

## Preparation and Stability Studies of Cyclic Boronate Derivatives of Functionally Diverse Catechols

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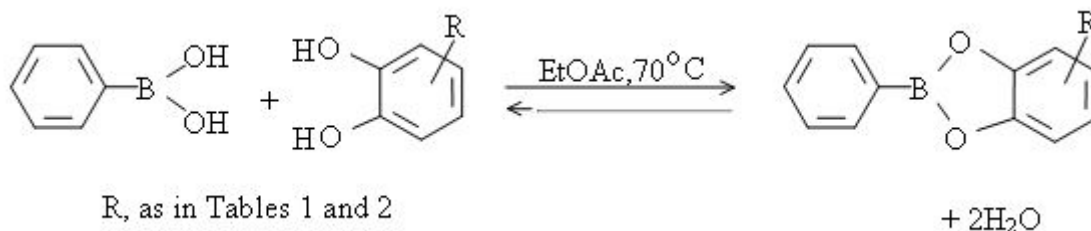
**Abstract:** Stable crystalline benzeneboronate derivatives of catecholic carboxyl methyl esters, N-acetyldopamine, coumarin and catechol estrogens were prepared in high yield. While related catechol compounds with extra polar functional group(s) (OH, NH<sub>2</sub>) did not form or partially formed unstable cyclic boronate derivatives.

**Keywords:** *Cyclic benzeneboronate, Catechols, Stability*

### Introduction

Selective reactions of boronic acids with compounds containing two or more suitably disposed proximal polar functional groups (OH, NH, SH, COOH) can afford cyclic derivatives of reduced polarity, of value in analytical characterisation and in separation of polyfunctional compounds. Crystalline benzeneboronates from the reactions of benzeneboronic acid with polyols [1], sugars [2,3], other carbohydrates [4,5,6], macrolide aglycones [7] and steroids[8] have been isolated and characterised. Depending on the substrates, the condensations could take place in aqueous and aqueous-methanol solutions [1], organic solvent [4], reactions by fusion techniques, or by reaction in anhydrous solvents followed by removal of water azeotropically [3]. By virtue of the high molecular weight and comparative rigidity of the areneboronic acids, the corresponding boronates are in general easier to crystallise than those derived from aliphatic boronic acids. A variety of cyclic boronates stable to hydrolysis has been studied by reversed-phase liquid chromatography (HPLC) [9].

In the present work I focused on the formation and stabilities of cyclic boronate esters of various types of biologically important catechols (Scheme 1). Several crystalline cyclic boronate esters of catechols type: 3,4-dihydroxy methyl esters [1-4]; N-acetyl-dopamine [5], estra-1,3,5(10)-triene-2,3- and -3,4-diols [6,7] and 4-methyl-7,8-dihydroxy coumarin [8] were obtained.



Scheme 1: Typical reaction of benzenboronic acid with catechols

## Results and Discussion

The compounds in Table 2, were readily prepared under neutral conditions in EtOAc at 70 oC, resulted from the spontaneous reactions of 0.1 molar excess of benzeboronic acid with the catechol groups as compounds [1-8], Table 1 .

The recovered crude yields of the cyclic boronates were high (84-99.8%). The esters were stable in anhydrous non-hydroxylic organic solvents (e.g. EtOAc, pyridine, hexane, toluene) and towards aerial oxidation to some extent and atmospheric moisture and remained stable on storage. However, they were unstable on Thin-layer chromatography (TLC) or on 'dry column' silica gel chromatography, undergoing disassociation with subsequent partial oxidation.

The Infra Red [IR] spectra of the cyclic boronate derivatives of compounds [1-8] exhibited two characteristic bands, for B-O and Ph-O absorption in the regions 1325-1380cm<sup>-1</sup> and 1390-1455cm<sup>-1</sup>, respectively. The other bands were characteristic for the remaining functional groups of the listed compounds [3,6,10].

The cyclic boronate derivatives of the compounds listed in Table 2 showed characteristic <sup>1</sup>H NMR chemical shifts for the five aromatic protons of the phenyl group bonded directly to the boron atoms [11,12]. The two proton ortho to the boron atom are deshielded, and resonated at δ 7.16-8.87; the two meta protons resonated at higher field, in the region δ 6.56-7.63; whilst the single para proton resonated at δ 7.26-7.98. The corresponding protons in the catechol boronate unit appeared in the region δ 6.91-7.96[12-16], as shown in Table 2.

The Gas Chromatography-Mass Spectrometre [GC-MS] results shown in Table 1, showed molecular ions as the base peaks for all the boronate esters, except for compounds [2] (97%) and [5] (6%).

Methyl 2,3-dihydroxybenzoate; 2,3-dihydroxybenzaldehyde; 2,3,4-trihydroxy-acetophenone; dopamine; 3-(3,4-dihydroxy-phenyl)-L-alanine methyl ester; α-propyl-dopacetamide; 3,4-dihydroxy- -(isopropyl-amino)acetophenone; salsolinol; 3,4-di-hydroxynomifensine; apomorphine; N-n-propylnorapomorphine and 2-hydroxy-estradiol; these compounds formed the cyclic boronate esters, as judged by GC-MS, but these

products were not stable and can not be isolated or purified, due to hydrolysis followed by arial oxidation at ambient temperature. 3,4-Dihydroxy- $\alpha$ -hydroxyphenylacetic acid, tetrahydroxy-terephthalic acid diethyl ester, brazilin and gossypol did not yield cyclic boronate derivatives either on an analytical or preparative scale. For some of these compounds, the failure to form stable cyclic boronates may reflect either additional polar functionality or may be due to a reduction in reactivity arising from the strong inter-molecular hydrogen bonding to the catechol hydroxyl groups.

### **Materials and methods**

The reagents were obtained from British Drugs House (BDH) except benzenboronic acid from Koch-Light Labs. Ltd. The substrates were obtained from Fluka, BDH, Sigma Chemicals Co., Aldrich Chem. Co., Koch-light Labs. Ltd., Makor and the rest from Professor C.J.W. Brooks (Glasgow University). The Infra Red (IR) spectra were measured on a Perkin-Elmer Grating Infra Red Spectrophotometer Model 257. The conditions and methods used for the Nuclear Magnetic Resonance (NMR) and GC-MS are noted at the footnotes of Table 1. Mass spectra (direct insertion probe) were measured on a VG MICROMASS 2S8 instrument. Melting points (m.p.) were recorded on a Kofler block.

### **Experimental section**

The typical procedure for the preparation of benzenboronate derivatives is exemplified below:-

Methyl 3,4-dihydroxydihydrocinnamate 3,4-benzenboronate [11]: Methyl 3,4-dihydroxy-dihydrocinnamate [3] (0.5 g: 2.5 mmole) was dissolved in EtOAc (5 ml); benzenboronic acid (0.317 g: 2.6 mmole) in EtOAc (2ml) was added, and the reaction mixture heated for 20 min at 70 °C. After removal of the solvent, the gummy product was dissolved in ether. Evaporation of the solvent with nitrogen yielded crystalline material (680mg: 95%), m.p. 60-62 °C. Gas liquid chromatography (GLC) showed a single well-defined peak. Vacuum sublimation yielded fine white crystals, m.p. 61-62 °C. For analytical data and Mass Spectrometre (MS) are as in Table 1.

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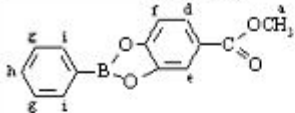
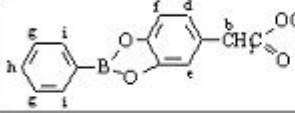
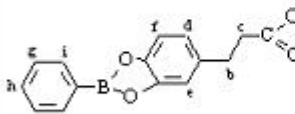
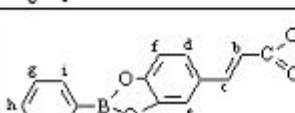
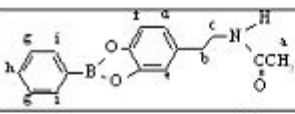
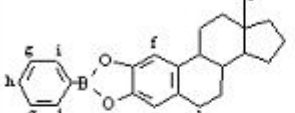
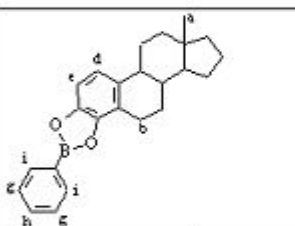
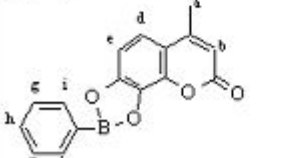
Table 1. Preparative benzeneboronate derivative formation from catechol type compounds

Parent compound	Compound No.	Amount used mg (mmole)	Benzeneboronic acid mg (mmole)	Data corresponding benzeneboronates					
				Amount recovered mg* (% crude yield)	m.p. °C	Mol. Formula (Mol. Wt)	Analysis		MS
							Found	Calc.	M <sup>+</sup> (%) <sup>b</sup>
Methyl 3,4-dihydroxybenzoate <sup>a</sup>	1	831 (4.50)	629.5 (5.15)	1050 (84)	109.5-110.5 <sup>d</sup>	C <sub>11</sub> H <sub>11</sub> BO <sub>4</sub> (254)	C, 65.90 H, 4.23 B, 4.78	C, 66.14 H, 4.33 B, 4.3	254 (100)
Methyl 3,4-dihydroxyphenylacetate	2	300 (1.65)	203 (1.67)	400 (90.4)	82-83 <sup>e</sup>	C <sub>11</sub> H <sub>11</sub> BO <sub>4</sub> (268)	C, 67.20 H, 4.95 B, 3.8	C, 67.16 H, 4.85 B, 4.1	268 (97)
Methyl 3,4-dihydroxydihydrocinnamate	3	500 (2.55)	317 (2.6)	680 (95)	61-62 <sup>f</sup>	C <sub>11</sub> H <sub>11</sub> BO <sub>4</sub> (282)	C, 68.24 H, 5.38 B, 3.83	C, 68.09 H, 5.32 B, 3.9	282 (100)
Methyl 3,4-dihydroxycinnamate	4	263 (1.36)	170 (1.39)	349 (92)	131-133 <sup>f</sup>	C <sub>11</sub> H <sub>11</sub> BO <sub>4</sub> (280)	C, 68.7 H, 4.35 B, 4.01	C, 68.57 H, 4.64 B, 4.0	280 (100)
N-Acetyltopamine	5	977 (5.01)	612 (5.02)	1405 (99.8)	159-160 <sup>h</sup>	C <sub>11</sub> H <sub>11</sub> BNO <sub>3</sub> (281)	C, 68.0 H, 5.90 B, 4.11 N, 5.06	C, 68.33 H, 5.69 B, 3.90 N, 4.98	281 (6)
Estra-1,3,5(10)-triene-2,3-diol	6	22 (0.08)	10 (0.08)	28 (96)	244-247 <sup>i</sup>	C <sub>21</sub> H <sub>17</sub> BO <sub>2</sub> (358)	j		358 (100)
Estra-1,3,5(10)-triene-3,4-diol	7	22 (0.08)	10 (0.08)	28 (96)	176-177 <sup>j</sup>	C <sub>21</sub> H <sub>17</sub> BO <sub>2</sub> (358)	C, 80.42 H, 7.34	C, 80.45 <sup>k</sup> H, 7.54	358 (100)
4-Methyl-7,8-dihydroxy coumarin <sup>l</sup>	8	260 (1.35)	165 (1.35)	370 (98.4)	191-193 <sup>m</sup>	C <sub>11</sub> H <sub>11</sub> BO <sub>4</sub> (278)	m		278 (100)

### Footnotes:- Table 1

- <sup>a</sup>GLC analysis of these crude products showed in each case a single peak corresponding to their benzenboronate derivatives. Traces of excess benzenboronic acid (eluted as triphenylboroxine) were also observed.
- <sup>b</sup>Mass spectra were recorded at electron energy 20 eV, using an LKB 9000 GC-MS instrument, fitted with a glass column (2m x 4mm, i.d.) of 1% OV-1 on Gas Chrom Q (100-120 mesh). The flash heater was at 250 oC, the molecular separator at 270 oC, and ion source at 265 oC. The helium carrier gas flow rate was 30 ml/min. The trap current was 60 mA, filament current 4A and accelerating voltage 3.5 KV. In Table I the abundances for the ion are shown in brackets ( ).
- <sup>c</sup>The isomeric methyl 2,3-dihydroxybenzoate did not react fully with benzenboronic acid, as judged by GLC. On recrystallisation of the crude reaction mixture, from acetone-hexane; the recovered material was largely benzenboronic acid. Vacuum sublimation of the crude product, also failed to yield any cyclic ester.
- <sup>d</sup>Recrystallisation from acetone-hexane; m.p. 107-108.5o; then vacuum sublimation: yield a middle fraction which was collected.
- <sup>e</sup>Vacuum sublimation at 55o/0.01 torr.
- <sup>f</sup>Vacuum sublimation at 55o/0.01 torr, yielded fine white crystals.
- <sup>g</sup>Recrystallisation from acetone-hexane; m.p. 125-127o; then followed by vacuum sublimation; a middle fraction was collected.
- <sup>h</sup>Vacuum sublimation at 130o/torr; m.p. 157-160o, a second sublimation yielded fine white crystals.
- <sup>i</sup>Vacuum sublimation at 140o/0.01 torr; yielded a viscous gum, which failed to crystallise from acetone, EtOAc or hexane. Trituration in hexane at low temperature yielded a semi-solid product, which crystallised on standing. GC showed traces of benzenboronic acid.
- <sup>j</sup>A satisfactory micro-analysis was not obtained for this compound.
- <sup>k</sup>Recrystallisation from acetone; then vacuum sublimation at 160o/0.01 torr. The sublimed material was recrystallised twice from actone. High resolution MS, C<sub>24</sub>H<sub>27</sub>BO<sub>2</sub>, requires 358.2810; found 358.2104.
- <sup>l</sup>The isomeric 4-methyl-6,7-dihydroxy coumarin benzenboronate was formed and showed GC-MS peak with M<sup>+</sup> 278(100) but attempts to isolate pure crystals were unsuccessful.
- <sup>m</sup>Two recrystallisation from CHCl<sub>3</sub>-hexane, then vacuum sublimation at 140o/0.01 torr, gave a middle fraction which was recrystallised from EtOAc-hexane. GLC analysis for this product showed the presence of ca. 0.1% of benzenboronic acid: the micro-analysis was not satisfactory for carbon. High resolution MS, C<sub>16</sub>H<sub>11</sub>BO<sub>4</sub>, requires 278.072; found 278.075.

Table 2. <sup>1</sup>H NMR, characteristics proton chemical shifts ( = ppm), of the catechol types benzeneboronate derivatives. Data measured in CDCl<sub>3</sub> + 0.4% tetramethylsilane, (400 MHz)a.

Compound	No.	a	b	c	d	e	f	g	h	i
	9	3.86 s	-	-	7.91 dd	7.97	6.89 d	7.54 m 2H	7.57 m 1H	8.08 m 2H
	10	3.70 s	3.66 s	-	7.14 dd	7.24	7.22 d	7.54 m 2H	7.57 m 1H	8.06 m 2H
	11	3.68 s	3.01 q	2.66 q	6.97 dd	6.72 d	6.78 d	7.47 m 2H	7.58 m 1H	8.07 m 2H
	12	3.77 s	6.24 d	5.56 d	6.99 dd	7.05 d	6.85 d	7.63 m 2H	7.56 m 1H	8.17 m 2H
	13	1.96 s	2.87 t	3.54 q	6.91 dd	7.13 d	7.26 d	7.49 m 2H	7.58 m 1H	8.08 m 2H
	14	0.91 s	2.87 m	-	-	6.58		6.56 m 2H	7.26 m 1H	7.16 m 2H
	15	0.76 s	2.88 m	-	7.09 ABq		-	7.48 m 2H	7.55 m 1H	8.09 m 2H
	16	2.33	6.09	-	6.99	7.36	-	7.69 m 2H	7.96 m 1H	8.03 m 2H

<sup>a</sup> JEOL, ND6-LA400, FT NMR SYSTEM