SYNTHESIS OF DESOXY DERIVATIVES OF β-1,6-ANHYDRO-D-GLUCOPYRANOSE (LEVOGLUCOSAN)

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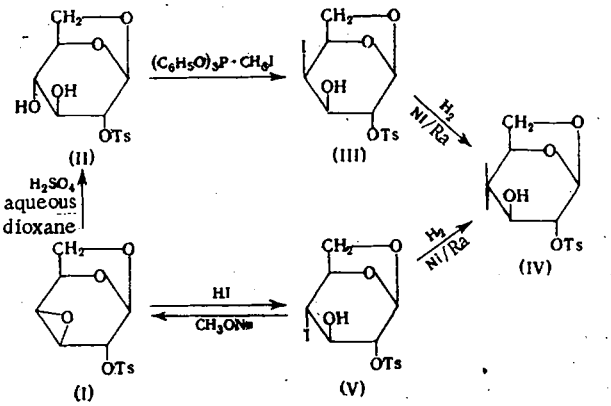
In order to obtain some new data on the synthetic application of β-1,6-anhydro-D-glucopyranose (levoglucosan) we studied the synthesis of its desoxy derivatives by two routes: 1) replacement of the free hydroxyl group in the tosyl esters of levoglucosan by treatment with triphenyl phosphite methiodide and subsequent reduction of the iododesoxy group, and 2) reduction of the α-oxide rings in the benzyl derivatives of the α-oxides of glycosans with aluminum lithium hydride and subsequent hydrogenolysis of the benzyl groups. The synthesis of the desoxy derivatives of levoglucosan is described in isolated publications and is quite difficult [1-4]. The results of studying the nucleophilic substitution of the hydroxyl groups in 2-O-tosyllevoglucosan (II) when treated with triphenyl phosphite methiodide are depicted in the following scheme.



The starting (II) was obtained by the hydrolysis of β-D-1,6:3,4-dianhydro-2-O-tosylgalactopyranose (I) [5]. The treatment of (II) with $(C_6H_5O)_3P \cdot CH_3I$ under the conditions described for the methylhexopyranosides [6, 7], with subsequent chromatographing of the reaction mixture on Al_2O_3, gave the iododesoxy derivative (III) in 44% yield. The fact that it contained the iododesoxy group at C_4 was proved by reduction over Raney nickel to the known 1,6-anhydro-2-O-tosyl-4-desoxy-β-D-xylohexopyranose (IV) [1]. In order to ascertain the configuration of compound (III) the α-oxide ring in (I) was opened by treatment with HI to give compound (V). The latter when treated with CH_3ONa gave the starting (I), while reduction over Raney nickel gave (IV), and consequently (V) was the 4-iodo-4-desoxy-β-D-1,6-anhydroglucopyranose. Derivative (III) had mp 158-159°, $[\alpha]_D^{20} -5.05°$ (C 3.03, $CHCl_3$), whereas derivative (V) differed from (III) in its properties and had mp 127-128° and $[\alpha]_D^{20} -88.8°$ (C 2.02, $CHCl_3$).

The obtained data show that the reaction of the 2-O-tosyl ester of levoglucosan with $(C_6H_5O)_3P \cdot CH_3I$ proceeds selectively at C_4, despite the fact that the hydroxyl group at C_4 occupies the exo position, and the endo position at C_3. These data differ from those obtained previously [8, 9], according to which the hydroxyl is not replaced by halogen when the exo-hydroxyl groups in condensed bicyclic systems like 1,2-O-isopropylidene-5,6-di-O-methyl-α-D-glucofuranose, 3,4-O-isopropylidene-β-D-methylgalactoside, and 1,4:3,6-dianhydro-D-sorbitol are treated with $(C_6H_5O)_3P \cdot CH_3I$. It may be assumed that the β-1,6-anhydro

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ring in the levoglucosan fails to exert a substantial shielding effect with respect to the backside approach of the nucleophile to C_4. At the same time, the bulky tosyloxy group at C_2 can hinder the approach to C_3 and prevent replacement of the endo-hydroxyl group.

An attempt to insert halogen in the C_3 position, both in β-1,6-anhydro-2-O-tosylglucopyranose and in β-1,6-anhydro-2,4-di-O-tosylglucopyranose, by using excess reagent proved unsuccessful. We were unable to detect in the reaction mixture any substances with an R_f value close to the R_f of halo derivative (III).

The reduction of the α-oxide rings of the benzyl derivatives of glucosan α-oxides with $LiAlH_4$, and subsequent hydrogenolysis of the benzyl groups, was accomplished for the purpose of synthesizing β-1,6-anhydro-3-desoxy-D-ribohexopyranose and β-1,6-anhydro-2-desoxy-D-arabinohexopyranose (3- and 2-desoxylevoglucosan). The new α-oxide derivatives, β-1,6:2,3-dianhydro-4-O-benzylallopyranose and β-1,6:2,3-dianhydro-4-O-benzylmannopyranose, were obtained by analogy with [1, 5, 10]. Communications on the synthesis of the indicated α-oxides [11, 12] and 2-desoxylevoglucosan [3] appeared at the time the present study was completed. As the starting product we used 4-O-benzyl-2-O-tosyllevoglucosan. 3-Desoxylevoglucosan, identical with that described in [2], was obtained via 4-O-benzyl-2,3-di-O-tosyllevoglucosan and β-1,6:2,3-dianhydro-4-O-benzyl-D-allopyranose. 2-Desoxylevoglucosan was synthesized via β-1,6:2,3-dianhydro-4-O-benzyl-D-mannopyranose. The product of opening the α-oxide was subjected to hydrogenolysis to give a substance with mp 145-150° and $[\alpha]_D^{20}$ −116°, (C 1.2, H_2O), which, based on the GLC data for its acetate, proved to be pure. The paper chromatography of the substance, with its detection using $NaIO_4$ solution and an acid solution of $NaIO_4$ and $AgNO_3$, established that it contains a glycol grouping, and 2-desoxyglucose was obtained as the result of hydrolysis. The known synthesis of 2-desoxylevoglucosan, starting with β-1,6:2,3-dianhydro-4-O-benzylmannopyranose [3], leads to a product with mp 159-160° and $[\alpha]_D^{20}$ −118° (C 1.3, H_2O). 2-Desoxylevoglucosan was obtained previously by the alkaline hydrolysis of 2-desoxy-α-D-phenylglucopyranoside, and was described as a sirup with $[\alpha]_D^{20}$ −33.1° (C 0.7, C_2H_5OH) [4].

The results of [3], and also our data, showed that [4] was wrong.

EXPERIMENTAL METHOD

The TLC was run in a loose layer of silica gel in 10 : 1 benzene—acetone (system A) and 3 : 1 chloroform—methanol (system B); the compounds were detected using H_2SO_4. The column chromatography was run on neutral Al_2O_3 (III activity), using a 4 : 1 benzene—ether mixture (system C) for elution, and on silica gel (100-150 mesh), using a 7 : 3 acetone—benzene mixture (system D) for elution. The paper chromatography was run on M paper by the ascending method in the system: 4 : 2 : 1 butanol—ethanol—water (system E). To detect the compounds we used $NaIO_4$ solution, with subsequent treatment using either an acid solution of p-nitroaniline or alkaline $AgNO_3$.

4-Iodo-4-desoxy-2-O-tosyl-1,6-anhydro-β-D-galactopyranose (III). Compound (II) (1.9 g), obtained as described in [5], was dissolved by heating in a mixture of 30 ml of absolute benzene and 2 ml of dry $CHCl_3$. The solution was added to a suspension of 3 g of $(C_6H_5O)_3P \cdot CH_3I$ in absolute benzene and the mixture was heated at 55°C for 6 h. The mixture was chromatographed on an Al_2O_3 column (system C). After a double recrystallization from alcohol we isolated 1.15 g (44%) of product with mp 158-159°; $[\alpha]_D^{20}$ −5.05° (C 3.0, $CHCl_3$); R_f 0.54 (system A). Found: C 36.90; H 3.79; I 29.64; S 7.55%. $C_{13}H_{15}IO_6S$. Calculated: C 36.62; H 3.52; I 29.80; S 7.51%.

4-Iodo-4-desoxy-2-O-tosyl-1,6-anhydro-β-D-glucopyranose (V). To 2 g of 1,6:3,4-dianhydro-2-O-tosyl-β-D-galactopyranose (I), obtained as described in [13], in 40 ml of dioxane was added a solution of 12 ml of HI in 40 ml of dioxane and the mixture was let stand in the dark at 20° for 18 h. The mixture was treated with 1% $Na_2S_2O_3$ solution until colorless, extracted with $CHCl_3$, and the chloroform extract was dried over $MgSO_4$ and evaporated to dryness; after two recrystallizations from alcohol the yield of (V) was 45%; mp 127-128°; $[\alpha]_D^{20}$ −88,8° (C 2.02, $CHCl_3$). Found: C 36.53; H 3.61; I 29.67; S 7,48%. $C_{13}H_{15}IO_6S$. Calculated: C 36.62; H 3.52; I 29.80; S 7.51%.

2-O-Tosyl-1,6-anhydro-4-desoxy-β-D-xylohexopyranose (IV). The compound was obtained from 4-iodo-4-desoxy-2-O-tosyl-1,6-anhydro-β-D-galactopyranose (III) by reduction over Raney nickel under the conditions described for the reduction of 1,6:3,4-dianhydro-2-O-tosyl-β-D-galactopyranose [1]. From 0.63 g of (III) we obtained 0.47 g (98%) of (IV), mp 92-94° (from alcohol); $[\alpha]_D^{20}$ −40° (C 2.0, $CHCl_3$); cf. [1]. Found: C 52.37; H 5.31; S 10.35%. $C_{13}H_{16}O_6S$. Calculated: C 51.99; H 5.37; S 10.65%.

3-Desoxylevoglucosan

The starting 1,6-anhydro-2-O-tosyl-4-O-benzyl-β-D-glucopyranose (VI) was obtained by the treatment of (I) with benzyl alcohol in the presence of p-toluenesulfonic acid as described in [10].

1,6-Anhydro-2,3-di-O-tosyl-4-O-benzyl-β-D-glucopyranose (VII) was obtained from (VI) by tosylation in pyridine, the same as the preparation of 1,6-anhydro-2,3-di-O-tosyl-4-desoxy-β-D-xylohexopyranose from 1,6-anhydro-2-O-tosyl-4-desoxy-β-D-xylohexopyranose [1]. The obtained sirup failed to crystallize; yield 90%. Based on the TLC data (system A), the compound is pure. Found: C 57.96; H 5.08; S 11.34%. $C_{17}H_{28}O_9S_2$. Calculated: C 57.80; H 5.05; S 11.42%.

1,6:2,3-Dianhydro-4-O-benzyl-β-D-allopyranose (VIII). Similar to the preparation of 1,6:2,3-dianhydro-4-desoxy-β-D-ribohexopyranose [1], (VIII) was synthesized by the treatment of (VII) with CH_3ONa. The obtained sirup crystallized on standing in a vacuum-desiccator. Recrystallization from alcohol gave the product in 46% yield and mp 74-75°; $[\alpha]_D^{20}$ −121° (C 0.5, $CHCl_3$); cf. [11].

1,6-Anhydro-4-O-benzyl-3-desoxy-β-D-ribohexopyranose (IX). Compound (IX) was obtained by the reduction of 1,6:2,3-dianhydro-4-O-benzyl-β-D-allopyranose (VIII) with $LiAlH_4$ under the conditions indicated for 2,3-anhydro-β-D-methylriboside [14], but the reaction time was increased to 5 h. The reaction mixture was worked up to give a hygroscopic crystalline substance, which, based on the TLC data (system A), was pure. The yield of crude product was 78%. After recrystallization from ether, mp 57-58°; $[\alpha]_D^{20}$ −76.4° (C 0.87, $CHCl_3$). Found: C 65.63; H 6.81%. $C_{13}H_{16}O_4$. Calculated: C 65.90; H 7.06%.

1,6-Anhydro-3-desoxy-β-D-ribohexopyranose (X). A solution of 0.5 g of (IX) in 10 ml of alcohol was subjected to hydrogenolysis on 10% Pd/C at atmospheric pressure for 24 h. After filtration and evaporation we obtained a hygroscopic crystalline substance in 83% yield, which, based on the TLC data (system B), was pure, $[\alpha]_D^{20}$ −76° (C 0.94, alcohol), cf. [2]. Found: C 49.84; H 6.87%. $C_6H_{10}O_4$. Calculated: C 49.31; H 6.84%.

2-Desoxylevoglucosan

1,6:2,3-Dianhydro-4-O-benzyl-β-D-mannopyranose (XI). Obtained in the same manner as 1,6:2,3-dianhydro-4-O-tritylmannopyranose [5] by treating (VI) with CH_3ONa in alcohol under reflux. The yield of the sirupy reaction product was ~100%. Based on the TLC data (system A), the compound is pure. After a double recrystallization from methanol we obtained a crystalline compound in 75% yield, mp 65-66°, $[\alpha]_D^{20}$ −23.5° (C 1.5, $CHCl_3$), cf. [12].

β-1,6-Anhydro-2-desoxy-D-arabinohexopyranose (XII). Compound (XII) was obtained by opening the α-oxide ring in (XI) with $LiAlH_4$ under the conditions described for 2,3-anhydro-β-D-methylriboside [14] and subsequent hydrogenolysis of the benzyl group. The product obtained in the first step was a sirup that crystallized on standing; yield 75%. Based on the TLC data (system B), the compound is pure. Hydrogenolysis gave a hygroscopic crystalline product in 99% yield. Based on the TLC data (system B), and the GLC data for its acetate, the compound is pure. When (XII) was chromatographed on paper it was developed by sprinkling with $NaIO_4$ solution, and then with an acid solution of p-nitroaniline, or else with $NaIO_4$ solution, and then with an acetone solution of $AgNO_3$ and alcoholic NaOH solution. The hydrolysis of (XII) with 1 N HCl solution at 110° for 1 h, followed by paper chromatography (system E) and TLC (system B), gave a product that was identical with 2-desoxyglucose. Product (XII) was passed through a silica gel column (system D); yield 60%. After a double recrystallization from ethyl acetate and drying, mp 145-150°; $[\alpha]_D^{20}$ −116° (C 1.23, H_2O), cf. [3]. Found: C 49.36; H 6.91%. $C_3H_{10}O_4$. Calculated: C 49.31; H 6.84%.

CONCLUSIONS

1. A study was made of the nucleophilic replacement of the hydroxyl groups in the partial tosyl esters of levoglucosan by treatment with triphenyl phosphite methiodide. When β-1,6-anhydro-2-O-tosyl-D-glucopyranose is reacted with this reagent the reaction goes selectively to give 4-iodo-4-desoxy-2-O-tosyl-β-D-1,6-anhydrogalactopyranose.

2. The 3- and 2-desoxy derivatives of levoglucosan were synthesized by opening the α-oxide rings in 4-O-benzyl-β-1,6:2,3-dianhydro-D-allopyranose and 4-O-benzyl-β-1,6:2,3-dianhydro-D-mannopyranose with aluminium lithium hydride.

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