The First Monocyclic 1,3,2-Dioxaphosphorinane in a Boat Form. Synthesis, Structure, and Stability

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Abstract: Single-crystal X-ray analysis of *cis*-2,5-di-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinane, *cis*-**10**, reveals that it crystallizes in the orthorhombic space group $Pmc2_1$ with two half-molecules per asymmetric unit ($Z = 4$) and $a = 9.729$ (3) Å, $b = 11.634$ (3) Å, $c = 11.945$ (4) Å, $R = 0.042$, and $R_w = 0.050$. The two independent molecules, which have crystallographic C_s symmetry, are in the boat conformation with the *tert*-butyl groups in cis positions. The existence of the boat structure, which is the first example of this type for phosphorinanes, is attributed to steric and lattice effects. Molecular mechanics shows that the normally more stable chair form undergoes strong steric repulsion between the two cis *tert*-butyl groups positioned on the ring. The boat form which relieves this repulsion is calculated to be more stable by 1.8 kcal/mol. This study supports low energy differences for boat, twist-boat, and chair conformations for phosphorinane molecules.
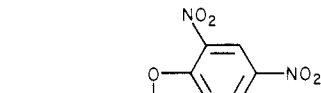
Most structural studies of phosphorinane derivatives reveal a chair conformation of the six-membered ring. For example, X-ray studies of cyclophosphamide **1**[2] and cyclophosphamide-like molecules **2**[3] and **3**[4,5] and the more complex, but related, *trans*-
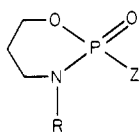
1, R = H; Z = N(CH₂CH₂Cl)₂
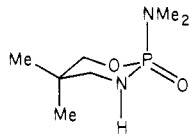2, R = CH₂CH₂Cl; Z = NHCH₂CH₂Cl
3, R = CH₂CH₂Cl; Z = N(CH₂CH₂Cl)₂
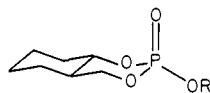
4, R = Ph
5, R = *p*-CH₃OPh

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decalin-type six-membered ring phosphorinane esters **4**,[6] **5**,[7] and **6**,[7] show that they all exist in chair conformations. In a related study,[8] we found the 1,3,2-oxazaphosphorinane **7** to possess a chair

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conformation, and like **6**, the phosphoryl group was situated in an equatorial position.

In general, interpretation of NMR data supports the retention of the chair conformation in solution, although, when the aryloxy group is in an equatorial position, as in **4** and **5**, or when the dimethylamino group is axial, as in **9**,[9] mixtures of chair and twist-boat conformations are indicated. Chair–twist equilibria also have been observed for other 1,3,2-dioxaphosphorinanes that have sterically strained chair structures.[10] In the cyclophosphamide-like oxazaphosphorinanes **8**, X-ray and NMR studies
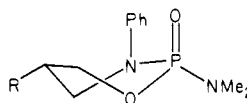
8a, R = *t*-Bu
8b, R = Ph

9, T = thymine

support twist conformations in both the solid and solution states,[11,12] with no more than minor amounts of other conformations indicated in solution. The latter twist structure is intermediate along the ring-puckering pseudorotational route between two boat forms which assume adjacent pairs of bow atoms.[11] This suggests that the twist-boat and boat form are not too different in energy. One X-ray study of an unsymmetrical twist-boat 1,3,2-dioxaphosphorinane also has been reported.[13] The observance of near 1:1 equilibrium mixtures of chair and twist-boat forms in solution for the *trans*-decalins **4** and **5**[14] and the 3:1 twist:chair equilibrium for **9**[10] shows that these conformations also have small energy differences. Twist-boat structures for 1,3,2-dithiaphosphorinanes also have been noted.[15]

Presumably, by suitable ligand construction, a boat conformation for this class of compounds might be formed as well. In

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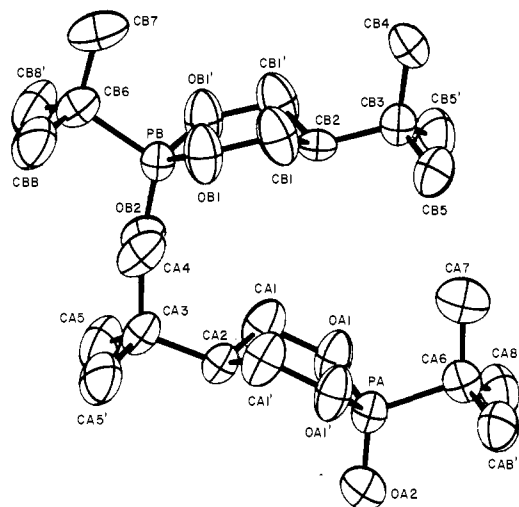
Figure 1. ORTEP plot showing the two independent molecules in crystalline (*t*-BuC$_3$H$_5$O$_2$)(*t*-Bu)PO, *cis*-**10**, with thermal ellipsoids at the 50% probability level. Hydrogen atoms have been omitted for purposes of clarity. Primed atoms are generated from unprimed ones by crystallographic mirror planes.

order to explore further the structural possibilities for this interesting class of substances, we undertook the synthesis, X-ray study, and a molecular mechanics study of the stability of the 1,3,2-dioxaphosphorinane **10**. It contains two *tert*-butyl groups

cis-**10**
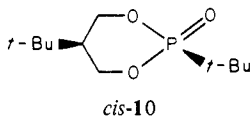
attached to the ring in cis positions. Because of symmetry, **10** is not biased toward a twist structure as are **4**, **5**, **8**, and **9**.

Experimental Section

Preparation of 2,5-Di-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinane (10). Sodium hydride (1.7 g, 0.071 mol) was placed in 100 mL of anhydrous ether under nitrogen. To this vigorously stirred mixture was added dropwise a solution of 2-*tert*-butyl-1,3-propanediol[16] (4.0 g, 0.030 mol) in 100 mL of anhydrous ether over a period of 20 min. The reaction mixture was then refluxed for $2^1/_4$ h. To it was added, with continued stirring over a 1-h period, a solution of *tert*-butylphosphonic dichloride, *t*-BuP(O)Cl$_2$, in 100 mL of anhydrous ether. After an additional $1^1/_2$ h of reaction, GLC analysis showed the reaction to be 97% complete and the product diastereomers present in 46/54 cis/trans ratio. Filtration and removal of solvent left 6.6 g of crude product. A 3.6-g portion of this material was dissolved in a minimum of CH$_2$Cl$_2$ and placed on a chromatography column that had been slurry packed with 300 g of 100–200 mesh Florosil in 700 mL of 20/80 ether/ligroin. Progressive elution with mixtures of these same solvents—2 L of 20/80, 3 L of 40/60, 7 L of 60/40, and 30 L of 80/20—gave 0.5 g of the trans isomer, mp 167–168 °C (100% pure by GLC analysis), and 0.25 g of solid material (94/6 cis/trans by GLC), mp 142–144 °C, after subsequent recrystallization from (bp 60–90 °C) ligroin (pure cis by GLC). For the trans isomer: Anal. Calcd for C$_{11}$H$_{23}$O$_3$P: C, 56.40; H, 9.90; P, 13.22. Found: C, 56.45; H, 9.94; P, 13.05. IR, cm^{-1} (KBr): 2950, 2900, 1800, 1470, 1390, 1320, 1250, 1220, 1140, 1050, 1010, 980, 890, 830, 800, 770, 663. ^{1}H NMR (CDCl$_3$): δ 0.950 (9 H, s, 5-*t*-Bu), 1.23 (9 H, d, J$_{HP}$ = 17 Hz, 2-*t*-Bu), 1.98 (1 H, m, methine), 4.25 (2 H, m, equatorial CH$_2$), 4.43 (2 H, m, axial CH$_2$). ^{31}P NMR (C$_6$D$_6$): +35.0. For the cis isomer: Anal. Calcd for C$_{11}$H$_{23}$O$_3$P: C, 56.40; H, 9.90; P, 13.22. Found: C, 56.34; H, 9.81; P, 12.46. IR, cm^{-1} (KBr): 2950, 2900, 1800, 1470, 1390, 1370, 1310, 1250, 1220, 1130, 1060, 1015, 980, 940, 900, 835, 815, 790, 760, 650. ^{1}H NMR (CDCl$_3$): δ 0.915 (9 H, s, 5-*t*-Bu), 1.18 (9 H, d, J$_{HP}$ = 17 Hz, 2-*t*-Bu), 4.10 (2 H, m, CH$_2$), 4.47 (2 H, m, CH$_2$), 2.43 (1 H, m, methine). ^{31}P NMR (C$_6$D$_6$): +33.4 (downfield from external H$_3$PO$_4$).

Crystallography of *cis*-10. Crystals of the cis isomer of **10**, suitable for X-ray diffraction, were obtained by vapor diffusion of a solution of the compound in ethyl ether with pentane. A crystal was mounted inside a sealed thin-walled glass capillary as a precaution against moisture

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Table I. Atomic Coordinates in Crystalline (*t*-BuC$_3$H$_5$O$_2$)(*t*-Bu)PO, *cis*-**10**^{a}

atom type^b	coordinates		
	10^4x	10^4y	10^4z
PA	5000	690 (2)	1630
PB	0	6846 (1)	3921 (2)
OA1	3715 (3)	20 (3)	2109 (4)
OB1	1278 (3)	7486 (3)	4439 (4)
OA2	5000	810 (5)	418 (5)
OB2	0	6836 (5)	2712 (4)
CA2	5000	−1778 (6)	1989 (6)
CA3	5000	−3097 (6)	2243 (6)
CA4	5000	−3330 (7)	3491 (7)
CA6	5000	2054 (6)	2363 (6)
CA7	5000	1830 (8)	3634 (6)
CB2	0	9278 (6)	4619 (5)
CB3	0	10488 (6)	5169 (7)
CB4	0	10424 (6)	6445 (7)
CB6	0	−5443 (6)	4559 (7)
CB7	0	5525 (8)	5822 (8)
CA1	3758 (5)	−1167 (4)	2444 (5)
CA5	3721 (6)	−3648 (5)	1696 (6)
CA8	3704 (6)	2701 (5)	2026 (5)
CB1	1247 (5)	8587 (5)	4920 (6)
CB5	1300 (7)	11141 (5)	4783 (6)
CB8	1301 (6)	4816 (5)	4145 (6)

^{a} Numbers in parentheses are estimated standard deviations. When these are omitted, the parameters were fixed. ^{b} Atoms are labeled to agree with Figure 1.

Table II. Selected Bond Lengths (Å) and Bond Angles (deg) for (*t*-BuC$_3$H$_5$O$_2$)(*t*-Bu)PO, *cis*-**10**^{a}

type^b	molecule A	molecule B
P–O1	1.581 (3)	1.576 (4)
P–O2	1.455 (6)	1.444 (5)
P–C6	1.813 (7)	1.801 (7)
O1–C1	1.438 (6)	1.404 (6)
C1–C2	1.503 (7)	1.499 (7)
O1–P–O2	114.1 (2)	113.4 (2)
O1–P–C6	104.9 (2)	105.2 (2)
O2–P–C6	113.4 (3)	114.6 (3)
O1–P–O1'	104.5 (3)	104.2 (3)
P–O1–C1	123.5 (3)	125.1 (3)
O1–C1–C2	112.1 (4)	114.1 (5)
C1–C2–C1'	107.0 (6)	108.0 (6)

^{a} Numbers in parentheses are estimated standard deviations.
^{b} Atoms are labeled to agree with Figure 1. Primed atoms go into unprimed ones by crystallographic mirror planes.

sensitivity. The X-ray crystallographic studies were done by using an Enraf-Nonius CAD4 diffractometer and graphite monochromated molybdenum radiation (λ Kα$_1$ = 0.70930 Å, λ Kα$_2$ = 0.71359 Å) at an ambient temperature of 23 ± 2 °C. Details of the experimental and computational procedures have been described previously.[17]

Crystal Data for *cis*-2,5-Di-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinane, C$_{11}$H$_{23}$O$_3$P (10). A colorless crystal of **10** was cut from a large triangular plate (triangular prism, edge = 0.30 mm, height = 0.25 mm), orthorhombic space group *Pmc*2$_1$ [C^7_{2v}—No. 26].[18] from *mmm* diffraction symmetry, extinctions, and successful solution and refinement; *a* = 9.729 (3) Å, *b* = 11.634 (3) Å, *c* = 11.945 (4) Å, *Z* = 4 (two half molecules per asymmetric unit), μ(Mo Kα) = 0.196 mm^{-1}, and D_{calcd} = 1.151 g/cm^3. A total of 1325 independent reflections (+*h*,+*k*,+*l*) were measured by using the θ–2θ scan mode for 2° ≤ 2θ(Mo Kα) ≤ 50°. No corrections were made for absorption.

The structure was solved by using a combination of direct methods (MULTAN) and Fourier difference techniques and was refined by full-matrix least-squares methods.[19] The 22 independent non-hydrogen

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atoms were refined anisotropically. Coordinates for the 26 independent hydrogen atoms were obtained by a combination of calculation and Fourier difference techniques. These were included in the refinement as fixed isotropic scatterers. Calculable coordinates were updated as refinement converged so that the final C–H bond lengths were 0.98 Å. The final agreement factors[20] were $R = 0.042$, $R_w = 0.050$, and GOF = 1.386 for the 974 reflections having $I \geq 2\sigma I$. A final Fourier difference synthesis showed a maximum density of 0.130 e/Å^3.

Results and Discussion

The atom labeling scheme for *cis*-10 is shown in the ORTEP plot of Figure 1. Atomic coordinates for non-hydrogen atoms appear in Table I, and important bond lengths and angles are given in Table II. Anisotropic thermal parameters, hydrogen atom parameters, and mean planes are provided as supplementary material.

As can be seen in Figure 1, the two independent molecules for *cis*-10 have very similar geometry. The six-membered rings are in the boat conformation with the *tert*-butyl groups in cis positions. The molecules have crystallographic C_s symmetry with C4, C3, C2, P, C6, and C7 lying on mirror planes.

The appearance of the boat conformation for *cis*-10 represents the first monocyclic example of this structural type for this class of molecules. The presence of the bulky *cis-tert*-butyl groups no doubt contributes in destabilizing the chair form for *cis*-10. On the basis of a molecular model, if the chair form (11) is con-

11
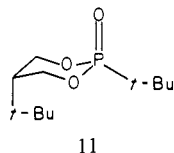
structed, which is flattened at phosphorus as in Figure 1, the two *tert*-butyl groups would produce a close contact between carbon centers of approximately 2.5 Å, suggesting steric repulsion. Also crystal packing effects of the symmetrically substituted molecule most likely contribute in favoring the boat over the twist-boat form for *cis*-10. A boat conformation for *cis*-10 in solution had been suggested earlier in ^{1}H NMR work.[21]

In order to establish in a more quantitative fashion the degree of steric interaction, we employed the molecular mechanics approach[22] using our previously developed methods and parameters.[23] The strain energies of both boat and chair conformations for *cis*-10 were calculated.

The starting coordinates for the *boat* conformation were the X-ray coordinates of the B molecule of *cis*-10. The starting coordinates for the *chair* conformation were obtained by a rotation of the flap carbon atom CB2 (with its hydrogen and *tert*-butyl substituents) about an axis perpendicular to the mirror plane and passing through CB1. The starting conformations were then minimized and the energies of the boat and chair forms were calculated to be 17.3 and 19.1 kcal/mol, respectively. The contribution of stretch, bend, and van der Waals terms as well as total strain energy is shown in Table III, calculation 1. The calculated structure for the boat conformation simulates the X-ray structure quite closely, with the average deviations of calculated and actual bond lengths and angles for the entire molecule equal to 0.01 Å and 2.4°, respectively.

While the absolute value of the strain energy has no physical significance, the 1.8-kcal calculated energy difference between the two conformation is significant. It is apparent from the *initial* coordinate of the chair conformation that the close approach of the *tert*-butyl groups causes a large steric strain. This steric contribution is diminished in the final minimum energy chair

Table III. Strain Energy (kcal/mol) of Minimum Energy Conformations of $(t\text{-BuC}_3\text{H}_5\text{O}_2)(t\text{-Bu})\text{PO}$. *cis*-10 (Boat and Chair Forms)

	calculation 1^a		calculation 2^b	
	boat	chair	boat	chair
bond stretch	2.54	2.81	0.03	0.02
bond bending	6.29	6.93	0.36	0.40
nonbonded interactions	8.45	9.36	0.90	0.48
total strain energy	17.28	19.10	1.29	0.90
nearest R–R' distance,^{c} CB4–CB7	5.77	4.03	5.44	2.51

^{a} All bond lengths, bond angles, and VDW parameters are as described in ref 23. ^{b} VDW radius for carbon and hydrogen atoms reduced to 0.3 and 0.2 Å, respectively. All other parameters as in calculation 1. ^{c} R = R' = *tert*-butyl; distance in Å.

conformation by a separation of the two *tert*-butyl groups. While the closest approach of carbon atoms is only 4.03 Å, this separation is achieved only by an increase in strain energy in all bond lengths and bond angles; hence the overall higher energy of the chair form as compared to the boat form.

To assess what the actual distance between *tert*-butyl groups would be without the distribution of strain into all bond lengths and bond angles, it was necessary to reduce the contribution of the van der Waals terms to the total strain energy. To do this, the parameters for the van der Waals radius for carbon and hydrogen were reduced to 0.3 and 0.2 Å, respectively. This in effect eliminates steric hindrance and allows the final minimum energy structure to reflect "strainless" bond lengths and bond angles only. Using the same starting conformations as in calculation 1, minimum energy conformations were calculated for the boat and chair forms. These results are shown in Table III, calculation 2. The conformation of the boat form again corresponds quite well to the conformation obtained from the X-ray structure. The average deviations of calculated and experimental bond lengths and angles for the entire molecule were 0.01 Å and 2.9°, respectively. In calculation 2, both conformations show a drop in energy due to the elimination of a large van der Waals contributions from carbon and hydrogen. Now the energy of the chair form (0.9 kcal/mol) is lower than that of the boat form (1.3 kcal/mol), thus supporting the contention that the appearance of the boat form for *cis*-10 is a result of increased steric interaction between the two *tert*-butyl groups in the chair form. The distance between *tert*-butyl groups in the chair form is 2.5 Å, based on the closest C–C distance, CB4–CB7. We see there is much less decrease for this distance in the less sterically hindered boat form between these two calculations, 0.33 Å compared to 1.52 Å for the chair. The energy terms resulting from this calculation are shown in Table III, calculation 2. While the axial *tert*-butyl group at C2 would of itself destabilize chair structure 11, these calculations suggest that 11 is rendered especially unstable by the interaction of the two *tert*-butyl substituents. Interestingly, the P=S analogue of *cis*-10 assumes the chair form corresponding to 11 in the solid state.[24]

The P–O–C bond angles for the boat conformation *cis*-10 deviate considerably from the tetrahedral value of 109° 28′ (123.5 (3)° for molecule A and 125.1 (3)° for molecule B). As a result, the extent of folding along O1–O1′ is less than that along C1–C1′. The atoms O1, O1′, C1, and C1′ are required by symmetry to be coplanar. For molecule A, the dihedral angle (α) between this four-atom plane and the plane defined by CA1, CA2, and CA1′ is 53.6°, while the dihedral angle (β) between the four atom plane and the plane defined by OA1, PA, and OA1′ is only 20.2°. For molecule B, the corresponding dihedral angles are 48.2° and 15.6°. For the calculated chair form (Table III, calculation 1), the latter dihedral angle (β) is 35.4°. For the chair structure found for the

(20) $R = \sum ||F_o| - |F_c||/\sum |F_o|$, $R_w = \{\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2\}^{1/2}$, and GOF = $[\sum w(|F_o| - |F_c|)^2/N_o - N_v]^{1/2}$, where $N_o = 974$ and $N_v = 156$. The inverse configuration gave $R_w = 0.050$ and GOF and 1.387.

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P=S analogue of cis-10,[24] this dihedral angle is 50.3°, suggesting that the tert-butyl groups are positioned further apart for greater steric relief. The presence of a larger sulfur atom in this compound compared to the oxygen atom in cis-10 may contribute to the relative stability of the observed chair structure. If the boat form were formed for the P=S analogue, larger sulfur atom repulsions with hydrogens at the C1 and C2 carbon atoms might arise.

The degree of flattening at the phosphorus end of the ring may be typical of boat and twist-boat 1,3,2-dioxaphosphorinanes. Thus the twist-boat cis-2-(tert-butylamino)-2-seleno-4,4,6-trimethyl-1,3,2-dioxaphosphorinane[13] displayed averaged endocyclic P–O–C bond angles of 122 (3)°. This feature could contribute to lowering the relative free energy of the boat or twist conformations of such ring systems.

The structural comparisons made here, particularly the suggestion that the boat form for cis-10 may be a result of steric and lattice interactions, support the low energy differences inherent between the three main ring conformations for phosphorinanes. All three forms have now been observed in the solid state on related derivatives.

Conformations of Saturated Six-Membered Ring Phosphorus Heterocycles. X-ray Crystallographic and ¹H NMR Study of cis-2-Oxo-2-(dimethylamino)-3,5-diphenyl-1,3,2-oxazaphosphorinane, a Cyclophosphamide-like Molecule in a Twist Conformation

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Abstract: The title compound (5) crystallized in the monoclinic space group $P2_1/n$ with $a = 16.225$ (4) Å, $b = 6.149$ (1) Å, $c = 16.496$ (3) Å, $\beta = 92.75$ (2)° ($Z = 4$), $R = 0.047$, and $R_w = 0.051$. The molecule adopts a twist conformation with the 5-phenyl and 2-dimethylamino substituents cis to one another in pseudoequatorial positions. Both the ring nitrogen and the dimethylamino nitrogen have planar geometries. The ring is somewhat flattened at the phosphorus end. ¹H NMR parameters measured at 300 MHz show that 5 is predominantly in the same twist conformation in solution. The chair conformer with 5-phenyl axial, significantly, is not populated. This appears to be the only example of a saturated six-membered ring system which is forced essentially completely out of the chair conformation by an axial substituent as small as phenyl and defines an important difference between the 1,3,2-oxaza- and 1,3,2-dioxaphosphorinane ring system. By contrast, at least 25% of the 2-oxo-2-tert-butyl-5-phenyl-1,3,2-dioxaphosphorinane in solution adopts a chair conformation with the 5-phenyl axial. It is concluded that the free energy change for the conversion of the chair conformation of a 1,3,2-oxazaphosphorinane into the corresponding twist form must be very small.

The effect on the conformational properties of the cyclohexane ring system of replacement of ring carbon atoms by heteroatoms (P, O, S, N, etc.) is of considerable basic interest. Consequences of the placement of heteroatoms within the rings include (1) the alteration of bond lengths and angles within the ring; (2) the replacement of ring hydrogen atoms by heteroatom electron lone pairs, and (3) the introduction of bond and molecular dipoles. All of these can have profound effects upon the relative energies of diastereomers, the axial and equatorial preferences of substituents, and the relative energies of various conformations, e.g., chair and twist conformers. Examples of such heterocyclic compounds whose conformational properties are unusual[2] are the 2-oxo-1,3,2-dioxaphosphorinanes (1). Related to them are the 2-oxo-1,3,2-oxazaphosphorinanes (2). The latter are of special interest, because the clinically important anticancer drugs[3] cyclophosphamide
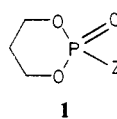
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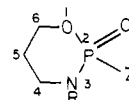
2a, R = H; Z = N(CH₂CH₂Cl)₂
  b, R = CH₂CH₂Cl; Z = NHCH₂CH₂Cl
  c, R = CH₂CH₂Cl; Z = N(CH₂CH₂Cl)₂

(2a), isophosphamide (2b), and trophosphamide (2c) all possess the 1,3,2-oxazaphosphorinane ring system. Carbon-substituted derivatives of cyclophosphamide also have been made and shown

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(2) The conformational properties of 1,3,2-dioxaphosphorinanes have been comprehensively reviewed: Maryanoff, B. E.; Hutchins, K. O.; Maryanoff, C. A. *Top. Stereochem.* **1979,** *11,* 187. For an earlier review see: Verkade, J. G. *Phosphorus Sulfur* **1976,** *2,* 251.

(3) Hill, D. L. "A Review of Cyclophosphamide"; C. C. Thomas: Springville, IL, 1975.