SYNTHESIS OF 2,3,4,5,6-PENTA-O-TOSYL-sn-MYOINOSITOL. IV.

É. G. Zhelvakova, O. G. Ul'yanova, V. I. Shvets, and N. A. Preobrazhenskii

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Among the lipids, phosphoinositides possess the highest metabolic activity and also some other properties which indicate for them an important role in the formation and activity of cell and subcell membranes.

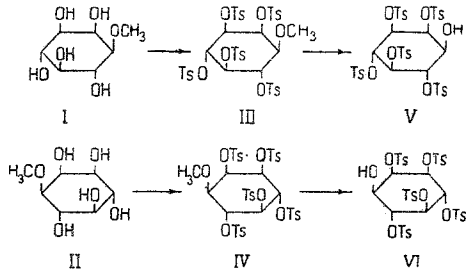
The synthesis of these substances has been retarded hitherto by the absence of methods for obtaining optically active asymmetrically-substituted derivatives of myoinositol of definite structure—the main structural elements of the natural phosphoinositides.

In this paper (which continues our investigations on the synthesis of optically active derivatives of myoinositol [1]), we describe a synthetic approach to 2,3,4,5,6-pentasubstituted sn-myoinositol from natural quebrachitol, 2-O-methyl-(−)-inositol, which, on further reactions, should lead to the natural monophosphoinositide, unlike the synthesis of 1,2,4,5,6-penta-O-benzyl-sn-myoinositol considered previously [2], using the same quebrachitol. In the latter case, it is possible to isolate only the antipode of the natural monophosphoinositide.

The work was based on the conversion of quebrachitol by a literature method [3] via the corresponding inosose into (−)-bornesitol, 1-O-methyl-sn-myoinositol (I), with the subsequent protection of all five free hydroxyl groups and the elimination of the methyl group.

As the protective group we selected tosyl, the use of which permits demethylation to be carried out successfully [4]. The stage of tosylation and demethylation was developed with racemic (±)-bornesitol and was then applied to (−)-bornesitol (I).

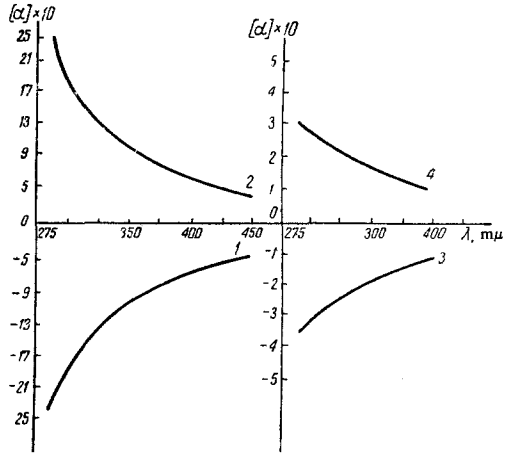
The pentatosyl derivative of (±)-bornesitol was obtained by its esterification with p-toluenesulfonyl chloride in pyridine (100° C). The use of the classical reagents (HI, HBr) for the elimination of the methyl group led to a complicated mixture containing the required product in only small amounts. It was not possible to effect demethylation by using boron trichloride as demethylating agent, either (the bulk of the starting material was recovered from the reaction mixture). The cleavage of the $O—CH_3$ bond was achieved successfully by the reaction of the pentatosyl ester of (±)-bornesitol with boron tribromide in methylene chloride at −55° C.



To check the optical purity of the 2,3,4,5,6-penta-O-tosyl-sn-myoinositol (V) obtained from (−)-bornesitol, we synthesized 1,2,4,5,6-penta-O-tosyl-sn-myoinositol (VI) from natural (+)-bornesitol (II).

The structures of the racemic 3-O-methyl-1,2,4,5,6-penta-O-tosylmyoinositol, 1,2,4,5,6-penta-O-tosylmyoinositol, and the corresponding optically active substances III and IV, and V and VI, were established by means of their IR and NMR spectra and their optical rotatory dispersion (ORD) curves. The IR spectra of 3-O-methyl-1,2,4,5,6-penta-O-tosylmyoinositol and of the optically active methyl ethers III and IV had the absorption bands characteristic for a sulfonate (1375, 1185 cm^{-1}), for the benzene nuclei of tosyl residues (1595, 1500 cm^{-1}), and for a methoxyl group (2840 cm^{-1}) but had no hydroxyl group absorption. The NMR spectra of the substances mentioned showed the presence of the methyl group in $O—CH_3$ (δ 3.60 ppm) and five $C—CH_3$ groups in $C_6H_4CH_3$ (δ 2.4, 2.5, 2.53, 2.6, 2.7 ppm).

The structures of 1, 2, 4, 5, 6-penta-O-tosylmyoinositol and of 2, 3, 4, 5, 6-and 1, 2, 4, 5, 6-penta-O-tosyl-sn-myoinositols (V and VI) were shown by comparing their chromatographic characteristics with those for the initial pentatosyl esters of (±), (−)-, and (+)-bornesitols (III and IV) and by the appearance in the spectra of the demethylated substances of the band of a hydroxyl group (3480 cm^{-1}) and the disappearance of the $O-CH_3$ absorption (2840 cm^{-1}). In the NMR spectra of the demethylated substances, the signals of the protons of the $O-CH_3$ group had disappeared, but all the signals of the protons of the methyl groups in $C_6H_4CH_3$ had remained unaffected.



Optical rotatory dispersion spectra of 1-O-methyl-2, 3, 4, 5, 6-penta-O-tosyl-sn-myoinositol (1), 3-O-methyl-1, 2, 4, 5, 6-penta-O-tosyl-sn-myoinositol (2), 2, 3, 4, 5, 6-penta-O-tosyl-sn-myoinositol (3), and 1, 2, 4, 5, 6-penta-O-tosyl-sn-myoinositol (4).

The ORD curves (figure) of compounds III and V and of IV and VI had a smooth nature but were opposite in sign and absolute magnitude of the rotation, which confirmed their antipodal relationship.

EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer model 257 spectrometer (paraffin oil or tablets with KBr), the NMR spectra on a JNM-4H-100 instrument (trichloroacetic acid), and the ORD curves on a Cary 60 spectropolarimeter (chloroform). Thin-layer chromatography was carried out on KSK silica gel in systems 1), benzene–acetone (9 : 1) and 2) benzene–acetone (15 : 1). After the chromatogram had been run, the substances on the plates were revealed by spraying them with chromic acid mixture and subsequent heating at 200–250° C.

3-O-Methyl-1, 2, 4, 5, 6-penta-O-tosylmyoinositol (pentatosyl ester of (±)-bornesitol). With stirring at 20° C, 7.6 g of p-toluenesulfonyl chloride was added to 0.55 g of (±)-bornesitol (mp 199–200° C) obtained by the previously-described method [5], in 15 ml of pyridine. The reaction mixture was stirred at 100° C for 10 hr and was left at 20° C for 16–18 hr. Then 100 ml of water was added and the substance was extracted with chloroform (3 × 50 ml). The extract was washed with 2% HCl (5 × 30 ml), with saturated sodium bicarbonate solution (3 × 50 ml), and with water (3 × 40 ml), and was dried with sodium sulfate. The chloroform was distilled off and the residue was washed with boiling methanol (3 × 50 ml). Yield 0.63 g (23.1%), mp 226–227° C, R_f 0.47 (1). IR spectrum (KBr), cm^{-1}: 2840 (OCH_3), 1595, 1500 (benzene rings), 1375, 1185 (sulfonates). NMR spectrum (δ, ppm); 3.60 (OCH_3), 2.4, 2.5, 2.53, 2.6, 2.7 (CH_3 in $C_6H_4CH_3$).

Found, %: C 52.31; H 4.80; S 16.49. Calculated for $C_{42}H_{44}O_{16}S_5$, %: C 52.29; H 4.56; S 16.59.

1, 2, 4, 5, 6-Penta-O-tosylmyoinositol. With stirring at −70° C a solution of 2.4 g of boron tribromide in 10 ml of methylene chloride was added to a solution of 0.6 g of 3-O-methyl-1, 2, 4, 5, 6-penta-O-tosylmyoinositol in 30 ml of methylene chloride. The reaction mixture was left at −55° C for 170 hr and was then poured into 150 ml of water and the mixture was vigorously shaken. The organic layer was separated off and washed with water (2 × 50 ml), and was then dried with magnesium sulfate. The solvent was distilled off and the residue was chromatographed on 10 g of hydrated silica. The 1, 2, 4, 5, 6-penta-O-tosylmyoinositol was diluted with benzene containing 5% of acetone. Yield 0.13 g (22.4%), mp 174–175° C, R_f 0.24 (2). IR spectrum (KBr), cm^{-1}: 3480, (OH), 1595, 1500 (benzene rings), 1375,

1185 (sulfonates). NMR spectrum (δ, ppm): 2.4, 2.5, 2.53, 2.6, 2.7 (CH_3 in $C_6H_4CH_3$).

Found, %: C 51.95; H 4.69; S 16.73. Calculated for $C_{41}H_{42}O_{16}S_5$, %: C 51.79 H 4.42; S 16.84.

1-O-Methyl-2,3,4,5,6-penta-O-tosyl-sn-myoinositol (III) was obtained by the method described for the pentatosyl ester of (±)-bornesitol, from 0.5 g of 1-O-methyl-sn-myoinositol, (−)-bornesitol (I). The yield of III was 0.12 g (25.4%). Amorphous substance; R_f 0.47 (1). The IR and NMR spectra were similar to the corresponding spectra for the sample of the pentatosyl ester of (±)-bornesitol. $[\alpha]_{450}^{20}$ − 46.8°; $[\alpha]_{425}^{20}$ − 56.3°; $[\alpha]_{400}^{20}$ − 65.7°; $[\alpha]_{375}^{20}$ − 81.3°; $[\alpha]_{350}^{20}$ − 101.7°; $[\alpha]_{325}^{20}$ − 136.3°; $[\alpha]_{300}^{20}$ − 181.2°; $[\alpha]_{285}^{20}$ − 240.3° (c 0.6; chloroform).

Found, %: C 52.01; H 4.71; S 16.31. Calculated for $C_{42}H_{44}O_{16}S_5$, %: C 52.29; H 4.56; S 16.59.

3-O-Methyl-1,2,4,5,6-penta-O-tosyl-sn-myoinositol (IV) was synthesized from 0.35 g of 3-O-methyl-sn-myoinositol, (+)-bornesitol (II), in the same way as compound III. Yield 0.10 g (30.2%). Amorphous substances. A mixture of equal amounts of III and IV had mp 225.5–226° C, R_f 0.47 (1). The IR and NMR spectra were identical with the spectra of the pentatosyl ester of (±)-bornesitol and of compound III: $[\alpha]_{450}^{20}$ + 45.9°; $[\alpha]_{425}^{20}$ + 55.6°; $[\alpha]_{400}^{20}$ + 65.5°; $[\alpha]_{375}^{20}$ + 81.9°; $[\alpha]_{350}^{20}$ + 101.2°; $[\alpha]_{325}^{20}$ + 133.8°; $[\alpha]_{300}^{20}$ + 180.6°; $[\alpha]_{285}^{20}$ + 239.5° (c 0.6; chloroform).

Found, %: C 52.10; H 4.69; S 16.42. Calculated for $C_{42}H_{44}O_{16}S_5$, %: C 52.29; H 4.56 S 16.59.

2,3,4,5,6-Penta-O-tosyl-sn-myoinositol (V) was isolated from 0.18 g of 1-O-methyl-2,3,4,5,6-penta-O-tosyl-sn-myoinositol (III) by the method described for the racemic pentatosyl ester. The 2,3,4,5,6-penta-O-tosyl-sn-myoinositol was isolated by thin-layer chromatography on hydrated silica. Yield 0.046 g (27 3%). Amorphous substance, R_f 0.24 (2). The IR and NMR spectra were similar to those of the racemic pentatosyl ester. $[\alpha]_{400}^{20}$ − 11.3°; $[\alpha]_{375}^{20}$ − − 17.0°; $[\alpha]_{350}^{20}$ − 19.2°; $[\alpha]_{325}^{20}$ − 22.6°; $[\alpha]_{300}^{20}$ − 28.2°; $[\alpha]_{290}^{20}$ − 33.8° (c 0.1; chloroform).

Found, %: C 51.97; H 4.52; S 16.64. Calculated for $C_{41}H_{42}O_{16}H_5$, %: C 51.79; H 4.42; C 16.84.

1,2,4,5,6-Penta-O-tosyl-sn-myoinositol (VI) was obtained from 0.15 g of substance IV as described for the racemic pentatosyl ester and compound V. Yield 0.041 g (28.1%). Amorphous substance. A mixture of equal amounts of substance V and VI had mp 173-174° C, R_f 0.24 (2). The IR and NMR spectra were identical with the spectra of the racemic pentatosyl ester and of compound V. $[\alpha]_{400}^{20}$ + 10.5°; $[\alpha]_{375}^{20}$ + 16.4°; $[\alpha]_{350}^{20}$ + 18.8°; $[\alpha]_{325}^{20}$ + 22.2°; $[\alpha]_{300}^{20}$ + 27.6°; $[\alpha]_{290}^{20}$ + 32.9° (c 0.1; chloroform).

Found, %: C 52.00; H 4.56; S 16.71. Calculated for $C_{41}H_{42}O_{16}S_5$, %: C 51.79; H 4.42; S 16.84.

CONCLUSIONS

The synthesis of 2,3,4,5,6-penta-O-tosyl-sn-myoinositol has been effected from (−)-bornesitol by its tosylation followed by demethylation with boron tribromide.

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Lomonosov Moscow Institute of Fine Chemical Technology