Chemistry of Heterocyclic Compounds, Vol. 44, No. 11, 2008

SYNTHESIS AND MOLECULAR STRUCTURE OF SUBSTITUTED 2-HYDROXYPERHYDRO-[1,3,2]DIOXABORININO[5,4-*c*]PYRIDINES, PERHYDRO[1,3]DIOXANO[5,4-*c*]PYRIDINE, AND THEIR PRECURSOR – 4-HYDROXY-3-(α-HYDROXYBENZYL)-1-METHYL-4-PHENYLPIPERIDINE

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4,8a-Diphenyl-substituted 2-(2-propoxy)perhydro[1,3,2]dioxaborinino[5.4-c]pyridine was obtained by the condensation of 4-hydroxy-3-(α-hydroxybenzyl)-1-methyl-4-phenylpiperidine with triisopropyl borate, and its 2-hydroxysubstituted analog in the presence of water. 1-Methyl-4,8a-diphenyl-perhidro[1,3]dioxano[5,4-c]pyridine was synthesized by the reaction of the same piperidol with formaldehyde. A comparative study of the molecular structures of the three products was carried out by X-ray crystallography.

Keywords: 4-hydroxy-3-(α-hydroxybenzyl)-1-methyl-4-phenylpiperidine, perhydro[1,3,2]dioxaborinino-[5,4-*c*]pyridines, perhydro[1,3]dioxano[5,4-*c*]pyridine, triisopropyl borate, molecular structures.

The synthesis of 2,4,8a-triarylperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridines with aryl substituents at the boron atom has been reported [1-3]. The preparation of indicated derivatives of new heterocyclic systems was dictated by the observation that many of them when subjected to the PASS program [4] should possess (to a high degree of probability) effects on the central nervous system. In the same connection the molecular structure of B-phenyl-substituted perhydrodioxaborininopyridine was studied in detail – a racemic diastereomer for which *cis*-fusion of the two heterocyclic units was established, with three chiral atoms, C(4), C(4a), and C(8a) with the *R*-, *S*-, and *S*-configurations respectively [2]. In the present paper the syntheses of B-(2-propoxy)- (**2a**) and B-hydroxyperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridine (**2b**) are described, based on the substituted γ-piperidol **1**, and also their structural analog **2c** in which the boron atom is replaced by the CH_2 group; the

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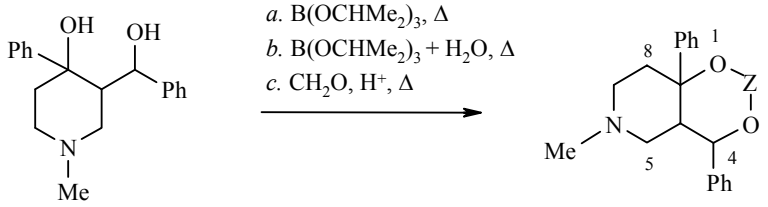
structures of compounds **1** and **2b,c**, determined by X-ray spectroscopy are discussed. The choice of he was based not only on the objective of comparing the most important characteristics with those of the dioxaborininopiperidine **2b** and the piperidol **1**, but also on the possibility that compound **2c** might possess a definite amount of bioisostery with its boron-containing analogs since computer screening with the PASS program showed that it was highly likely to affect the central nervous system; the possibility of treatment of disturbance of the cognitive function of the brain (74% probability) and treatment of Alzheimer's disease (57%), antagonism of the receptor of the GABA neuromediator (69%).

The dioxaborinine **2a** was synthesized in 56% yield by boiling the piperidol **1** with triisopropyl borate in dry hexane in a nitrogen atmosphere (variant *a*). Carrying out this reaction in the presence of moisture (variant *b*) gave compound **2b**, the product of the partial hydrolysis of its predecessor **2a**, in 70% yield.



1 **2a–c**

2 a Z = $BOCHMe_2$, **b** Z = BOH, **c** Z = CH_2

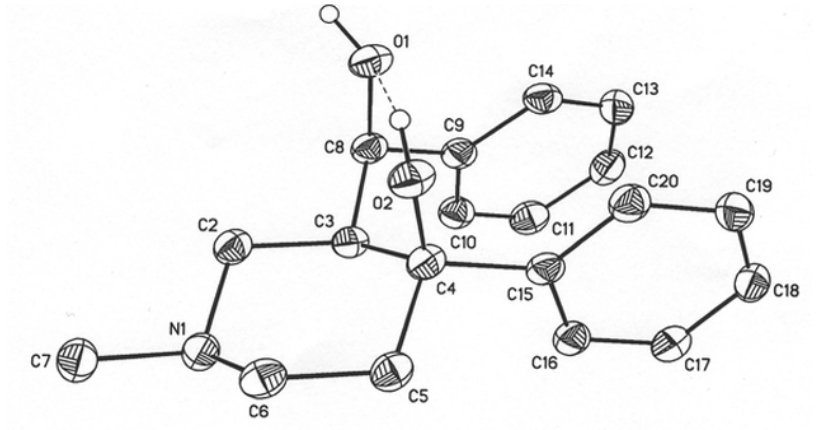
The dioxane derivative **2c** was obtained in 84.5% yield by condensation of formaldehyde with the diol **1** on heating in an acid medium (variant *c*). In order to establish the structures, refining the relative configuration of the stereogenic centers, and to determine other stereochemical characteristics of compounds **1**, **2b**, and **2c**, they were examined by X-ray crystallography. The general shape of molecules **1**, **2b**, and **2c** and their packing in the crystal are shown in Fig. 1-4 (the atoms are given with their crystallographic numbering). Bond lengths, bond and torsional angles of these substances are given in Tables 1-3 respectively. Lenghts of valence and hydrogen bonds, and also angles between them in the fragments of compound **1** D–H···A (D – donor atom, A – acceptor atom) are given in Table 4. The structure of compound **1** is shown in Fig. 1. It crystallized in the triclinic space group $P\bar{1}$,

Table 1. Lengths (*l*) of Some Bonds in the Molecules **1**, **2b**, and **2c**

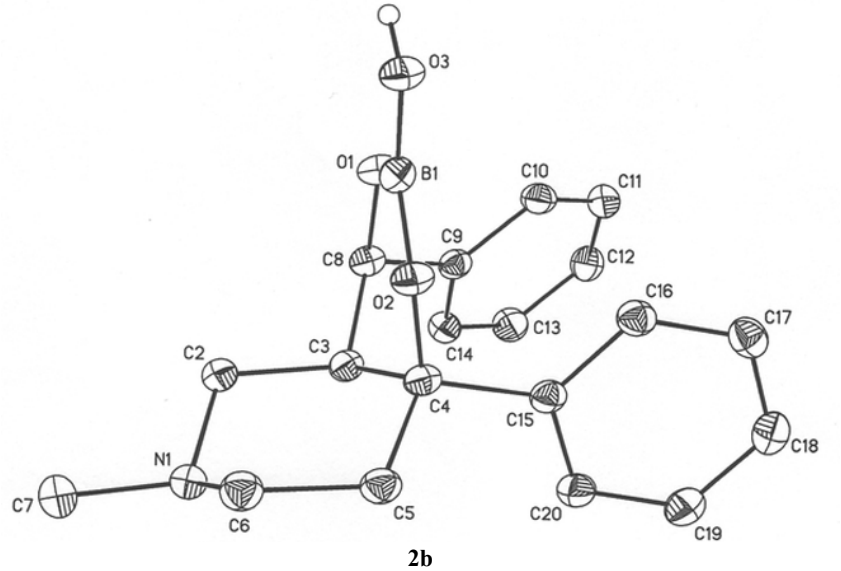
Bond	*l*, Å		
	1*	**2b**	**2c**
N(1)–C(2)	1.472(3)	1.469(2)	1.471(2)
N(1)–C(6)	1.473(3)	1.477(2)	1.463(2)
N(1)–C(7)	1.465(3)	1.462(2)	1.468(2)
C(2)–C(3)	1.524(3)	1.528(2)	1.534(2)
C(3)–C(4)	1.550(3)	1.550(2)	1.544(2)
C(3)–C(8)	1.540(3)	1.544(2)	1.541(2)
C(4)–O(2)	1.435(3)	1.443(2)	1.449(2)
C(4)–C(5)	1.537(3)	1.539(2)	1.530(2)
C(4)–C(15)	1.525(3)	1.532(2)	1.535(2)
C(5)–C(6)	1.511(3)	1.518(2)	1.520(2)
C(8)–O(1)	1.429(3)	1.434(2)	1.435(2)
C(8)–C(9)	1.515(3)	1.517(2)	1.511(2)
B(1)–O(1)		1.377(2)	
B(1)–O(2)		1.371(2)	
B(1)–O(3)		1.355(2)	
C(1)–O(1)			1.409(2)
C(1)–O(2)			1.412(2)

* Average values for the two independent molecules are cited.

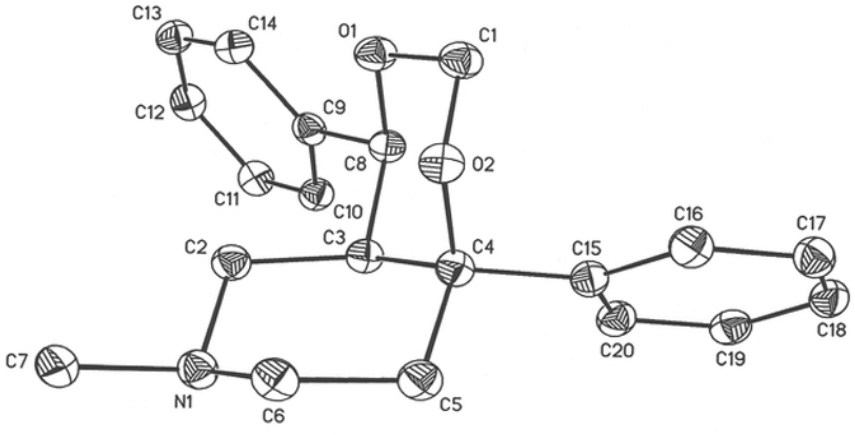
with two crystallographically independent molecules in the unit cell. The geometric parameters of these molecules are very close (average values are cited in Table 1), consequently we have carried out an averaged description of molecule **1**, which is a diastereomer with the asymmetric atoms C(3), C(4), and C(8) in the first independent molecule, and C(22), C(23), and C(27) in the second molecule. The relative configurations of these chiral centers are *rac*-3*S**,4*S**,8*R** and *rac*-22*S**,23*S**,27*R** respectively.



1



2b



2c

Fig. 1. Molecular structures of compounds **1**, **2b**, and **2c.**

The piperidine ring in the piperidol **1** has an almost ideal *chair* conformation (the ranges of the moduli of the torsion angles of the two independent molecules are 53.0(2)-63.2(2) and 55.4(2)-59.0(2)° respectively). The substituents Me, CH(OH)Ph, and Ph take equatorial positions in these molecules, while the hydroxy group takes an axial position. The plane of the phenyl substituent in the piperidine ring is essentially perpendicular to the plane C(2)C(3)C(5)C(6) or C(22)C(23)C25)C(26) (the angles between these rings are 88.2 and 86.1° respectively). The phenyl rings are placed practically one above the other and in each of the independent molecules their planes are almost parallel (the angles between them are 16.8 and 17.5° respectively). In

Table 2. Some Valence Angles (ω) in the Molecules of Compounds **1**, **2b**, and **2c**

Angle	ω, deg		
	1*	**2b**	**2c**
C(2)–N(1)–C(6)	109.6(2)	109.1(1)	110.2(1)
C(2)–N(1)–C(7)	110.4(2)	110.5(1)	108.6(1)
C(6)–N(1)–C(7)	110.2(2)	110.5(1)	109.0(1)
N(1)–C(2)–C(3)	112.0(2)	111.1(1)	113.4(1)
C(2)–C(3)–C(4)	109.3(2)	112.1(1)	111.1(1)
C(2)–C(3)–C(8)	109.4(2)	108.6(1)	109.8(1)
C(4)–C(3)–C(8)	116.4(2)	112.4(1)	108.7(1)
O(2)–C(4)–C(3)	109.9(2)	109.6(1)	107.8(1)
O(2)–C(4)–C(5)	105.9(2)	105.6(1)	106.3(1)
O(2)–C(4)–C(15)	110.6(2)	110.1(1)	109.1(1)
C(3)–C(4)–C(5)	107.7(2)	110.8(1)	109.6(1)
C(3)–C(4)–C(15)	113.0(2)	111.4(1)	115.1(1)
C(5)–C(4)–C(15)	109.4(2)	109.1(1)	108.5(1)
C(4)–C(5)–C(6)	112.8(2)	113.6(1)	112.2(1)
N(1)–C(6)–C(5)	111.0(2)	110.2(1)	110.5(1)
O(1)–C(8)–C(3)	109.8(2)	112.2(1)	109.1(1)
O(1)–C(8)–C(9)	111.6(2)	110.3(1)	108.5(1)
C(3)–C(8)–C(9)	115.0(2)	115.8(1)	113.8(1)
O(1)–B(1)–O(2)		122.8(1)	
O(1)–B(1)–O(3)		119.5(1)	
O(2)–B(1)–O(3)		117.7(1)	
B(1)–O(1)–C(8)		122.4(1)	
B(1)–O(2)–C(4)		120.2(1)	
C(1)–O(1)–C(8)			110.6(1)
C(1)–O(2)–C(4)			111.8(1)
O(1)–C(1)–O(2)			112.4(1)

* Average values for the two independent molecules are cited.

Table 3. Some Torsion Angles (θ) in the Molecules of Compounds **1**, **2b**, and **2c**

Angle	θ, deg		
	1*	**2b**	**2c**
C(8)–C(3)–C(4)–O(2)	64.3(2)	51.6(1)	54.9(1)
C(8)–C(3)–C(4)–C(15)	-59.8(2)	-70.5(1)	-67.2(1)
C(4)–C(3)–C(8)–C(9)	75.5(2)	86.3(1)	-177.5(1)

* Average values for the two independent molecules are cited.

addition, the phenyl rings of one independent molecule are practically perpendicular to the phenyl rings of the other. This distribution of the substituents is evidently determined by a system of strong intramolecular O-H···H and intermolecular O-H···N hydrogen bonds (Table 1, Fig. 1 and 2). The molecules are packed in a chain along the *b* axis (Fig. 2).

2-Hydroxydioxaborininopiperidine **2b** has *cis* fusion of the heterocycles (Fig.1) which is explained by the position of the hydroxyl groups in the starting material **1** at which the cyclization occurs. The conformation of the piperidine ring is a slightly distorted *chair* [the range of the values of the torsion angles is 45.3(1)-64.1(1)°], the conformation of the borinine ring is a slightly distorted *sofa* with a deviation of atom C(3) from the mean square of the remaining atoms by 0.578 Å. The boron atom has a generally planar configuration (the sum of its valence angles is 360.0°). Just as in the piperidol **1**, compound **2b** is a diastereomer with three asymmetric atoms C(3), C(4), and C(8). The relative configuration of these chiral centers is retained on cyclization – *rac*-3*S**,4*S**,8*R**.

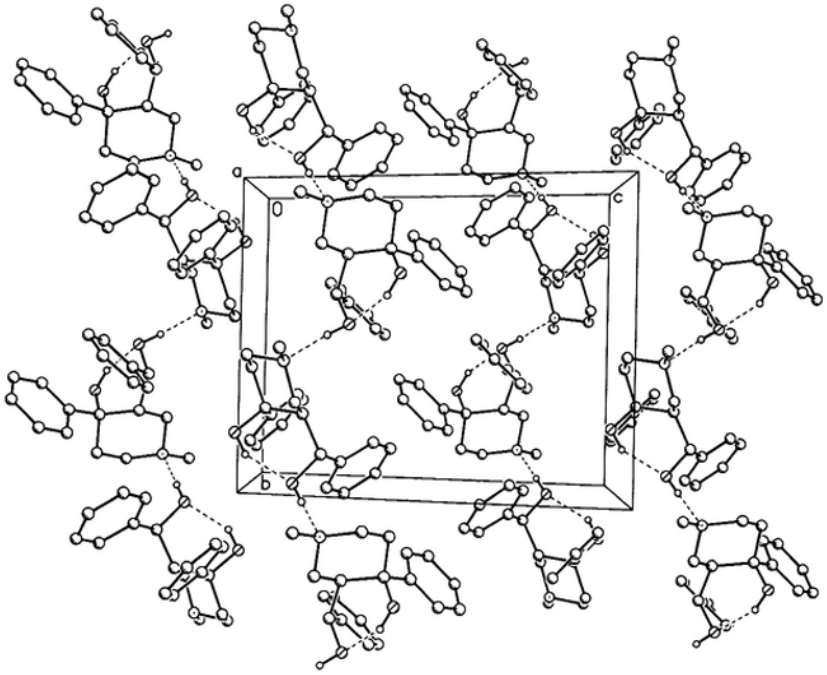


Fig. 2. Packing of the molecules in the crystal of compound **1** along the *a* axis.

The general structure of the molecule of **2b** is identical to that of the molecule of piperidol **1** starting material. The phenyl substituent in the piperidine ring is effectively perpendicular to the C(2)C(3)C(5)C(6) (the angle between these planes is 84.0°). The two phenyl groups are distributed *cis*-perpendicularly relative to the borininine ring, however as a result of the formation of the latter ring the angle between them is increased to 37.2°. It is interesting that in the crystal of **2b** overall chain structural motive along the *b* axis is also retained because of the intermolecular O(3)–H···N(1) hydrogen bonds [O(3)···N(1) 2.792(2), H···N 1.89 Å, and O–H···N 171°] (Fig. 3).

In the dioxanopiperidine **2c** *cis* fusion of the heterocycles also occurs (Fig.1) which is determined for the same reason as for compound **2b**. The normal *chair* conformation is characteristic for the piperidine ring [the range of the moduli of the torsion angles is 49.4(2)-59.8(2)°]. It should be noted that in the formation of 1,3-dioxane ring, which also has the general *chair* conformation [range of the values of the moduli of the torsion angles 54.9(1)-61.9(2)°], an inversion of the asymmetric atom C(8) occurs. As a result the relative configurations of the chiral centers C(3), C(4), and C(8) in the diastereomer **2c** becomes *rac*-3*S**,4*S**,8*S**. In

consequence the planes of the phenyl substituents are positioned *anti*-periplanar relatively to the newly formed dioxane ring, with an angle between them of 44.8°. Moreover, the position of the phenyl substituent in the piperidine ring is changed – it is considerably tilted from the perpendicular position to the C(2)C(3)(C5)(C6) plane found in compounds **1** and **2b** (the angle between these planes equals 53.2°).

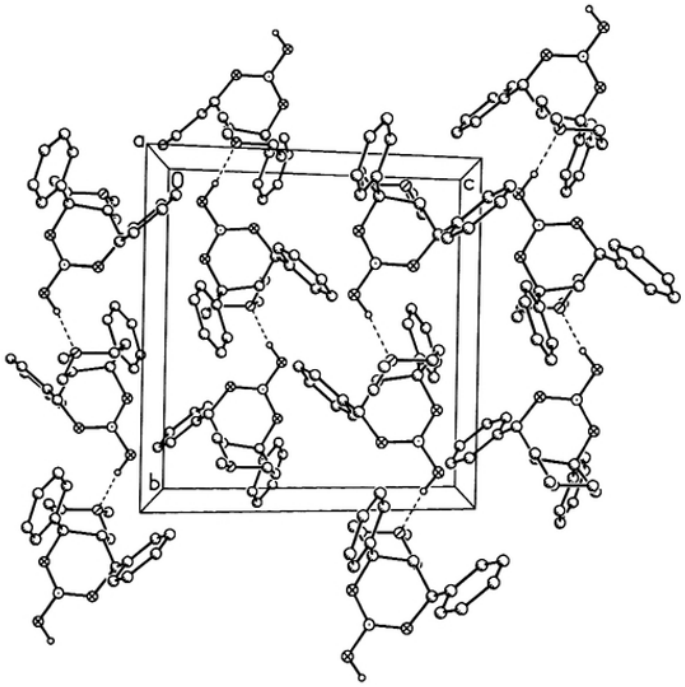


Fig. 3. Packing of the molecules in the crystal of compound **2b** along the *a* axis.

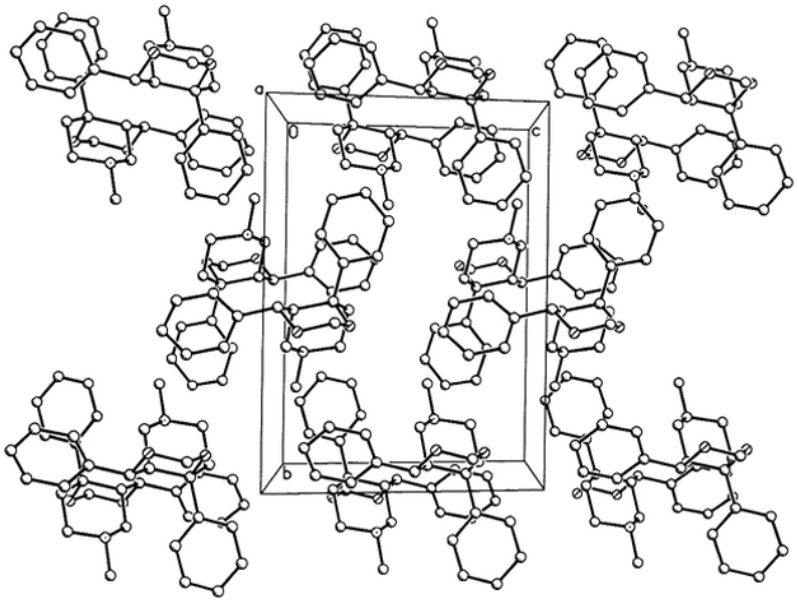


Fig. 4. Packing of the molecules in the crystal of compound **2c** along the *a* axis.

Table 4. Lengths (*l*) of Valence and Hydrogen Bond in the Units D–H···A in Compound **1**, Distance (*d*) between Atoms D and A, Angles (θ) D–H···A

Unit D–H···A	*l*, Å		*d*, Å	θ, deg
	D–H	H···A		
O(2)–H···O(1)	0.86	1.94	2.714(2)	149
O(4)–H···O(3)	0.88	1.93	2.716(2)	148
O(1)–H···N(2)*	0.91	1.82	2.727(3)	178
O(3)–H···N(1)	0.92	1.80	2.722(3)	173

* The symmetry operation $x, y + 1, z$ was used to generate equivalent atoms.

Table 5. Basic Crystallographic Data and Parameters for the Refinement of Compounds **1**, **2b**, and **2c**

	1	**2b**	**2c**
Empirical formula	$C_{19}H_{23}NO_2$	$C_{19}H_{22}BNO_3$	$C_{20}H_{23}NO_2$
Molecular mass	297.38	323.19	309.39
T, K	120	115	120
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$	$P2_1/c$
a, Å	10.426(3)	11.1303(11)	10.796(2)
b, Å	11.190(3)	12.8639(16)	14.304(3)
c, Å	14.416(5)	12.5271(16)	10.6135(19)
α, deg	89.556(8)	90	90
β, deg	71.331(7)	107.045(5)	102.105(6)
γ, deg	88.007(10)	90	90
V, Å^3	1592.4(8)	1714.8(4)	1602.6(5)
Z	4	4	4
d_c, g cm^{-3}	1.240	1.252	1.282
F(000)	640	688	664
μ, mm^{-1}	0.080	0.083	0.082
$2\theta_{max}$, deg.	54	56	56
No. of reflexions			
measured	14760	17682	11032
independent	6823	4133	3768
observed with $I > 2\sigma(I)$	4119	3342	3110
No. of parameters refined	399	218	209
R_1 ($I > 2\sigma(I)$)	0.0645	0.0494	0.0521
wR_2 (all data)	0.1553	0.1305	0.1243
GooF	1.007	1.028	1.008

The packing of molecules **2c** in the crystal is stacked along the *a* axis. The molecules are distributed at van der Waals distances, there are no short contacts in the structure.

Comparison of the X-ray crystallographic data for compounds **2b** and **2c** shows that both have isosteric *cis* fusion of the heterocycles. The single structural difference is the *cis*-1,3-diaxial relative position of the phenyl substituents in the borinine nucleus of molecules **2b** and their *trans* position in the dioxane ring of molecules **2c**.

EXPERIMENTAL

IR spectra of KBr disks were recorded with an IR-75 instrument. Mass spectra were recorded with a Finnigan MAT Incos 50 instrument with direct introduction of the sample into the ion source with an ionizing current of 70 eV. ^{1}H and ^{13}C NMR spectra in $CDCl_3$ solution with TMS as internal standard were recorded with a Bruker WM-400 instrument (400 and 100 MHz respectively).

X-ray structural analysis of compounds 1, 2b, and 2c. Monocrystals of compounds **1** and **2b** were grown from acetone, of compound **2c** were measured from diethyl ether. Unit cell parameters and the intensities of reflexions for compounds **1**, **2b**, and **2c** were measured on a Bruker SMART 1000 CCD automatic three-circle diffractometer (λMoKα-radiation, graphite monochromator, φ- and ω-scanning). The basic crystallographic data are presented in Table 5. The structures of all compounds were solved by direct methods and refined by full matrix least squares method in the anisotropic approximation for non-hydrogen atoms. The hydrogen atoms of the hydroxyl groups in compounds **1** and **2b** were localized objectively in difference Fourier syntheses and refined in the isotropic approximation with fixed positions and thermal parameters. The positions of the remaining hydrogen atoms in the compounds **1**, **2b**, and **2c** were calculated geometrically and refined in the isotropic aproximation with fixed positions (the "riding" model) and thermal parameters [U_{iso}(H) = 1.5U_{eq}(C) for CH_3 groups and U_{iso}(H) = 1.2U_{eq}(C) for all other groups]. All calculations were carried out with SHELXTL PLUS (version 5.10) suite of programs [5]. Tables of atomic coordinates, bond lengths, valence and torsional angles, and anisotropic thermal parameters for compounds **1**, **2b**, and **2c** have been deposited in the Cambridge Structural Data Bank (deposit CCDC 693537-693539).

6-Methyl-4,8a-diphenyl-2-(2-propoxy)perhydro[1,3,2]dioxaborinino[5,4-*c*]pyridine (2a). A mixture of piperidol **1** (1 g, 3.37 mmol) and triisopropyl borate (2.07 g, 11.0 mmol) in dry hexane (50 ml) was boiled for 2 h under a nitrogen atmosphere in a Dean-Stark apparatus with a calcium chloride tube. The hexane was evaporated off and the residue was crystallized from acetone to give 0.69 g (56%) of product, mp 185-186°C (colorless crystals). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 and 1.33 (6H, two d, $J_1 = J_2 = 6.1$, $CH(C\underline{H}_3)_2$); 1.79 and 2.01 (2H, two m, H-8); 2.38 (3H, s, NCH_3); 2.46 (1H, t, $^2J = 10.8$, H-4a); 2.63-2.95 (4H, m, NCH_2); 4.03 (1H, m, $C\underline{H}CH_3$); 4.95 (1H, br. s, H-4); 6.75-6.99 (10H, m, H Ph). Mass spectrum, *m/z* (I_{rel}, %): 365 $[M]^+$ (2), 323 $[M\text{-}C(CH_3)_2]^+$ (29), 322 (5), 251 (7), 191 (11), 172 (38), 159 (26), 105 (20), 77 (26), 71 (35), 70 (52), 57 (67), 44 (100), 43 (72), 42 (65). Found, %: C 72.41; H 7.55; N 3.62. $C_{22}H_{28}BNO_3$. Calculated, %: C 72.34; H 7.73; N 3.83.

2-Hydroxy-6-methyl-4,8a-diphenylperhydro[1,3,2]dioxaborinino[5,4-*c*]pyridine (2b). A mixture of piperidol **1** (4 g, 13.4 mmol), triisopropyl borate (2.6 g, 13.83 mmol, and hexane (50 ml) was boiled in a Dean Stark apparatus for 8 h in moist air. The reaction mixture was treated as described above for compound **2a** to give product **2b** (3.04 g, 70%, colorless crystals), mp > 230°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.78 and 2.06 (2H, two m, H-8); 2.40 (3H, s, NCH_3); 2.43 and 2.70 (2H, two m, NCH_2); 2.46 and 2.53 (1H, t, $^3J = 11.0$, H-4a); 2.90-3.10 (2H, m, NCH_2); 4.90 (1H, m, H-4); 6.70-7.05 (10H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 25.3 (C-8); 40.7 (NCH_3); 45.2 (C-5); 45.9 (C-7); 56.9 (C-4a); 65.7 (C-4); 74.0 (C-8a quat), 124.5-128.8 (10C, C_6H_5); 141.6 (C Ph quat); 141.4 (C quat arom). Mass spectrum, *m/z* (I_{rel}, %): 323 $[M]^+$. Found, %: C 70.37; H 7.05; N 4.20. $C_{19}H_{22}BNO_3$. Calculated, %: C 70.61; H 6.86; N 4.33.

6-Methyl-4,8a-diphenylperhydro[1,3]dioxano[5,4-*c*]pyridine (2c). A mixture of piperidol **1** (2.0 g, 6.7 mmol), formaldehyde (0.31 g, 10.1 mmol), water (14 ml), and conc. H_2SO_4 (7 ml) was boiled for 5.5 h, then cooled and extracted with ethyl acetate (2×20 ml, extract 1). The aqueous layer was basified with 20% NaOH solution to pH 10, and extracted with ethyl acetate (3×10ml, extract 2). Extract 2 was dried over $MgSO_4$. The residue after evaporating extract 2 was crystallized from ether to give compound **2c** (1.75 g, 84.5%, white crystals), mp 133-135°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80 (2H, m, H-8); 2.17 (3H, s, CH_3); 2.22-2.60 (4H, m, H-5,7); 2.81 (1H, m, H-4a); 4.83 (1H, d, $^3J = 2.5$, H-4); 5.01 and 5.10 (2H, two, d, $J_1 = J_2 = 6.4$, H-2); 7.21-7.50 (10H, m, H Ph). Mass spectrum, *m/z* (I_{rel}, %): 309 $[M]^+$. Found, %: C 77.82; H 7.55; N 4.32. $C_{20}H_{23}NO_2$. Calculated, %: C 77.64; H 7.49; N 4.53.

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