

## 2-(6-Bromopyridin-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and (6-bromopyridin-3-yl)boronic acid, new bifunctional building blocks for combinatorial chemistry

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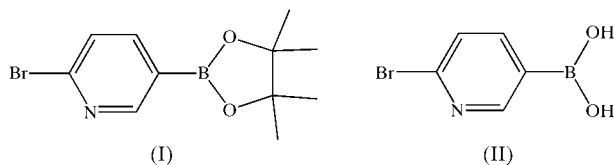
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The first comparative study between two new heterocyclic boron derivatives, *viz.* a (6-bromopyridin-3-yl)boronic ester,  $C_{11}H_{15}BBrNO_2$ , and (6-bromopyridin-3-yl)boronic acid,  $C_5H_5BBrNO_2$ , shows a small but not significant difference in their C—B bond lengths, which cannot explain the experimentally observed difference in their stabilities. The crystal packing of the boronic ester consists principally of van der Waals interactions, while the boronic acid molecules interact in their crystal through hydrogen bonds.

### Comment

For the past few years, we have been focusing on a general method for the synthesis of new pyridinylboronic acids and esters of use in combinatorial approaches, with the aim of obtaining mild and flexible strategies for the design of new pyridine libraries. In particular, we have concentrated on the synthesis of new (halopyridinyl)boronic acids and esters likely



to offer double reactivity, *via* their boronic acid moiety and their halogen atom. We have recently published a very efficient and general method for the synthesis and isolation of novel (6-halopyridin-3-yl)boronic acids and esters (Bouillon *et al.*, 2002a). In this paper, the crystal structure of 2-(6-bromopyridin-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (I), is described. Even though the structure of (6-bromopyridin-3-yl)boronic acid, (II), has already been solved (Parry *et al.*, 2002), we report this structure here also, as solved in our laboratory, in order to make a comparison between the

tetramethylethylene ester and its corresponding acid. The structural data for (6-halopyridin-3-yl)boronic acid are not available in the Cambridge Structural Database (CSD, Version 5.23; Allen, 2002) at the time of writing.

Figs. 1 and 2 show views of the asymmetric units of the ester, (I), and the acid, (II), respectively. The asymmetric unit consists of one molecule for each compound.

The five-membered ring in (I) is in a half-chair conformation and its best plane is oriented approximately coplanar to the pyridine ring, at an angle of 2.6 (3)°. The deviation of the  $BO_2$  group from a coplanar arrangement with respect to the pyridine ring is about 6.5 (6)° in (I), compared with 10.5 (5)° in (II). The greater deviation in (II) most probably results from crystal-packing interactions. In the crystal of (II), the packing is principally mediated by electrostatic interactions (hydrogen bonds), with the molecules grouped into dimers. The two molecules in a dimer are coplanar, facing each other *via* the boronic acid groups (Fig. 3), and they are linked by a pair of symmetry-equivalent  $O2-H2 \cdots O1$  hydrogen bonds (Fig. 3 and Table 3) related by inversion centres. Furthermore, the presence of one hydrogen-bond acceptor, atom N1 in the six-membered ring, allows interaction between neighbouring dimers through another hydrogen bond,  $O1-H1 \cdots N1(1-x, y-\frac{1}{2}, \frac{3}{2}-z)$ . The involvement of O atoms in several hydrogen bonds influences the spatial orientation of the boronic acid group in (II). In contrast, the crystal packing of (I) is mediated principally by van der Waals interactions, and the orientation of the  $BO_2$  group is dictated only by its position in the ester ring.

In (I), a shorter bond length is observed for the C—B bond, with  $C5-B = 1.557$  (6) Å (Table 1), compared with  $C5-B =$

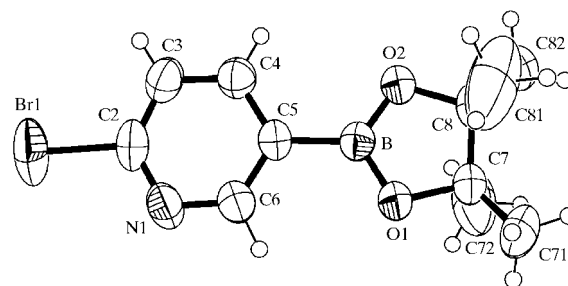


Figure 1

A view of the molecule of the ester, (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small circles of arbitrary radii.

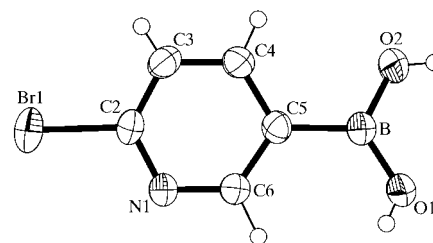
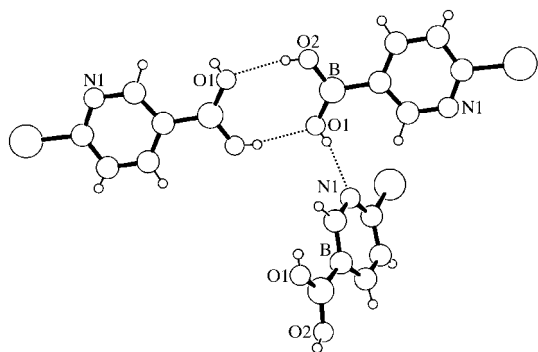


Figure 2

A view of the molecule of the acid, (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small circles of arbitrary radii.



**Figure 3**  
A view of the hydrogen bonds (dotted lines) in the crystal packing of (II).

1.580 (5) Å in (II) (Table 2). Another difference observed in the spatial arrangement of the  $\text{BO}_2$  group concerns the C—B—O bond angles. In (II), a slight asymmetry is observed between these angles (Table 2) which is not detected in (I) (Table 1). The existence of this asymmetry in (II) is probably due to the involvement of the boronic acid group in intermolecular interactions, which is not the case in (I).

In the five-membered ring of (I), an elongation of the displacement ellipsoids in a direction perpendicular to the mean plane of the five-membered ring is observed. This is the result of either static or dynamic conformational disorder, which is not of sufficient magnitude (if static) to permit refinement of separate atoms for the disordered components. The disorder, which is progressively greater as one traverses the ring from B out to the tetramethylethylene fragment, also affects the terminal methyl groups. The individual atomic sites were modelled with anisotropic displacement parameters so as to reproduce correctly the average scattering density in this part of the cell in a manner consistent with such a disorder. The bond distances, especially those involving the methyl C atoms, should be considered 'apparent distances' and it is not recommended that they be used in comparisons with other C—C distances. The C— $\text{CH}_3$  distances (Table 1) differ significantly from the reference value of 1.53 Å (Glusker *et al.*, 1994).

As has already been mentioned, the molecules of (I) interact principally through van der Waals interactions. Dimeric aggregation can be seen in the crystal packing. Two molecules are oriented facing each other *via* their boronic ester groups, related by inversion centres. The intermolecular distances between methyl C atoms are in the vicinity of 4 Å. These dimers interact through weak electrostatic interactions between Br atoms and methyl groups. Strong interactions between the N and B atoms are not observed, either in the crystal packing of the ester, (I), or in that of the acid, (II).

The observed difference between the C—B bond length in the boronic ester and boronic acid is not statistically significant and cannot in itself explain the greater experimentally observed stability of the ester compound with respect to the boronic acid during chemical reactions. We are currently working to characterize other isomers of these pyridinylboronic acid and pyridinylboronate esters, for which we have recently published the syntheses (Bouillon *et al.*, 2002*b,c*).

## Experimental

The title compounds were synthesized from 2,5-dibromopyridine using the method described by Bouillon *et al.* (2002*a*). Suitable crystals of the title ester, (I), and the acid, (II), were obtained by slow evaporation from acetonitrile at room temperature.

### Compound (I)

#### Crystal data

$\text{C}_{11}\text{H}_{15}\text{BBrNO}_2$   
 $M_r = 283.96$   
 Monoclinic,  $P2_1/c$   
 $a = 6.4672$  (4) Å  
 $b = 12.4977$  (10) Å  
 $c = 16.1074$  (8) Å  
 $\beta = 95.024$  (6)°  
 $V = 1296.88$  (15) Å<sup>3</sup>  
 $Z = 4$

$D_x = 1.454$  Mg m<sup>-3</sup>  
 Mo  $K\alpha$  radiation  
 Cell parameters from 25 reflections  
 $\theta = 18\text{--}25^\circ$   
 $\mu = 3.15$  mm<sup>-1</sup>  
 $T = 293$  (2) K  
 Prism, translucent colourless  
 0.60 × 0.44 × 0.36 mm

#### Data collection

Enraf-Nonius CAD-4 diffractometer  
 $\theta/2\theta$  scans  
 Absorption correction: Gaussian (*JANA98*; Petříček & Dušek, 1998)  
 $T_{\min} = 0.241$ ,  $T_{\max} = 0.358$   
 3893 measured reflections  
 3772 independent reflections

1849 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.048$   
 $\theta_{\text{max}} = 30^\circ$   
 $h = -9 \rightarrow 9$   
 $k = 0 \rightarrow 17$   
 $l = 0 \rightarrow 22$   
 3 standard reflections  
 frequency: 60 min  
 intensity decay: 8.1%

#### Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.068$   
 $wR(F^2) = 0.217$   
 $S = 1.02$   
 3772 reflections  
 149 parameters  
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0981P)^2 + 1.1126P]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\text{max}} = 0.001$   
 $\Delta\rho_{\text{max}} = 0.54$  e Å<sup>-3</sup>  
 $\Delta\rho_{\text{min}} = -0.74$  e Å<sup>-3</sup>

**Table 1**

Selected geometric parameters (Å, °) for (I).

C5—B	1.557 (6)	C7—C72	1.638 (11)
B—O1	1.342 (5)	C8—C82	1.459 (9)
B—O2	1.351 (6)	C8—C81	1.626 (11)
C7—C71	1.434 (7)		
O1—B—O2	113.3 (4)	O2—B—C5	123.9 (4)
O1—B—C5	122.8 (4)		

### Compound (II)

#### Crystal data

$\text{C}_5\text{H}_5\text{BBrNO}_2$   
 $M_r = 201.82$   
 Monoclinic,  $P2_1/c$   
 $a = 7.4991$  (9) Å  
 $b = 6.9178$  (5) Å  
 $c = 13.8251$  (15) Å  
 $\beta = 96.574$  (12)°  
 $V = 712.49$  (13) Å<sup>3</sup>  
 $Z = 4$

$D_x = 1.881$  Mg m<sup>-3</sup>  
 Mo  $K\alpha$  radiation  
 Cell parameters from 25 reflections  
 $\theta = 18\text{--}25^\circ$   
 $\mu = 5.70$  mm<sup>-1</sup>  
 $T = 293$  (2) K  
 Prism, translucent colourless  
 0.65 × 0.40 × 0.18 mm

## Data collection

Enraf–Nonius CAD-4 diffractometer	1326 reflections with $I > 2\sigma(I)$
$\theta/2\theta$ scans	$R_{\text{int}} = 0.041$
Absorption correction: Gaussian (JANA98; Petříček & Dušek, 1998)	$\theta_{\text{max}} = 30^\circ$
$T_{\text{min}} = 0.073$ , $T_{\text{max}} = 0.381$	$h = -10 \rightarrow 10$
2150 measured reflections	$k = 0 \rightarrow 9$
2071 independent reflections	$l = 0 \rightarrow 19$
	3 standard reflections
	frequency: 60 min
	intensity decay: 2.4%

## Refinement

Refinement on $F^2$	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.049$	$w = 1/[\sigma^2(F_o^2) + (0.0712P)^2]$
$wR(F^2) = 0.129$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.03$	$(\Delta/\sigma)_{\text{max}} < 0.001$
2071 reflections	$\Delta\rho_{\text{max}} = 0.62 \text{ e } \text{Å}^{-3}$
93 parameters	$\Delta\rho_{\text{min}} = -0.83 \text{ e } \text{Å}^{-3}$

Table 2

Selected geometric parameters (Å, °) for (II).

C5—B	1.580 (5)	B—O1	1.356 (5)
B—O2	1.347 (4)		
O2—B—O1	120.2 (3)	O1—B—C5	123.1 (3)
O2—B—C5	116.7 (3)		

The possibility of disorder of the pyridinyl ring in (I) by a rotation of  $180^\circ$  about the C5—B bond was tested. Only one of the two possible orientations led to a stable refinement, and this is the position described here for (I). A full *PLATON* (Spek, 2003) check indicates small displacement parameters for atom C2 compared with its neighbours. Atom C2 has three neighbouring atoms, viz. C3, N1 and Br1. The displacement parameters of atoms C2, N1 and C3, all part of the pyridine ring, are comparable [ $U_{\text{eq}}(\text{C2}) = 0.0657$ ,  $U_{\text{eq}}(\text{C3}) = 0.0689$  and  $U_{\text{eq}}(\text{N1}) = 0.0709 \text{ Å}^2$ ]. The only significant difference is between the displacement parameters of C2 and Br1, the latter of which is exocyclic [ $U_{\text{eq}}(\text{Br1}) = 0.1081 \text{ Å}^2$ ]. Furthermore, during the refinement, density peaks corresponding to H atoms were observed,

and a density peak was detected in the vicinity of atom C3, but none in the vicinity of atom N1. H-atom parameters were constrained, with C—H distances in the range 0.93–0.96 Å and O—H distances of 0.82 Å.

For both compounds, data collection: *CAD-4-PC Software* (Enraf–Nonius, 1996); cell refinement: *CAD-4-PC Software*; data reduction: *JANA98* (Petříček & Dušek, 1998); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA1004). Services for accessing these data are described at the back of the journal.

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