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THE PREPARATION OF 1-O-TOSYL-(−)-INOSITOL FROM QUEBRACHITOL

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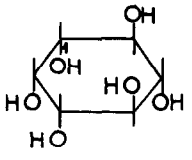
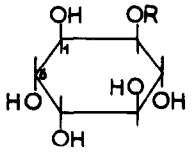
Many optically active derivatives of myoinositol, such as glycosides, methyl ethers and phosphates occur in Nature [1]. It has been firmly established that the phosphatidyl group of the naturally occurring inositol phosphatides is attached to the L-1 position of the myoinositol ring [2](I). The biological interest of these substances suggests that a rational synthesis of the inositol phospholipides would be valuable in promoting further biological studies.

The previously described [3] 1,2-O-cyclohexylidene-myoinositol and 1,4,5,6-tetra-O-acetyl-myoinositol have received a great deal of attention and have proved very useful for the preparation of substituted myoinositol derivatives. The resolution of these racemic compounds, however, presents serious difficulties.



(I.)



(II.) R = H

(III.) R = CH_3

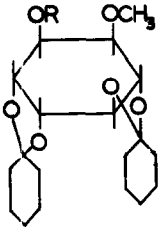
We report in this communication a simple preparative route to the hitherto unknown 1-O-tosyl and penta-O-benzoyl-1-O-tosyl-(-)inositol (IX and X).

It can be seen that, in (-)-inositol (II), 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 myoinositol.

A direct introduction of the tosyl group at the required position [C-1 of the (-)-inositol] seemd a very hard task. Therefore, quebrachitol (III) [2-O-methyl-(-)-inositol], in which the twofold axis of symmetry of (-)-inositol is destroyed by the methyl substituent, was chosen as starting material. For the attainment of our objective - the preparation of IX and X - we required :

a) - a convenient method for the preparation of a 3,4:5,6-di-O-alkylidene-2-O-methyl-(-)-inositol and its O-tosylester (IV and V),

b) - a reagent which would demethylate the methyl ether without cleavage of the sulphonyl ester.



(IV) R=H

(V) R=Ts

(VI) R=Ac

(VII) R=Ms

It has been shown previously[3] that, under energetic conditions, even trans pairs of hydroxyl groups in myoinositol react with cyclohexanone. Accordingly, quebrachitol was heated for 4 hours with cyclohexanone and p-toluenesulphonic acid in benzene with azeotropic removal of water. 3,4:5,6-di-O-cyclohexylidene-2-O-methyl-(-)-inositol (IV)* was obtained in 72% yield (m.p. 117-118,5°, $[\alpha]_D^{29} = -19.3°$

* Professor S. J. Angyal has kindly informed us that this compound has also been prepared in his department (see the recent note [6]).

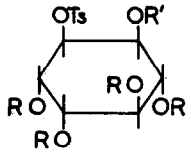
(c = 0.775, $CHCl_3$). Calc. for $C_{19}H_{30}O_6$: C 64.38 ; H 8.53. Found: C 64.28 ; H 8.32).

The hydroxyl group is axial in the diketal (IV) (n. m. r. spectra : δ 2.13 for the acetoxy (VI) and δ 3.12 for the mesyloxy (VII) protons) and consequently its tosylation at room temperature gave an unsatisfactory yield. However, when the diketal (IV) was heated with tosyl chloride (1.5 mol) in pyridine at 70° for 3 hours and then was left at room temperature for 3 days, 3,4:5,6-di-O-cyclohexylidene-2-O-methyl-1-O-tosyl-(−)-inositol (V) was obtained in a yield of 82% [m. p. 128,5°-129,5°, $[\alpha]_D^{29} = -12°$ (c = 0.733, $CHCl_3$). Calc. for $C_{26}H_{36}O_8S$: C 61.40 ; H 7.14 ; S 6.29. Found: C 61.13 ; H 7.01 ; S 6.08].

Next, we turned our attention to the selective removal of the methyl ether.

It was quite obvious that the classical ether cleavage reagents - hydriodic or hydrobromic acid - could not be useful for our purpose. It appeared, however, that an approach using Lewis acids such as BF_3 etherate or BCl_3 - through the formation of intermediate complexes with the ether oxygen - might effect the desired nucleophilic cleavage of the CH_3-O bond.

Boron trifluoride etherate-acetic anhydride has been used to cleave different types of steroidal methyl ethers [4]. In most of the cases the epimeric acetates and elimination products were isolated. The use of boron trichloride for dealkylation, deacylation and deacetalation was reported by Bonner et al. [5].



(VII) R = R' = Ac

(IX) R = R' = H

(X) R = R' = COPh

(XI) R = H ; R' = CH_3

3,4:5,6-di-O-cyclo hexylidene-2-O-methyl-1-O-tosyl-(-)-inositol (V) was treated with 43 moles of boron trichloride in dichloromethane at -80°. The progress of the demethylation was readily followed by acetylating the crude reaction product and observing the change in the pattern of its n.m.r. spectrum. After a reaction time of 15 hours, the crude peracetylated product (VIII) showed the disappearance of the methoxyl proton signals. The presence of the tosyl group is shown by the aromatic and methyl proton signals.

The elusive 1-O-tosyl-(-)-inositol (IX) was thus obtained in a yield of 90% (m.p. 162,5-164° ; $[\alpha]_D^{30}$ = -37.7 (c = 0.45, methanol). Calc. for $C_{13}H_{18}O_8S$: C 46.67 ; H 5.38 ; S 9.28. Found: C 46.82 ; H 5.59 ; S 9.08).

Benzoylation of (IX) with benzoyl chloride in anhydrous pyridine furnished penta-O-benzoyl-1-O-tosyl-(-)-inositol (X) in a yield of 63% (m.p. 102-104° ; $[\alpha]_D^{25}$ = -40.3 (c = 0.62 , $CHCl_3$). Calc. for $C_{48}H_{38}O_{13}S$: C 67.50 ; H 4.44 ; S 3.74. Found: C 67.72 ; H 4.37 ; S 3.94).

When the amount of the BCl_3 was decreased, a second product was present in the crude reaction mixture. The latter product was identical with authentic 2-O-methyl-1-O-tosyl-(-)-inositol (XI), prepared by acidic treatment of 3,4:5,6-di-O-cyclohexylidene-2-O-methyl-1-O-tosyl-(-)-inositol (m.p. 178-179,5° ; $[\alpha]_D^{24}$ = - 68° (c = 0.50, methanol). Calc. for $C_{14}H_{20}O_8S,H_2O$; C 45.90 ; H 6.00 ; S 8.74. Found: C 45.96 ; H 5.82 ; S 8.70).

It is believed that these derivatives will serve as key intermediates for the synthesis of "optically active" 1-O-substituted myoinositols.

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