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.

Acknowledgment. The support of this research by the National Institutes of Health (GM 21466 to R.R.H. and CA 11045 to W.G.B.) is gratefully acknowledged. We also thank the University of Massachusetts Computer Center for generous allocation of computer time.

Registry No. *cis*-**10**, 35365-45-8; *trans*-**10**, 35365-44-7; *t*-BuP(O)Cl_2, 4707-95-3; 2-*tert*-butyl-1,3-propanediol, 2819-05-8.

Supplementary Material Available: Thermal parameters (Table A), fixed hydrogen atom parameters (Table B), least-squares mean planes (Table C), and a listing of observed and calculated structure factor amplitudes for *cis*-**10** (9 pages). Ordering information is given on any current masthead page.

Conformations of Saturated Six-Membered Ring Phosphorus Heterocycles. X-ray Crystallographic and ^{1}H 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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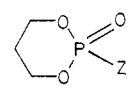
Received January 24, 1983

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, β = 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. ^{1}H NMR parameters measured at 300 MHz show that **5** also 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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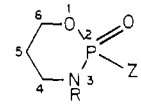

2a, R = H; Z = $N(CH_2CH_2Cl)_2$
b, R = CH_2CH_2Cl; Z = $NHCH_2CH_2Cl$
c, R = CH_2CH_2Cl; Z = $N(CH_2CH_2Cl)_2$

(**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

(1) (a) University of Utah. (b) University of Massachusetts, Amherst.

(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.

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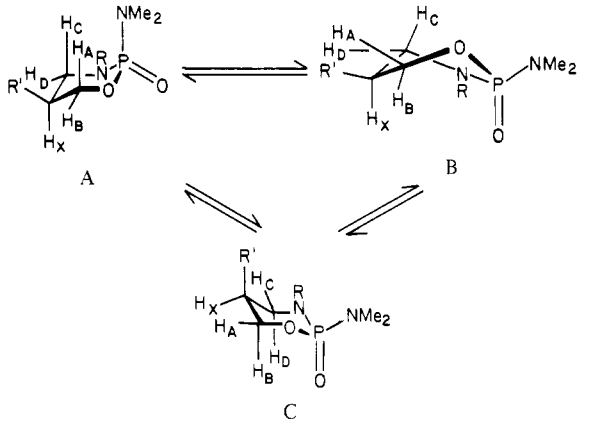
Scheme I



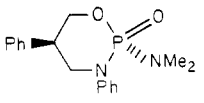
A B C

3, R = Ph, R′ = *t*-Bu; **4**, R = H, R′ = *t*-Bu; **5**, R = Ph, R′ = Ph

to be biologically active.[4] Moreover, the microsomal activation of cyclophosphamide (and likely **2b** and **2c** as well) involves initial hydroxylation at C(4), giving potentially two diastereomers. Knowledge of the possible effect of ring substitution and conformation on the ease of both hydroxylation and subsequent ring opening, all necessary to activation, requires a thorough understanding of the conformational properties of ring-substituted 2-oxo-1,3,2-oxazaphorinanes.

In an earlier paper[5] we showed by X-ray crystallography that **3**, *cis*-2-oxo-2-(dimethylamino)-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane, adopts a twist-boat conformation (B of Scheme I) in the crystal and also very predominately so in solution, as demonstrated by ^{1}H NMR. The apparent larger steric size of the Me_2N in this compound compared to **4**, which populates A,[5] was ascribed to a repulsive steric interaction in A between the axial Me_2N and the *N*-phenyl substituent which is relieved in B in which the Me_2N is pseudoequatorial. However, conformation C is also without Me_2N/PhN strain, yet it is populated to less than 5%. Evidently the conformational energy (*A* value) of the axial *tert*-butyl in C is sufficient to cause depopulation of C in favor of B.

Whether the failure of C to be populated stems from an unusually high conformational energy of the axial *tert*-butyl or a relatively low change in free energy in isomerization from the chair conformation was not clear. An important question, consequently, is whether a smaller R will result in depopulation of B in favor of C. To this end we have examined *cis*-2-oxo-2-(dimethylamino)-3,5-diphenyl-1,3,2-oxazaphosphorinane (**5**) by X-ray crystallographic and ^{1}H NMR techniques. The conformation of the trans diastereomer, **6**, was also investigated by ^{1}H NMR.



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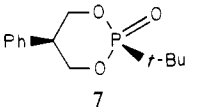

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Evidently, the 5-phenyl substituent is still relatively large in this ring system because **5**, like **3**, was found to be in a twist conformation, B, in solution and in the crystal. This represents the first study of the effects of the steric size of a substituent at the 5-position of a 2-oxo-1,3,2-oxazaphosphorinane on the conformational equilibria of such rings. Furthermore, this is to our knowledge the first six-membered ring system for which a substituent as small as phenyl on a carbon atom β to two heteroatoms (here O and N) causes an essentially complete depopulation of a chair conformation (C), in favor of a twist boat (B). This also defines another important difference between the 2-oxo-1,3,2-oxaza- (**2**) and 2-oxo-1,3,2-dioxaphosphorinane (**1**) ring systems, since **7** is found in solution in two conformations in rapid equilibrium analogous to B ⇄ C.[6]

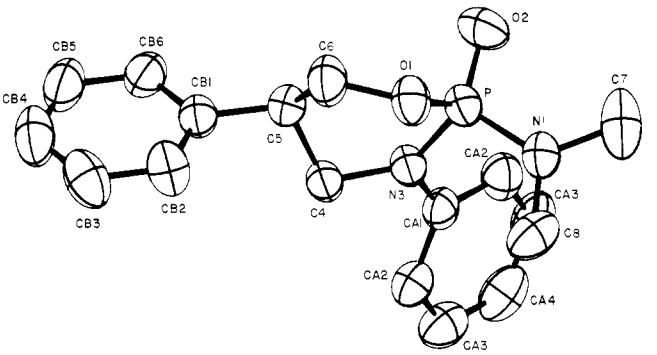


Figure 1. ORTEP plot of $(PhC_3H_5ONPh)(Me_2N)PO$ (**5**), with thermal ellipsoids at the 50% probability level. Hydrogen atoms have been omitted for purposes of clarity.

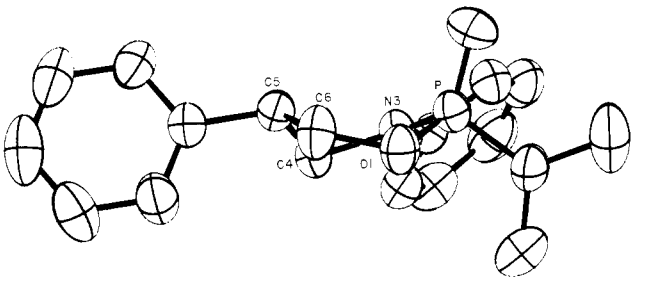
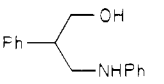


Figure 2. ORTEP plot of $(PhC_3H_5ONPh)(Me_2N)PO$ (**5**) showing the twist-boat conformation of the phosphorus-containing six-membered ring.

Results and Discussion

Preparation of 5 and 6. The 1,3,2-oxazaphosphorinanes **5** and **6** were readily prepared on reaction of $Me_2NP(O)Cl_2$ with amino alcohol **8**, synthesized in several steps from diethyl phenylmalonate



8

by a route analogous to that published earlier[7] for *N*-phenyl-2-(hydroxymethyl)-3,3-dimethylbutylamine. Column chromatography (MPLC) separated the diastereomers **5** and **6**. The assignment of cis stereochemistry (Ph and Me_2N) to **5** was tentatively made from the ordering of ^{31}P NMR chemical shifts, δ ^{31}P (cis) < δ ^{31}P (trans), and confirmed by X-ray crystallography.

X-ray Structure of 5. The atom labeling scheme is shown in Figure 1, while Figure 2 portrays the twist-boat conformation for **5**. 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.

The six-membered ring of **5**, Figures 1 and 2, has a twist-boat conformation with pseudoequatorial dimethylamino and phenyl groups cis to one another. Both the ring nitrogen atom, N(3) and the dimethylamino nitrogen, N(1), have essentially planar ge-

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(5) Bajwa, G. S.; Bentrude, W. G.; Panteleo, N. S.; Newton, M. G.; Hargis, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1602, and unpublished X-ray data for **3**.

(6) Bentrude, W. G.; Tan, H. W.; Yee, K. C., unpublished work.

(7) Bajwa, G. S.; Chandrasekaran, S.; Hargis, J. H.; Sopchik, A. E.; Blatter, D.; Bentrude, W. G. *J. Am. Chem. Soc.* **1982**, *104*, 6385.

Table I. Atomic Coordinates in Crystalline $(PhC_3H_5ONPh)(Me_2N)PO$ (5)[a]

atom type[b]	coordinates		
	10^4x	10^4y	10^4z
P	1476.7 (7)	6140 (2)	9502.0 (6)
O1	675 (2)	7182 (4)	9852 (1)
O2	1580 (2)	3817 (5)	9647 (2)
N1	1405 (2)	6732 (6)	8544 (2)
N3	2199 (2)	7741 (5)	9921 (2)
C4	1997 (2)	9179 (6)	10606 (2)
C5	1416 (2)	7997 (6)	11158 (2)
C6	582 (3)	7591 (8)	10704 (2)
C7	1404 (3)	5086 (10)	7919 (3)
C8	1376 (3)	9001 (9)	8276 (3)
CA1	2986 (2)	7942 (7)	9593 (2)
CA2	3346 (3)	6170 (7)	9224 (2)
CA3	4126 (3)	6381 (9)	8912 (2)
CA4	4543 (3)	8337 (10)	8966 (3)
CA5	4183 (3)	10084 (9)	9327 (3)
CA6	3404 (2)	9914 (8)	9630 (2)
CB1	1314 (2)	9274 (7)	11934 (2)
CB2	935 (3)	11276 (8)	11918 (3)
CB3	861 (3)	12454 (8)	12632 (4)
CB4	1163 (3)	11604 (10)	13362 (3)
CB5	1554 (3)	9631 (10)	13378 (3)
CB6	1630 (3)	8467 (7)	12667 (2)

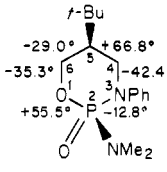
[a] Numbers in parentheses are estimated standard deviations. [b] Atoms are labeled to agree with Figure 1.

Table II. Selected Bond Lengths (Å) and Bond Angles (deg) for $(PhC_3H_5ONPh)(Me_2N)PO$ (5)[a]

P-O1	1.584 (3)	N1-C7	1.445 (5)
P-O2	1.457 (3)	N1-C8	1.463 (5)
P-N3	1.656 (3)	C4-C5	1.526 (5)
P-N1	1.620 (3)	C6-C5	1.534 (5)
O1-C6	1.444 (4)	N3-CA1	1.415 (5)
N3-C4	1.485 (4)	C5-CB1	1.518 (5)
O1-P-N1	104.0 (2)	P-O1-C6	123.4 (2)
O1-P-O2	115.3 (2)	P-N3-C4	119.6 (2)
O1-P-N3	100.7 (2)	O1-C6-C5	111.6 (3)
N1-P-N3	106.8 (2)	C4-C5-C6	110.0 (3)
O2-P-N3	116.1 (2)	C5-C4-N3	109.6 (3)
O2-P-N1	112.5 (2)	P-N1-C7	122.4 (3)
C4-C5-CB1	110.6 (3)	P-N1-C8	120.6 (3)
C6-C5-CB1	111.6 (3)	C7-N1-C8	116.9 (4)
C4-N3-CA1	118.4 (3)	P-N3-CA1	121.7 (2)

[a] Numbers in parentheses are estimated standard deviations. Atoms are labeled to agree with Figure 1.

ometries. The sum of the bond angles about N(3) is 359.7 (7)° while that about N(1) is 359.9 (10)°. The ring is skewed from that of a true boat structure in the same manner as is the ring of **3**.[5] Comparisons of the ring torsional angles for the two structures are given in **9** and **10**. The pseudorotational skewing



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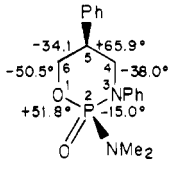

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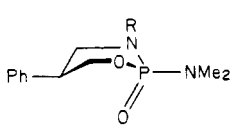
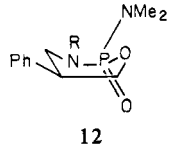
of the P and C(5) atoms away from their opposed positions in the bow positions of the true boat **11** toward the O(1)–C(4) bow,



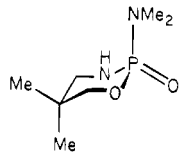
11



12

true boat **12**, is greater in **10** than in **9**. Dreiding models clearly show that the C(6)–O(1) torsional angle (−35.3° vs. −50.5°) is particularly sensitive to this motion.

Similarities in the exocyclic P–N(1) bond lengths of **3** (1.622 (3) Å)[5] and **5** (1.620 (3) Å) also can be noted. Both are significantly *shorter* than those of **13**,[8] 1.644 (5) Å, and **14**,[9] 1.661



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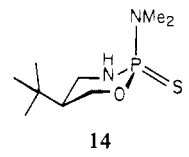

14

(2) Å. The longer exocyclic P–N bond of **13** and **14** and the pyramidal nature of the nitrogen ($\sum\angle$ = 349.3 (13)° in **13**, 345° for **14**) can be ascribed[8,9] to loss of optimal P–N rotational geometry (and presumably loss of P–N π-bonding[10]) in which the coplanar P=O/NMe_2 geometry seen for **3** and **5** is precluded for steric reasons. The torsional angle O(2)–P–N(1)–C(7) is 2.93° for **5**, and **3** is similarly close to having the Me_2N completely in the O(2)–P–N(1) plane.[5] This geometry is seen without exception for equatorial (or pseudoequatorial) R_2N attached to P=O of 1,3,2-oxazaphosphorinanes[5,11-16] and 1,3,2-dioxaphosphorinanes.[17] Apparently P–N π-bonding is optimal in this geometry.[10]

The endocyclic P–N(3) bonds of **3** and **5** are of nearly the same length at 1.656 (3) Å for **5** and 1.661 (2) Å for **3**.[5] Notably, they are considerably *longer* than the pseudoequatorial exocyclic P-(O)–NMe_2 bonds of **3** (1.622 (3) Å) and **5** (1.620 (3) Å) discussed earlier.

Solution Conformation of 5. Tables III and IV give the ^1H NMR spectral parameters for **5** taken at 300 MHz in two solvents. The H_C, H_D, and H_X parts of the spectra were not completely first order, so it was necessary to iteratively refine approximate spectral parameters obtained by inspection, through use of the LAOCN3 program (see Experimental Section). Also in Table III are spectral parameters for the corresponding 5-*tert*-butyl compound **3** which was earlier shown to be in the twist conformation in solution.[5,7] $^3J_{HP}$ values follow a Karplus-like relationship.[18] Therefore, most diagnostic for this conformation is the combination of large J_{AX} *and* large J_{AP}, which is most clearly seen for **3**, which is almost entirely in the twist conformation B of Scheme I. In structure B, H_A is pseudoequatorial (hence the relatively large J_{AP}) and at the same time the dihedral angle H_A–C(6)–C(5)–H_X is still close enough to 180° for J_{AX} to remain large. (Angle H_A–C-

(8) Holmes, R. R.; Day, R. O.; Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G., unpublished work.
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(12) (a) Brassfield, H. A.; Jacobsen, R. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1975**, *97*, 4143. (b) Perales, A.; Garcia-Blanco, S. *Acta Crystallog., Sect. B* **1977**, *33B*, 1935.
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(14) Sternglanz, H.; Einspahr, H. M.; Bugg, C. E. *J. Am. Chem. Soc.* **1974**, *96*, 4014.
(15) Camerman, N.; Camerman, A. *J. Am. Chem. Soc.* **1973**, *95*, 5038.
(16) Camerman, N.; Smith, H. W.; Camerman, N. *Acta Crystallogr., Sect. B* **1977**, *33B*, 678.
(17) Newton, M. G.; Pantaleo, N. S.; Bajwa, G. S.; Bentrude, W. G. *Tetrahedron Lett.* **1977**, 4454. Wagner, R. E.; Jensen, W.; Wadsworth, W.; Johnson, Q. *Acta Crystallogr., Sect. B* **1973**, *29B*, 2160.
(18) For a recent example of such a relationship for J_{HCOP} see: Kung, W.; Marsh, R. E.; Kainosho, M. *J. Am. Chem. Soc.* **1977**, *99*, 5471.

Table III. ^{1}H NMR Coupling Constants (J, Hz) Measured at 300 MHz, 25 °C

case	compd[d]	solvent	J_{AB}	J_{AX}	J_{BX}	J_{AP}	J_{BP}	J_{CD}	J_{CX}	J_{DX}	J_{CP}	J_{DP}	J_{BD}	J_{Me_2N}	ref
1	5[c]	acetone-d_6	−10.6	9.8	5.7	14.2	8.9	−11.7	10.3	3.9	4.2	13.0	1.3	10.2	*a*
2	5[c]	C_6D_6	−10.7	9.4	6.1	17.0	6.0	−10.6	11.3	3.6	4.3	12.2	1.0	10.1	*a*
3	3	C_6D_6	−10.8	10.5	7.0	20.0	5.0	−10.5	10.5	3.5	2.0	16.0	1.3	10.5	*b*
4	3	$CDCl_3$	−10.6	10.6	6.8	18.0	5.0	−11.0	11.0	4.0	2.6	14.4	1.4	10.5	*b*
5	6[c]	C_6D_6	−11.6	11.3	4.6	3.2	22.4	−11.8	11.5	4.7	2.8	20.2	2.3	9.6	*a*
6	16	C_6D_6	−10.8	11.0	4.0	4.0	22.0	−10.5	11.0	3.0	5.0	17.5	2.6	9.6	*e*

[a] This work. [b] References 5, 7. [c] From iterative LAOCN3 analysis of 300-MHz spectra. [d] Concentrations 1–2%. [e] Reference 7.

Table IV. ^{1}H NMR Chemical Shifts Measured at 300 MHz,[a] 25 °C

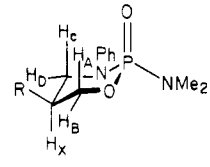
case	compd[e]	solvent	H_A	H_B	H_C	H_D	H_X	other	ref
1	5[d]	acetone-d_6	4.40	4.54	4.05	3.72	3.65	2.53, Me_2N 7.51–7.02, C_6H_5	*b*
2	5[d]	C_6D_6	3.96	4.40	3.53	3.42	3.37	2.42, Me_2N 7.17–6.84, C_6H_5	*b*
3	3	C_6D_6	3.78	4.35	3.27	3.41	2.28	0.53, *t*-Bu 2.50, Me_2N 6.93–7.41, C_6H_5	*c*
4	3	$CDCl_3$	4.04	4.50	3.49	3.60	2.42	0.94, *t*-Bu 2.50, Me_2N 7.04–7.34, C_6H_5	*c*
5	6	C_6D_6	4.60	3.95	3.76	3.30	3.17	2.42, Me_2N 7.49–6.78, C_6H_5	*b*
6	16	C_6D_6	4.38	4.07	3.49	3.37	1.83	0.55, *t*-Bu 2.48, Me_2N 7.01–7.55, C_6H_5	*c*

[a] Chemical shifts downfield from Me_4Si. [b] This work. [c] Reference 7. [d] From iterative LAOCN3 analysis of 300-MHz spectra. [e] Concentrations 1–2%.

(6)–C(5)–H_X was 153° for **3** in the crystal.[5]) H_C and H_D, which are equatorial and axial, respectively, in conformer A, remain pseudoequatorial and pseudoaxial in conformer B and are expected to display more or less normal J_{AP} (equatorial) and J_{BP} (axial) values in either A or B, as they in fact do.

The coupling constants for **5** in C_6D_6 are roughly similar to those of **3**, which shows that it too is largely in conformation B, Scheme I. Differences could result from several sources. The J values of conformation B, as is clear from Dreiding models, depend strongly on the degree of twisting. As noted above this is different in the crystal structures of **3** and **5**. The population for **5** of small amounts of other twist conformations encountered on the pseudorotational cycle would also affect the J values. To attempt to say anything more definitive would be unjustified. In acetone-d_6 there also must be an appreciable population of conformation A in view of the increase in J_{BP} and decrease in J_{AP}. A similar effect on conformational equilibria was noted for **3** in $CDCl_3$.[5,7] What is very clear for both **3** and **5**, however, is that *conformation C or any other in which the R′ (t-Bu or Ph) is axial or pseudoaxial is not significantly populated.* Otherwise J_{AX} and J_{CX} both would have to fall much below the ~10 Hz values found.

Solution Conformation of 6. On inspection of the coupling constants for **6**, the trans diastereomer of **5**, it is readily apparent that **6** very predominantly, if not entirely, populates the chair conformation, **15**, with both phenyl and dimethylamino equatorial.



15, R = Ph
16, R = *t*-Bu

The large values of J_{BP} and J_{DP} compared to the corresponding small J_{AP} and J_{CP} values are most indicative. The equatorial position of the 5-phenyl is clear from J_{AX} and J_{CX}. The relatively large J_{BD} for equatorial hydrogens in a W arrangement also supports structure **15**. (Note the small J_{BD} value for **5** by contrast.) Essentially similar coupling constants are seen for **16**, the trans diastereomer of **3**.

Table V. Phosphoryl Stretching Frequencies for 1,3,2-Oxazaphosphorinanes

compd	$\nu_{P=O}$, cm^{-1} KBr	$\nu_{P=O}$, cm^{-1} CCl_4
3	1222	1236
5	1226	1240
6 (15)	1226	1242
16	1224	1234

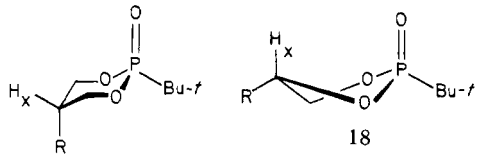
Infrared spectroscopic analysis of **3** and **5** also supports the twist conformation B assignment for these molecules. The P=O stretching frequencies of 2-oxo-1,3,2-oxazaphosphorinanes can be utilized *with some caution* to determine the relative geometrical orientations (axial or equatorial) of phosphoryl oxygens,[19] especially those of diastereomers.[4a] The P=O stretch for compounds with axial P=O occurs at *lower* frequency than that for compounds with equatorial P=O. The phosphoryl stretching frequencies for **3** and **5** along with related compounds are listed in Table V. These data suggest that the phosphoryl oxygen in each compound, both in the solid state as well as in solution, adopts the same orientation, pseudoaxial or axial; i.e. the P=O stretches for **3** and **5** are very close to those of **6** and **16**. Of course such comparisons must be made in the same media and only between molecules that have the *same* substituents on phosphorus.

Conclusions

The failure of **5** to exist in conformation C (Scheme I) means that the 5-phenyl is sterically large enough to destabilize structure C in favor of either B or A. The latter, however, is not greatly populated because of the steric size of Me_2N when the ring nitrogen is phenyl substituted.[7] Thus structure B is of lowest energy. It is surprising that C is relatively so unstable since for the analogous 1,3,2-dioxaphosphorinane (**17**, **18**, R = Ph) considerable amounts (>25%)[20] of conformer **17** are present in solution, al-

(19) (a) Roca, C.; Kraemer, R.; Majoral, J. P.; Navech, J. *Org. Magn. Reson.* **1976**, *8*, 407. (b) Arshinova, R.; Kraemer, R.; Majoral, J.-P.; Navech, J. *Ibid.* **1975**, *7*, 309. (c) Durrieu, J.; Kraemer, R.; Navech, J. *Ibid.* **1973**, *5*, 407.

(20) Bentrude, W. G.; Yee, K. C. *J. Chem. Soc., Chem. Commun.* **1972**, 169. A paper concerning *cis*-2-oxo-2-*tert*-butyl-5-phenyl-1,3,2-dioxaphosphorinane is in preparation.[6]



17 18

though the 5-*tert*-butyl compound (**17**, **18**, R = *t*-Bu) like **3** and **5** in C_6D_6 is entirely in the twist form analogous to **18**.[20] Evidently an axial 5-phenyl is sterically "larger" in the 1,3,2-oxazaphosphorinanes than it is in the 1,3,2-dioxaphosphorinanes. *This demonstrates a significant difference between these two ring systems.*

$\Delta G°$ for the conversion of C to B ($\Delta G°_{C\rightarrow B}$, eq 1) or **17** to **18**

$$\Delta G°_{C\rightarrow B} = \Delta G°_{5\text{-}R'} + \Delta G°_{c\rightarrow t} \quad (1)$$

is determined according to eq 1 by the balance between the favorable relief of steric strain associated with the 5-axial substituent ($\Delta G°_{5\text{-}R'}$) and the opposing increase in energy which accompanies the conversion of the chair-form ring in C into the twist conformation B ($\Delta G°_{c\rightarrow t}$). We earlier estimated that $\Delta G°_{c\rightarrow t}$ for a 2-oxo-1,3,2-oxazaphosphorinane ring is a little less than 2 kcal/mol.[7] In fact $\Delta G°_{c\rightarrow t}$ may be 1 kcal/mol or less.[8] 2-Oxo-1,3,2-dioxaphosphorinanes also have low $\Delta G°_{c\rightarrow t}$ values of about 1 kcal/mol.[21] Whether the greater effective size of the 5-phenyl in **5** results from the $\Delta G°_{c\rightarrow t}$ or $\Delta G°_{5\text{-}R'}$ term of eq 1 is not evident. $\Delta G°_{c\rightarrow t}$ may be smaller in the 2-oxo-1,3,2-oxazaphosphorinane system because of the increased P–N vs. P–O bond lengths and potential consequent flattening of the ring about phosphorus. These factors could relieve torsional and cross-ring repulsions in B. The 5-phenyl in C may experience greater destabilization than in **17**, perhaps as a result of the presence of the phenyl on N(3). Studies on the conformational aspects of the N(3)H analogue of **5** are in progress.

The extreme sensitivity of the conformational equilibria (A, B, C) available to 5-substituted-2-oxo-1,3,2-oxazaphosphorinanes to the steric size of R′ is quite striking. *There does not appear to be another six-membered ring system which undergoes a virtually complete chair to twist conformational change in response to a substituent as small as a phenyl group.* From this and previous studies regarding the low value[7,8] for $\Delta G°_{c\rightarrow t}$ it is possible that the antitumor agents **2a–c** on interaction with oxidative enzymes systems assume conformations different from those normally populated in solution. *The greater sensitivity of the 2-oxo-1,3,2-oxazaphosphorinane ring system to axial 5-substituents along with the previously reported dramatic effect on the equilibrium A ⇌ C on the nature of R (R = H vs. Ph) provide two examples of important differences between the conformational properties of the 2-oxo-1,3,2-dioxaphosphorinane rings.*

Experimental Section

Methods and Materials. Analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN. Melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 298 spectrophotometer. ^{1}H NMR spectra were taken on a Varian SC 300 spectrometer, operated in the FT mode, or on a Varian EM 390 CW instrument. Coupling constants in Table II were measured at 300 MHz, 100-Hz expansions, 32K data base, 5.459-s acquisition times, and are probably accurate to ±0.2 Hz. ^{31}P NMR spectra were made at 32.2 MHz on a Varian FT-80A spectrometer under proton noise decoupling conditions. Positive ^{31}P chemical shifts are in δ, ppm downfield from external 85% H_3PO_4. The mass spectrometer used was a VG Micromass 7070 double focusing high resolution instrument operating in the EI mode, with VG Data System 2000 direct inlet sampling.

The X-ray crystallographic studies were done by using an Enraf-Nonius CAD4 diffractometer and graphite monochromated molybdenum radiation (λ K_{α_1} = 0.70930 Å, λ $K\alpha_2$ = 0.71359 Å) at an ambient temperature of 23 ± 2 °C. Details of the experimental and computational procedures have been described previously.[22] Clear colorless crystals of **5** were obtained by vapor diffusion of a solution of the compound in ethyl ether with pentane. A well-formed crystal was mounted in a sealed thin-walled glass capillary as a precaution against moisture sensitivity.

Crystal Data for $C_{17}H_{21}O_2N_2P$ (5). Colorless crystal 0.13 × 0.18 × 0.35 mm, monoclinic space group $P2_1/n$, alternating setting of $P2_1/c$ [C^5_{2h}—No. 14],[23] a = 16.225 (4) Å, b = 6.149 (1) Å, c = 16.496 (3) Å, β = 92.75 (2)°, Z = 4, D_{calcd} = 1.278 g/cm^3, and μ(Mo K$\bar{\alpha}$) = 0.181 mm^{-1}. A total of 2900 independent reflections ($+h,+k,\pm l$) were measured by using the θ–2θ scan mode for 2° ≤ 2θ(Mo K$\bar{\alpha}$) ≤ 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.[24] The 22 independent non-hydrogen atoms were refined anisotropically. Coordinates for the 21 independent H atoms were obtained by a combination of difference Fourier techniques and calculation. 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[25] were R = 0.047 and R_w = 0.051 for the 1608 reflections having $I \geq 2\sigma(I)$.

2-Carboethoxyphenylacetic Acid. Solid potassium hydroxide (13.0 g, 0.232 mol) was added to a solution at 0 °C of diethyl phenylmalonate (54.6 g, 0.230 mol) in absolute ethanol (240 mL). The reaction mixture was stirred while a temperature of 10–20 °C was maintained. The reaction mixture was monitored periodically by GLC and upon completion of the reaction (ca. 3.5 h) the ethanol was removed by rotary evaporation at 15–20 °C. The residue was cooled to 0 °C. Ice water (500 mL) was added, and the mixture was extracted with ethyl ether (3 × 100 mL). The aqueous phase was acidified at 0 °C with 10% aqueous HCl and extracted with ethyl ether (4 × 100 mL). The ethereal extracts from the acidified solution were combined and dried over anhydrous $MgSO_4$, and the ether was removed by rotary evaporation, leaving 30.3 g (63.3% yield) of 2-carbethoxyphenylacetic acid as a colorless crystalline solid: mp 65–72 °C (lit.[26] 76–77 °C); ^{1}H NMR (90 MHz, acetone-d_6) δ 1.23 (t, 3 H, J = 6.0 Hz, $CO_2CH_2CH_3$), 4.16 (q, 2 H, J = 6.0 Hz, $CO_2CH_2CH_3$), 4.75 (s, 1 H, methine CH), 6.0 (s, 1 H, CO_2H), 7.3 (m, 5 H, Ph); IR (KBr) 3300–2900 (s, b, OH), 1740 (s, C=O), 1720 (s, C=O), 1190 (CO), 1170 (CO) cm^{-1}.

***N*-Phenyl-(2-carbethoxyphenyl)acetamide.** A solution of (2-carbethoxyphenyl)acetic acid (15.6 g, 0.075 mol) in anhydrous dichloromethane (40 mL) was treated, at 0 °C, with phosphorus pentachloride (15.6 g, 0.75 mol). The reaction mixture was stirred at room temperature for 5 h. The volatile materials were removed in vacuo. The residue was dissolved in anhydrous ethyl ether (100 mL), and aniline (15.0 mL, 0.158 mol) was added slowly at room temperature. The reaction mixture was stirred at room temperature for 10 h and refluxed for an additional 2 h. The aniline hydrochloride was filtered off and the ether removed from the filtrate by rotary evaporation. The residual solid was twice recrystallized from absolute ethanol to give 7.91 g (37.2% yield) of *N*-phenyl-(2-carbethoxyphenyl)acetamide as a yellow crystalline solid: mp 84–86 °C; ^{1}H NMR (90 MHz, acetone-d_6) δ 1.1 (t, 3 H, J = 6 Hz, $CO_2CH_2CH_3$), 2.7 (s, 1 H, NH), 4.1 (q, 2 H, J = 6 Hz, $CO_2CH_2CH_3$), 4.85 (s, 1 H, methine CH), 7.3 (m, 10 H aromatic); IR (KBr) 3320 (N–H), 2990, 1745 (C=O), 1655 (C=O), 1600, 1532, 1500, 1445, 1335, 1315, 1275, 1210, 1175–1160, 1030, 755, 740, 695 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.19; H, 5.54; N, 8.41.

***N*-Phenyl-2-phenyl-3-aminopropan-1-ol (8).** A slurry of *N*-phenyl-(2-carbethoxyphenyl)acetamide (2.83 g, 10.0 mmol) in anhydrous ethyl ether (200 mL) was added slowly to a stirred suspension of lithium aluminum hydride (0.87 g, 23 mmol) in ethyl ether (100 mL). The reaction mixture was heated to gentle reflux for 6 days. The reaction mixture was quenched with a mixture of ethyl ether (100 mL) and water (1.9 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Anhydrous magnesium sulfate (10 g) was added and stirring continued for 15 min. The reaction mixture was filtered and the solids washed with ether (4×). The ether was removed from the filtrate by rotary evaporation and the residue distilled from bulb to bulb with an air bath temperature of 150 °C at 0.020 mm, to give 2.16 g (95% yield) of *N*-phenyl-2-phenyl-3-aminopropan-1-ol **(8)** as a yellow

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(24) The function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w^{1/2} = 2F_oLp/\sigma_I$. Mean atomic scattering factors were taken from ref 23 (Vol. IV, 1974, pp 72–98). Real and imaginary dispersion corrections for O and P were taken from the same source, pp 149–150.

(25) $R = \sum||F_o| - |F_c||/\sum|F_o|$, $R_w = \{\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2\}^{1/2}$

(26) Corey, E. J. *J. Am. Chem. Soc.* **1952**, *74*, 5897.

oil: bp 168 °C (0.050 mm); ^{1}H NMR (90 MHz, acetone-d_6) δ 2.95-3.75 (m, 4 H, $-CH_2N-$, NH, methine CH), 3.85 (d, 2 H, $-CH_2O-$), 4.70 (broad s, 1 H, OH), 6.55-730 (m, 10 H aromatic); IR (thin film) 3600-3200 (s, b O-H, N-H), 3055, 3027, 2925, 2875, 1603, 1505, 1454, 1433, 1320, 1260, 1182, 1072, 1056, 1030, 756, 706, 700 cm^{-1}. Anal. Calcd for $C_{15}N_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.41; H, 7.75; N, 6.09.

***cis*- and *trans*-2-(Dimethylamino)-2-oxo-3,5-diphenyl-1,3,2-oxazaphosphorinane (5 and 6).** A solution of $Me_2NP(O)Cl_2$ (1.62 g, 10.0 mmol) in ethyl acetate (15 mL) was added to a solution of *N*-phenyl-2-phenyl-3-aminopropan-1-ol (2.27 g, 10.0 mmol) and triethylamine (2.02 g, 20.0 mmol) in ethyl acetate (10 mL). The reaction mixture was refluxed for 2 days and then filtered. The filtrate was treated with activated charcoal and the solvent removed under reduced pressure, leaving 5.50 g of residue. The residual product was dissolved in benzene, treated with pentane, cooled in ice, and then filtered. The solvents were removed from the filtrate, leaving 2.67 g (85% crude yield) of yellow crystalline residue. A 1.00-g sample of the residue was purified by MPLC on a silica gel column eluting with tetrahydrofuran/hexane (1:1) to give 496 mg of pure *trans*-2-(dimethylamino)-2-oxo-3,5-diphenyl-1,3,2-oxazaphosphorinane (**6**) [mp 129-131 °C; ^{31}P NMR (C_6D_6) δ 9.78 ppm; IR (KBr) 3040, 2985, 2950, 2930, 2875, 2845, 2815, 1600, 1496, 1250, 1224, (s, P=O), 1132, 1023, 1010, 1002, 966, 899, 869, 810, 780, 765, 752, 711, 705 cm^{-1}; mass spectrum, *m/e* 316 (M^+, 16%), 106 (16%), 105 (100%), 104 (41%), 77 (14%), 43 (12%)], 110 mg of pure *cis*-2-(dimethylamino)-2-oxo-3,5-diphenyl-1,3,2-oxazaphosphorinane (**5**) [mp 173-175 °C; ^{31}P NMR (C_6D_6) δ 6.69 ppm; IR (KBr) 2910, 1600, 1496, 1478, 1456, 1312, 1300, 1264, 1226 (s, P=O), 1138, 1099, 1077, 1042, 1036, 1008, 1000, 965, 888, 800, 774, 760, 745, 708, 700 cm^{-1}; mass spectrum, *m/e* 316 (M^+, 16%), 106 (14%), 105 (100%), 104 (36%), 77 (12%), 43 (10%)], and a 100-mg mixture of the two diastereomers (706 mg total, 59.4% yield). Anal. Calcd for $C_{17}H_{21}N_2O_2P$: C, 64.54; H, 6.71; N, 8.85; P, 9.79. Found: C, 64.45; H, 6.63; N, 8.76; P, 9.76.

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Supplementary Material Available: Thermal parameters (Table A), fixed hydrogen atom parameters (Table B), least-squares mean planes (Table C), and a listing of observed and calculated structure factors amplitudes for **5** (9 pages). Ordering information is given on any current masthead page.

Synthesis and Crystal and Molecular Structure of a Cu(I) Complex of Vitamin B_1, Cu(thiamin)Cl_2

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Abstract: The structure of the complex Cu(thiamin)Cl_2 has been determined by single-crystal X-ray diffraction methods. Yellow, bladelike crystals were obtained by vapor diffusion of acetone into an aqueous reaction mixture of $Cu_2(CH_3CO_2)_4 \cdot 2H_2O$ and thiamin chloride hydrochloride (1:4 mole ratio). The triclinic cell, space group $P\bar{1}$, containing two complex molecules, has cell parameters (25 °C) a = 9.203 (4) Å, b = 14.866 (6) Å, c = 5.985 (2) Å, α = 99.56 (3)°, β = 94.59 (3)°, γ = 104.23 (3)°, V = 776.36 Å^3, ρ_{calcd} = 1.711 g/cm^3, and ρ_{obsd} = 1.699 (2) g/cm^3. The structure has been refined by the full-matrix least-squares technique to a final error index of R_1 = 0.035 for the 264 variables and 3227 unique, absorption-corrected data for which $I > 3\sigma(I)$. The Cu(I) ion is coordinated to two chloride ions and the N(1′) atom of the pyrimidine ring of the thiamin molecule in a distorted trigonal-planar arrangement. The effect of metal-ion complexation on the organic ligand is similar to that observed in the only other metal-thiamin complex, Cd(thiamin)$Cl_3 \cdot 0.6H_2O$. The torsion angles ϕ_T = −10.1° and ϕ_P = −83.8° correspond to the frequently observed *F* conformation. A hydrogen-bonding network and base-stacking interactions between parallel pyrimidine planes are the predominant intermolecular forces in the crystal.

Research efforts by several workers[1-4] directed toward preparing metal-ion complexes of thiamin have led only to the isolation of thiamin salts with a metal-containing anion. These repeated failures led Richardson[3] to conclude that it was not possible to prepare such complexes. However, the successful preparation and structure determination of the first metal-ion comlex of thiamin, Cd(thiamin)$Cl_3 \cdot 0.6H_2O$, proved that metal-thiamin complexes exist.[5]

Continuing our research on the interaction of metal ions with this biomolecule, we have investigated its reaction with copper. Our interest in this metal ion is due to the possible role that Cu(II) may have in the oxidation of thiamin to thiochrome.[6] Previous attempts to prepare a copper-thiamin complex have failed. The crystal structure of a tetrachlorocuprate(II) salt of thiamin showed no bonding between the Cu(II) ion and the ligand.[2] Another structural report on the complex [(thiamin pyrophosphate)(1,10 phenanthroline)aquacopper(II)] demonstrated that the metal ion coordinated to the thiamin moiety only via the pyrophosphate chain.[7] We have now prepared a Cu(I)-thiamin complex, Cu(thiamin)Cl_2, and report its crystal and molecular structure.

Experimental Section

Preparation of Cu(thiamin)Cl_2. The complex Cu(thiamin)Cl_2 was prepared by reacting 2.5 mmol (0.9982 g) of $Cu_2(CH_3CO_2)_4 \cdot 2H_2O$ with 10 mmol of thiamin hydrochloride (3.373 g) in 20 mL of distilled water at room temperature. Yellow, bladelike crystals were obtained after 4 days by vapor diffusion of acetone into the cooled solution. The crystals were allowed to grow for another week, after which they were collected by suction filtration and washed with small amounts of water and ace-

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