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A boron-containing estrogen mimic

PAUL D. ROBINSON[a] AND MICHAEL P. GROZIAK[b]

[a]*Department of Geology, Southern Illinois University-4324, Carbondale, IL 62901, USA, and* [b]*Pharmaceutical Discovery Division, SRI International, Menlo Park, CA 94025-3493, USA. E-mail: paul@geo.siu.edu or michael.groziak@sri.com*

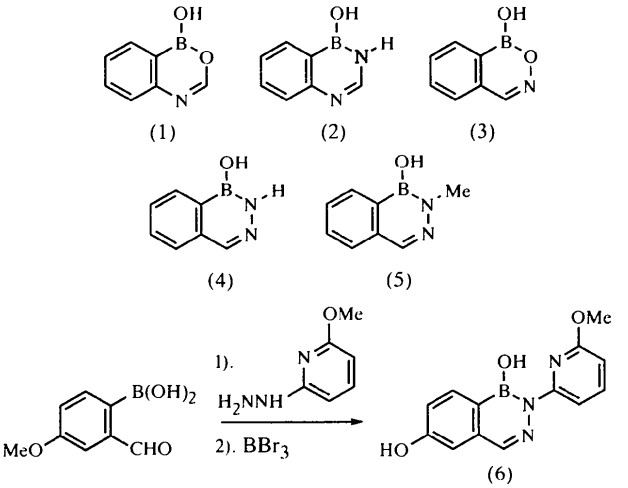
(*Received 19 April 1999; accepted 3 June 1999*)

Abstract

A prototype of a new class of 2,3,1-benzodiazaborine-based estrogen mimics is described. 1,2-Dihydro-1,6-dihydroxy-2-(2-methoxy-6-pyridyl)-2,3,1-benzodiazaborine, (6), was obtained as a crystalline monohydrate ($C_{13}H_{12}BN_3O_3 \cdot H_2O$) after regioselective BBr_3-mediated O-demethylation of the condensation product formed from 2-formyl-4-methoxybenzeneboronic acid and 2-hydrazino-6-methoxypyridine. As intended by design, the solid-state structure of (6) features an intramolecular hydrogen-bond association between the donor B—OH group and the acceptor pyridine ring N, a connection which constitutes an additional 'virtual' six-membered ring, thereby providing for an overall topography closely matching that of a tetracyclic steroid. Specifically, prototype (6) can be viewed as a boron-containing mimic of the O17-methyl ether derivatives of dihydroequilenin or estradiol.

Comment

The well considered placement of a B atom within a molecular framework can generate classes of boron heterocycles that are quite stable to hydrolysis, and thus very useful as new 'platforms' for a biomimicry-based approach to the development of novel classes of bioactive compounds. In the most in-depth investigations of 2,4,1-benzodiheteraborines like (1) and (2) (Groziak *et al.*, 1994) and 2,3,1-benzodiheteraborines like (3) and



(4) (Groziak *et al.*, 1997) yet undertaken, we provided extensive physicochemical characterization data for both classes of heterocycles and clearly documented their hydrolytic stability. Interestingly, heterocycles (1) and (2) are susceptible to a facile, zwitterion-forming 1,4-addition of water and alcohols. The zwitterionic solid-state structure we determined for the bis-methanol adduct of (2) (Groziak *et al.*, 1994) is closely related to those determined more recently for certain indolo-fused 1-hydroxy-2,4,6-triazaborines (Andrade-López *et al.*, 1998). In contrast, (3), (4), and (5) all exist in planar, neutral form in aprotic and protic solvents and also in the solid state (Groziak *et al.*, 1997; Robinson *et al.*, 1998). Variants of (5) which are dialkylated at N2 cannot do so, and form trimeric boroxine solid-state structures instead (Robinson *et al.*, 1996). For the purpose of developing mimics of endogenous and synthetic bioactive compounds, our attention was drawn to the 2-substituted 2,3,1-benzodiazaborines like (5), since it is these boracinnoline heterocycles which are likely the most versatile platforms for new bioactive compound construction. There are already a few classes of bioactive boron heterocycles known. Some of the 2-aryl(alkyl)sulfonylated derivatives of (4) (Grassberger *et al.*, 1984) are antibacterial by virtue of inhibiting enoyl-acyl carrier protein reductase (Baldock *et al.*, 1998), and some of the 2-arylated derivatives of (2) have been found to have activity against tuberculosis (Davis *et al.*, 1998).

Within the intermolecular hydrogen-bonding pattern discovered for (5), the O—H bond was oriented antiperiplanar with respect to the endocyclic B1—N2 bond.

We reasoned that this orientation would change to *syn* coplanar if an intramolecular hydrogen bond were to be introduced between the B—OH donor and an imine N acceptor contained within an N2 substituent. This hydrogen bond would structurally define a 'virtual' ring flexibly annelated onto the B1—N2 edge of the formally bicyclic 2,3,1-benzodiazaborine. If, additionally, the imine N acceptor were made part of a heterocyclic substituent like a pyridyl, the molecule's topography would take on the characteristics of the familiar steroidal cyclopentanophenanthrene framework. Finally, the substitution pattern of the *A*-ring aromatic estrogens and *AB*-ring aromatic equilenins could be established by equipping both the benzodiazaborine's benzene ring and the N2 substituent with oxygen-based substituents at appropriate loci. To test these design features of our novel class of biomimetic boron heterocycles, we prepared the title compound, (6)·H_2O, as a prototype.

An *ORTEP* (Johnson, 1965) view of the molecule of crystalline (6)·H_2O, together with its atom numbering, is provided in Fig. 1. The estrogen-like molecular shape of (6) is immediately obvious, and is a direct consequence of the intentionally engineered intramolecular hydrogen bond between the B—OH group and pyridine ring. This is a reasonably strong hydrogen bond. Besides acting as a hydrogen-bond donor, O1 acts as an acceptor for the hydrogen-bond donor H_2O, which apparently was introduced by the atmosphere during the crystallization procedure.

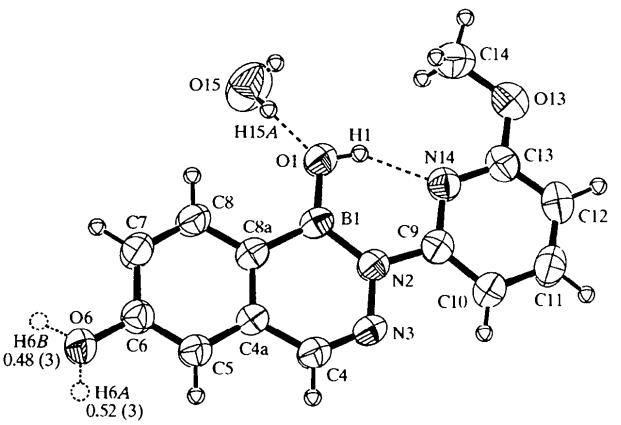


Fig. 1. The molecular structure and atom-numbering scheme for (6)·H_2O with displacement ellipsoids at the 50% probability level. The H6 atom is disordered over two sites (H6*A* and H6*B*) with occupancy factors as shown.

As shown in Table 1, the relative sizes of the three bond angles centered about the B atom no longer show the distinctive 'leaning' of the O1 atom away from the benzene ring that was remarkable in (3), (4), and (5) (Groziak *et al.*, 1997, Robinson *et al.*, 1998). This could be due to the effect of the intramolecular hydrogen bond, the donation of electrons to B1 from O6 through the benzene ring, or both. To compare, in (6), the C8a—B1—O1, O1—B1—N2, and N2—B1—C8a angles are 122.04 (15), 121.79 (16), and 116.17 (14)°, respectively, whereas in (5), they are 128.2 (2), 116.3 (2), and 115.5 (2)°, respectively.

All of the non-hydrate heavy atoms of (6) are close to coplanar, as evidenced by the small torsion angles of O1—B1—N2—C9 at −0.8 (3), B1—N2—C9—N14 at 2.1 (2), and C14—O13—C13—N14 at −2.2 (3)°. The B1—O1 distance in (6) of 1.363 (2) Å is similar to that found in (5) [1.357 (3) Å] and midway between those in (3) [1.350 (6) Å] and (4) [1.371 (3) Å]. The phenolic C6—O6 distance in (6) [1.368 (2) Å] is short and nearly identical to that of B1—O1. The B1—N2 distance of 1.455 (2) Å is the longest, and the C8a—B1 distance of 1.529 (3) Å the shortest yet when compared to counterparts in (3), (4), and (5). The N2—N3 distance of 1.3930 (19) Å is only slightly longer than that in the other two 2,3,1-benzodiazaborines, but the N2—C9 distance of 1.422 (2) Å is distinctly shorter than in (5) by 0.035 Å. This fact is highly suggestive of some amount of resonance electron donation from N2 into the pyridine ring.

The O6···O13 *trans*-molecular distance in (6) of 10.602 (4) Å is quite close to the 10.8 Å one apparent for equilenin in a recent crystallographic study of the enzyme Δ^5-3-ketosteroid isomerase (Kim *et al.*, 1997). This is truly remarkable, given that (6) has a pyridine-based rather than cyclopentane-based '*D* ring'. Thus, in the solid state this first prototype of our new class of 2,3,1-benzodiazaborine-based estrogen mimics is already extremely close in structure to its endogenous counterparts. To be truly valuable, though, the biomimetic characteristics of this class of compounds need to extend to their solution structures as well. The engineered intramolecular hydrogen bond in (6) responsible for its estrogenic molecular shape is clearly maintained in $(CD_3)_2SO$ solution as evidenced by the downfield-shifted placement of the H1 resonance in its ^1H NMR spectrum. In fact, by this assessment both H1 and H6 are fairly Brønsted acid labile in solution. The former is labile because of the intramolecular hydrogen bond, while the latter is labile because of the electron-withdrawing effect of B1 on O6 transmitted through the benzene ring.

The molecules of (6) pack in corrugated layers roughly parallel to (100). Individual molecules within the layers are interconnected by hydrogen bonds as shown in Fig. 2. Pairs of interlayer O15 water molecules connect adjacent molecular layers *via* additional hydrogen bonds. Hydrogen-bond geometry is given in Table 2. The refinement clearly indicates that the H6 atom is disordered between sites H6*A* and H6*B*. Thus, when an O6—H6*A*···O6 hydrogen bond is present, the adjacent O6—H6*B*···O15 hydrogen bond is not. The H6*A*:H6*B* site occupancy ratio is essentially 50:50 [0.52 (3):0.48 (3)].

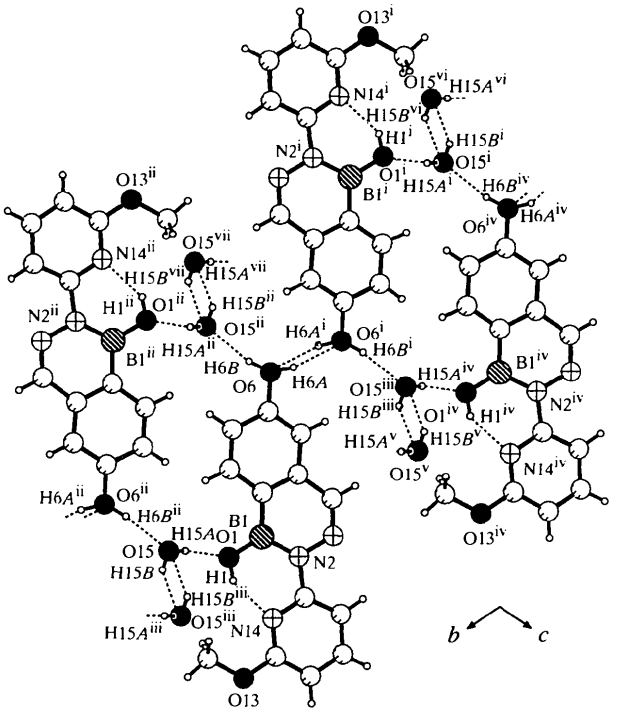


Fig. 2. View of the hydrogen bonding and the molecular packing in (6)·H_2O. The hydrogen bonding produces layers of molecules roughly parallel to (100). The molecular layer shown is connected to other molecular layers above and below (not shown) through pairs of interlayer water molecules (for example, O15 and $O15^{iii}$). The H6*A* and H6*B* atoms are only partially occupied with occupancy factors of 0.52 (3) and 0.48 (3), respectively. [Symmetry codes: (i) $2-x, -y, -1-z$; (ii) $2-x, 1-y, -1-z$; (iii) $2-x, 2-y, -z$; (iv) $x, -1+y, z$; (v) $2-x, 1-y, -z$; (vi) $x, -2+y, -1+z$; (vii) $x, -1+y, -1+z$.]

Experimental

A mixture of 2-chloro-6-methoxypyridine (2.87 g, 20 mmol, Aldrich) and anhydrous hydrazine (11 ml, excess, Aldrich) was heated under argon on a steam bath (*ca* 386 K) overnight. The mixture was allowed to cool to 296 K and was then extracted with diethyl ether (10 × 10 ml), and the organic extracts were combined and rotary evaporated to give 1.58 g (57%) of 2-hydrazino-6-methoxypyridine as a yellow liquid that was *ca* 95% pure by ^{1}H NMR; ($CDCl_3$) δ 7.38 (pseudo-*t*, 1), 6.20 (*d*, J = 8.0 Hz, 1), 6.09 (*d*, J = 8.0 Hz, 1), 5.71 (*bs*, exchanges with D_2O, 1, NH), 3.84 (*s*, 3, OCH_3), 3.1 (*bs*, exchanges with D_2O, 2, NH_2). A solution of this hydrazine (1.58 g, 11 mmol) in absolute ethanol (10 ml) was added to a solution of 2-formyl-4-methoxybenzeneboronic acid (1.8 g, 10 mmol, Frontier Scientific Inc.) in absolute ethanol (20 ml). A precipitate began forming within a few minutes. The mixture was allowed to stand at 296 K overnight and the product was collected by suction filtration, washed with a small amount of ethanol, and then dried *in vacuo* to give 1.65 g of the direct precursor to (6). An additional 510 mg was obtained by concentration of the filtrate (combined yield: 2.15 g, 76%); m.p. 434–435 K (ethanol). ^{1}H NMR [$(CD_3)_2SO$]: δ 10.45 (*s*, exchanges with D_2O, 1, OH), 8.25 (*s*, 1, H4), 8.04 (*d*, J = 8.2 Hz, 1), 7.88 (pseudo-*t*, 1), 7.54 (*d*, J = 8.2 Hz, 1), 7.36 (*s*, 1), 7.26 (*d*, J = 8.25 Hz, 1), 6.68 (*d*, J = 7.9 Hz, 1), 6.64 (pseudo-*t*, 1), 3.92 (*s*, 3, OCH_3), 3.90 (*s*, 3, OCH_3), low-resolution DCI mass spectrum, *m/z* 284 (100%, MH^+). Exposure of this precursor to BBr_3 in dichloromethane solution at 296 K overnight effected a regioselective demethylation, giving (6); m.p. 471–472 K (ethanol). ^{1}H NMR [$(CD_3)_2SO$]: δ 10.41 (*s*, exchanges with D_2O, 1, OH), 10.26 (*s*, exchanges with D_2O, 1, OH), 8.17 (*s*, 1, H4), 7.98 (*d*, 1), 7.88 (pseudo-*t*, 1), 7.54 (*d*, 1), 7.12 (*m*, 3), 6.67 (*d*, 1), 3.92 (*s*, 3, OCH_3), low-resolution DCI (direct chemical ionization) mass spectrum, *m/e* 270 (100%, MH^+). X-ray quality crystals of (6) were grown *via* slow evaporation of an absolute ethanol solution exposed to the atmosphere. The crystallographic determination of (6) obtained in this manner revealed a non-covalent monohydrate, a fact confirmed by comparing the ^{1}H NMR [$(CD_3)_2SO$] spectra of the compound recorded before and after the addition of a trace amount of H_2O.

Crystal data

$C_{13}H_{12}BN_3O_3·H_2O$
M_r = 287.08
Triclinic
$P\bar{1}$
a = 8.885 (3) Å
b = 10.2996 (19) Å
c = 8.5543 (15) Å
α = 111.952 (11)°
β = 98.61 (3)°
γ = 103.04 (3)°
V = 683.2 (3) Å^3
Z = 2
D_x = 1.396 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 23 reflections
θ = 6.3–14.8°
μ = 0.104 mm^{-1}
T = 296 K
Irregular fragment
0.43 × 0.38 × 0.24 mm
Pale brown

Data collection

Rigaku AFC-5*S* diffractometer
ω scans (rate: 4° min^{-1} in ω)
Absorption correction: none
2585 measured reflections
2416 independent reflections
1582 reflections with $I > 2\sigma(I)$

R_{int} = 0.008
θ_{max} = 25°
$h = 0 \rightarrow 10$
$k = -12 \rightarrow 11$
$l = -10 \rightarrow 10$
3 standard reflections every 150 reflections
intensity decay: 0.40%

Refinement

Refinement on F^2
$R(F)$ = 0.036
$wR(F^2)$ = 0.118
S = 1.029
2416 reflections
206 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0640P)^2 + 0.0583P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.144 e Å^{-3}
$\Delta\rho_{min}$ = −0.144 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.009 (3)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

B1—O1	1.363 (2)	N3—C4	1.287 (2)
C6—O6	1.368 (2)	C4a—C8a	1.399 (2)
N2—N3	1.3930 (19)	C4—C4a	1.449 (2)
N2—C9	1.422 (2)	C8a—B1	1.529 (3)
B1—N2	1.455 (2)		
N3—N2—C9	111.99 (13)	C8—C8a—B1	124.45 (14)
N3—N2—B1	122.73 (14)	C4a—C8a—B1	117.93 (14)
C9—N2—B1	125.26 (14)	O1—B1—N2	121.79 (16)
C4—N3—N2	118.01 (13)	C8a—B1—O1	122.04 (15)
N3—C4—C4a	127.65 (15)	N2—B1—C8a	116.17 (14)
C8a—C4a—C4	117.49 (15)		
C9—N2—N3—C4	−177.96 (15)	C14—O13—C13—N14	−2.2 (3)
B1—N2—N3—C4	0.5 (2)	O1—B1—N2—C9	−0.8 (3)
N2—N3—C4—C4a	−0.7 (3)	C8—C8a—B1—O1	−2.4 (3)
N3—C4—C4a—C8a	−0.4 (3)	C4a—C8a—B1—O1	178.11 (16)
C4—C4a—C8a—B1	1.4 (2)	C8—C8a—B1—N2	177.99 (15)
N3—N2—C9—N14	−179.52 (13)	C4a—C8a—B1—N2	−1.5 (2)
B1 N2 C9 N14	2.1 (2)		

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1···N14	0.82	1.89	2.599 (2)	144
O6—H6*A*···O6^{i}	0.82 (2)	1.90 (5)	2.699 (2)	163 (5)
O6—H6*B*···O15^{ii}	0.84 (2)	1.92 (4)	2.754 (3)	167 (5)
O15—H15*A*···O1	0.82 (3)	2.02 (3)	2.833 (3)	171 (3)
O15—H15*B*···O15^{iii}	0.78 (3)	2.57 (4)	2.751 (3)	95 (3)

Symmetry codes: (i) $2-x, -y, -1-z$; (ii) $2-x, 1-y, -1-z$; (iii) $2-x, 2-y, -z$.

Fourier maps and the circular Fourier hydrogen-locating method available in *SHELXL*97 (Sheldrick, 1997) both strongly indicated that the H(—O6) atom was split over two sites. The two positions, designated H6*A* and H6*B*, were refined with fixed isotropic displacement factors and restrained O—H distances. In addition, the sum of their site occupancies was constrained to equal 1.0 resulting in occupancy values of 0.52 (3) and 0.48 (3), respectively. Sites H15*A* and H15*B* were refined in a similar manner although no site occupancy refinement was required. All other H atoms are riding. The rotational orientation of the methyl group was refined by the circular Fourier method available in *SHELXL*97 (Sheldrick, 1997).

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1996). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *PROCESS* in *TEXSAN* (Molecular Structure Corporation, 1997). Program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990). Program(s) used to refine structure: *LS* in *TEXSAN* and *SHELXL*97 (Sheldrick, 1997). Molecular graphics: *ORTEP* (Johnson, 1965) in *TEXSAN*. Software used to prepare material for publication: *TEXSAN*, *SHELXL*97 and *PLATON* (Spek, 1990).

This work was supported in part by grant GM44819 (to MPG) from the National Institute of General Medical Sciences, National Institutes of Health, USA.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1557). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1999). C**55**, 1704–1706

A zwitterionic Meisenheimer complex of 2,4,6-trinitrobenzene

OLEG YA. BORBULEVYCH,[a] OLEG V. SHISHKIN[b] AND VICTOR N. KNYAZEV[c]

[a]*A. N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences, 28 Vavilov Street, Moscow 117813, Russia,* [b]*Scientific Research Department of Alkali Halide Crystals, STC 'Institute for Single Crystals' of the National Academy of Sciences of Ukraine, 60 Lenina Avenue, Khar'kov 310001, Ukraine, and* [c]*Timiryazev Agricultural Academy, 49 Timiryazevskaya Street, Moscow 127550, Russia. E-mail: oleg@xrlab.ineos.ac.ru*

(*Received 15 March 1999; accepted 29 April 1999*)

Abstract

In molecules of the zwitterionic Meisenheimer complex 4-(*N*-pyridiniomethyl)-1,3-dioxolane-2-spiro-1′-2′,4′,6′-trinitrocyclohexadienide ($C_{14}H_{12}N_4O_8$), the nitro groups do not possess equivalent geometries. The C—N bond to the nitro group *para* to the saturated C atom is shorter than those of the others, and bond lengths vary