Synthesis and molecular structure of 2,4,8a-triaryl-6-methylperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridines

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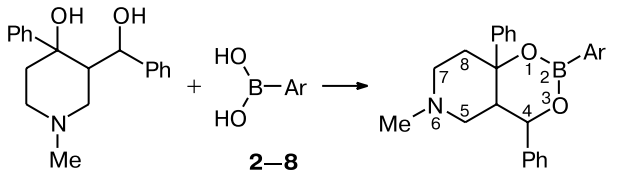
Condensation of arylboronic acids with 4-hydroxy-3-(α-hydroxybenzyl)-1-methyl-4-phenylpiperidine afforded 2,4,8a-triarylperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridines. The molecular structure of 6-methyl-2,4,8a-triphenylperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridine was established by X-ray diffraction analysis.

Key words: arylboronic acids, 4-hydroxy-3-(α-hydroxybenzyl)-1-methyl-4-phenylpiperidine, 2,4,8a-triarylperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridines, molecular structure.

In recent years, the chemistry of organic derivatives of boric acid has attracted increasing attention. In particular, the Suzuki reaction, in which new C—C bonds are constructed with the use of arylboronic acids[1] and their cyclic esters (for example, 2-aryl-1,3,2-dioxaborinanes),[2] has gained wide acceptance as an important procedure for the synthesis of difficultly accessible *ortho*-substituted biaryls[1,2] and phenols.[3] Certain derivatives of arylboronic acids hold considerable promise as a tool in developing molecular sensors that react highly selectively and reversibly with natural mono- and oligosaccharides.[4—6] The configurations and conformations of substituted 1,3,2-dioxaborinanes were systematically studied by NMR spectroscopy and quantum-chemical methods.[7—11] Computer-aided predictions of biological activities of substituted perhydro[1,3,2]dioxaborinino[5,4-*c*]pyridines using the PASS Internet program[12] demonstrated with high probability that these compounds will exhibit antispasmodic (73—93% probability), psychotropic (81—89%), sedative (80—82%), and other activities (>50%). Taking into account this fact and with the aim of revealing stereochemical features of these compounds, we performed condensation of 1,3-diol **1** with arylboronic acids **2—8** giving rise to 2,4,8a-triaryl-6-methylperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridines **9—15**, which are representatives of a new heterocyclic system (for preliminary communication, see Ref. 13) (Scheme 1).

Scheme 1



1 **2—8** **9—15**

	2, 9	**3, 10**	**4, 11**	**5, 12**	**6, 13**	**7, 14**	**8, 15**
Ar	Ph	4-Tol	3-Tol	2-Tol	2,4,6-$Me_3C_6H_2$	3-$CF_3C_6H_4$	4-Py

A characteristic feature of the ^{1}H NMR spectra of compounds **9—15** is that the C(4)H proton resonates at low field (δ ~5.1) as a broadened singlet with $J_{1/2}$ = 15.6—16.2 Hz, which is indicative of its *trans* arrangement with respect to the C(4a)H proton.[9] It is difficult to unambiguously determine whether two heterocyclic fragments are *cis*- or *trans*-fused. However, based on the re-

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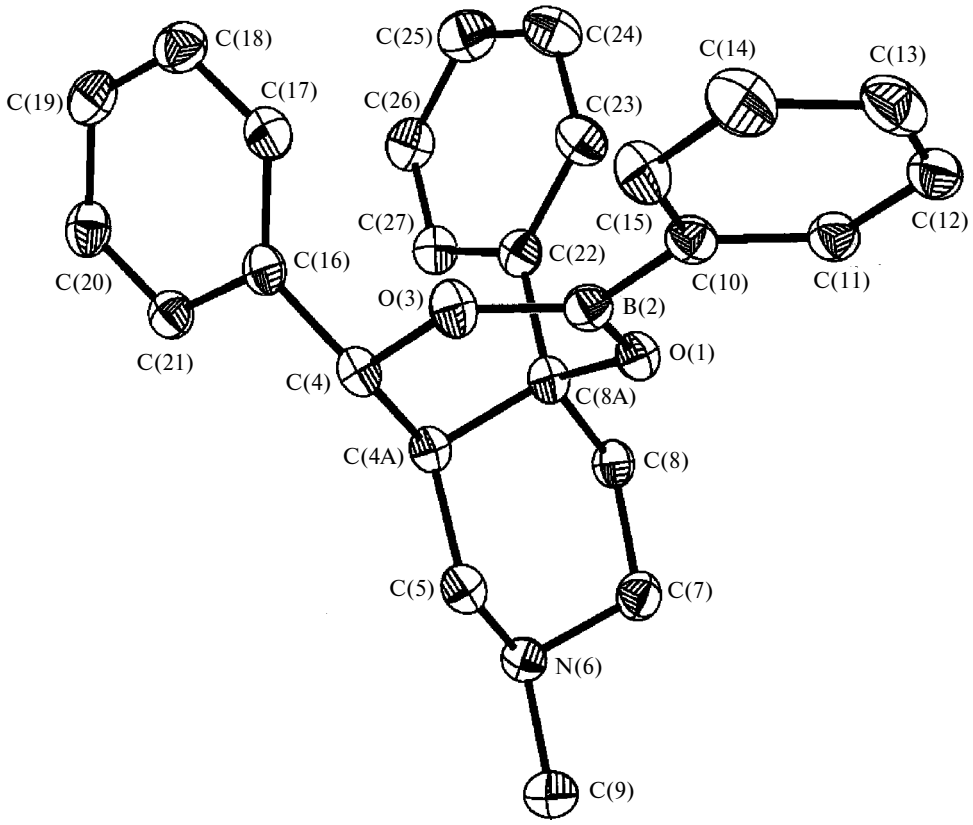

Fig. 1. Molecular structure of compound **9** with thermal ellipsoids drawn at the 40% probability level.

sults of X-ray diffraction data for related 3-benzoyl-4-hydroxy-4-phenylpiperidine[14] and the ^{1}H NMR spectroscopic data for 1,3-diol **1**,[13] we concluded that the γ-phenyl, β-benzoyl, and β-phenylhydroxymethyl substituents are in equatorial positions of the piperidine ring. Hence, both heterocycles in perhydrodioxaborinino-pyridines **9—15** should be *cis*-fused.

To unambiguously establish the molecular structures of perhydrodioxaborininopyridines, we performed an X-ray diffraction analysis of compound **9**. The general view of molecule **9** is shown in Fig. 1. The bond lengths and bond angles are given in Tables 1 and 2, respectively (the numbering of atoms in the piperidinodioxaborinane moiety follows the IUPAC nomenclature and is identical to that used in the text). Compound **9** is a racemic diastereomer containing three asymmetric carbon atoms, *viz.*, C(4), C(4a), and C(8a). Molecule **9** has the *rac*-*R*,*S*,*S* configuration with the *cis*-fused six-membered heterocycles. The dioxaborinane ring adopts a half-chair conformation. The C(4a) and C(8a) atoms deviate from the plane (within 0.013 Å) through the other atoms of the heterocycle by +0.313 and −0.403 Å, respectively. The piperidine ring adopts a virtually ideal chair conformation (the torsion angles vary in magnitude from 50.1(2) to 61.2(2)°). The B and N atoms have a planar and pyramidal configuration, respectively (the corresponding sums of the bond angles are 360.0° and 330.2°). The phenyl substituents at the C(4) and C(8a) atoms are in axial positions. The methyl substituent at the N atom is in an equatorial position. In the crystal, the molecules are stacked along the *x* axis at the van der Waals distances.

Table 1. Selected bond lengths (*d*) in molecule **9**

Bond	*d*/Å	Bond	*d*/Å
O(1)—B(2)	1.354(3)	C(4a)—C(8a)	1.542(3)
O(1)—C(8a)	1.453(2)	C(5)—N(6)	1.453(3)
B(2)—O(3)	1.364(3)	N(6)—C(9)	1.456(3)
B(2)—C(10)	1.566(3)	N(6)—C(7)	1.466(3)
O(3)—C(4)	1.445(2)	C(7)—C(8)	1.513(3)
C(4)—C(16)	1.514(3)	C(8)—C(8a)	1.518(3)
C(4)—C(4a)	1.528(3)	C(8a)—C(22)	1.533(3)
C(4a)—C(5)	1.531(3)		

To summarize, we developed a preparative procedure for the synthesis of 2,4,8a-triarylperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridines, which are of interest because certain representatives of this new heterocyclic system can exhibit biological activities. The piperidine and dioxaborinane fragments were found to be *cis*-fused.

Table 2. Selected bond angles (ω) in molecule **9**

Angle	ω/deg
B(2)—O(1)—C(8a)	117.43(15)
O(1)—B(2)—O(3)	123.65(19)
O(1)—B(2)—C(10)	118.55(18)
O(3)—B(2)—C(10)	117.80(19)
B(2)—O(3)—C(4)	122.87(16)
O(3)—C(4)—C(16)	110.60(16)
O(3)—C(4)—C(4a)	110.93(15)
C(16)—C(4)—C(4a)	115.01(16)
C(4)—C(4a)—C(5)	110.21(17)
C(4)—C(4a)—C(8a)	112.46(16)
C(5)—C(4a)—C(8a)	110.43(16)
N(6)—C(5)—C(4a)	112.03(17)
C(5)—N(6)—C(9)	110.97(19)
C(5)—N(6)—C(7)	109.93(16)
C(9)—N(6)—C(7)	109.34(18)
N(6)—C(7)—C(8)	111.07(17)
C(7)—C(8)—C(8A)	112.99(18)
O(1)—C(8a)—C(8)	107.20(15)
C(11)—C(10)—B(2)	121.74(19)
C(17)—C(16)—C(4)	122.94(18)
C(21)—C(16)—C(4)	118.42(19)
O(1)—C(8a)—C(22)	108.15(15)
C(8)—C(8a)—C(22)	109.87(16)
O(1)—C(8a)—C(4a)	108.08(15)
C(8)—C(8a)—C(4a)	109.86(17)

Experimental

Compounds were isolated and purified by crystallization and column chromatography on silica gel L-60 (40/100); TLC was carried out on Silufol UV-254 plates (acetone; visualization with iodine vapor). The ^{1}H NMR spectra were recorded on a Bruker WM-400 instrument (400 MHz) in $CDCl_3$ with Me_4Si as the internal standard. The mass spectra were obtained on an MKh-1303 spectrometer; the energy of ionizing electrons was 70 eV. Compound **1** was synthesized according to a known procedure.[15] Compounds **2—8** (97% purity) were purchased from Aldrich.

6-Methyl-4,8a-diphenyl-2-(4-tolyl)perhydro[1,3,2]dioxaborinino[5,4-*c*]pyridine (10). A solution of *p*-tolylboronic acid (**3**) (0.37 g, 2.72 mmol) and 4-hydroxy-3-(α-hydroxybenzyl)-1-methyl-4-phenylpiperidine (**1**) (0.8 g, 2.69 mmol) in toluene (50 mL) was refluxed using a Dean—Stark trap for 3 h. Compound **10** was isolated by column chromatography (toluene and then acetone) as yellowish crystals. The yield was 1.01 g (95%), m.p. 104—106 °C, R_f 0.53. Found (%): C, 78.30; H, 7.23; N, 3.41. $C_{26}H_{28}BNO_2$. Calculated (%): C, 78.59; H, 7.05; N, 3.53. ^{1}H NMR, δ: 2.40 (s, 3 H, NMe); 2.43 (br.m, 1 H, H(5)); 2.45 (s, 3 H, CMe); 2.72 (br.m, 1 H, H(5)); 6.91 and 7.00 (both m, 8 H and 2 H, respectively, C(4)Ph, C(8a)Ph); 7.31 and 8.00 (both d, 2 H each, BC_6H_4, AA´BB´ system, J = 7.5 Hz). MS, m/z (I_{rel} (%)): 397 $[M]^+$ (46), 396 (32), 326 (18), 325 (23), 265 (27), 174 (38), 172 (38), 159 (26), 105 (31), 91 (23), 77 (30), 70 (57), 57 (71), 44 (100), 43 (69), 42 (70).

Compounds **9** and **11—15** were prepared analogously.

6-Methyl-2,4,8a-triphenylperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridine (9). The yield was 72%, m.p. 150 °C. Found (%): C, 78.20; H, 7.01; N, 3.56. $C_{25}H_{26}BNO_2$. Calculated (%): C, 78.33; H, 6.79; N, 3.66. ^{1}H NMR, δ: 2.40 (s, 3 H, NMe); 2.44 and 2.69 (both br.m, 2 H, H(5)); 6.93 (br.m, 8 H, C(4)Ph, C(8a)Ph); 7.09 (br.m, 2 H, C(4)Ph, C(8a)Ph); 7.05 and 7.57 (both m, 2 H and 1 H, respectively, BPh); 8.12 (d, 2 H, BPh, J = 7.0 Hz). MS, m/z (I_{rel} (%)): 383 $[M]^+$ (100), 382 (25), 312 (23), 251 (18), 174 (22), 172 (32), 159 (12), 115 (11), 105 (24), 91 (10), 77 (15), 70 (16), 57 (18), 44 (19), 43 (14), 42 (11).

6-Methyl-4,8a-diphenyl-2-(3-tolyl)perhydro[1,3,2]dioxaborinino[5,4-*c*]pyridine (11). The yield was 90%, m.p. 52—54 °C, R_f 0.46. Found (%): N, 3.32. $C_{26}H_{28}BNO_2$. Calculated (%): N, 3.53. ^{1}H NMR, δ: 2.44 (br.s, 6 H, Me); 2.53 and 2.80 (both br.m, 1 H each, H(5)); 6.89 and 7.05 (both br.m, 8 H and 2 H, respectively, C(4)Ph, C(8a)Ph); 7.42 and 7.91 (both m, 2 H, BC_6H_4). MS, m/z (I_{rel} (%)): 397 $[M]^+$ (55), 396 (16), 326 (15), 325 (19), 265 (22), 174 (33), 172 (42), 159 (21), 105 (48), 91 (40), 77 (44), 70 (51), 57 (77), 44 (100), 43 (83), 42 (95).

6-Methyl-4,8a-diphenyl-2-(2-tolyl)perhydro[1,3,2]dioxaborinino[5,4-*c*]pyridine (12). The yield was 76%, m.p. 50—52 °C, R_f 0.4. Found (%): N, 3.47. $C_{26}H_{28}BNO_2$. Calculated (%): N, 3.53. ^{1}H NMR, δ: 2.44 (s, 3 H, NMe); 2.50 (br.t, 1 H, H(5), J = 11.2 Hz); 2.71 (s, 3 H, CMe); 2.73 (br.m, 1 H, H(5)); 6.92 and 7.07 (both br.m, 8 H and 2 H, respectively, C(4)Ph, C(8a)Ph); 7.30 and 7.42 (both m, 2 H and 1 H, respectively, BC_6H_4); 8.12 (m, 1 H, BC_6H_4). MS, m/z (I_{rel} (%)): 397 $[M]^+$ (32), 396 (18), 326 (11), 325 (13), 265 (11), 174 (29), 172 (33), 159 (21), 105 (38), 91 (38), 77 (33), 70 (49), 57 (65), 44 (100), 43 (62), 42 (72).

6-Methyl-2-mesityl-4,8a-diphenylperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridine (13). The yield was 85%, m.p. 60 °C, R_f 0.42. Found (%): N, 3.33. $C_{28}H_{32}BNO_2$. Calculated (%): N, 3.29. ^{1}H NMR, δ: 2.40 (s, 3 H, NMe); 2.43 (s, 3 H, 4-Me); 2.49 (br.s, 6 H, 2-Me, 6-Me); 2.50—2.80 (br.m, 3 H, H(4a), H(5)); 6.91 and 6.98 (both s, 2 H, BC_6H_2); 7.10 and 7.26 (both br.m, 8 H and 2 H, respectively, C(4)Ph, C(8a)Ph). MS, m/z: 425 $[M]^+$.

6-Methyl-2-(3-trifluoromethylphenyl)-4,8a-diphenylperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridine (14). The yield was 65%, m.p. 95—96 °C, R_f 0.35. Found (%): N, 2.73. $C_{26}H_{25}BF_3NO_2$. Calculated (%): N, 2.97. ^{1}H NMR, δ: 2.38 (s, 3 H, NMe); 2.48 and 2.70 (both br.m, 1 H each, H(5)); 6.85—7.05 (br.m, 10 H, C(4)Ph, C(8a)Ph); 7.57 (dd, 1 H, BC_6H_4, H(5´), J = 7.1 Hz, J = 7.6 Hz); 7.76 (d, 1 H, BC_6H_4, H(6´), J = 7.6 Hz); 8.21 (d, 1 H, BC_6H_4, H(4´), J = 7.1 Hz); 8.27 (s, 1 H, BC_6H_4, H(2´)). MS, m/z: 471 $[M]^+$.

6-Methyl-4,8a-diphenyl-2-(4-pyridyl)perhydro[1,3,2]dioxaborinino[5,4-*c*]pyridine (15). The yield was 52%, m.p. 132—134 °C, R_f 0.40. Found (%): N, 7.03. $C_{24}H_{25}BN_2O_2$. Calculated (%): N, 7.29. ^{1}H NMR, δ: 2.32 (s, 3 H, NMe); 2.33 and 2.62 (both br.m, 2 H, H(5)); 6.93 and 7.05 (br.m, 8 H and 2 H, respectively, C(4)Ph, C(8a)Ph); 7.83 (d, 2 H, Py, H(2), H(6), J = 3.8 Hz); 8.86 (d, 2 H, Py, H(3), H(5), J = 3.8 Hz). MS, m/z: 384 $[M]^+$.

Crystals of compound **9** ($C_{25}H_{26}BNO_2$, M = 383.28) are monoclinic, space group $P2_1/n$, at T = 120 K, a = 9.6256(12), b = 18.699(2), c = 11.7919(14) Å, β = 100.832(3)°, V = 2084.6(4) Å, Z = 4, d_{calc} = 1.221 g cm^{-3}, F(000) = 816, μ = 0.076 mm^{-1}. The unit cell parameters and intensities of 14166 reflections were measured on an automated Bruker

SMART CCD-1000 diffractometer (λ-MoKα radiation, graphite monochromator, $\theta_{max} = 26°$). The structure was solved by direct methods and refined by the full-matrix least-squares method with anisotropic thermal parameters for all nonhydrogen atoms. The hydrogen atoms were revealed from difference Fourier syntheses and refined isotropically. The final reliability factors were as follows: $R_1 = 0.0546$ for 2786 independent reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1021$ for all 4065 independent reflections. All calculations were carried out using the SHELXTL PLUS (Version 5.10) program package.[16] The atomic coordinates and anisotropic thermal parameters were deposited with the Cambridge Structural Database.

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