Heteroatom Chemistry
Volume 5, Number 2, 1994

New Phenylboronic Esters Derived from Inositol [1]

Verónica Salazar-Pereda, Laura Martínez-Martínez,
Angelina Flores-Parra,* María de Jesús Rosales-Hoz,
Armando Ariza-Castolo, and Rosalinda Contreras*

Departamento de Química, Centro de Investigacion y de Estudios Avanzados del Instituto Politécnico Nacional, 0700 México D. F., México

Received 12 October 1993; revised 4 January 1994

ABSTRACT

We have prepared two new tetracyclic phenylboronic esters **4** *and* **5** *derived from myo-inositol and from 1,2-O-isopropylidene-myo-inositol, respectively. The structures of these compounds were established from NMR and IR spectra, elemental analyses, and an X-ray diffraction study in the case of* **4**. *Compound* **4** *is a tetracyclic derivative of the less stable conformer of inositol (five axial hydroxy groups and one equatorial) with two dioxaboroline rings at opposite faces of the six-membered ring, one formed between the boron atom and the axial hydroxyl groups at C-3 and C-5 and the other between the boron atom and the hydroxyl groups at C-4 and C-6, and a dioxaborolidine ring bridging C-1 and C-2 at axial and equatorial positions. A similar structure was found for* **5** *with the difference that bridging C-1 and C-2 there is a dioxolane ring. The boron atoms are planar with their attached atoms, stabilized by retrocoordination between the boron and oxygen and carbon atoms, respectively. The two phenyl rings that are in the same face of the molecule are essentially parallel, with a dihedral angle between planes of 28.26 ± 0.79°.*

INTRODUCTION

We are involved in the study of organic boron derivatives of cyclitols principally derived from biologically active molecules such as quinic acid [2]. The study of the reactivity of polyfunctional organic molecules toward the boron reagents affords relevant information about the structures. In addition, the possibility of introducing several boron atoms in a small organic molecule could be of interest in the search for boron targets for neutron cancer therapy. We are also interested in the electronic behavior of boron and in knowing how coordination or retrocoordination may stabilize new structures [3].

Myo-inositol **1** is a very important biological substance involved in several cell functions and its derivatives are being actively studied [4]. Compound **1** contains a cyclohexane ring with six hydroxy groups. Its preferred conformation has five equatorial oxygen atoms and one axial oxygen [5]. The polyfunctional character of **1** makes it possible to obtain several polycyclic compounds by reaction with phenylboronic acid. One, two, or three boronate groups can be introduced.

Reaction of **1** with 2,2-dimethoxypropane affords selectively compound **2** showing that the equatorial and axial hydroxy groups (C-1 and C-2 or C-2 and C-3) are more reactive than the other groups [6]. Under stronger acidic conditions, a second compound **3**, among others, can be obtained corresponding to a second dioxolane ring bridging C-4 and C-5. In both dioxolane derivatives, the cyclohexane conformation is the same as in **1** [7].

We were interested in investigating the reaction of **1** with different amounts of phenylboronic acid in order to see if it followed the same behavior as that observed in the dioxolane formation and whether it was possible to obtain products with

---

*To whom correspondence should be addressed.

1042-7163/94/$5.00 + .25

different degrees of substitution. In all the reactions of *myo*-inositol with phenylboronic acid, only one compound (**4**) was formed. The same reactivity was found for compound **2**, which also gave only one compound (**5**, Figure 1).

NMR STUDY

The structures of compounds **4** and **5** were deduced from NMR analysis. The ^{11}B NMR spectra exhibit a broad singlet at $\delta = +28.6$ and $+28.9$ for **4** and **5**, respectively, characteristic of phenylboronic esters [8]. The chemical shift assignments of ^1H and ^{13}C NMR were made by HETCOR $^{13}C/^1H$, COSY, and H-coupled ^{13}C NMR spectra. The ^1H NMR spectra of **4** and **5** show three and two sets of aromatic protons, respectively, indicating the introduction of three phenylboronic groups in **4** and two in **5**.

The presence in the ^1H NMR spectra of four W ^4J coupling constants in **4** [^4J(H–H): (H_1–H_3) = (H_3–H_5) = 1, (H_1–H_5) = 1.1, and (H_4–H_6) = 1.8 Hz] and also in **5** [^4J(H–H): (H_1–H_3) = 1.3, (H_1–H_5) = 1.2, (H_3–H_5) = 1.6, and (H_4–H_6) = 2 Hz] was indicative of a preferred chair conformation with five equatorial protons. Therefore, the conformations of **4** and **5** correspond to the less stable chair conformer of inositol, **1a**. The phenylboronic acid reacted with the two axial hydroxy groups in **5** at each face of the molecule and with the same two groups in **4** as well as with the axial and the equatorial hydroxy functions at C-2 and C-1. The NMR spectra of **4** and **5** are very similar, indicating analogous structures. The correct assignment of the coupling constants was corroborated by the simulated spectra [9], the dihedral angles being calculated from coupling constants ^3J(H–H) (Table 1). The ^{13}C NMR chemical shifts of the aromatic C-*para* indicate trigonal hybridization of the boron atom. These atoms appear shifted at higher frequency (5 ppm) than those of phenyl groups attached to tetracoordinated boron atoms. This is attributed to the retrocoordination effect from the phenyl group to the boron atom [3a]. The C-*ipso* are identified because they give rise to broad signals due to the quadrupolar effect of boron atoms.

X-RAY DIFFRACTION STUDY OF COMPOUND 4

The X-ray diffraction structure of **4** confirmed the NMR results. The structure is depicted in Figure 2. Compound **4** is a tetracyclic compound, with two dioxaboroline rings at opposite faces of the six-membered ring, one between the boron atom and the axial hydroxy groups at C-3 and C-5 and the other with the hydroxy groups at C-4 and C-6; the dioxaborolidine ring bridges C-1 and C-2 that have axial and equatorial oxygens, respectively. From this structure, it is deduced that the less favorable

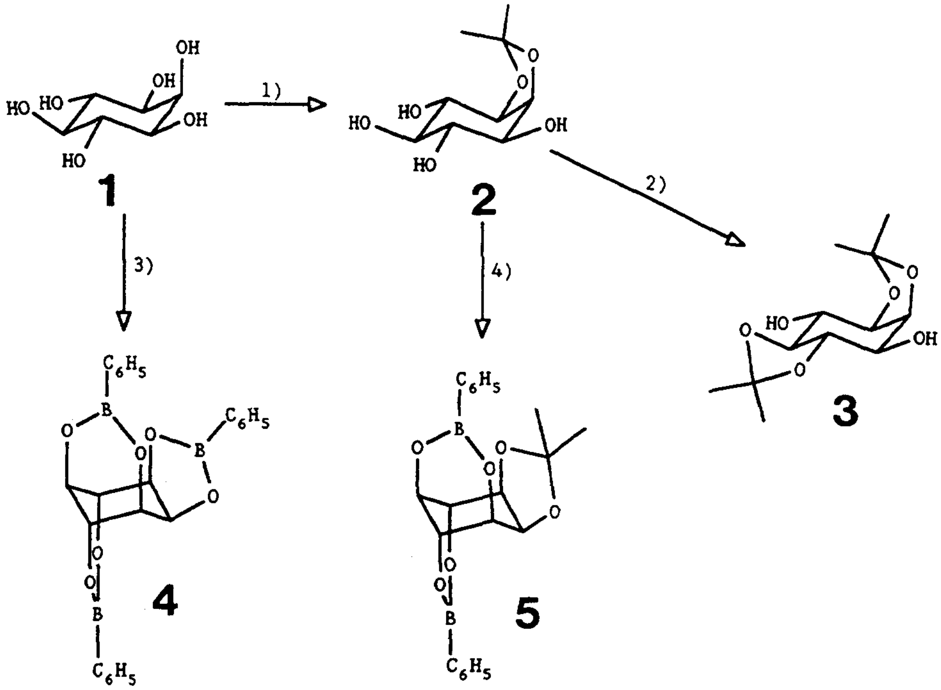

FIGURE 1 (1) 2,2-Dimethoxypropane/DMSO (40%); (2) 2,2-dimethoxypropane/acetone, H^+ (20%); (3) 3 equivalents of $C_6H_5B(OH)_2$; and (4) 2 equivalents of $C_6H_5B(OH)_2$.

TABLE 1 Coupling Constants ($^3J_{H-H}$, Hz) and Dihedral Angles (°) of Compounds **1**, **3**, and **4** [10]

	Compound Number		
$^3J_{H-H}$	**1**^{a}	**4**	**5**
H_1–H_2	2.9/57	6.3/39	5.8/
H_2–H_3	2.9/57	3.2/46	4.6/
H_3–H_4	9.4/177	4.0/53	4.8/
H_4–H_5	9.0/186	4.3/55	4.4/
H_5–H_6	9.0/186	4.2/60	3.5/
H_6–H_1	9.5/177	2.2/66	3.5/

[a] $^3J_{Hx-OH}$ if: $x = 1$, $J = 5.8$; $x = 2$, $J = 3.4$; $x = 3$, $J = 5.8$; $x = 4$, $J = 4.6$; $x = 5$, $J = 4.3$; and $x = 6$, $J = 4.6$ Hz.

conformer **1a** gave the more stable boron heterocycle. Compound **4** is a rigid molecule without any possibility of inverting its conformation. The crystal, distance, and angle data are shown in Tables 2–6.

Both six-membered rings are almost planar, with one atom C5 in ring **C** and with C4 in ring **B** outside of the main plane, as can be deduced from the selected torsion angles shown in table 5. Conversely, the five-membered ring is not planar but exists in a twist conformation with very open dihedral angles. The cyclohexane ring has a distorted chair conformation (Figure 2).

The boron atoms are planar with the other atoms to which they are bonded, indicating retrocoordination from the oxygen and carbon atoms. The B–O length (1.35–1.39 compared with a calculated single bond distance of 1.5 Å, Table 3) indicates partial double bond character. The same is observed to a lesser extent in the C–B bond (1.48–1.52 compared with the calculated C–B distance of 1.59 Å).

The distances between the *ipso*- and *ortho*-carbon atoms in the phenyl rings are longer than those between *meta*- and *para*-carbons. This is also indicative of an interaction between the *ipso*-carbon and boron atoms. This interaction is also deduced from the fact that the phenyl ring is almost coplanar with the boron ring, with dihedral angles being between 5 and 12°. A very interesting finding is the relative position between the two boron and two phenyl rings that are nearly parallel, with a dihedral angle between the phenyl ring planes of 28.26 ± 0.81°. In Table 6, the nonbonding distances between the two rings are reported, showing that oxygen atoms O1 and O5 are the nearest atoms with a distance of 3.01 Å and that the farthest are C10 and C22 with a distance of 4.87 Å.

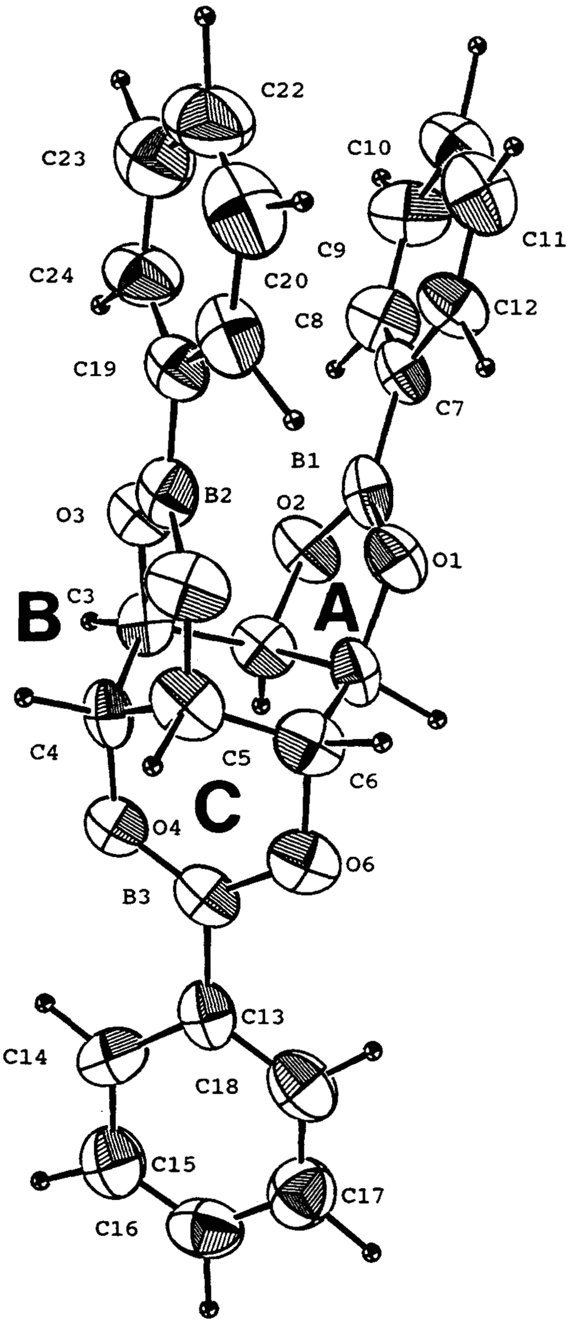

FIGURE 2 X-ray diffraction structure of compound **4**.

EXPERIMENTAL

Melting points were measured on a Gallenkamp apparatus and are uncorrected. The infrared spectra were taken in KBr-discs using a Nicolet MX-1-FT infrared spectrometer. All the NMR spectra were obtained on a JEOL GXS-270 spectrometer in DMSO-d_6 or D_2O solution. The ^1H, ^{13}C, and ^{11}B NMR spectra were obtained at 270, 67.8, and 86.55 MHz, respectively. ^1H and ^{13}C NMR spectra were measured with TMS as the internal reference. ^{11}B NMR spectra were obtained with BF_3-OEt_2 as an external reference. *myo*-Inositol 1 was purchased from

TABLE 2 Crystal Data of Compound **4**

Formula	$C_{24}H_{21}B_3O_6$
FW	437.86
Crystal dimensions	0.50 × 0.40 × 0.50 mm
System	monoclinic P
Space group	$P2_{1/a}$
a/Å	11.486(7)
b/Å	13.624(5)
c/Å	14.303(8)
β, °	105.08
V, Å^3	2161.2
Z	4
μ (Mo K_α), cm^{-1}	0.9
F (000)	912
d_{calcd}, g cm^{-3}	1.35
2θ range, °	2.8–20.4
Scan type	$\omega/2\theta$
Scan width, °	1.2 + 1.500 tan θ
Scan speed, ° min^{-1}	4–20
Diffractometer	CAD4F
No. of reflections collected	1899
No. of unique reflections	1899
No. of reflections with I > $3\sigma(I)$	1899
R	0.091
R_w	0.084
Abs coeff cor	0.68 < coeff < 1
No. of variables	378
Weighting scheme	unity
Residual electron density e/A^3	0.4/0

TABLE 3 Bond Distances (Å) of Compound **4**

01–C1	1.450(7)	C1-C6	1.545(9)	C13-C18	1.39(1)
01–B1	1.390(9)	C2-C3	1.52(1)	C13-B3	1.52(1)
02–C2	1.442(7)	C3-C4	1.516(9)	C14-C15	1.387(9)
02–B1	1.377(9)	C4-C5	1.52(1)	C15-C16	1.36(1)
03–C3	1.432(7)	C5-C6	1.51(1)	C16-C17	1.37(1)
03–B2	1.379(9)	C7-C8	1.395(9)	C17-C18	1.39(1)
04–C4	1.426(7)	C7-C12	1.395(9)	C19-C20	1.40(1)
04–B3	1.35(1)	C7-B1	1.506(9)	C19-C24	1.41(1)
05–C5	1.423(8)	C8-C9	1.37(1)	C19-B2	1.48(1)
05–B2	1.370(9)	C9-C10	1.38(1)	C20-C21	1.39(1)
06–C6	1.424(7)	C10-C11	1.40(1)	C21-C22	1.37(1)
06–B3	1.37(1)	C11-C12	1.37(1)	C22-C23	1.40(1)
C1–C2	1.54(1)	C13-C14	1.40(1)	C23-C24	1.37(1)

TABLE 4 Some Selected Bond Angles (°) of Compound **4**

C1–01–B1	106.6(5)	C6–06–B3	118.7(6)	04–B3–06	121.7(6)
C2–02–B1	107.0(5)	01–B1–02	111.5(5)	01–B1–C7	125.0(6)
C3–03–B2	122.1(5)	02–B1–C7	123.5(6)	03–B2–C19	121.1(7)
C5–05–B2	120.5(5)	03–B2–05	119.6(6)	04–B3–C13	120.6(7)
C4–04–B3	121.6(5)	05–B2–C19	119.3(7)	06–B3–C13	117.6(7)

Aldrich, and compounds **2** and **3** were prepared as described in Ref. [6].

1:2, 3:5, 4:6-*O^1:O^2, O^3:O^5, O^4:O^6-tris(Phenylboronate)-myo-inositol* **4**

myo-Inositol (1 g, 5.55 mmol), phenylboronic acid (0.6767 g, 5.5 mmol), and dried benzene (75 mL) were refluxed for 48 hours under vigorous stirring. Then, the mixture was filtered to remove the inositol that had not reacted. The solvent was evaporated in vacuum and a white solid was obtained, 75% yield, mp 204–208°C. Anal. calcd for $C_{24}H_{21}O_8B_3[C_6H_6]_{1/5}$: C, 66.7: H, 4.93. Found: C, 67.0: H, 4.8. NMR ^{11}B (86.55 MHz, $CDCl_3$): δ 28.9. NMR ^1H (270 MHz. $CDCl_3$): δ 4.79 (1H, dd, H-1); 4.84 (1H, dd, H-2); 4.71 (1H, dddd, H-3); 4.77 (1H, dd, H-4); 4.63 (1H, dddt, H-5); 5.02 (1H, ddd, H-6); 7.40 (1H, dt, H*o*); 6.99 (1H, t, H*m*); 7.21 (1H, dd, H*p*); 7.50 (1H, dt, H*o*); 7.13 (1H, t, H*m*); 7.33 (1H, dd, H*p*); 7.82 (1H, dt, H*o*); 7.58 (1H, t, H*m*); 7.52 (1H, dd, H*p*). NMR ^{13}C (67.8 MHz, $CDCl_3$): δ 74.44 (C-1); 73.95 (C-2); 67.29 (C-3); 66.67 (C-4); 64.95 (C-5); 68.74 (C-6); 134.81 (C*o*); 127.87 (C*m*); 131.84 (C*p*); 134.36 (C*o*); 127.43 (C*m*); 131.50 (C*p*); 134.05 (C*o*); 127.09 (C*m*); 130.90 (C*p*).

1:2-*O-Isopropyliden*-**3:5, 4:6**-*O^3:O^5, O^4:O^6-bis(phenylboronate)-myo-inositol* **5**

Compound **2** (1 g, 4.54 mmol), dried benzene (75 mL), and phenylboronic acid (0.553 g 4.54 mmol) were refluxed for 48 hours under vigorous stirring, and then the reaction mixture was filtered in order to remove the compound **2** that had not reacted. Evaporation of the solvent afforded a white solid, 68% yield, mp 172–173°C. Anal. calcd for $C_{21}H_{22}O_6B_2$: C, 64.3%; H, 5.6%. Found: C, 64.6%: H, 5.9%. NMR ^{11}B (86.55 MHz, $CDCl_3$) δ 28.6. NMR ^1H (270 MHz, $CDCl_3$): δ 4.57 (1H, ddd, H-1); 4.45 (1H, dd, H-2); 4.61 (1H, t, H-3); 4.70 (1H, ddd, H-4); 4.58 (1H, ddd, H-5); 4.91 (1H, ddd, H-6); 7.81 (1H, d, H*o*); 7.36 (1H, t, H*m*); 7.43 (1H, t, H*p*); 7.85 (1H, d, H*o*); 7.37 (1H, t, H*m*); 7.45 (1H, t, H*p*); 1.33 (3H, s, CH_3); 1.27 (3H, s, CH_3). NMR ^{13}C (67.8 MHz, $CDCl_3$); δ 75.51 (C-1); 72.38 (C-2); 67.08 (C-3); 67.58 (C-4); 64.90 (C-5); 68.21 (C-6); 134.37 (C*o*); 127.81 (C*m*); 131.71 (C*p*); 134.28 (C*o*); 127.64 (C*m*); 131.10 (C*p*); 110.48 (-C-); 25.61 (CH_3); 25.15 (CH_3).

Crystal Data

Selected crystals were set up on an automatic diffractometer, and diffraction data were collected using molybdenum radiation. Unit-cell dimensions with estimated standard derivations were obtained from least-squares refinements of the set-

TABLE 5 Selected Torsion Angles (°) of Compound **4**

Atoms					*Atoms*				
1	*2*	*3*	*4*	*Angles*	*1*	*2*	*3*	*4*	*Angles*
B1	O1	C1	C2	−23.23(0.64)	C2	C3	C4	C5	64.48(0.67)
B1	O2	C2	C1	−29.01(0.64)	C3	C4	C5	C6	−68.73(0.66)
C3	O3	B2	O5	−8.25(1.04)	C4	C5	C6	C1	57.96(0.75)
C4	O4	B3	O6	−5.22(0.94)	C5	C6	C1	C2	41.13(0.89)
B2	O5	C5	C4	−29.32(0.87)	C6	C1	C2	C3	35.59(0.79)
C5	O5	B2	O3	4.29(1.06)	O4	C4	C5	O5	176.42(0.49)
B3	O6	C6	C5	37.89(0.76)	O5	C5	C6	O6	174.56(0.48)
C6	O6	B3	O4	−4.08(0.92)	C12	C7	B1	O1	−10.95(1.11)
O1	C1	C2	O2	31.62(0.57)	C14	C13	B3	O4	−5.21(1.00)
O2	C2	C3	O3	−40.83(0.65)	C20	C19	B2	O5	12.29(1.14)
C1	C2	C3	C4	−48.08(0.76)					

TABLE 6 Nonbonding Distance (Å) of Compound **4**

B1–B2	3.1379	C9–C23	4.8165
O1–O5	3.0117	C10–C22	4.8774
O2–O3	2.6597	C11–C21	4.4507
C7–C19	3.8358	C12–C20	3.9489
C8–C24	4.3017		

ting angles of 25 well-centered reflections. Two standard reflections were monitored periodically; they showed no change during data collection. Crystallographic data and other pertinent information are summarized in Table 1. Corrections were made for Lorentz and polarization effects. An empirical absorption correction (PSISCAN) was applied. Atomic scattering factors for neutral S, C, N, O, and H were taken from Ref. [11].

The structure was solved by direct methods using MOLEN and refined by full matrix least-squares cycles. Anisotropic temperature factors were introduced for all nonhydrogen atoms. The hydrogen atoms were found on difference electron density maps and refined isotropically.

Tables 3–5 contain interatomic distances and bond angles. Positional parameters for all atoms, final thermal parameters, and a list of calculated and observed structure factor tables have been deposited with the Cambridge Crystallographic Data Center.

ACKNOWLEDGMENTS

We thank Mr. Guillermo Uribe Rojas for NMR spectra recording and Mr. Efren Garcia Báez for his technical assistance in the X-ray diffraction study.

REFERENCES

[1] This work was presented at the "Eighth IMEBORON Meeting," University of Tennessee, Knoxville, TN, July 11–15, 1993.

[2] (a) A. Flores-Parra, C. Paredes-Tepox, P. Joseph-Nathan, R. Contreras, *Tetrahedron, 46,* 1990, 4137; (b) M. A. Bello-Ramirez, M. E. Rodriguez-Martinez, A. Flores-Parra, *Heteroatom Chem., 4,* 1993, 613.

[3] (a) N. Farfan, R. Contreras, *J. Chem. Soc., Perkin Trans. II,* 1987, 771; (b) A. Ariza-Castolo, A. Paz-Sandoval, R. Contreras, *Magn. Reson. Chem., 30,* 1992, 520; (c) I. I. Padilla-Martinez, A. Ariza-Castolo, R. Contreras, *Magn. Reson. Chem., 31,* 1993, 189.

[4] (a) M. J. Berridge, R. F. Irvine, *Nature 341,* 1989, 197; (b) A. B. Reitz (ed): *Inositol Phosphates and Derivatives,* ACS Symposium Series, Vol. 463, 1991; (c) M. Ghisletta, H.-P. Jalett, T. Gerfin, K. Hegetschweiler, *Helv. Chim. Acta, 75,* 1992, 2233; (d) Ch. Yuan, H. Zhai, Y. Li, S. Wang, *Phosphorus, Sulfur, and Silicon, 69,* 1992, 71.

[5] V. Salazar-Pereda: Ms.D. Thesis, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, México, 1993.

[6] J. Gigg, R. Gigg, S. Payne, R. Conant, *Carbohydr. Res., 142,* 1985, 132.

[7] V. Salazar-Pereda, A. Flores-Parra, R. Contreras, unpublished work.

[8] (a) H. Nöth, B. Wrackmeyer: *Nuclear Magnetic Spectroscopy of Boron Compounds,* Springer-Verlag, Berlin, 1978; (b) B. Wrackmeyer, *Ann. Rep. NMR Spectrosc., 20,* 1988, 61.

[9] A. Bothner-Dy, S. M. Castillano: in F. Datar (ed), *Computer Programs for Chemistry,* W. A. Benjamin Inc., New York, 1968.

[10] MOLEN, *An Interactive Structure Solution Procedure,* ENRAF-NONIUS, Delft Instruments X-ray Diffraction, Delft, The Netherlands, 1990.

[11] *International Tables for X-ray Crystallography,* Vol. IV, Kynoch Press, Birmingham, England, 1974.