For each structure, the positions of all H atoms were initially located in a difference electron-density map. The positions of the amine and amide H atoms were refined freely, as were their individual isotropic displacement parameters. The positions of all other H atoms were geometrically idealized and refined with a riding model (including free rotation about C—C bonds), with U_{iso} constrained to be $1.2U_{eq}$ ($1.5U_{eq}$ for methyl groups) of the parent C atom. For (2*a*), five reflections were considered to be severe outliers and were excluded from the final refinement.

For all compounds, data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1991); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1989); program(s) used to solve structure: *SHELXS*86 (direct methods) (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

The Swiss National Science Foundation and F. Hoffmann–La Roche AG, Basel, are thanked for financial support, and DMA is grateful to the Swiss Federal Government for the provision of a National Scholarship for Foreign Students (Bundesstipendium).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1546). Services for accessing these data are described at the back of the journal.

References

Aggarwal, V., Ila, H. & Junjappa, H. (1982). *Synthesis*, pp. 65–68.
Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–19.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
García Trimiño, M. I., Linden, A., Heimgartner, H. & Macías Cabrera, A. (1993). *Helv. Chim. Acta*, **76**, 2817–2829.
García Trimiño, M. I., Macías Cabrera, A. & Vélez Castro, H. (1992). *Synth. Commun.* **22**, 1319–1331.
García Trimiño, M. I., Macías Cabrera, A., Vélez Castro, H., Rosado Pérez, A., Moya Argilagos, D., Linden, A. & Heimgartner, H. (1998). *Helv. Chim. Acta*, **81**, 718–728.
García Trimiño, M. I., Moya Argilagos, D., Macías Cabrera, A., Linden, A. & Heimgartner, H. (1994). 10th IUPAC Conference on Organic Synthesis, Bangalore, India. Abstract P-TUE-33.
Goerdeler, J. & Gnad, J. (1965). *Chem. Ber.* **98**, 1531–1543.
Gompper, R. & Schaefer, H. (1967). *Chem. Ber.* **100**, 591–604.
Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Linden, A., Heimgartner, H., García Trimiño, M. I. & Macías Cabrera, A. (1994). *Acta Cryst.* C**50**, 421–424.
Molecular Structure Corporation (1989). *TEXSAN. Single Crystal Structure Analysis Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Molecular Structure Corporation (1991). *MSC/AFC Diffractometer Control Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Moya Argilagos, D., García Trimiño, M. I., Macías Cabrera, A., Linden, A. & Heimgartner, H. (1997). *Helv. Chim. Acta*, **80**, 273–292.
Moya Argilagos, D., Kunz, R. W., Linden, A. & Heimgartner, H. (1998). *Helv. Chim. Acta*, **81**, 2388–2406.
Pomés Hernández, R., Duque Rodríguez, J., García Trimiño, M. I., Novoa de Armas, H. & Toscano, R. A. (1995). *Acta Cryst.* C**51**, 1392–1394.
Rajappa, S. (1981). *Tetrahedron*, **37**, 1453–1480.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997). *SHELXL*97. *Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.

Acta Cryst. (1999). C**55**, 1698–1701

6,7,8,9-Tetrahydro-3-methyl-1*H*-pyrano-[4,3-*b*]quinolin-1-one

DUY H. HUA,[a] YI CHEN,[a] HONG-SIG SIN,[a] PAUL D. ROBINSON,[b] CAL Y. MEYERS,[c] ELISABETH M. PERCHELLET,[d] JEAN-PIERRE PERCHELLET,[d] PETER K. CHIANG[e] AND JEAN-FRANCOIS BIELLMANN[f]

[a]*Department of Chemistry, Kansas State University, Manhattan, KS 66506, USA,* [b]*Department of Geology, Southern Illinois University 4324, Carbondale, IL 62901, USA,* [c]*Department of Chemistry, Southern Illinois University 4409, Carbondale, IL 62901, USA,* [d]*Department of Biology, Kansas State University, Manhattan, KS 66506, USA,* [e]*Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100, USA, and* [f]*Faculté de Chimie, Université Louis Pasteur, 67008 Strasbourg, France. E-mail: robinson@geo.siu.edu*

(*Received 6 May 1999; accepted 26 May 1999*)

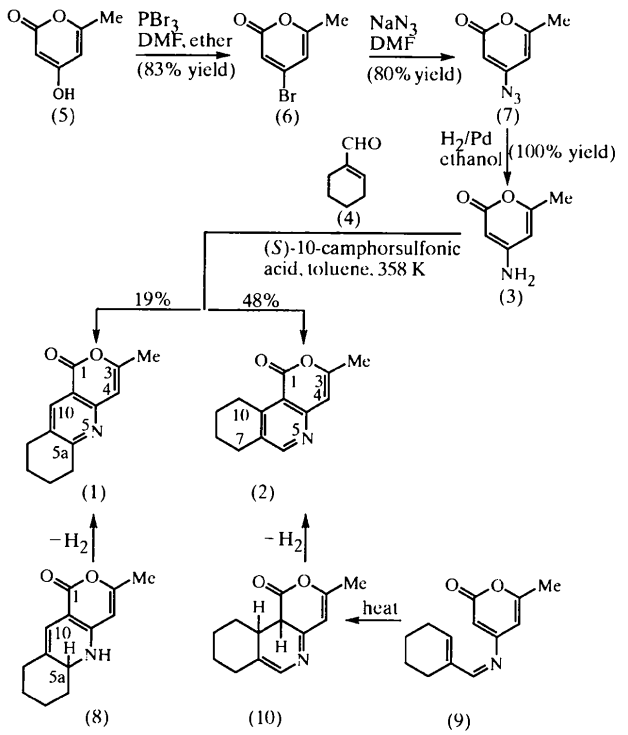
Abstract

The condensation reaction of 4-amino-6-methyl-2-pyrone with 1-cyclohexenecarboxaldehyde and a catalytic amount of (*S*)-(+)-10-camphorsulfonic acid in toluene at 358 K gave a 1:2.5 ratio of the title compound, (1) ($C_{13}H_{13}NO_2$), and 7,8,9,10-tetrahydro-1*H*-pyrano[4,3-*c*]isoquinoline-1-one, (2). The formation of (2) presumably proceeds through an intermediate imine. Both (1) and (2) show inhibitory activities against acetylcholinesterase and human aldose reductase. Of the three linear-fused rings of (1), both ring *A* and ring *B* are planar and the angle between these planes is 0.46 (13)°. While the two C atoms of cyclohexane ring *C* attached to its common atoms with ring *B* are in the plane of the latter, as expected, the remaining two C atoms of ring *C* are out of this plane, by 0.342 (4) and −0.402 (3) Å, respectively.

Comment

In the search for new biologically active compounds, a class of tricyclic pyranopyrones was synthesized by Hua *et al.* (1997). In this reaction, 6-substituted 4-hydroxy-2-pyrones were condensed with 1-cyclo-

hexenecarboxaldehydes to give exclusively linearly fused 3-substituted 1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-*b*][1]benzopyrans. Because several compounds from this class of tricyclic pyrones possess anticancer (Newell *et al.*, 1998) and acetylcholinesterase (AChE) inhibitory activities, the synthesis of a 5-*N* analog, *e.g.* (1), was carried out.



The structure of (1) is somewhat similar to that of tacrine, a cholinesterase inhibitor used for the treatment of Alzheimer's disease (Zacharias & Glusker, 1988). Hence, 4-amino-6-methyl-2-pyrone, (3), was prepared from 4-hydroxy-6-methyl-2-pyrone, (5), by the reported procedure (Cervera *et al.*, 1990), as depicted in the scheme. To our surprise, under reaction conditions similar to those described earlier by Hua *et al.* (1997), no product was formed. Several different catalysts and reaction conditions were tried. Ultimately, in the presence of 0.1 equivalent of (*S*)-(+)-10-camphorsulfonic acid, aminopyrone (3) underwent condensation with enal (4) to give a mixture of linear tricyclic pyranoquinoline (1) [19% yield, based on recovered (3)] and the isomeric L-shaped pyranoisoquinoline (2) (48% yield). It was not possible to determine the structures of (1) and (2) by ^1H or ^{13}C NMR. For example, although H10 resonates at 8.15 p.p.m. in (1) and at 8.5 p.p.m. (H6) in (2), neither affords a feature identifying the isomeric structure. Thus, single-crystal X-ray analysis was needed to determine the respective structures. Compound (1), a white solid, was recrystallized from EtOH:diethyl ether (1:1) to give crystals suitable for X-ray analysis. However, crystals of (2) were unamenable to X-ray analysis. From the X-ray structure of (1), it is reasonably presumed that isomeric (2) has the L-shaped structure. As shown in the scheme, the formation of (1) most likely proceeds *via* a mechanism similar to that described previously by Hua *et al.* (1997), through amine (8), while (2) is reasonably formed *via* a 6π electrocyclic reaction of imine (9).

In addition to the study of tricyclic pyranopyrones for the inhibition of DNA synthesis (Perchellet *et al.*, 1998), other biological applications of this class of compounds, such as inhibition of acetylcholinesterase (AChE) and aldose reductase (AR), were carried out. The competitive AChE inhibition constants, *Ki*, of (1) and (2) were determined to be 33 and 14 μM, respectively, using electric eel AChE (Ralston *et al.*, 1985), and their corresponding IC_{50} values in human AR inhibition were 40 and 80 μM (inhibition of the conversion of xylose and NADPH into xylitol and NADP, catalyzed by human AR).

The X-ray structure with atom numbering (Fig. 1) shows (1) to be a linear tricyclic pyrone. Of the three linear-fused rings, rings *A* and *B* are both planar, although they are not coplanar, the angle between the two planes being 0.46 (13)°. In cyclohexane ring *C*, C6 and C9 are in the plane of ring *B*, as expected, although C7 and C8 are out of this plane by 0.342 (4) and −0.402 (3) Å, respectively. The bond lengths and angles are mostly within the expected range. However, C4a—C10a [1.394 (3) Å], C9a—C10 [1.374 (3) Å] and C10—C10a [1.381 (3) Å] are shorter than the respective bonds of tacrine hydrochloride [C10—C11 1.406 (2), C9—C13 1.406 (2) and C9—C10 1.441 (2) Å; Zacharias &

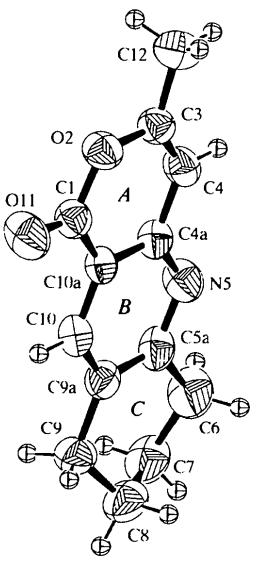


Fig. 1. The molecular structure and atom-numbering scheme for (1) with displacement ellipsoids at the 50% probability level.

Glusker, 1988], while C5a—C9a [1.408 (3) Å] is longer than the corresponding C12—C13 bond [1.389 (2) Å] of the aforementioned tacrine. The angles C4a—N5—C5a [117.7 (2)°] and C5a—C9a—C10 [116.7 (2)°] are smaller than the respective angles of the tacrine [C11—N1—C12 123.2 (1) and C9—C13—C12 119.2 (1)°], while C9a—C10—C10a [121.0 (2)°] and N5—C4a—C10a [122.4 (2)°] are larger than the corresponding angles of the same tacrine [C10—C9—C13 119.6 (1) and N1—C11—C10 119.6 (1)°]. Some additional bond distances and angles of interest are given in Table 1.

Experimental

A mixture of of 1-cyclohexenecarboxaldehyde, (4) (250 mg, 2.28 mmol), 4-amino-6-methyl-2-pyrone, (3) (190 mg, 1.52 mmol) and (*S*)-(+)-10-camphorsulfonic acid (35 mg, 0.15 mmol) in toluene (12 ml) was heated at 358 K under argon for 3 d. The mixture was cooled to room temperature and the solids were removed by filtration and carefully washed with ethyl acetate (20 ml). The filtrate and ethyl acetate wash were combined, diluted with methylene chloride (100 ml), washed with water (50 ml) and brine (50 ml), dried ($MgSO_4$), concentrated and column chromatographed on silica gel using ethyl acetate–hexane (2:1) as eluant, to give 13.3 mg of (1) (19% yield based on unrecovered starting material), 33 mg of (2) (48% yield) and 150 mg of pyrone (3) (79% recovery). Compound (1): white solid, m.p. 344–345 K; ^{1}H NMR ($CDCl_3$; δ, p.p.m.): 8.15 (*s*, 1H, C10-H), 6.44 (*s*, 1H, C4-H), 3.01 (*t*, J = 7 Hz, 2H, CH_2), 2.88 (*t*, J = 7 Hz, 2H, CH_2), 2.31 (*s*, 3H, Me), 1.95 (*m*, 2H, CH_2), 1.86 (*m*, 2H, CH_2); ^{13}C NMR ($CDCl_3$; δ, p.p.m.): 168 (*s*, C1), 165.71 (*s*), 157.69 (*s*), 152.22 (*s*, C3), 137.2 (*d*, C10), 132.34 (*s*), 114.0 (*s*), 105.48 (*d*), 33.34 (*t*, CH_2), 28.69 (*t*, CH_2), 22.59 (*t*, CH_2), 22.32 (*t*, CH_2), 19.89 (*q*, Me); MS (FAB): 216 (M + 1). Compound (2): white solid, m.p. 346–347 K; ^{1}H NMR ($CDCl_3$; δ, p.p.m.): 8.50 (*s*, 1H, C6-H), 6.43 (*s*, 1H, C4-H), 3.35 (*t*, J = 6 Hz, 2H, CH_2), 2.82 (*t*, J = 6 Hz, 2H, CH_2), 2.29 (*s*, 3H, Me), 1.90–1.80 (*m*, 4H, CH_2); ^{13}C NMR ($CDCl_3$; δ, p.p.m.): 162.5 (*s*, C1), 157.4 (*s*), 156.4 (*d*), 154.4 (*s*), 151.4 (*s*), 132.7 (*s*), 114.6 (*s*), 106.5 (*d*, C4), 28.6 (*t*, CH_2), 27.6 (*t*, CH_2), 22.6 (*t*, CH_2), 21.7 (*t*, CH_2), 19.8 (*q*, Me); MS (FAB): 216 (M + 1), 215, 188, 154, 136.

Crystal data

$C_{13}H_{13}NO_2$
M_r = 215.24
Triclinic
$P\bar{1}$
a = 7.6535 (9) Å
b = 10.8255 (10) Å
c = 7.4067 (9) Å
α = 92.436 (10)°
β = 117.023 (8)°
γ = 81.610 (9)°
V = 540.62 (10) Å^3
Z = 2
D_x = 1.322 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 10.2–12.1°
μ = 0.090 mm^{-1}
T = 296 K
Irregular fragment
0.28 × 0.25 × 0.17 mm
Colorless

Data collection

Rigaku AFC-5*S* diffractometer
$\omega/2\theta$ scans (2° min^{-1} in ω)
Absorption correction: none
2065 measured reflections
1910 independent reflections
873 reflections with $I > 2\sigma(I)$
R_{int} = 0.029
θ_{max} = 25.04°
h = 0 → 9
k = −12 → 12
l = −8 → 7
3 standard reflections
every 100 reflections
intensity decay: 0.80%

Refinement

Refinement on F^2
$R(F)$ = 0.038
$wR(F^2)$ = 0.127
S = 1.02
1910 reflections
146 parameters
H atoms riding
$w = 1/[\sigma^2(F_o^2) + (0.0475P)^2 + 0.0809P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.13 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

O11—C1	1.206 (3)	O2—C3	1.387 (3)
C3—C4	1.318 (3)	C4—C4a	1.436 (3)
N5—C4a	1.349 (3)	N5—C5a	1.341 (3)
C3—C12	1.488 (3)	C1—C10a	1.451 (3)
O11—C1—O2	116.7 (2)	C3—C4—C4a	121.1 (2)
N5—C5a—C9a	123.8 (2)	C7—C8—C9	110.4 (2)
C8—C7—C6	110.4 (2)		

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

DHH gratefully acknowledges financial support from the American Heart Association, Kansas Affiliate (KS-96-GS-69), BioServe Space Technologies (grant NAGW-1197), Great Plains Diabetes Inc., Wichita, KS, and a Special Group Incentive Research Award from Kansas State University.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1560). Services for accessing these data are described at the back of the journal.

References

Cervera, M., Moreno-Manas, M. & Pleixats, R. (1990). *Tetrahedron*, **46**, 7885–7892.

Hua, D. H., Chen, Y., Sin, H.-S., Maroto, M. J., Robinson, P. D., Newell, S. W., Perchellet, E. M., Ladesich, J. B., Freeman, J. A., Perchellet, J.-P. & Chiang, P. K. (1997). *J. Org. Chem.* **62**, 6888–6896.

Johnson, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

Molecular Structure Corporation (1996). *MSC/AFC Diffractometer Control Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Molecular Structure Corporation (1997). *TEXSAN. Single Crystal Structure Analysis Software*. Version 1.03 (Windows). MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Newell, S. W., Perchellet, E. M., Ladesich, J. B., Freeman, J. A., Chen, Y., Liu, L., Hua, D. H., Kraft, S. L., Basaraba, R. J. & Perchellet, J.-P. (1998). *Int. J. Oncol.* **12**, 433–442.
Perchellet, E. M., Ladesich, J. B., Chen, Y., Sin, H.-S., Hua, D. H., Kraft, S. L. & Perchellet, J.-P. (1998). *Anti-Cancer Drugs*, **9**, 565–576.
Ralston, J. S., Rush, R. S., Doctor, B. P. & Wolfe, A. D. (1985). *J. Biol. Chem.* **260**, 4312–4318.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997). *SHELXL97. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
Spek, A. L. (1990). *Acta Cryst.* A**46**, C-34.
Zacharias, D. & Glusker, J. P. (1988). *Acta Cryst.* C**44**, 1656–1658.

Acta Cryst. (1999). C**55**, 1701–1704

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*

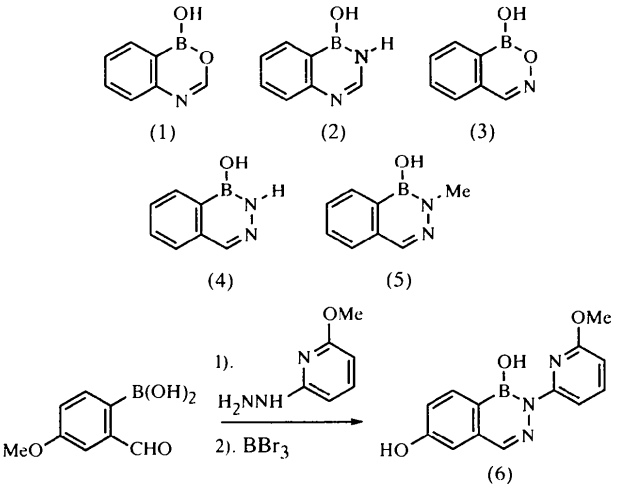
(*Received 19 April 1999; accepted 3 June 1999*)

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.