Conformational Study of Some Saturated 2-[Bis(2-chloroethyl)amino]-1,3,2-benzoxazaphosphorinane 2-Oxides

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Conformational analyses of cis- and trans-fused 2-[bis(2-chloroethyl)amino]-3,4,4a,5,6,7,8,8a-octahydro-1,3,2-benzoxazaphosphorinane 2-oxides and their 3-methyl and 3-benzyl derivatives were performed by ^{1}H, ^{13}C, ^{31}P, and variable-temperature NMR methods. Depending on the P-2 configuration and the substituent on N-3, different equilibria between chair−chair and chair−twist-boat conformations were found for the trans-fused isomers. The N-3 substituent shifts the equilibrium toward the chair−twist-boat to an extent varying in the sequence methyl > benzyl > hydrogen. In the cis-fused isomers, the nature of the N-3 substituent affects the equilibrium between the *O-in* and *O-out* conformations in the same sequence.

Introduction

A number of studies have been carried out on the conformational behavior of the 2-oxo-1,3,2-oxazaphosphorinane ring. The important findings include that these compounds relatively easily populate conformations other than the chair and that the chair−chair and chair−twist equilibria are strongly influenced by the size of the substituent R^1 and the steric and electronic properties of Z (Figure 1).[1] Relatively small electronegative substituents (Z = MeO, PhO) prefer the axial position of the ring, independently of the substituent R^1 (R^1 = H, *i*-C_3H_7, Ph).[2] The orientation of the amine (Z = NR_2) substituents depends on their relative steric size and the size of the R^1 group. Me_2N prefers the axial position when R^1 is small (R^1 = H), but its orientation is clearly equatorial when R^1 is phenyl. Sterically more demanding amine substituents prefer the equatorial ring position, even in the case of small substituents R^1.[3] Studies of 2-anilino-5,5-dimethyl-substituted compounds have shown the important role of the electron-withdrawing capacity of Z.[4]

The twist conformation becomes populated when the ring conformation is locked (R^2 = *tert*-butyl, phenyl) and the substituent on the phosphorus occupies a nonpreferred orientation.[5] Such compounds can populate two different twist conformations: those with the O atom and C-4 (Figure 1: form C) or the N atom and C-6 (Figure 1: form D) in the bow positions. There are only a few examples of the latter case, e.g., 2-(*p*-nitrophenoxy)-2-oxo-5,6-tetramethylene-1,3,2-oxazaphosphorinane; due to the trans-fused cyclohexane, this has no possibility to attain any twist form other than D.[6] 2-Methoxy-2-oxo-1,3,2-oxazaphosphorinane favors form D in the absence of a bulky R^1 substituent,[2a] whereas some 2-aryl derivatives of 2-oxo-1,3,2-oxazaphosphorinane are mixtures of three different conformations.[7] The literature contains no examples of compounds with conformation D when there is an amine substituent on position 2. The reason for the appearance of no twist conformation other than

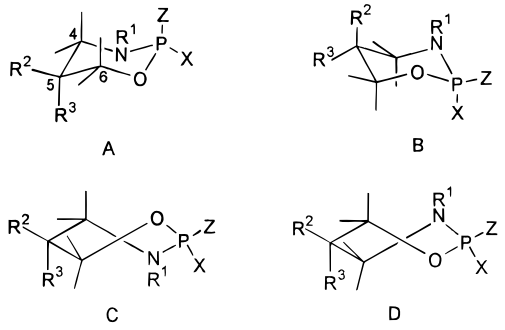

Figure 1. Oxazaphosphorinanes studied earlier.

(1) (a) Bentrude, W. G.; Setzer, W. N.; Newton, M. G.; Meehan, E. J., Jr.; Ramli, E.; Khan, M.; Ealick, S. *Phosphorus, Sulfur, Silicon* **1991**, *57*, 25. (b) Bentrude, W. G.; Setzer, W. N.; Kergaye, A. A.; Ethridge, V.; Saadein, M. R.; Arif, A. M.; *Phosphorus, Sulfur, Silicon* **1991**, *57*, 37. (c) Spassov, S. L.; Lyapova, M. J.; Ivanova, M. E. *Phosphorus Sulfur* **1988**, *37*, 199. (d) Bajwa, G. S.; Bentrude, W. G.; Pantaleo, N. S.; Newton, M. G.; Hargis, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1602.

(2) (a) Bentrude, W. G.; Setzer, W. N.; Sopchik, A. E.; Bajwa, G. S.; Burright, D. D.; Hutchinson, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 6669. (b) Roca, C.; Kraemer, R.; Majoral, J.-P.; Navech, J.; Brault, J. F.; Savignac, P. *Org. Magn. Reson.* **1976**, *8*, 407.

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(4) Bentrude, W. G.; Setzer, W. N.; Khan, M.; Sopchik, A. E.; Ramli, E. *J. Org. Chem.* **1991**, *56*, 6127.

(5) (a) Chandrasekaran, S.; Bentrude, W. G. *Tetrahedron Lett.* **1980**, *21*, 4671. (b) Bajwa, G. S.; Chandrasekaran, S.; Hargis, J. H.; Sopchik A. E.; Blatter, D.; Bentrude, W. G. *J. Am. Chem. Soc.* **1982**, *104*, 6385. (c) Bentrude, W. G.; Beres, J.; Chandrasekaran, S.; Nelson, K.; Quin, G. S.; Setzer, W. N.; Sopchik, A. E.; Tomasz, J. *Phosphorus Sulfur* **1983**, *18*, 389. (d) Bentrude, W. G.; Day, R. O.; Holmes, J. N.; Quin, G. S.; Setzer, W. N.; Sopchik, A. E.; Holmes, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 106. (e) Holmes, R. R.; Day, R. O.; Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1984**, *106*, 2353.

(6) (a) Gorenstein, D. G. Rowell, R. *J. Am. Chem. Soc.* **1979**, *101*, 4925. (b) Gorenstein, D. G.; Rowell, R.; Findlay, J. *J. Am. Chem. Soc.* **1980**, *102*, 5077.

(7) Bentrude, W. G.; Setzer, W. N.; Sopchik, A. E.; Chandrasekaran, S.; Ashby, M. T. *J. Am. Chem. Soc.* **1988**, *110*, 7119.

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Scheme 1. Synthesis of the Studied Compounds

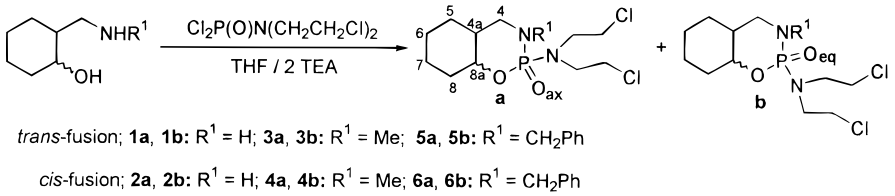


Table 1. ^{31}P Chemical Shifts in CD_2Cl_2 at 200 K for 4b and at 203 K for 6b, and the First Coalescences (400 MHz) for 4b and 6b. $\Delta G_1^{\ddagger}$ Represents the Barrier for *O-in* → *O-out* (see Figure 4) and $\Delta G_2^{\ddagger}$ the Barrier for the Reverse Reaction at the Coalescence Temperature

	δ_1/ppm	δ_2/ppm	$\Delta G_1^{\ddagger}$/kJ mol^{-1}	$\Delta G_2^{\ddagger}$/kJ mol^{-1}	T_c/K
4b	11.8	9.5	44.0	42.7	228
6b	12.4	10.0	42.3	42.6	226

C in these derivatives is not known. To study this question, we have prepared the derivatives of 1,3,2-oxazaphosphorinanes with *trans*-ring fusion at positions 5 and 6. These compounds cannot populate twist forms other than D (Figure 1). The corresponding cis derivatives were also synthesized in order to study the effect of R^1 on the equilibrium between the *O-in* and *O-out* conformations.

Results

Synthesis. The amino alcohols were prepared according to literature procedures.[8] They were cyclized with bis(2-chloroethyl) phosphoramidic dichloride[9] at 0 °C or at ambient temperature (Scheme 1). In all cases, two diastereomers were formed. The temperature of cyclization did not notably affect the ratio of the isomers or the yields. Compounds **1a** and **1b** had been prepared earlier by Yang et al.,[10] but since there was some controversy as regards the interpretation of their NMR data, we decided to study them again. Since we were not able to separate the isomers **2a** and **2b**, they were prepared in the pure state by removing the benzyl group from isomers **6a** and **6b** by the method described by Sato et al.[11]

Characterization of Structures (Assignment of Diastereomers). The diastereomers can be divided into two categories: the **a** series and the **b** series. In the **a** series (Figures 6 and 7), the P═O group is axial (in the cis-fused isomers the ring O is also axial, i.e., the *O-in* form), while in the **b** series (Figures 6 and 8) it is equatorial. Assignment of the configuration of the P atom is based on NMR data: the ^{31}P NMR shifts for the **a** series of compounds are downfield from those for the **b** series (Table 2). The chemical shifts for C-8a are upfield and those for H-8a are downfield in the **a** series as compared with those for the **b** series (Tables 2 and 3). Further, the chemical shift of C-4 in series **a** is always downfield from that in series **b**, for any given pair of diastereomers. That the geometry was correctly assigned to the diastereomers of **1** and **5** is confirmed by the X-ray structures of **1a**[10] and **5a**.[12]

Table 2. Selected ^{1}H (δ_{TMS} = 0 ppm) and ^{31}P NMR ($\delta_{H_3PO_4}$ = 0 ppm) Chemical Shifts in $CDCl_3$[a]

	4ax	4eq	4a	5ax	5eq	8ax	8eq	8a	P
1a	3.13	3.11	1.64	1.00	1.7	1.40	2.06	4.15	13.4
1b	2.81	3.10	1.7	0.89	1.63	1.51	2.00	3.88	11.0
2a	3.6	2.98	1.61	1.5	1.82	1.5	1.96	4.80	14.5
2b	3.28	3.10	1.67	1.93	1.43	1.6	1.99	4.50	10.6
3a	2.93	2.89	1.7	1.02	1.7	1.35	2.06	4.08	15.6
3b	2.94	2.98	1.98	0.99	1.74	1.51	2.05	3.88	11.0
4a	3.40	2.72	1.68	1.76	1.5	1.46	1.97	4.77	16.8
4b	3.08	3.18	2.15	1.5	1.8	1.77	2.0	4.40	11.0
5a	2.72	2.85	1.65	0.94	1.60	1.38	2.08	4.12	15.6
5b	2.82	2.88	1.79	0.90	1.58	1.52	2.05	3.91	11.1
6a	3.19	2.72	1.63	1.82	1.4	1.5	1.99	4.81	17.1
6b	3.04	3.00	2.0	1.25	1.75	1.75	2.0	4.45	10.7

[a] In the case of cis derivatives, the assignments refer to the *O-in* conformation.

Variable-Temperature NMR Measurements. Low-temperature NMR measurements were performed on the **b** forms of the molecules to find out if any conformational processes could be frozen out. The **a** forms were not subjected to low-temperature measurements because they apparently all exist in biased chair−chair conformations with axial P═O bonds, as will be shown. The **a** compounds are the most stable in the latter conformations, and there is no rational reason to expect them to assume any other geometry. The **b** forms, however, should be treated in two separate categories: the cis-fused and the trans-fused isomers.

The Trans-Fused Cases. The ^{31}P NMR measurements on the trans-fused **b** series were performed in $CHFCl_2$ as solvent. For **1b** and **5b**, no line splitting was observed in the range from 135 to 298 K and the signal remained narrow even at the lowest temperatures, especially for **5b**. In **3b**, the ^{31}P signal split into two at about 153 K, which was approximated as the coalescence temperature in the field of a 400 MHz magnet from the peak widths. According to the integration and peak heights, the two separate forms were present in a ratio of about 7:93 at 138 K. The main signal corresponds to the chair−chair form, which is also the major contributor in **1b** and **5b**. The minor signal is 1.6 ppm downfield from that for the postulated chair−chair form, which indicates that the minor conformer has a more axial P═O bond than that in the chair form. This is possible if the heterocyclic part of the molecule is in a twist-boat[13] or a boat conformation. The exact conformation of the minor form, however, cannot be assigned on the basis of the low-temperature spectral data. The absolute difference in the chemical shifts in **3b** could not be measured due to the inability to lower the temperature further, and it was therefore not possible to assess the relative ratio of the two conformers at room temperature from the measured data.

(8) (a) Fülöp, F.; Huber, I.; Bernáth, G.; Hönig, H.; Seufer-Wasserthal, P. *Synthesis* **1991**, 43. (b) Fülöp, F.; Bernáth, G. *Tetrahedron* **1984**, *40*, 2053.

(9) Frieman, O. M.; Seligman, A. M. *J. Am. Chem. Soc.* **1954**, *76*, 655.

(10) Yang, J.-C.; Shah, D. O.; Rao, N. U. M.; Freeman, W. A.; Sosnovsky, G.; Gorenstein, D. G. *Tetrahedron* **1988**, *44*, 6305.

(11) Sato, T.; Ueda, H.; Nakagawa, K.; Bodor, N. *J. Org. Chem.* **1983**, *48*, 98.

(12) Unpublished result from our laboratory.

(13) Refers to a conformation which is not purely twist or boat but rather something between them.

Table 3. ^{13}C NMR Chemical Shifts ($\delta_{HCDCl_3} = 77.0$) in $CDCl_3$

	4	4a	5	6	7	8	8a	9	10	11,15	12,14	13	16,18	17,19
1a	47.4	40.6	28.1	24.8	24.2	33.3	80.7						49.0	42.5
1b	47.1	41.4	28.0	24.7	24.2	33.2	83.0						48.6	42.0
2a	46.7	35.2	25.0	24.8	19.7	31.8	76.4						48.9	42.5
2b	45.8	35.7	24.5	24.3	20.1	31.6	79.1						48.6	42.1
3a	56.2	41.1	28.1	24.7	24.1	33.0	80.1	35.6					49.7	42.5
3b	55.8	40.1	28.7	24.6	24.1	33.3	82.3	35.6					49.4	42.3
4a	55.9	36.4	25.4	25.1	19.6	31.4	75.8	35.6					49.6	42.5
4b	52.6	35.7	26.6	22.4	22.5	30.1	79.8	36.0					49.6	42.4
5a	52.4	41.1	28.1	24.7	24.1	33.1	80.4	51.7	137.0	128.7	128.4	127.6	49.6	42.5
5b	52.2	40.5	28.4	24.6	24.2	33.3	82.8	51.8	137.6	128.7	128.5	127.6	49.3	42.3
6a	51.7	36.3	25.1	25.0	19.7	31.3	76.1	51.2	136.9	128.6	128.1	127.4	49.3	42.4
6b	49.2	35.8	26.0	22.8	21.8	30.5	79.7	51.9	137.2	128.7	128.6	127.6	49.4	42.4

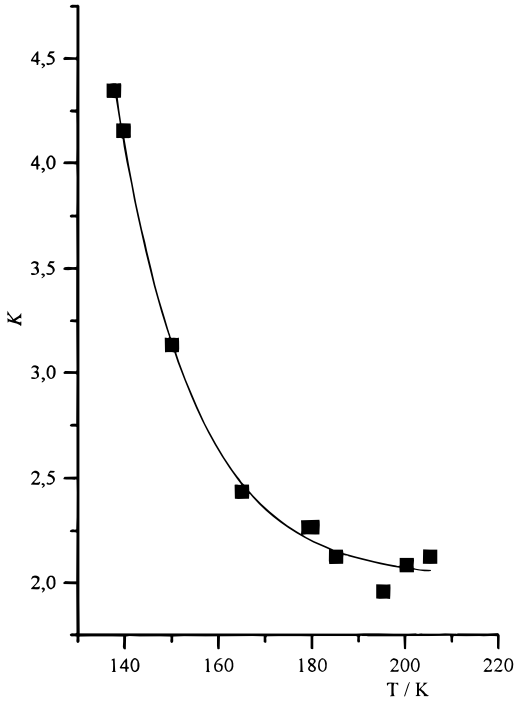


Figure 2. Equilibrium constant K vs T for the barrier of the process *O-in* → *O-out* for **4b**. The curve illustrates a fit $K = 2.01974 + 2.41599 \exp(-(T - 137.30821)/16.56191)$.

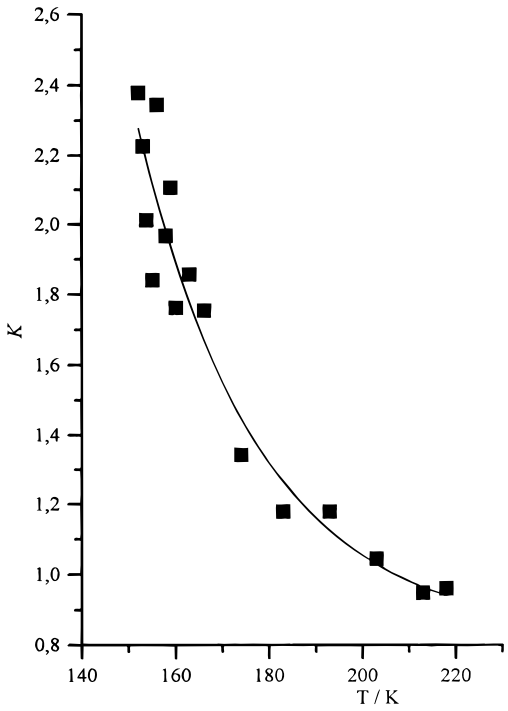
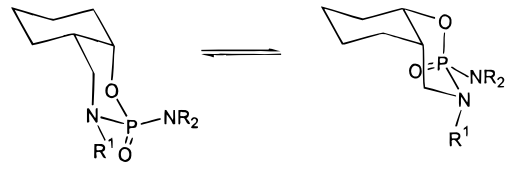


Figure 3. Equilibrium constant K vs T for the barrier of the process *O-in* → *O-out* for **6b**. The curve illustrates a fit $K = 0.83034 + 1.32651 \exp(-(T - 154.25709)/25.72159)$.

The ^{31}P NMR spectra of **1b**, **3b**, and **5b** were also measured at several temperatures as mixtures with the corresponding **a** diastereomer in CD_2Cl_2. The ^{31}P peak separations were observed and plotted against temperature. If both diastereomers existed in one exclusively populated conformation, the peak separation would not vary considerably on change of the temperature. However, for **1b** and **5b**, the peak separation approached a certain limiting value as the temperature was lowered, indicating that a conformational process is affected by the change of temperature. This is consistent with the idea that **1b** and **5b** consist of small amounts of entropy-favored chair−twist-boat conformations at room temperature, but the population decreases with decreasing temperature and finally no peak splitting is observed. This limit is reached at about 165 K for **1b**, and at about 180 K for **5b**. For **3b**, the peak separation does not reach a limit, at least above 180 K, which is consistent with the small amount of chair−twist-boat conformation observed at ca. 153 K.

The Cis-Fused Cases. Low-temperature ^{31}P NMR measurements were carried out for **2b**, **4b**, and **6b** in $CHFCl_2$ in the temperature range from 137 to 298 K; no signal splitting was observed for **2b**, but the signal broadened considerably below 273 K. The ^{31}P signals of **4b** and **6b** split into two below 228 K, while that of **6b** splits a second time to give three signals at 159 K.

The conformational processes, which slowed to an observable rate on an NMR time scale at about 227 K, can readily be rationalized to be the interconversion of different cis conformers for both **4b** and **6b**. The ratio of the two conformers was measured below 227 K in CD_2Cl_2 and $CHFCl_2$ and is plotted as a function of temperature in Figure 2 for **4b** and in Figure 3 for **6b**. Different solvents did not seem to affect the equilibrium significantly. The chemical shifts of the frozen conformers at about 200 K are listed in Table 1. Below 207 K, the less populated conformation for both **4b** and **6b** was assigned as the *O-in* chair−chair form (I) illustrated in Figure 4. The ratio of the *O-in* and *O-out* forms for **6b** is reversed above ca. 207 K. For both **4b** and **6b**, the more populated form below 207 K is the *O-out* form (II) in Figure 4. Exponential decay curves were fitted to the equilibrium constant vs temperature plots in Figures 2 and 3 with the Origin program, and acceptable equations were obtained to represent the K values at different temper-



O-in I		*O-out* II
4b; R^1 = Me	33%	67% [a]
6b; R^1 = CH_2Ph	54%	46% [a]
(**2b**; R^1 = H	91%	9%) [b]

Figure 4. Contributions of *O-in*/*O-out* forms to the cis-fused **b** isomers: [a]from low temperature measurements; [b]from C7 chemical shift.

atures. Thus, **4b** was extrapolated to be a 33:67 (I:II) mixture and **6b** to be a 54:46 (I:II) mixture at 300 K in CD_2Cl_2.

The coalescences in CD_2Cl_2 in the field of a 400 MHz magnet for **4b** and **6b** are shown in Table 1. The ratio of the two frozen forms of **4b** and **6b** was calculated at the coalescences, and the rate constants k for the exchange processes were evaluated by treatment with the unequally populated doublets method described in the book by Sandström,[14a] originally developed by Shanan-Atidi and Bar-Eli.[15] From the rate constants at the coalescences, the $\Delta G^{\ddagger}$ values (Table 1) were calculated with the Eyring eq 1:[14b]

$$\Delta G^{\ddagger}/\text{kJ mol}^{-1} = 1.914 \times 10^{-2}\, T\, [10.319 + \log(T/k)] \quad (1)$$

The $\Delta G^{\ddagger}$ values for **4b** and **6b** (Table 1) are similar to those for other six-membered heterocyclanes.[16]

In **2b**, an exchange process between two interconverting chair−chair forms similar to those in **4b** and **6b** can be expected. **2b** was examined by measuring the ^{31}P signal intensities for a mixture[17] of **2a** and **2b** in CD_2Cl_2 at different temperatures. **2a** was chosen as a reference molecule because it is closely related to **2b** but it is not affected by an exchange process. The intensity of the ^{31}P signal of **2b** relative to that of **2a** is plotted as a function of temperature in Figure 5. When the temperature is lowered from about 300 K down to 230 K, the intensity of the signal of **2b** drops quite linearly. The intensity starts to grow again when the temperature is lowered below ca. 223 K. No signal splitting is, however, observed because the population of the minor *O-out* form (see below) has diminished to an undetectable level and only the signal of the *O-in* form is observed. From the temperature dependence of the intensity, the coalescence for **2b** can be approximated to occur in the temperature range of 220−225 K. The free energy of activation for **2b** is therefore approximately equal to those of **4b** and **6b**; thus, an exchange process between the two interconverting cis conformations of **2b**, similar to those for **4b** and **6b**, can indeed be postulated.

The additional splitting of the ^{31}P signals of **6b** to give a third peak at 159 K in $CHFCl_2$ seems to reflect a similar

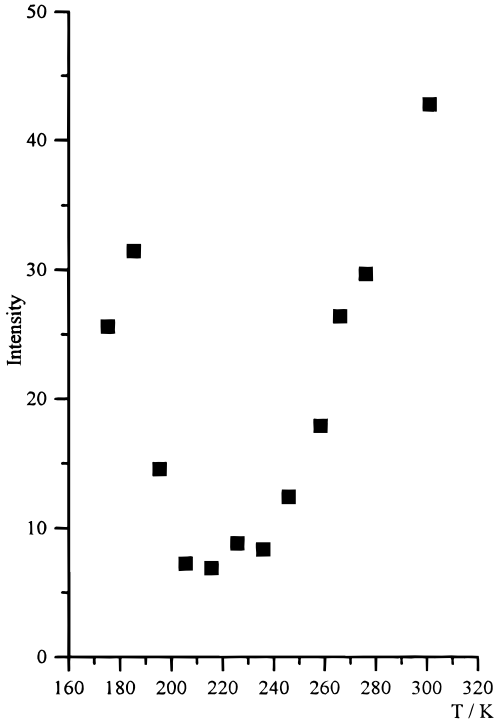


Figure 5. Intensity of the ^{31}P NMR signal of **2b** relative to that of **2a** (= 100 at all temperatures) vs temperature. In the lowest temperature the intensity drops probably because of the vicinity of the melting point of CD_2Cl_2 and thus the decreased solubility.

phenomenon as in **3b**. At 166 K, the spectrum contains two signals, at 13.2 and 11.0 ppm, in an intensity ratio of ca. 64:36, respectively, but at 137 K there are three signals, at 12.9, 12.1 and 10.3 ppm, with intensities of 13:58:29. The low-field signal at 166 K corresponds to the *O-out* form with an axial P═O bond (Figure 4) and the high-field signal to the *O-in* form. The ^{13}C chemical shifts are also consistent with this assignment, since C-6 and C-8 are more shielded in **4b** and **6b** than in **2b**, for the reason that the P═O oxygen is located spatially close to them in the *O-out* form II, which is almost absent in **2b**. The third signal found at 137 K is low-field from both of the other signals, and thus the P═O bond must be "axial" as in the *O-out* form, but the phosphorus is not shielded as in the *O-out* form, where the P═O is spatially especially close to the atoms at position 8. This is possible when the heteroring in **6b** is in a boat or a twist-boat conformation of the *O-in* type (Figure 9).

Conformations. The Trans-Fused Isomers. The **a** series of diastereomers is readily characterized conformationally by ^1H and ^{13}C NMR spectroscopy. Signals were assigned with the aid of NOEDIF, COSY, and HMQC measurements. The trans-fused isomers in the **a** series have large ^3J(H4a,H4ax) and ^3J(H4a,H8a) and intermediate ^3J(H4a,H4eq) coupling constants (Table 4). The P couplings to H-4eq are large (varying from 24.1 to 27.1 Hz) while those to H-4ax and H-8a are small (varying from 1.3 to 1.8 Hz) (see Table 5). These isomers also involve P coupling to C-7 as a result of the W-type arrangement of the P and C-7 atoms. These characteristic couplings and the data from Tables 2−5 show that they assume chair−chair conformations (Figure 6). Further characteristic features for the whole **a** series are the smaller ^3J coupling between the P and C-4a and the larger coupling between the P and C-8 than for the

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(15) Shanan-Atidi, H.; Bar-Eli, K. H. *J. Phys. Chem.* **1970**, *74*, 961.
(16) Delpuech, J.-J. In *Cyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH: New York, 1992; p 184.
(17) A readily available approximately 70:30 (**2a**:**2b**) mixture was used.

Table 4. Selected Geminal and Vicinal H, H Coupling Constants (Hz)[a]

	4ax,4eq	4a,4ax	4a,4eq	4a,5ax	4a,5eq	4a,8a	5ax,5eq	5ax,6ax	5ax,6eq	8ax,8eq	8a,8ax	8a,8eq
1a	−11.0	10.8	4.5	12.5	<3	10.4	−12.5	12.5	4.1	−12	11	4.4
1b	−12.8	11.1	4.5	11	4	9.4	−13.5	12.5	4.0	−12.7	11.1	4.4
2a	−11.6	3.9	2.0	12.2	3.9	3.9						
2b	−13.1	3.9	3.5	11.2	3.7	2.6	−13.4	11.2	3.5	−13.6	5.1	2.6
3a	−11.0	11.3	4.6	12.8		10.2	−12.8	12.8			10.2	4.3
3b	−11.13	11.16	5.26	12.6	3.1	10.7	−12.6	12.6	3.7	−12.8	11	4.5
4a	−11.5	3.7	1.7	12.5	3.7	3.7	−12.6	12.6	3.7	−10.9	3.2	
4b	−11.6	4.9	7.6	4.1	4.6	3.9	−13.6			−13.5	3.9	8.9
5a	−11.2	11.2	4.6	12.8		10.56	−12.8	12.7	3.6	−12.1	10.56	4.54
5b	−11.97	10.65	4.65	11.91	3.40	10.42	−13.36	12.6	3.54	−12.78	11.04	3.86
6a	−11.7	3.7	2.0	12.4	2	2	−13.9	13.0	3.8			
6b	−12.0	4.8	6.6			3.5					3.5	7.8

[a] The assignments of couplings for cis-isomers refer to the *O-in* conformations.

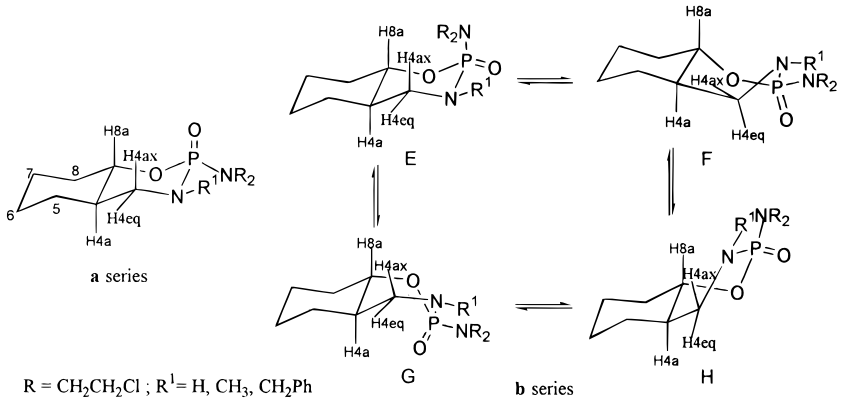

Figure 6. Possible heteroring conformations for the trans-fused isomers.

Table 5. Selected Phosphorus Proton and Phosphorus Carbon Coupling Constants (Hz)[a]

	H4ax,P	H4eq,P	H8a,P	C4,P	C4a,P	C7,P	C8,P	C8a,P
1a	1.6	27.1	1.3	2.6	3.7	2.1	8.6	6.2
1b	3.5	21.2	1.3	2.8	8.3	2.2	7.1	7.7
2a	*b*	28.5	*b*	2.3	3.1		8.7	6.0
2b	6.2	19.9	4.9	2.4	6.4		6.5	7.6
3a	1.3	24.6	1.8		3.1	2.3	9.2	6.1
3b	8.83	10.66	1.6	2.5	8.3	2.5	6.6	7.4
4a	1.5	26.3	*b*	0.8	2.5		8.7	6.2
4b	16.2	7.4	13.0		4.6		3.7	7.9
5a	1.8	24.1	1.4	0.9	2.6	1.7	9.0	6.4
5b	5.4	13.7	1.9	2.3	7.6	2.3	6.9	8.0
6a	2.0	26.5	*b*		2.0		8.8	6.1
6b	12.1	10.3	11.0		4.5		3.8	8.4

[a] The assignments of couplings for cis-isomers refer to the *O-in* conformations. [b] Not resolvable.

compounds in the **b** series (Table 5). This should be the case if the heterocyclic ring in the **a** series is in an almost perfect chair form and the **b** isomers display some distortion or exist in conformational equilibrium. The values for geminal coupling between H-4eq and H-4ax (ranging from −11.0 to −11.2 Hz, see Table 4) in the trans-fused **a** forms indicate that the substituent on the ring nitrogen is in the equatorial position.[18]

The coupling constants either reveal that the heterocyclic ring in the **b** forms of the trans-fused compounds exists in a somewhat flattened chair form (more flattened than is usual for the 1,3,2-oxazaphosphorinane ring)[1b] or there is a conformational equilibrium between the chair, twist-boat, and boat conformations (Figure 6). The coupling constants between the P and H-4eq and H-4ax are considerably different for the **b** series than those for the corresponding **a** series (Table 5). The trans-fused **b** isomers exhibit a combination of intermediate ^3J(H4ax,P) and large ^3J(H4a,H4ax) couplings (Tables 4 and 5) indicative of the presence of a certain amount of the chair−twist-boat or chair−boat conformation.[19] At the same time, ^3J(H4eq,P) is smaller than it is in the **a** series. The ^4J(C7,P) coupling, however, is of the same size as in the corresponding **a** series of compounds, and this, together with the small value for ^3J(H8a,P), shows that a considerable amount of chair−boat conformation G (Figure 6) cannot be present. It remains to be decided whether conformation F or H or both are responsible for the observed changes in coupling constants. In chair-boat conformation F, the dihedral angle between H-4a and H-4eq would be very small, and therefore the presence of any substantial amount of conformation F would increase the time average coupling constant between H-4a and H-4eq significantly. No increase in this coupling can be observed on going from **1a** to **1b** or from **5a** to **5b**. A small increase in the coupling does occur on going from **3a** to **3b** (0.66 Hz), but this can be explained in terms of the chair−twist-boat conformation H (Figure 6), which will increase this coupling, but to a much lesser extent. Moreover, a considerable amount of conformation F would significantly decrease the coupling between H-4a and H-4ax, but this coupling remains almost the same for the pairs of isomers. Consequently, we conclude that the amount of conformation F is not significant.

A Karplus-type dihedral angular dependence of ^3J(P-NCH) has been noted.[20] However, since this coupling is affected by the nature of the ring N substituent, probably

(18) Pihlaja, K.; Sillanpää, R.; Dahlqvist, M.; Stájer, G.; Ahlgren, M. *Struct. Chem.* **1993**, *4*, 203.

(19) Bentrude, W. G. In *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis*; Quin, L. D., Verkade, J. G., Eds.; VCH: New York, 1994; Chapter 4.

through an altered hybridization of the N, only compounds with the same or closely related substituents R^1 can be compared with each other.[5b] Because of this and the small number of compounds with a type D conformation (Figure 1) to be found in the literature, we do not have good model values for couplings between the P and H-4ax and H-4eq for the pure chair−twist-boat conformation, and therefore we cannot calculate the proportion of conformation H for an equilibrium between conformations E and H (Figure 6). However, if we consider that changing the heteroring conformation from a chair to a twist-boat interchanges the couplings between the P and the protons at position 4, we can roughly estimate the amount of conformation H in this equilibrium by using the coupling values for the **a** series (Table 5) and the well-known eq 2:

$$X_{\text{twist-boat}} = [{}^3J(\text{H4ax,P})(\text{obs}) - {}^3J(\text{H4ax,P})(\mathbf{a}\ \text{ser})]/[{}^3J(\text{H4eq,P})(\mathbf{a}\ \text{ser}) - {}^3J(\text{H4ax,P})(\mathbf{a}\ \text{ser})] \quad (2)$$

According to eq 2, the amount of conformation H is about 7% in **1b**, about 32% in **3b**, and close to 16% in **5b**. This estimation, of course, is somewhat crude, since the idea of interchangeability of couplings is not necessarily completely true. The difference between coupling constants ^3J(C8,P) is the smallest when **1a** and **1b** are compared and the largest for the pair **3a** and **3b**. The couplings between the P and C-4a show a similar trend. These values indicate that the amount of conformation H is indeed largest in **3b**. The same is indicated by the less negative ^2J(H4eq,H4ax) value for **3b** than for **1b** and **5b**.

In the **b** series, the more negative values for the geminal ^2J(H4eq,H4ax) coupling (Table 4) shows that R^1 displays some tendency to occupy an axial position.[18] In **3b**, the proportion of axial R^1 is small; in **5b**, the proportion is somewhat larger; and in **1b**, the ^2J(H4eq,H4ax) value (−12.8 Hz) even indicates that the proton on N(3) is largely axial.

The Cis-Fused Isomers. The cis-fused isomers in the **a** series have small ^3J(H4a,H4eq), intermediate ^3J(H4a,H4ax) and ^3J(H4a,H8a), and large ^3J(H4a,H5ax) values (Table 4). Additionally, they have large ^3J(H4eq,P) (from 26.3 to 28.5 Hz) and small ^3J(H4ax,P) (from 1.5 to 2.0 Hz) phosphorus couplings (Table 5). The H-8a signal in these cases is a narrow, poorly resolved multiplet showing only small or intermediate couplings, and this proton always resonates at lower field than is the case in the corresponding **b** series of compounds (Table 2), whereas C-8a resonates at higher field in the **a** series, due to the γ-effect of the axial P═O group (Table 3). The ^{31}P chemical shift is larger for the **a** than for the **b** series, as it was in the trans-fused isomers. Further, H-4ax resonates at lower and H-4eq at higher field than in the **b** isomers. Characteristic features for the whole series are the larger couplings ^3J(C8,P) and the smaller couplings ^3J(C4a,P) and ^2J(C8a,P) for the **a** than for the **b** forms. These values and those in Tables 2−5 indicate that the cis-fused **a** series isomers exist largely in the *O-in* chair−chair conformation (Figure 7). They have slightly more negative geminal couplings between H-4eq and H-4ax (from −11.5 to −11.7 Hz, see Table 4) than

(20) Bentrude, W. G.; Setzer, W. N. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH: Deerfield Beach, FL, 1987; Chapter 11.2.

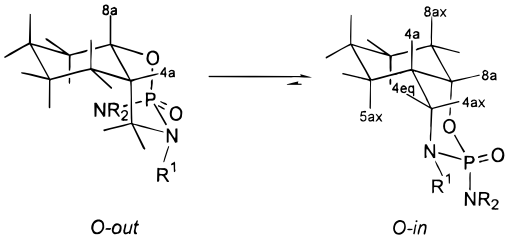

Figure 7. *O-in*/*O-out* equilibria for **a** series cis-fused isomers.

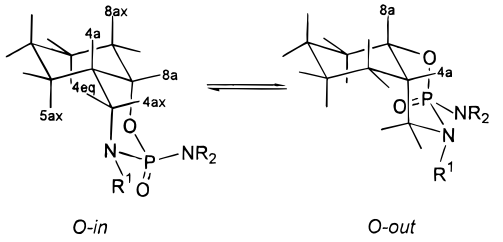

Figure 8. *O-in*/*O-out* equilibria for **b** series cis-fused isomers.

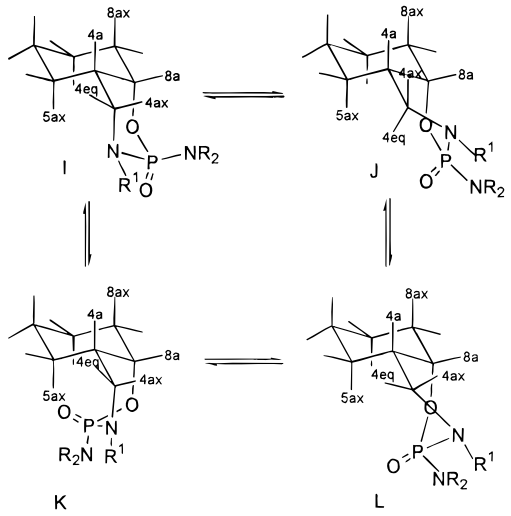

Figure 9. Possible heteroring conformations for *O-in* **b** series cis-fused isomers.

those for the trans-fused **a** forms. However, we believe that R^1 remains largely equatorial in both cases.

In the cis-fused **b** series the situation is clearly the most complicated, since these compounds can exist in two different chair−chair conformations, the *O-in* and *O-out* forms, and additionally the heteroring can adopt a twist-boat or a boat conformation (Figures 8 and 9).

Low-temperature measurements proved that the amount of the *O-out* form is 67% for **4b** and 46% for **6b** at ambient temperature (Figure 4). For **2b**, we did not succeed in estimating the amount of the *O-out* form from the low-temperature ^{31}P results. However, it can be calculated by using eq 2 again. The shift value for C-7 (Table 3) is probably the most suitable for this purpose since it is not greatly affected, if at all, by the possible twist-boat or boat forms of the heteroring. By using eq 2 and the shift value from the corresponding trans-fused **a** series compound (**1a**) to represent the *O-out* value and that of the cis-fused **a** series compound (**2a**) to represent the *O-in* value, we can calculate that **2b** contains 9% of the *O-out* conformation. Similarly, values of 64% and 48% of the *O-out* form were obtained for **4b** and **6b**,

respectively, in close agreement with the values extrapolated from the low-temperature measurements.

There is no reason to believe that the *O-out* form would have any tendency to escape to a chair−twist-boat or chair−boat conformation, since the substituents on the P occupy their most stable positions. In contrast, the *O-in* form, with an exocyclic P−N bond in the axial position, does have some driving force toward a chair−twist-boat or chair−boat conformation, in the same way as for the trans-fused compounds in the **b** series (Figure 9). The question that arises is whether this driving force just inverts the chair−chair conformation or whether there is additionally some amount of other than chair conformations present. By means of low-temperature measurements, we detected a third ^{31}P signal for isomer **6b**; this signal has a lower field ^{31}P shift value than the other two and it represents a chair−boat or chair−twist-boat conformation (Figure 9).

In principle, we can also estimate the populations of the *O-out* type conformations for the cis-fused **b** isomers from the ^3J(H4a,H4), ^3J(H8a,P), and ^3J(H4,P) couplings via eq 2, although this is complicated by the choice of proper model values (it is not completely justified to select model values from configurationally different molecules), especially since at least **4b** and **6b** also involve chair−twist-boat conformations. Nevertheless, the agreement for **4b** and **6b** is good (X_{O-out} 60−65 and 40−45%, respectively) as concerns the estimates based on low-temperature measurements and C-7 chemical shifts. For **2b**, however, somewhat higher contributions of the *O-out* form are obtained (15−20% as compared to 9%), which is mainly due to the approximate model values for the coupling constants (use of the trans-^3J(H4a,H5) coupling gives X_{O-in} 90%), and may even partly reflect some twist contribution in **2b**.

Discussion

For the trans-fused **b** series of compounds we did not succeed in calculating the contribution of the minor conformation from the low-temperature measurements. However, the observations made are in agreement with the approximate ratios obtained in the room-temperature region. For **3b**, which was found to consist of 32% of the chair−twist-boat conformation at 298 K, a small amount of this entropy-favored form was observed at low temperatures, but for **1b** and **5b**, which contained less of the chair−twist-boat conformation at 298 K than did **3b**, no signal splitting was observed. The relative amount of the chair−twist-boat conformation should increase with increasing temperature.[21]

As stated earlier, the amount of the chair−twist-boat conformation depends strongly on the size and nature of R[1]. In our case, the effective size of the substituent decreases in the sequence methyl > benzyl > hydrogen. The benzyl group, however, is normally clearly bulkier than methyl. It is possible that there are some unfavorable steric interactions between the phenyl and the other parts of molecule in the chair−twist-boat form, which would explain why in this case the effective steric size of benzyl is smaller than that of methyl. The other possibility is that the benzyl group makes the electron lone pair of the ring N less available for $n_N \rightarrow \sigma^*$ interaction with the "axial" P═O bond, the chair−twist-boat conformation therefore being less favorable. This anomeric effect[22] favors the orientation in which an energetically relatively high, filled orbital (lone pair of ring N n_N) is trans-diaxially oriented with a relatively low-energy empty antibonding orbital (in our case $\sigma^*_{P=O}$). In the present case, this requirement favors the chair−twist-boat conformation in the **b** series. $\Delta G°$ is 2.2 kJ mol^{-1} less favorable for **5b** than for **3b** (Table 6), which could represent the energy released due to the lone pair delocalization if it is assumed that the steric requirements for methyl and benzyl are not significantly different in this case. This energy difference is of the same magnitude as found by Bentrude et al.[1b,4] from a comparison of 2-*p*-aryl-substituted derivatives of oxazaphosphorinanes. A comparison of **1b** with **3b** or **5b** or other previously published compounds of the same type is not straightforward, because of the probable hydrogen bonding in **1b**. The possibility of hydrogen bonding of N(3)H-substituted derivatives has been noted previously.[23] In **1b**, hydrogen bonding was observed in the variable-temperature ^{1}H NMR measurements, where the shift of the N(3)H proton changed greatly with variation of temperature relative to the shifts of other protons. Hydrogen bonding in **1b** is also supported by the observed axial preference of N(3)H. Whether the hydrogen bonding is intra- or intermolecular remains to be established since our measurements cannot exclude either type of hydrogen bonding.

Table 6. Equilibrium Constant and $\Delta G°$ at 298 K for 1b−6b in Conformational Equilibrium (Chair−Chair → Chair−Twist in 1b, 3b, and 5b; *O-in* → *O-out* in 2b, 4b, and 6b)

	K	$\Delta G°$/ kJ mol^{-1}	K^a	$\Delta G°$ [a]/ kJ mol^{-1}	$\Delta G°$(av)/ kJ mol^{-1}	$\Delta\Delta G°$ [b]/ kJ mol^{-1}
1b	0.0753	6.4			6.4	0
2b			0.0989	5.7	5.7	0
3b	0.471	1.9			1.9	−4.5
4b	2.02	−1.7	1.78	−1.4	−1.6	−7.3
5b	0.190	4.1			4.1	−2.3
6b	0.835	0.45	0.923	0.20	0.3	−5.4

[a] Calculated from the C-7 chemical shifts. [b] Relative to $\Delta G°$ for **1b** in **3b** and **5b** and for **2b** in **4b** and **6b**.

The energetic ease with which the chair−twist-boat structure is populated for these derivatives can be reasonably estimated by using formula 3:[3,24]

$$\Delta G°\,(\mathrm{E} \rightarrow \mathrm{H}) = \Delta G°_{\mathrm{CT}} + \Delta G°_{\mathrm{NR2}} \qquad (3)$$

where $\Delta G°_{NR2}$ represents the free-energy difference between axial and equatorial NR_2. Cyclophosphamide (Figure 1: $R^1 = R^2 = R^3 = H$, X = ═O, and Z = $N(CH_2CH_2Cl)_2$) and its 5,5-dimethyl derivative exhibit a 3.4 and a 2.7 kJ mol^{-1} preference, respectively, for the 2-bis(2-chloroethyl)amine substituent to be equatorial.[3] This gives an average $\Delta G°_{NR2}$ of 3.1 kJ mol^{-1}. Use of this value, the equilibrium constant for **1b** (Table 6), and eq 3 leads to $\Delta G°_{CT}$ = 9.5 kJ mol^{-1} for **1b**, which is considerably more than what was estimated for the 5-*tert*-butyl-substituted cyclophosphamide,[3] where the O-type

(21) Eliel, E. R.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 689−690.

(22) See for example: (a) Salzner, U. *J. Org. Chem.* **1995**, *60*, 986. (b) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019 and references therein.

(23) White, D. W.; Gibbs, D. E.; Verkade, J. G. *J. Am. Chem. Soc.* **1979**, *101*, 1937.

(24) Perrin, C. L. *Tetrahedron* **1995**, *51*, 11901.

twist conformation is populated (Figure 1: form C). Even though the error in our estimation may be relatively large, this result explains the apparent population of only forms of type C for compounds where both types of twist forms are feasible.

For the cis-fused **b** isomers, the $\Delta G°$ values for the *O-in*/*O-out* equilibria were obtained from the C-7 chemical shifts, and in some cases from the ^{31}P low-temperature measurements (Table 6). The substituent on the ring N was found to alter the position of the equilibrium toward the *O-out* conformation in the sequence methyl > benzyl > hydrogen. Thus, change of the substituent from hydrogen to methyl shifts the equilibrium toward *O-out*, but when methyl is replaced by benzyl, the equilibrium shifts back toward the *O-in* form. Furthermore, in the case of the benzyl substituent, a chair−twist-boat conformation L (Figure 9) is present in equilibrium with the *O-in* chair−chair form, as shown by the low-temperature measurements on **6b**. The other cis **b** forms **2b** and **4b** were also postulated to involve some chair−twist-boat conformation at room temperature. The sequence of the substituent effects is the same as for the trans-fused **b** isomers; thus, we postulate a similar variation in the anomeric effect when the N substituent is changed from methyl to benzyl.

In **2b**, the ring N hydrogen is probably inter- or intramolecularly hydrogen bonded, as in **1b** in the trans series. This was shown by variable-temperature ^1H NMR measurements, where the signal of the NH proton was shifted considerably relative to those of the other protons in **2b**, and additionally by the fact that in **2b** this proton is mostly axial.

Experimental Section

General Procedures. Melting points were recorded on an electrothermal apparatus and are uncorrected. ^1H, $^1H\{^{31}P\}$, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$, ^1H NOEDIF, ^1H COSY, and ^1H,^{13}C HMQC NMR spectra were recorded in $CDCl_3$ solution at 25 °C on JEOL JNM LA400 (^1H, 399.78 MHz; ^{13}C, 100.53 MHz; and ^{31}P, 161.84 MHz) and on JEOL A500 (^1H, 500.16 MHz; ^{13}C, 125.77 MHz; and ^{31}P, 202.47 MHz) Fourier transform spectrometers, with the deuterium signal of the solvent as the lock. TMS was used as an internal standard in ^1H NMR measurements (0.00 ppm), whereas the middle line of the solvent signal was used in ^{13}C NMR measurements (77.00 ppm) and external 85% H_3PO_4 in an inner tube was used in ^{31}P measurements (0.00 ppm, values not corrected). Positive ^{31}P chemical shifts (ppm) are downfield from the external standard. Samples were dissolved in 0.5 mL of solvent, and the measurements were made in 5-mm diameter Wilmad 7-in. 507PP NMR tubes. Spectral analyses were performed for several cases with the PERCH[25] program on a Pinus Pentium 100-MHz personal computer. This was needed to resolve the overlapping signals or in some cases to iterate the non-first-order portions of spectra. For example, the signals of H-4ax and H-4eq form an AB-type system in many cases. The criteria for accepting the iterated signals were the best-looking fits of the iterated and measured spectra. For low-temperature measurements, samples were dissolved in CD_2Cl_2 or in $CHFCl_2$. $CHFCl_2$ samples were prepared by cooling Wilmad 528JY valve NMR tubes in dry ice and letting the gas flow into the tubes and condense. A quick degassing was performed for the $CHFCl_2$ samples with the freeze−pump−thaw method (freezing with liquid nitrogen) and in a CD_2Cl_2 solution of **2b** by bubbling nitrogen through the sample. Variable-temperature NMR measurements were performed by cooling with a nitrogen flow. Temperatures were calibrated with a methanol sample method.[26] The signal of external 85% H_3PO_4 signal in an inner tube in $CDCl_3$ at 25 °C was used as a reference (0.00 ppm) for all low-temperature ^{31}P measurements. Chemicals were generally of highest purity. For column chromatography, Merck silica gel 60 Art. 9385 was used. Preparative thin-layer chromatography was performed with Merck silica gel 60 F_{254}S Art. 13792.

General Method for Ring-Closure Reactions. To a stirred solution of triethylamine (2 equiv) and bis(2-chloroethyl) phosphoramidic dichloride (1 equiv) in 100 mL of dry THF at room temperature in dry nitrogen atmosphere was added a solution of the appropriate amino alcohol (4.4 mmol) in 50 mL of dry THF dropwise. The reaction mixture was stirred overnight. The amine salt was filtered off, and filtrate was evaporated to dryness to yield a crude mixture of two isomers in each case.

Separation and Purification of Isomers. Trans-Fused 2-[Bis(2-chloroethyl)amino]-3,4,4a,5,6,7,8,8a-octahydro-1,3,2-benzoxazaphosphorinane 2-Oxides 1a and 1b. The crude product (ratio of isomers 1:1, based on the ^{31}P NMR spectrum of the crude product) was purified by flash column chromatography (methanol−chloroform 3:97). The more mobile component was crystallized from ethyl acetate−*n*-hexane to yield isomer **1a** (11.7%, mp 119.6−120.4 °C): ^1H NMR ($CDCl_3$) δ 1.00 (m, 1 H, 5ax), 1.25 (m, 1 H, 6ax), 1.3 (m, 1 H, 7ax), 1.40 (m, 1 H, 8ax) 1.64 (m, 1 H, 4a), 1.7 (m, 2 H, 5eq, 6eq) 1.82 (m, 1 H, 7eq), 2.06 (m, 1 H, 8eq), 2.57 (bs, 1 H, NH), 3.11 (m, 1 H, 4eq), 3.13 (m, 1 H, 4ax), 3.33−3.42 (m, 2 H, 16b, 18b), 3.47−3.56 (m, 2 H, 16a, 18a), 3.62 (m, 4 H, 17a, 17b, 19a, 19b), 4.15 (tq, 1 H, 8a); ^{13}C NMR ($CDCl_3$) δ 24.2 (d, 7, $^4J_{CP}$ = 2.1 Hz), 24.8 (s, 6), 28.1 (s, 5), 33.3 (d, 8, $^3J_{CP}$ = 8.6 Hz), 40.6 (d, 4a, $^3J_{CP}$ = 3.7 Hz), 42.5 (s, 2 C, 17, 19), 47.4 (d, 4, $^2J_{CP}$ = 2.6 Hz) 49.0 (d, 2 C, 16, 18, $^2J_{CP}$ = 4.6 Hz), 80.7 (d, 8a, $^2J_{CP}$ = 6.2 Hz); ^{31}P NMR ($CDCl_3$) δ 13.4. Anal. Calcd for $C_{11}H_{21}N_2O_2PCl_2$: C, 41.92; H, 6.72; N, 8.89. Found: C, 42.32; H, 6.71; N, 8.57.

The middle fraction contained a pure mixture of isomers (^1H NMR, 48.3%). The less mobile component was purified by flash chromatography, eluting first with ethyl acetate and then with chloroform. The chloroform fraction was evaporated to yield isomer **1b** in pure form (13.8%, mp 98.8−99.6 °C): ^1H NMR ($CDCl_3$) δ 0.89 (m, 1 H, 5ax), 1.2 (m, 1 H, 6ax), 1.25 (m, 1 H, 7ax), 1.51 (m, 1 H, 8ax), 1.63 (m, 1 H, 5eq), 1.66 (m, 1 H, 6eq), 1.7 (m, 1 H, 4a), 1.8 (m, 1 H, 7eq), 2.00 (m, 1 H, 8eq), 2.81 (m, 1 H, 4ax), 3.10 (m, 1 H, 4eq), 3.29−3.47 (m, 5 H, 16a, 16b, 18a, 18b, NH), 3.63 (m, 4 H, 17a, 17b, 19a, 19b), 3.88 (m, 1 H, 8a); ^{13}C NMR ($CDCl_3$) δ 24.2 (d, 7, $^4J_{CP}$ = 2.2 Hz), 24.7 (d, 6, $^5J_{CP}$ = 0.3 Hz), 28.0 (d, 5, $^4J_{CP}$ = 0.6 Hz), 33.2 (d, 8, $^3J_{CP}$ = 7.1 Hz), 41.4 (d, 4a, $^3J_{CP}$ = 8.3 Hz), 42.0 (d, 2 C, 17, 19, $^3J_{CP}$ = 2.8 Hz), 47.1 (d, 4, $^2J_{CP}$ = 2.8 Hz), 48.6 (d, 2 C, 16, 18, $^2J_{CP}$ = 3.7 Hz), 83.0 (d, 8a, $^2J_{CP}$ = 7.7 Hz); ^{31}P NMR ($CDCl_3$) δ 11.0. Anal. Calcd for $C_{11}H_{21}N_2O_2PCl_2$: C, 41.92; H, 6.72; N, 8.89. Found: C, 41.78; H, 6.75; N, 8.53.

Trans-Fused 3-Methyl-2-[bis(2-chloroethyl)amino]-3,4,4a,5,6,7,8,8a-octahydro-1,3,2-benzoxazaphosphorinane 2-Oxides 3a and 3b. The crude product (ratio of isomers 2:3, based on the ^{31}P NMR spectrum of the crude product) was purified by column chromatography (acetone−ethyl acetate 1:9). The more mobile component was further purified by preparative thin-layer chromatography eluting with 1% methanol/9% acetone/90% ethyl acetate. The compound with R_f = 0.35 was identified as pure isomer **3a** (23.8%, colorless oil): ^1H NMR ($CDCl_3$) δ 1.02 (m, 1 H, 5ax), 1.25 (m, 2 H, 6ax, 7ax), 1.35 (m, 1 H, 8ax), 1.7 (m, 3 H, 4a, 5eq, 6eq), 1.82 (m, 1 H, 7eq), 2.06 (m, 1 H, 8eq), 2.57 (d, 3 H, NMe), 2.89 (m, 1 H, 4eq), 2.93 (m, 1 H, 4ax), 3.31−3.52 (m, 4 H, 16a, 16b, 18a, 18b), 3.63 (m, 4 H, 17a, 17b, 19a, 19b), 4.08 (tq, 1 H, 8a); ^{13}C NMR ($CDCl_3$) δ 24.1 (d, 7, $^4J_{CP}$ = 2.3 Hz), 24.7 (s, 6), 28.1

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(s, 5), 33.0 (d, 8, $^3J_{CP}$ = 9.2 Hz), 35.6 (s, 9), 41.1 (d, 4a, $^3J_{CP}$ = 3.1 Hz), 42.5 (s, 2 H, 17, 19), 49.7 (d, 2 C, 16, 18, $^2J_{CP}$ = 4.6 Hz), 56.2 (s, 4), 80.1 (d, 8a, $^2J_{CP}$ = 6.1 Hz); ^{31}P NMR ($CDCl_3$) δ 15.6.

The less mobile component was dissolved in diethyl ether, the solution was filtered, and the filtrate was evaporated to yield isomer **3b** in pure form (17.3%, colorless oil): ^{1}H NMR ($CDCl_3$) δ 0.99 (m, 1 H, 5ax), 1.24 (m, 1 H, 6ax), 1.27 (m, 1 H, 7ax), 1.51 (m, 1 H, 8ax), 1.7 (m, 1 H, 7eq), 1.74 (m, 1 H, 5eq), 1.82 (m, 1 H, 6eq), 1.98 (m, 1 H, 4a), 2.05 (m, 1 H, 8eq), 2.70 (d, 3 H, NMe), 2.94 (m, 1 H, 4ax), 2.98 (m, 1 H, 4eq), 3.28−3.44 (m, 4 H, 16a, 16b, 18a, 18b), 3.64 (m, 4 H, 17a, 17b, 19a, 19b), 3.88 (tq, 1 H, 8a); ^{13}C NMR ($CDCl_3$) δ 24.1 (d, 7, $^4J_{CP}$ = 2.5 Hz), 24.6 (s, 6), 28.7 (s, 5), 33.3 (d, 8, $^3J_{CP}$ = 6.6 Hz), 35.6 (d, 9, $^2J_{CP}$ = 3.3 Hz), 40.1 (d, 4a, $^3J_{CP}$ = 8.3 Hz), 42.3 (d, 2 C, 17, 19, $^3J_{CP}$ = 1.7 Hz), 49.4 (d, 2 C, 16, 18, $^2J_{CP}$ = 4.1 Hz), 55.8 (d, 4, $^2J_{CP}$ = 2.5 Hz), 82.3 (d, 8a, $^2J_{CP}$ = 7.4 Hz); ^{31}P NMR ($CDCl_3$) δ 11.0.

Cis-Fused 3-Methyl-2-[bis(2-chloroethyl)amino]-3,4,-4a,5,6,7,8,8a-octahydro-1,3,2-benzoxazaphosphorinane 2-Oxides 4a and 4b. The crude product (ratio of isomers 3:2, based on the ^{31}P NMR spectrum of the crude product) was purified by column chromatography (methanol−acetone−ethyl acetate 1:9:90). The more mobile component was identified as isomer **4b** (47.4%, colorless oil): ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 2 H, 6ax, 7ax), 1.5 (m, 1 H, 5ax), 1.77 (m, 1 H, 8ax), 1.8 (m, 2 H, 5eq, 7eq), 2.0 (m, 1 H, 8eq), 2.15 (m, 1 H, 4a), 2.65 (d, 3 H, NMe), 3.08 (m, 1 H, 4eq), 3.18 (m, 1 H, 4ax), 3.35 (m, 2 H, 16b, 18b), 3.40 (m, 2 H, 16a, 18a) 3.63 (m, 4 H, 17a, 17b, 19a, 19b), 4.40 (m, 1 H, 8a); ^{13}C NMR ($CDCl_3$) δ 22.4 (s, 7), 22.5 (s, 6), 26.6 (s, 5), 30.1 (d, 8, $^3J_{CP}$ = 3.7 Hz), 35.7 (d, 4a, $^3J_{CP}$ = 4.6 Hz), 36.0 (d, 9, $^2J_{CP}$ = 2.8 Hz), 42.4 (d, 2 C, 17, 19, $^3J_{CP}$ = 1.6 Hz) 49.6 (d, 2 C, 16, 18, $^2J_{CP}$ = 4.6 Hz), 52.6 (s, 4), 79.8 (d, 8a, $^2J_{CP}$ = 7.9 Hz); ^{31}P NMR ($CDCl_3$) δ 11.0.

The less mobile component was dissolved in diethyl ether, the solution was filtered, and the filtrate was evaporated to yield isomer **4a** (25.5%, colorless oil): ^{1}H NMR ($CDCl_3$) δ 1.32 (m, 1 H, 6ax), 1.46 (m, 1 H, 8ax), 1.5 (m, 2 H, 5eq, 7ax), 1.54 (m, 1 H, 7eq), 1.68 (m, 1 H, 4a), 1.76 (m, 1 H, 5ax), 1.82 (m, 1 H, 6eq), 1.97 (m, 1 H, 8eq), 2.55 (d, 3 H, NMe), 2.72 (qd, 1 H, 4eq), 3.40 (m, 1 H, 4ax), 3.35−3.44 (m, 2 H, 16b, 18b), 3.49−3.58 (m, 2 H, 16a, 18a), 3.63−3.70 (m, 4 H, 17a, 17b, 19a, 19b), 4.77 (s, 1 H, 8a); ^{13}C NMR ($CDCl_3$) δ 19.6 (s, 7), 25.1 (s, 6), 25.4 (s, 5), 31.4 (d, 8, $^3J_{CP}$ = 8.7 Hz), 35.6 (d, 9, $^2J_{CP}$ = 0.8 Hz), 36.4 (d, 4a, $^3J_{CP}$ = 2.5 Hz), 42.5 (s, 2 C, 17, 19), 49.6 (d, 2 C, 16, 18, $^2J_{CP}$ = 4.5 Hz), 55.9 (s, 4), 75.8 (d, 8a, $^2J_{CP}$ = 6.2 Hz); ^{31}P NMR ($CDCl_3$) δ 16.8.

Trans-Fused 3-Benzyl-2-[bis(2-chloroethyl)amino]-3,4,4a,5,6,7,8,8a-octahydro-1,3,2-benzoxazaphosphorinane 2-Oxides 5a and 5b. The crude product (ratio of isomers 1:3, based on the ^{31}P NMR spectrum of the crude product) was purified by column chromatography (*n*-hexane−ethyl acetate 1:9). The more mobile component was identified as pure isomer **5b** (44.8%, colorless oil): ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 1 H, 5ax), 1.19 (m, 1 H, 7ax), 1.25 (m, 1 H, 6ax), 1.52 (m, 1 H, 8ax), 1.58 (m, 1 H, 5eq), 1.6 (m, 1 H, 7eq), 1.79 (m, 1 H, 4a), 1.8 (m, 1 H, 6eq), 2.05 (m, 1 H, 8eq), 2.82 (td, 1 H, 4ax), 2.88 (ddd, 1 H, 4eq), 3.38 (m, 2 H, 16b, 18b), 3.44 (m, 2 H, 16a, 18a), 3.67 (t, 4 H, 17a, 17b, 19a, 19b), 3.91 (tdd, 1 H, 8a), 4.01 (q, 1 H, 9a), 4.38 (q, 1 H, 9b), 7.25−7.38 (m, 5 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 24.2 (d, 7, $^4J_{CP}$ = 2.3 Hz), 24.6 (s, 6), 28.4 (d, 5, $^4J_{CP}$ = 0.76 Hz), 33.3 (d, 8, $^3J_{CP}$ = 6.9 Hz), 40.5 (d, 4a, $^3J_{CP}$ = 7.6 Hz), 42.3 (d, 2 C, 17, 19, $^3J_{CP}$ = 2.3 Hz), 49.3 (d, 2 C, 16, 18, $^2J_{CP}$ = 4.2 Hz), 51.8 (d, 9, $^2J_{CP}$ = 3.8 Hz), 52.2 (d, 4, $^2J_{CP}$ = 4.2 Hz), 82.8 (d, 8a, $^2J_{CP}$ = 8.0 Hz), 127.6 (s, 13), 128.5 (s, 2 C, 12, 14), 128.7 (s, 2 C, 11, 15), 137.6 (d, 10, $^3J_{CP}$ = 4.6 Hz); ^{31}P NMR ($CDCl_3$) δ 11.1.

The less mobile component was dissolved in diethyl ether, the solution was filtered, and the filtrate was evaporated to yield isomer **5a** in pure form (13.5%, mp 96.0−97.0 °C): ^{1}H NMR ($CDCl_3$) δ 0.94 (m, 1 H, 5ax), 1.22 (m, 1 H, 6ax), 1.26 (m, 1 H, 7ax), 1.38 (m, 1 H, 8ax), 1.60 (m, 1 H, 5eq), 1.65 (m, 1 H, 4a), 1.67 (m, 1 H, 6eq), 1.81 (m, 1 H, 7eq), 2.08 (m, 1 H, 8eq), 2.72 (td, 1 H, 4ax), 2.85 (ddd, 1 H, 4eq), 3.31−3.41 (m, 2 H, 16b, 18b), 3.54−3.64 (m, 6 H, 16a, 18a, 17a, 17b, 19a, 19b), 3.89 (q, 1 H, 9b), 4.12 (tdd, 1 H, 8a), 4.28 (q, 1 H, 9a) 7.25−7.36 (m, 5 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 24.1 (d, 7, $^4J_{CP}$ = 1.7 Hz), 24.7 (s, 6), 28.1 (s, 5), 33.1 (d, 8, $^3J_{CP}$ = 9.0 Hz), 41.1 (d, 4a, $^3J_{CP}$ = 2.6 Hz), 42.5 (s, 2 C, 17, 19, $^3J_{CP}$ = 0.9 Hz), 49.6 (d, 2 C, 16, 18, $^2J_{CP}$ = 4.7 Hz), 51.7 (d, 9, $^2J_{CP}$ = 2.1 Hz), 52.4 (d, 4, $^2J_{CP}$ = 0.9 Hz), 80.4 (d, 8a, $^2J_{CP}$ = 6.4 Hz), 127.6 (s, 13), 128.4 (s, 2 C, 12, 14), 128.7 (s, 2 C, 11, 15), 137.0 (d, 10, $^3J_{CP}$ = 8.1 Hz); ^{31}P NMR ($CDCl_3$) δ 15.6. Anal. Calcd for $C_{18}H_{27}N_2O_2PCl_2$: C, 53.34; H, 6.71; N, 6.91. Found: C, 52.95; H, 6.68; N, 6.54.

Cis-Fused 3-Benzyl-2-[bis(2-chloroethyl)amino]-3,4,-4a,5,6,7,8,8a-octahydro-1,3,2-benzoxazaphosphorinane 2-Oxides 6a and 6b. The crude product (ratio of isomers 2:3, based on the ^{31}P NMR spectrum) was purified by column chromatography (ethyl acetate). The more mobile component was identified as pure isomer **6b** (42.6%, colorless oil): ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 1 H, 5ax), 1.30 (m, 1 H, 6ax), 1.35 (m, 1 H, 7ax), 1.47 (m, 1 H, 6eq), 1.75 (m, 3 H, 5eq, 7eq, 8ax), 2.0 (m, 2 H, 4a, 8eq), 3.00 (ddd, 1 H, 4eq), 3.04 (td, 1 H, 4ax), 3.37 (m, 2 H, 16b, 18b), 3.47 (m, 2 H, 16a, 18a), 3.65 (t, 4 H, 17a, 17b, 19a, 19b), 4.06 (q, 1 H, 9a), 4.20 (q, 1 H, 9b), 4.45 (m, 1 H, 8a) 7.24−7.36 (m, 5 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 21.8 (s, 7), 22.8 (s, 6), 26.0 (s, 5), 30.5 (d, 8, $^3J_{CP}$ = 3.8 Hz), 35.8 (d, 4a, $^3J_{CP}$ = 4.5 Hz), 42.4 (d, 2 C, 17, 19, $^3J_{CP}$ = 1.5 Hz), 49.2 (s, 4), 49.4 (d, 2 C, 16, 18, $^2J_{CP}$ = 4.5 Hz), 51.9 (d, 9, $^2J_{CP}$ = 3.8 Hz), 79.7 (d, 8a, $^2J_{CP}$ = 8.4 Hz), 127.6 (s, 13), 128.6 (s, 2 C, 12, 14), 128.7 (s, 2 C, 11, 15), 137.2 (d, 10, $^3J_{CP}$ = 6.0 Hz); ^{31}P NMR ($CDCl_3$) δ 10.7. Anal. Calcd for $C_{18}H_{27}N_2O_2PCl_2$: C, 53.34; H, 6.71; N, 6.91. Found: C, 53.10; H, 6.79; N, 6.71.

The less mobile component was identified as pure isomer **6a** (23.5%, colorless oil): ^{1}H NMR ($CDCl_3$) δ 1.27 (m, 1 H, 6ax), 1.4 (m, 1 H, 5eq), 1.5 (m, 2 H, 7ax, 8ax), 1.55 (m, 1 H, 7eq), 1.63 (m, 1 H, 4a), 1.8 (m, 1 H, 6eq), 1.82 (m, 1 H, 5ax), 1.99 (m, 1 H, 8eq), 2.72 (qd, 1 H, 4eq), 3.19 (dq, 1 H, 4ax), 3.33−3.47 (m, 2 H, 16b, 18b), 3.62−3.72 (m, 6 H, 16a, 18a, 17a, 17b, 19a, 19b), 3.76 (q, 1 H, 9b), 4.36 (q, 1 H, 9a), 4.81 (bs, 1 H, 8a), 7.26−7.37 (m, 5 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 19.7 (s, 7), 25.0 (s, 6), 25.1 (s, 5), 31.3 (d, 8, $^3J_{CP}$ = 8.8 Hz), 36.3 (d, 4a, $^3J_{CP}$ = 2.0 Hz), 42.4 (s, 2 C, 17, 19), 49.3 (d, 2 C, 16, 18, $^2J_{CP}$ = 4.4 Hz), 51.2 (d, 9, $^2J_{CP}$ = 2.7 Hz), 51.7 (d, 4), 76.1 (d, 8a, $^2J_{CP}$ = 6.1 Hz), 127.4 (s, 13), 128.1 (s, 2 C, 12, 14), 128.6 (s, 2 C, 11, 15), 136.9 (d, 10, $^3J_{CP}$ = 9.8 Hz); ^{31}P NMR ($CDCl_3$) δ 17.1. Anal. Calcd for $C_{18}H_{27}N_2O_2PCl_2$: C, 53.34; H, 6.71; N, 6.91. Found: C, 53.60; H, 6.87; N, 7.22.

Cis-Fused 2-[Bis(2-chloroethyl)amino]-3,4,4a,5,6,7,8,-8a-octahydro-1,3,2-benzoxazaphosphorinane 2-Oxide 2a. 6a (130 mg, 0.32 mmol) was dissolved in toluene (30 mL). Under stirring, 5.5 g of concentrated sulfuric acid was added. After the completion of the addition, the mixture was stirred for 2 h. The mixture was then poured into ice−water (50 mL), *n*-hexane (30 mL) was added, and the organic layer was separated and extracted with water (2 × 25 mL). The combined water layers were extracted with chloroform (3 × 25 mL), and the chloroform layer was dried over anhydrous magnesium sulfate and evaporated to dryness to give the crude product as a colorless oil. Purification of the crude product by flash chromatography, eluting first with ethyl acetate and then with chloroform, afforded pure **2a** (23.0%, mp 107.9−108.9 °C): ^{1}H NMR ($CDCl_3$) δ 1.32 (m, 1 H, 6ax), 1.5 (m, 4 H, 5ax, 7ax, 7eq, 8ax), 1.61 (m, 1 H, 4a), 1.82 (m, 2 H, 5eq, 6eq), 1.96 (m, 1 H, 8eq), 2.27 (bd, 1 H, NH), 2.98 (m, 1 H, 4eq), 3.32−3.45 (m, 2 H, 16b, 18b), 3.53−3.67 (m, 7 H, 4ax, 16a, 18a, 17a, 17b, 19a, 19b), 4.80 (bs, 1 H, 8a); ^{13}C NMR ($CDCl_3$) δ 19.7 (s, 7), 24.8 (s, 5), 25.0 (s, 6), 31.8 (d, 8, $^3J_{CP}$ = 8.7 Hz), 35.2 (d, 4a, $^3J_{CP}$ = 3.1 Hz), 42.5 (d, 2 C, 17, 19, $^3J_{CP}$ = 0.7 Hz), 46.7 (d, 4, $^2J_{CP}$ = 2.3 Hz), 48.9 (d, 2 C, 16, 18, $^2J_{CP}$ = 4.8 Hz), 76.4 (d, 8a, $^2J_{CP}$ = 6.0 Hz); ^{31}P NMR ($CDCl_3$) δ 14.5. Anal. Calcd for $C_{11}H_{21}N_2O_2PCl_2$: C, 41.92; H, 6.72; N, 8.89. Found: C, 42.10; H, 6.40; N, 8.76.

Cis-Fused 2-[Bis(2-chloroethyl)amino]-3,4,4a,5,6,7,8,-8a-octahydro-1,3,2-benzoxazaphosphorinane 2-Oxide 2b. By a procedure analogous to that for the preparation of **2a**, the reaction of **6b** (130 mg, 0.32 mmol) afforded pure **2b** (16.8%, mp 93.9−95.1 °C): ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 1 H, 6ax), 1.43 (m, 1 H, 5eq), 1.47 (m, 1 H, 7eq), 1.6 (m, 1 H, 8ax),

1.67 (m, 1 H, 4a), 1.71 (m, 1 H, 7ax), 1.73 (m, 1 H, 6eq), 1.93 (m, 1 H, 5ax), 1.99 (m, 1 H, 8eq), 2.93 (q, 1 H, NH), 3.10 (m, 1 H, 4eq), 3.28 (m, 1 H, 4ax), 3.32−3.46 (m, 4 H, 16a, 16b, 18a, 18b), 3.62−3.68 (m, 4 H, 17a, 17b, 19a, 19b), 4.50 (m, 1 H, 8a); ^{13}C NMR ($CDCl_3$) δ 20.1 (s, 7), 24.3 (s, 6), 24.5 (s, 5), 31.6 (d, 8, $^3J_{CP}$ = 6.5 Hz), 35.7 (d, 4a, $^3J_{CP}$ = 6.4 Hz), 42.1 (d, 2 C, 17, 19, $^3J_{CP}$ = 2.9 Hz), 45.8 (d, 4, $^2J_{CP}$ = 2.4 Hz), 48.6 (d, 2 C, 16, 18, $^2J_{CP}$ = 3.7 Hz), 79.1 (d, 8a, $^2J_{CP}$ = 7.6 Hz); ^{31}P NMR ($CDCl_3$) δ 10.6.

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Supporting Information Available: ^{1}H and ^{31}P{^{1}H} NMR spectra on **2b**−**4b** and **5b** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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