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9-Ethyl-1,4-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9*H*-carbazole and 6-bromo-9-ethyl-1,4-dimethyl-9*H*-carbazole

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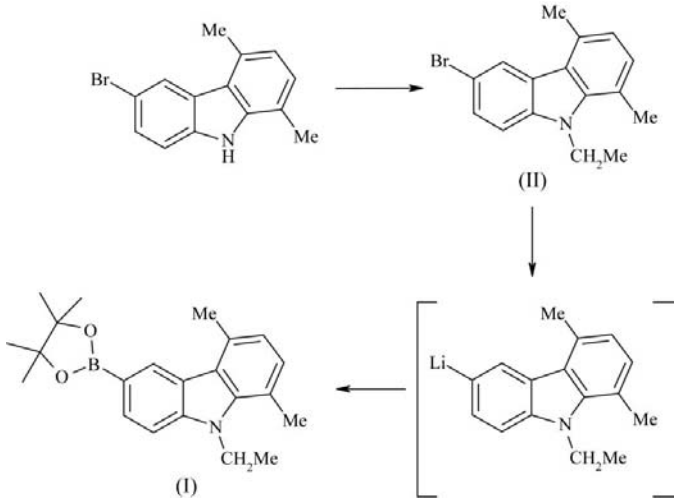
The title carbazolyl boronic ester, $C_{22}H_{28}BNO_2$, (I), is a building block for the synthesis of new carbazole derivatives of potential utility as pharmaceutically active compounds. The crystal structure of (I) and of the title bromocarbazole compound, $C_{16}H_{16}BrN$, (II), the synthetic precursor of (I), were solved and analysed with the aim of understanding the lack of reactivity of (I) under Suzuki cross-coupling reaction conditions. In both structures, the methyl groups are coplanar with the carbazole ring system, and the ethyl group lies out of the carbazole plane. The dioxaborolane ring of boronic ester (I) adopts a half-chair conformation but lies approximately in a planar orientation with respect of the carbazole ring system, whereas the Br atom of (II) is coplanar with the carbazole plane. In (I), the carbazole–boronic ester C—B bond length is 1.5435 (14) Å, which is somewhat shorter than the usual value of 1.57 Å.

Comment

Ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) is a well known alkaloid with antitumor properties, acting as a DNA intercalating agent and inhibiting the activity of topoisomerase II. Many structural modifications of the original molecule have been designed in order to obtain derivatives with a better pharmacological profile. In particular, 9-hydroxyellipticine, Celiptium, has been shown to possess a higher DNA affinity than ellipticine itself, measured on L1210 mice leukaemia, and a lack of toxicity at therapeutic doses (Le Pecq *et al.*, 1974; Searle *et al.*, 1984; Poljakova *et al.*, 2007; Ho & Hsieh, 2006).

We have described recently a general method for the synthesis of 9-alkyl-1,4-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9*H*-carbazoles starting from 9-alkyl-6-bromo-1,4-dimethyl-9*H*-carbazole (Caruso *et al.*, 2007). Using a similar synthesis pathway, we were able to prepare 9-ethyl-1,4-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9*H*-carbazole, (I), from 6-bromo-1,4-dimethyl-9*H*-carbazole, with 6-bromo-9-ethyl-1,4-dimethyl-9*H*-carbazole, (II), as an intermediate product. The crystal structures of the final product (I) and the intermediate (II) are described in this article.



The boronic acids and esters constitute very interesting and reactive intermediates for the preparation of various compounds; for example, they can be used in metal-catalysed reactions of the Suzuki type (Suzuki, 1999; Gérard *et al.*, 2006). Metallo-catalysed cross-coupling chemistry has considerably upset the existing medicinal chemistry strategies, making the majority of classical synthetic pathways obsolete. This generally convergent strategy, which is the source of great diversity, makes possible the synthesis of a wide range of chemical libraries starting from a few valuable scaffolds. In this context, we are interested in the production of boronic compounds which are directly carriers of a potent therapeutic skeleton and have cancerology applications (de Koning *et al.*, 2000). However, the title boronic ester has a lower activity than expected, and we have undertaken the crystal structure analysis of (I) and (II) to find an explanation.

Figs. 1 and 2 show views of the molecules of (I) and (II), respectively. The asymmetric unit of (I) contains one molecule and that of (II) contains two molecules.

Structure analysis showed that the carbazole system is planar in both compounds. The methyl substituents are coplanar with the aromatic rings. The ethyl group lies out of the carbazole plane in both structures. The dihedral angle between the carbazole plane and the plane formed by the ethyl C and carbazole N atoms (C9*A*—N9—C10—C11) is −69.9 (1)° in (I), and thus the ethyl group is oriented 'downwards' with respect to the carbazole plane. In (II), the dihedral angles are 96.2 (3) and 93.7 (3)°, and the ethyl group is oriented 'upwards' with respect to the carbazole ring system.

The dioxaborolane ring of (I) is in a half-chair conformation, with an O1—C14—C15—O2 torsion angle of 30.80 (9)°.

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The BO_2 group is rotated away from the plane of the carbazole ring system by 10.90 (5)°, and the angle between the dioxaborolane ring and the carbazole plane is 16.85 (4)°. The bond length between the carbazole system and the dioxaborolane ring is 1.5435 (14) Å, which is smaller than usual (1.57 Å; Hall, 2005). Thus, it seems that the boron electron deficiency pumps the π electrons from the carbazole ring system, and this could be a reason for the lower reactivity of (I).

The stacking interaction appears to be the principal interaction in the crystal packing of (I). The carbazole ring systems stack in parallel planes, forming columns in the *b*-axis direction. The interplanar spacing is between 3.50 and 3.54 Å.

In (II), the carbazole ring systems stack in parallel planes, forming columns in the *b*-axis direction. The interplanar spacing is 3.50–3.54 Å. Columns in the *b*-axis direction are also formed in (I). However, in this case, each second ring in the column is slipped (in the *a* direction) and the planes of neighbouring carbazole ring systems in the columns are twisted; the angle formed between the planes is about 37°.

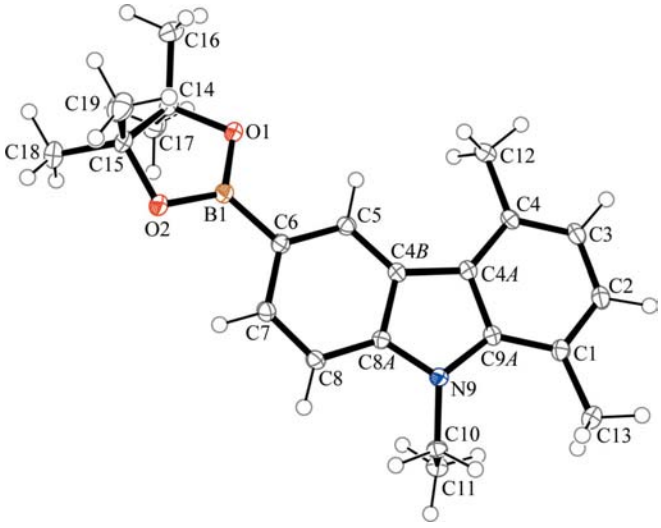

Figure 1
The asymmetric unit of (I), showing the labelling of the non-H atoms. Displacement ellipsoids are shown at the 50% probability level and H atoms are drawn as small circles of arbitrary radii.

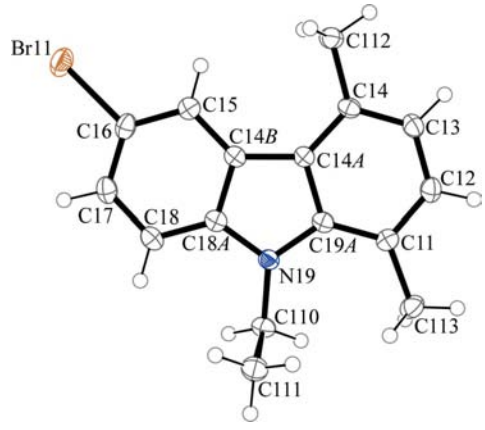

Figure 2
One of the two molecules of the asymmetric unit of (II), showing the labelling of the non-H atoms. Displacement ellipsoids are shown at the 50% probability level and H atoms are drawn as small circles of arbitrary radii.

Experimental

6-Bromo-1,4-dimethyl-9*H*-carbazole was prepared by the reaction of 5-bromoindole (25.0 g, 127.5 mmol) with hexane-2,4-dione (16.79 g, 147.0 mmol) in the presence of *p*-toluenesulfonic acid (18.65 g, 98.0 mmol) in ethanol (300 ml). 6-Bromo-1,4-dimethyl-9*H*-carbazole (2.0 g, 7.3 mmol) in dry dimethylformamide (60 ml) was *N*-ethylated with iodoethane (1.73 ml, 21.9 mmol)/sodium hydride (0.44 g, 10.9 mmol) under standard conditions to give (II). Lithiation–boronation of this intermediate (1.5 g, 4.97 mmol), at very low temperature (183 K), using *n*-BuLi (2.58 ml, 6.46 mmol), triisopropyl borate (1.26 ml, 5.47 mmol) and pinacol (0.59 g, 4.97 mmol) in dry tetrahydrofuran (120 ml), gave (I) after a typical hydrolytic work-up. Transparent crystals of (I) and (II) suitable for X-ray analysis were grown from an acetonitrile solution at room temperature.

Compound (I)

Crystal data

$C_{22}H_{28}BNO_2$
M_r = 349.26
Monoclinic, $P2_1/c$
a = 8.6357 (3) Å
b = 8.1068 (3) Å
c = 28.2057 (9) Å
β = 96.673 (2)°
V = 1961.24 (12) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.07 mm^{-1}
T = 150 (2) K
0.51 × 0.36 × 0.35 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
96221 measured reflections
8529 independent reflections
6728 reflections with $I > 2\sigma(I)$
R_{int} = 0.048

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.143
S = 1.08
8529 reflections
347 parameters
All H-atom parameters refined
$\Delta\rho_{max}$ = 0.59 e Å^{-3}
$\Delta\rho_{min}$ = −0.28 e Å^{-3}

Compound (II)

Crystal data

$C_{16}H_{16}BrN$
M_r = 302.21
Monoclinic, $P2_1$
a = 15.3210 (14) Å
b = 4.6518 (5) Å
c = 18.6647 (17) Å
β = 94.239 (5)°
V = 1326.6 (2) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 3.08 mm^{-1}
T = 150 (2) K
0.41 × 0.36 × 0.34 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
Absorption correction: numerical (*SAINT*; Bruker, 2006)
T_{min} = 0.366, T_{max} = 0.507
32267 measured reflections
9080 independent reflections
7897 reflections with $I > 2\sigma(I)$
R_{int} = 0.033

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.030$	H-atom parameters constrained
$wR(F^2) = 0.067$	$\Delta\rho_{max} = 0.59$ e Å^{-3}
$S = 1.01$	$\Delta\rho_{min} = -0.33$ e Å^{-3}
9080 reflections	Absolute structure: Flack (1983), 3979 Friedel pairs
332 parameters	
1 restraint	Flack parameter: 0.265 (4)

The Flack (1983) parameter for (II) was determined with a BASF/TWIN refinement. For (I), all H atoms were located *via* a difference Fourier map and refined with isotropic displacement parameters [C—H = 0.948 (17)–1.031 (16) Å]. For (II), H atoms were placed in calculated positions and treated as riding on their parent atoms in an ideal geometry (C—H = 0.93–0.97 Å).

For both compounds, data collection: *APEX2* (Bruker, 2006); cell refinement: *APEX2*; data reduction: *SAINT* (Bruker, 2006); program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); 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: SK3248). Services for accessing these data are described at the back of the journal.

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