solid was dissolved in $CHCl_3$, the soln filtered, and taken to dryness *in vacuo* and recrystallized from EtOH, yield: 380 mg, 71%. The product was recrystallized once more from $CHCl_3$/MeOH as needles, 290 mg, m.p. 197–199°, $[\alpha]_D^{25} = -13 \pm 2$ (*c*, 1·74 in $CHCl_3$). Found: P, 3·35. Calc. for $C_{53}H_{31}O_{14}P$: P, 3·35%.

1L-myo-*inositolphosphate dicyclohexylamine salt*. 1 L-diphenylphosphoryl-*myo*-inositol penta-O- benzoate (220 mg) was dissolved (almost) in EtOAc (10 ml) and PtO_2 (110 mg) added. The mixture was stirred under H_2 at 35° for 18 hr and the Pt filtered off. The total H_2 uptake was about 130 ml. The soln was evaporated to dryness *in vacuo*, dry MeOH added and evaporated twice and the final syrup which on TLC showed no trace of the starting material or dephosphorylated pentabenzoyl *myo*-inositol, was dissolved in dry MeOH (2 ml). IN-NaMeOH (0·7 ml) was added and the soln allowed to stand at room temp for 3 hr. Crystals were deposited. After neutralization with CO_2, the mixture was dissolved in water (20 ml) and diethyl ether (20 ml) and the aqueous layer separated, washed once with ether and deionized with Amberlite IR 120 H^+. The acidic soln was washed once more with ether, cyclohexylamine (0·1 ml) added and evaporated to dryness *in vacuo*. The syrupy product was dissolved in water (0·4 ml) and acetone added to turbidity. Standing at first at room temp and then at 2° gave needles of 1 L-*myo*-inositol phosphate dicyclohexylamine salt, 60 mg, 56%, after one recrystallization from water/acetone, m.p. 190–192°, $[\alpha]_D^{22} = -4·9° \pm 1·0$ (*c*, 5·68 in water, pH 9) lit[7] ($[\alpha]_D^{25} = -3·2°$ in water pH 9). On Whatman No. 1 paper, using isopropanol–ammonia–water, 7:1:2 as solvent, the product chromatographed identically with an authentic sample, m.p. 192–193°, kindly provided by Professor C. E. Ballou. It contained no trace of 2-phosphate: Found: N, 5·95; P, 7·1; calc. for $C_{18}H_{39}N_2O_9P$: N, 6·1; P, 6·8%.

Preparation of pyranyl derivatives of the mixed myo-*inositol penta*-O-*benzoates* **8** and **11**. The mixed pentabenzoates **7** and **10** from the NaF solvolysis reaction (1·92 g) were dissolved in dry CH_2Cl_2 (10 ml) and dihydropyran (25 ml) added, followed by a soln of HCl in dry dioxan (0·6 ml; 5N). The mixture was stirred magnetically for 16 hr and then K_2CO_3 (500 mg) added and all poured into ice/sat $NaHCO_3$. The mixture was extracted with $CHCl_3$, washed, dried and evaporated to dryness *in vacuo*. TLC on silica gel G, using benzene–MeOH 98:2, showed two spots which were separated by preparative chromatography and crystallized from EtOH. The slower moving product, 1,3,4,5,6-penta-O-benzoyl-2-O-pyranyl-*myo*-inositol had m.p. 220°–231°, $[\alpha]_D^{25} = 0 \pm 1°$. Found: C, 70·7; H, 5·35; O, 24·3. Calc. for $C_{46}H_{40}O_{12}$, C, 70·4; H, 5·15; O, 24·5%. It was debenzoylated with NaOMe and gave a mono-pyranyl myo-inositol indistinguishable on paper chromatography, using n-butanol–ethanol–water (40:11:19) as solvent from authentic 2-O-pyranyl-*myo*-inositol.[16]

The faster moving spot was 1L-2,3,4,5,6-penta-O-benzoyl-1-O-pyranyl-*myo*-inositol, m.p. 172–175°, $[\alpha]_D^{25} = -20°$ (*c*, 2·14 in $CHCl_3$). Found: C, 70·5; H, 5·0; O, 24·7; calc. for $C_{46}H_{40}O_{12}$: C, 70·4; H, 5·15; O, 24·5%. It was debenzoylated to a monopyranyl-*myo*-inositol indistinguishable on paper chromatography from DL-1-O-pyranyl-*myo*-inositol.[16]

Acknowledgements—The authors wish to express their sincere gratitude to Professor E. Lederer for the constant encouragement with which he supported this work. Thanks are expressed to Professor C. E. Ballou for a sample of 1L-*myo*-inositol 1-phosphate. This work has been supported by a research grant

from the Délégation Générale à la Recherche Scientifique et Technique auprès du Premier Ministre, n° 67-0192.

This research was made possible by a generous gift of quebrachitol from Uniroyal Plantation, Baltimore.

One of us, J.E.G.B. wishes to thank the University of Southampton for sabbatical leave and also the Royal Society for a European travelling fellowship.

Note added in Proof

In the conversion of 1L-2,3,4,5,6-penta-O-benzoyl-1-O-toluene-*p*-sulphonyl-*chiro*-inositol to 1D-1,2,4,5,6-penta-O-benzoyl-*myo*-inositol the temperature is very critical. If the temperature is raised by a few degrees, an optically inactive compound m.p. is formed with the same analysis and chromatographic mobility as 1D-1,2,4,5,6-penta-O-benzoyl-*myo*-inositol, which may be the racemic DL-*myo*-inositol pentabenzoate, since 1L-1,2,4,5,6-penta-O-benzoyl-*myo*-inositol can be obtained from the 1D by a series of phenoxonium ion rearrangements of the *trans* positions of the ring as have recently been described by Paulson and his colleagues for acetoxonium ions. (H. Paulson, F. G. Espinosa, W. P. Trautwein and K. Heyns, *Chem. Ber.* **101**, 179 (1968).)

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