BENZENEBORONIC ESTERS OF 1,6-ANHYDRO SUGARS

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ABSTRACT

Benzeneboronic acid reacts with 1,6-anhydro sugars to form cyclic boronic esters. The structures of these compounds have been established by chemical methods and found to be generally similar to those of the corresponding isopropylidene derivatives. However, 1,6-anhydro-β-D-glucopyranose, which lacks vicinal *cis*-hydroxyl groups, still forms a benzeneboronate.

INTRODUCTION

The interaction of boric acid with carbohydrate compounds, in aqueous solutions, is well known[1–3] and is extensively employed for conformational studies and separation of sugar derivatives by column chromatography[4] and ionophoresis[5]. However, with a few exceptions[6–8], the reaction has been detected by changes in such physical properties as optical rotation and electrical conductivity, rather than by the isolation of crystalline products. This is in sharp contrast to the reaction of benzeneboronic acid with sugar derivatives, under dehydrating conditions, which provides crystalline compounds[9,10]. These compounds are useful as synthetic intermediates[11,12], for crystallization, and for isolation of sugar derivatives[13–17].

We now report on the reaction of benzeneboronic acid with several 1,6-anhydro sugars.

RESULTS AND DISCUSSION

Under dehydrating conditions, benzeneboronic acid reacts with 1,6-anhydro-β-D-glucopyranose and other 1,6-anhydro sugars to provide the crystalline, cyclic boronic esters listed in Table I. These esters were generally stable in non-polar solvents but are readily hydrolyzed in water. However, further investigations indicated that the stability of a benzeneboronic ester and its utility as a protective group depends on the structure of the molecule. There was a considerable difference in the behaviour

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of 1,6-anhydro-β-D-glucopyranose benzeneboronate and the esters of other anhydro sugars investigated.

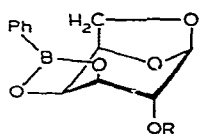
TABLE I

BENZENEBORONIC ESTERS OF 1,6-ANHYDROHEXOPYRANOSES

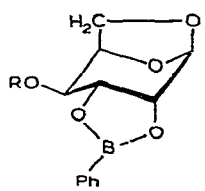
Ester	*Yield* (%)	*M.p.* (*degrees*)	$[\alpha]_D^{25}$ (*degrees*)	*Found* (%)		*Calc.* (%)	
				C	*H*	*C*	*H*
1,6-Anhydro-β-D-glucopyranose 2,4-benzeneboronate	90.0	122–124	−70.4	57.92	5.32	58.10	5.29
1,6-Anhydro-β-D-galactopyranose 3,4-benzeneboronate	68.3	169–170	−114	57.95	5.17	58.10	5.29
1,6-Anhydro-β-D-gulopyranose 2,3-benzeneboronate	72.8	212–216	+43.7	57.78	5.20	58.10	5.29
1,6-Anhydro-β-D-mannopyranose 2,3-benzeneboronate	65.1	149–150	−104.9	58.03	5.14	58.10	5.29
1,6-Anhydro-β-D-altropyranose 3,4-benzeneboronate	81.9	166–167	−129.6	58.21	5.22	58.10	5.29

1,6-Anhydro-β-D-galactopyranose benenzeboronate (**1**) was stable in pyridine and gave a monotoluene-*p*-sulfonate (**2**) in good yield. The positions of the benzeneboronic ester and the tosyl group were determined as follows.

Conversion of 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose[18] into the 2-toluene-*p*-sulfonate, followed by replacement of the isopropylidene group with benzeneboronic acid, gave ester **2**, indicating that benzeneboronic acid reacts with the vicinal *cis*-hydroxyl groups in the anhydro sugar to give **1**.



1 R = H
2 R = Ts



3 R = H
4 R = Ts

A similar sequence of reactions was applied to 1,6-anhydro-β-D-mannopyranose to show that the benzeneboronic acid had again reacted with vicinal *cis*-hydroxyl groups to give the 2,3-benzeneboronate. In both of the above cases, participation of other hydroxyl groups in the reaction is not very likely. However, for 1,6-anhydro-β-D-altropyranose, the pair of equatorial *trans*-hydroxyl groups at C-2 and C-3 provides a possible alternative to the vicinal *cis*-hydroxyl groups at C-3 and C-4; investigation of the reaction products by g.l.c. after trimethylsilylation indicated the presence of the 2,3- and 3,4-benzeneboronates in the ratio of 1:10. The major product (82% yield) was shown to be the 3,4-benzeneboronate by a reaction sequence similar to that used for the *galacto* and *manno* analogues.

Application of the above scheme to 1,6-anhydro-β-D-gulopyranose presented

major problems, partly because few derivatives of this sugar are known and partly because of the hindered nature of HO-4 as a result of the proximity of the 1,6-anhydro ring. Richtmyer[19] found that a ditoluene-*p*-sulfonate is readily formed from 1,6-anhydro-β-D-gulopyranose, but tosylation of the third hydroxyl group proceeds very slowly and requires considerable excess of reagent. In this study, benzeneboronic acid reacted readily with 1,6-anhydro-β-D-gulopyranose, but the crystalline reaction product **3** could not be tosylated under the standard conditions (2 mol. of *p*-tolylsulfonyl chloride). However, with a five-fold excess of reagent, the toluene-*p*-sulfonate **4** was obtained. The position of the tosyl group at position 4 was established by hydrolysis of the benzeneboronate and periodate oxidation of the resulting diol. Reduction of the dialdehyde formed, followed by hydrolysis of the product, gave glycolaldehyde (identified as the 2,4-dinitrophenylosazone), indicating that the tosyl group must have been at C-4 and the benzeneboronic ester at C-2 and C-3.

To our knowledge, an isopropylidene derivative of 1,6-anhydro-β-D-glucopyranose has not been obtained[18], presumably because of the lack of vicinal *cis*-hydroxyl groups in the semi-rigid structure. However, benzeneboronic acid (having a planar, trigonal structure) readily reacts with 1,6-anhydro-β-D-glucopyranose to provide a cyclic benzeneboronate. Theoretically, the anhydride could react in the *1C*(D) chair conformation to form a 2,4-cyclic ester or in the boat conformation (*B3*) to form either a 2,3- or a 3,4-benzeneboronate. Unfortunately, the benzeneboronate was not sufficiently stable in pyridine to allow the synthesis of any derivative that could be used for structural determination. However, based on analogy with methyl α- and β-D-xylopyranoside 2,4-benzeneboronate and the general preference of the sugar for reacting in the *1C*(D) conformation[20–23], the derivative tentatively is considered to be the 2,4-benzeneboronate.

In contrast to the other benzeneboronic esters described above, the 1,6-anhydro-β-D-glucopyranose derivative was unstable under the conditions of trimethylsilylation, and g.l.c. of the reaction product revealed only the anhydride [as the tris(trimethylsilyl) ether]. The instability of this benzeneboronate may be attributed to the formation of a six-membered ring, which contrasts with the formation of five-membered rings by the other anhydro sugars. However, other reasons must be involved, because methyl α- and β-D-xylopyranoside 2,4-benzeneboronates are stable in pyridine and can be used for the synthesis of monosubstituted derivatives[11].

One of the original objectives of this investigation was to find a convenient method for isolation of 1,6-anhydro-β-D-glucopyranose from the pyrolysis products of cellulose[24] and starch[25]. However, although the tarry materials obtained (44% yield) from the pyrolysis of starch contained 69% of the anhydride (g.l.c.), which reacted quantitatively with benzeneboronic acid, the pure benzeneboronate could not be isolated.

EXPERIMENTAL

General. — Reagents were dried and distilled before use. Solutions were concentrated *in vacuo* with bath temperatures no higher than 50°. Melting points (Fisher–

Johns apparatus) are uncorrected. G.l.c. was carried out with a Varian Model 1800 instrument (equipped with dual flame-ionization detectors and columns containing 3% SE-30 on Varaport) connected to a Varian Model 475 digital integrator; the column temperature was programmed from 100–200° at a rate of 8°/min.

Benzeneboronate derivatives[11]. — A mixture of 1,6-anhydro-β-D-altropyranose (0.6174 g), benzeneboronic acid (1.0598 g) and benzene was heated under reflux, and water was removed with a Dean and Stark apparatus. After the reaction was complete (*ca.* 6 h), the solvent was removed and 1,6-anhydro-β-D-altropyranose 3,4-benzeneboronate was recrystallized from benzene–petroleum ether. This procedure was also applied to several other 1,6-anhydro sugars. The products obtained are listed in Table I.

*Toluene-*p*-sulphonates of the benzeneboronate derivatives.* — (*a*) Tosylation was carried out by dissolving the boronic esters in dry pyridine at 0° (20 ml/g of ester) and adding a two-fold excess of *p*-tolylsulfonyl chloride. After 3 days, the pyridine was removed, and the syrup was extracted with dry benzene. The material left after evaporation of the solvent was recrystallized from benzene–petroleum ether. This procedure was used for all the anhydro sugars except 1,6-anhydro-β-D-gulopyranose, where it was necessary to use a five-fold excess of *p*-tolylsulfonyl chloride to obtain the monosulfonate. The yield and physical constants for the tosylated products are given in Table II.

TABLE II

TOSYL DERIVATIVES OF THE BENZENEBORONIC ESTERS

Tosyl derivative	*Yield* (%)	*M.p.* (*degrees*)	$[\alpha]_D^{25}$ (*degrees*)	*Found* (%)		*Calc.* (%)	
				C	*H*	*C*	*H*
1,6-Anhydro-2-*O*-tosyl-β-D-galactopyranose 3,4-benzeneboronate	47.7	135–136	+50.0	56.74	4.74	56.73	4.76
1,6-Anhydro-4-*O*-tosyl-β-D-gulopyranose 2,3-benzeneboronate	13.8	140–141	+83.9	57.20	4.71	56.73	4.76
1,6-Anhydro-4-*O*-tosyl-β-D-mannopyranose 2,3-benzeneboronate	84.3	157–158	−104	56.84	4.67	56.73	4.76
1,6-Anhydro-2-*O*-tosyl-β-D-altropyranose 3,4-benzeneboronate	63.1	173–175	−112	57.15	4.76	56.73	4.76

(*b*) The isopropylidene derivatives of 1,6-anhydro-β-D-galactopyranose[18], β-D-mannopyranose[26], and β-D-altropyranose[27] were prepared and tosylated by the literature procedures. Each sulphonate was treated with 0.1M hydrochloric acid to remove the isopropylidene group, and the resulting, crystalline monosulfonate was treated with benzeneboronic acid by the procedure described earlier. The products were identical with the corresponding compounds prepared in (*a*).

Periodate oxidation of 1,6-anhydro-4-O-tosyl-β-D-gulopyranose. — Sodium metaperiodate (79.7 mg) was dissolved in a methanol–water solution (1:4) containing 29.9 mg of 1,6-anhydro-4-*O*-tosyl-β-D-gulopyranose. After 48 h, the excess of perio-

date was removed, and the product was reduced and hydrolyzed[28]. The hydrolysate was added to 30 ml of 0.5M hydrochloric acid containing 50 mg of 2,4-dinitrophenylhydrazine. This gave a flocculent, yellow precipitate that was identified as glyoxal bis(2,4-dinitrophenylhydrazone) by t.l.c.[29] and u.v. spectroscopy[30].

Preparation of 1,6-anhydro-β-D-glucopyranose from the pyrolysis of starch. — Starch was pyrolyzed[31], and the crude, viscous distillate was extracted with methanol and concentrated under reduced pressure. A sample of the concentrated residue was trimethylsilylated and analyzed by g.l.c. using D-glucitol as an internal standard. This showed the presence of 69% of 1,6-anhydro-β-D-glucopyranose and other materials. The pyrolysis product was treated with benzeneboronic acid under dehydrating conditions. The crude, crystalline benzeneboronate could not be purified by repeated crystallization from petroleum ether–benzene.

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