Conformations of Saturated Six-Membered Ring Phosphorus Heterocycles.[1a] *cis*- and *trans*-2-Oxo- and 2-Thio-2-(dimethylamino)-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinanes: Molecules Related to Cyclophosphamide

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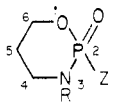
Abstract: Several 5-*tert*-butyl-2-(dimethylamino)-1,3,2-oxazaphosphorinanes have been prepared. Included are the NH (**3** and **4**) and NPh (**5** and **6**) oxides and sulfides. The individual diastereomers of **3–6** were separated and the cis and trans geometries determined for **4** and **5** by X-ray crystallography (reported elsewhere) and for **3** and **6** by analogy and use of ^{1}H and ^{31}P NMR data. ^{1}H NMR analysis established that the trans diastereomer (*t*-Bu and Me_2N) in all cases is in the chair conformation in solution with *t*-Bu and Me_2N both equatorial. *cis*-**3** and *cis*-**4** are largely in a chair conformation with *t*-Bu equatorial and Me_2N axial. For *cis*-**3** it is estimated that at room temperature about 22% of the molecules are in a twist conformation, **15**. By contrast, *cis*-**5** and *cis*-**6** are largely in the twist form, **15**. For *cis*-**5**, the percentage of **15** at room temperature is estimated to be at least 80% and *decreases* with increasing temperature. The percentage **15** for *cis*-**3** *increases* with increasing temperature, estimates ranging only 8–15% at 18 °C, about 22% at 25 °C, and 35–44% at 97 °C. It is suggested that the effect of NPh in place of NH in the ring is a steric one in which repulsive interactions between the Ph and axial Me_2N destabilize the chair conformer for *cis*-**5**. These repulsions are relieved in the twist conformation (**15**) in which the Me_2N is pseudoequatorial. The Ph/Me_2N repulsions are estimated to be at least 1.6 kcal/mol. By use of the steric size of the nitrogen mustard substituent, $N(CH_2CH_2Cl)_2$, as an estimate for that of Me_2N, an upper limit value for the chair → twist conformational isomerization **21** → **20** of 1.8 kcal/mol can be approximated. This low value compared to those for cyclohexane and 1,3-dioxane is for formation of the specific twist conformation **20**, in which the 5-carbon is opposite a pseudoaxial phosphoryl oxygen rather than the pseudoaxial Z as in **23**. The energy of **23** is probably higher than that of **20** and dependent on the steric size of Z. To our knowledge, this work represents the first complete conformational analysis, based on ^{1}H NMR, of non-fused-ring 1,3,2-oxazaphosphorinanes for which chair–twist equilibria can be defined.

The 1,3,2-oxazaphosphorinane cyclophosphamide (**1a**) and its



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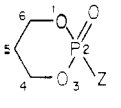

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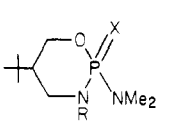
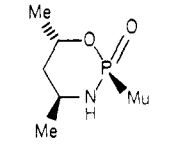
1a, R = H, Z = $N(CH_2CH_2Cl)_2$
1b, R = CH_2CH_2Cl, Z = $NHCH_2CH_2Cl$
1c, R = CH_2CH_2Cl, Z = $N(CH_2CH_2Cl)_2$

analogues isophosphamide (**1b**) and trophosphamide (**1c**) are clinically useful anticancer drugs. Furthermore, carbon-substituted derivatives of these molecules have been made and have undergone biological testing.[2] To be able to correlate potential effects of diastereomeric constitution and conformational differences on biological activity is of considerable interest. Moreover, the 1,3,2-oxazaphosphorinane ring system is worthy of conformational study on its own merits. It is closely related to the far more thoroughly investigated 1,3,2-dioxaphosphorinane ring (**2**),[3] which displays structural properties, including conformational features, quite different from the parent cyclohexane and 1,3-dioxane rings. Ring system **1**, however, has the added possibility of steric and electronic interactions between various R and Z substituents on the P–N system. Furthermore, the bond angles and lengths about N will differ from those about O.

In this particular study,[4] we have sought to define for this ring system the effect of variation in the nature of the substituent R on the conformational properties of the individual diastereomers of phosphoramidates **3–6**. The important finding reported here



3, R = H, X = O
4, R = H, X = S
5, R = Ph, X = O
6, R = Ph, X = S



Mu = $N(CH_2CH_2Cl)_2$
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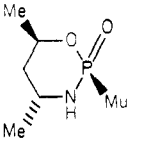

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is the large effect of the size of R on the chair–twist conformational equilibrium available to the diastereomers with *t*-Bu and Me_2N cis to each other. More particularly it will become apparent that Me_2N is axial in *cis*-**3** and *cis*-**4** but not in the cis diastereomers of **5** and **6** because of the influence of the PhN moiety.

The *possibility* that the equatorial or axial preference of substituents on phosphorus in certain unsubstituted or 5,5-disubstituted 1,3,2-oxazaphosphorinanes may be influenced by the nature of the substituent on ring nitrogen was proposed earlier.[5]

(1) (a) For the previous full paper in this series, see: Finocchiaro, P.; Recca, A.; Bentrude, W. G.; Tan, H.-W.; Yee, K. C. *J. Am. Chem. Soc.* **1976**, *98*, 3537. (b) University of Utah. (c) Auburn University.

(2) (a) Kinas, R.; Pankiewicz, K.; Stec, W. J.; Farmer, P. B.; Foster, A. B.; Jarman, M. *J. Org. Chem.* **1977**, *42*, 1650. (b) Cox, P. J.; Farmer, P. B.; Jarman, M. *Biochem. Pharmacol.* **1975**, *24*, 599. (c) Struck, R. F.; Thorpe, M. C.; Coburn, W. C., Jr.; Kirk, M. C. *Cancer Res.* **1975**, *35*, 3160. (d) Montgomery, J. A.; Struck, R. F. *Cancer Treat. Rep.* **1976**, *60*, 381. (e) Ludeman, S. M.; Zon, G. *J. Med. Chem.* **1975**, *18*, 1251. (f) Farmer, P. B.; Jarman, M.; Facchinetti, T.; Pankiewicz, K.; Stec, W. J. *Chem.-Biol. Interact.* **1977**, *18*, 47. (g) Abel, G.; Cox, P. J.; Farmer, P. B.; Haskins, N. J.; Jarman, M.; Merai, K.; Stec, W. J. *Cancer Res.* **1978**, *38*, 2592. (h) Shih, Y. E.; Wang, J. S.; Chen, C. T. *Heterocycles* **1978**, *9*, 1277. (i) Boyd, V. L.; Zon, G.; Himes, V. L.; Stalick, J. K.; Mighell, A. D.; Secor, H. V. *J. Med. Chem.* **1980**, *23*, 372.

(3) For a thorough review, see: Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Phosphorus Chem.* **1979**, *11*, 187.

(4) Part of this work was reported earlier: (a) Bajwa, G. S.; Bentrude, W. G.; Pantaleo, N. S.; Newton, M. G.; Hargis, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1602. (b) Chandrasekaran, S. Bentrude, W. G. *Tetrahedron Lett.* **1980**, 4671. (c) A full paper with details of the X-ray structure of *cis*-**5** will appear elsewhere, along with the structure of *trans*-**5**.

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However, configurational assignments were based only on rather tenuous interpretations of variations in the P=O IR stretching frequencies. (See below.) The results we report here are also related to NMR studies published earlier for cyclophosphamide (**1a**)[6,7] and for the methyl-substituted compounds **7** and **8**[7] and related systems and allow us to better define the conformational equilibria involved. Nonetheless our work represents the first complete conformational analysis of the individual diastereomers of a non-fused-ring 1,3,2-oxazaphosphorinane for which chair–twist equilibria can be defined.

Results

Synthesis. Compounds **5** and **6** were prepared in a straightforward manner (Experimental Section) by reaction of amino alcohol **13** with $(Me_2N)_3P$ followed by S_8 or N_2O_4 oxidation. Oxide **3** was synthesized via reaction of **11** with Me_2NPOCl_2 in the presence of Et_3N. Reaction of amino alcohol **11** with $PSCl_3$ followed by treatment with Me_2NH gave **4**. Separation of the individual diastereomers in each case was accomplished by elution column chromatography on SiO_2. The sequence for preparation of the amino alcohols is shown in Scheme I.

Characterization of Diastereomers. Cis and trans geometries were correctly assigned to the diastereomers of **5** on the basis of an X-ray crystallographic study of *cis*-**5**.[4a] Both diastereomers of **4** were similarly characterized.[8] Since 2-oxo and 2-thio derivatives in 1,3,2-dioxaphosphorinanes have generally similar conformational properties,[3] diastereomers of **3** and **6** were defined structurally by analogy to **4** and **5** once the ^1H NMR parameters had been measured for all. Assignments also were consistent with the relative ^{31}P chemical shifts (Table II) for the two diastereomers in nearly every case; i.e., the ^{31}P chemical shift of the cis isomer was *upfield* of that for the trans isomer except for the nearly equal shifts for *cis*- and *trans*-**3**. Furthermore, the trans isomers all had shorter GLC retention times. These correlations we have also found to be true of the corresponding 2-oxo- and 2-thio-2-Z-5-*tert*-butyl-1,3,2λ^5-dioxaphosphorinanes.[9]

Conformations and Proton Coupling Constants. The trans diastereomers of **3–6** are readily characterized conformationally by ^1H NMR spectroscopy. From the data of Table I, it is apparent that they are very largely in the chair conformation, i.e., one analogous to **14** but with substituents *t*-Bu and Me_2N both equatorial. Variations in $^3J_{HH}$ and $^3J_{HP}$ are both known to follow Karplus-like relationships.[10] Thus, e.g., *trans*-**3** (cases 6 and 7) shows exactly the combination of large J_{AX} and J_{CX} expected for equatorial placement of the *tert*-butyl, since axial A and C are both antiperiplanar to X,[9] and the chair geometry at the phosphorus end of molecule *trans*-**3** is clear from the combination of large J_{BP} and J_{DP} values along with small J_{AP} and J_{CP}. Similar coupling constants are noted for *trans*-**4–6**, i.e. (values in Hz): J_{AX} = 11.0–11.3; J_{CX} = 11.0–11.8; J_{BX} = 4.0–4.5; J_{DX} = 3.0–4.6; J_{AP} = 4.0–5.6; J_{BP} = 22.0 (oxide), 23.2–26.0 (sulfides); J_{CP} = 4.5–6.8; J_{DP} = 17.5 (oxide), 24.0–28.0 (sulfides). Also notable are the large four-bond cross-ring couplings (J_{BD}) between equatorial ring hydrogens, which, for *trans*-**3–6**, range 2.0–2.6 Hz as a result of the W configuration of H_BCCH_D. The greatly increased couplings J_{BP} and J_{DP} to phosphorus for the equatorial hydrogens of the sulfides, compared to those for the oxides, are characteristic of 1,3,2-dioxaphosphorinanes as well.[3,9] The sums

Table I. Coupling Constants (Hz) for **3–6** Measured at 300 MHz and Ambient Probe Temperature (~25 °C)

case	compd	diast	R	X	solvent	concn, %	J_{AB}[a]	J_{AX}	J_{AP}	J_{BX}	J_{BP}	J_{CD}	J_{CX}	J_{CP}	J_{DX}	J_{DP}	J_{BD}	J_{YC}	J_{YD}	J_{YP}	J_{Me_2N}[b]
1	3	cis	H	O	C_6D_6	~10	−10.8	10.7	6.2	4.7	17.0	−12.6	11.1	2.4	4.4	23.6	2.0	5.2[d]	6.6	6.6	10.8
2	3	cis	H	O	C_7D_8[c]	2	−10.4	10.7	6.5	4.6	16.8	−12.8	11.3	2.7	4.5	23.2	2.0	5.8[e]	6.9	6.4	10.8
3	3	cis	H	O	$CDCl_3$	~10	−11.0	10.7	5.6	4.6	17.0	−12.6	11.1	3.3	4.4	23.6	2.0	5.7[e]	6.6	6.7	10.8
4	3	cis	H	O	$CDCl_3$	0.1	−10.9	10.6	6.3	4.7	17.0	−13.0	11.4	4.4	4.4	20.8	2.1	6.2[e]	6.5	6.6	10.9
5	3	cis	H	O	Me_2SO-d_6	1	−11.0	11.0	5.0	4.5	18.0	−12.4	11.3	4.1	4.5	22.0	2.0	5.0	6.5	7.2	10.7
6	3	trans	H	O	C_6D_6	1	−11.0	11.0	4.0	3.8	20.8	−11.0	11.0	5.4	4.3	22.0	2.4	2.4[e,f]	4.4	g	9.9
7	3	trans	H	O	C_6D_6	20	−11.0	11.0	4.4	4.0	20.0	−11.0	11.0	6.2	4.3	21.6	2.0	2.4[d,f]	4.4	g	10.0
8	4	cis	H	S	C_6D_6	10	−10.8	11.0	4.5	4.0	20.2	h	11.4[i]	h	4.5[i]	h	2.2[j]	7.1[e]	7.1	10.4	13.5
9	4	cis	H	S	C_6D_6	20	−11.0	11.0	4.4	4.2	20.2	−13.4	11.2	2.0	4.4	24.0	2.4	6.8[d]	7.4	10.4	13.7
10	4	cis	H	S	$CDCl_3$	10	−11.0	11.0	4.1	4.1	20.4	h	11.4[i]	h	4.4[i]	h	2.3[j]	k	k	k	13.7
11	4	cis	H	S	Me_2SO-d_6	10	−11.2	11.2	3.6	4.0	20.6	−12.6	11.5	2.4	4.0	24.4	2.4	6.3[d]	6.4	12.8	13.7
12	4	trans	H	S	C_6D_6	20	−11.2	11.2	5.6	4.0	23.4	−11.4	11.0	6.2	4.6	27.8	2.4	1.6[e]	4.6	4.0	11.6
13	4	trans	H	S	C_6D_6	10	−11.2	11.2	5.2	4.0	23.6	−11.1	11.0	6.2	5.2	27.6	2.4	1.6[e]	4.1	4.1	11.4
14	4	trans	H	S	C_6D_6	1	−11.2	11.2	5.2	4.0	23.8	−11.2	11.0	6.0	4.4	28.0	2.4	1.6[d]	4.5	4.0	11.4
15	4	trans	H	S	$CDCl_3$	10	−11.2	11.2	5.4	4.1	23.2	−11.0	11.0	6.8	4.4	28.0	2.2	1.4[e]	4.4	4.2	11.7
16	5	cis	Ph	O	C_6D_6	1–2	−10.8	10.5	20.0	7.0	5.0	−10.5	10.5	2.0	3.5	16.0	1.3				10.5
17	5	cis	Ph	O	$CDCl_3$	1–2	−10.6	10.6	18.0	6.8	5.0	−11.0	11.0	2.6	4.0	14.4	1.4				10.5
18	5	cis[l]	Ph	O	MDCB[m]	1–2	−10.5	10.5	18.1	6.5	5.7	−11.1	11.0	3.5	3.1	15.1	1.0				10.9
19	5	trans	Ph	O	C_6D_6	1–2	−10.8	11.0	4.0	4.0	22.0	−10.5	11.0	5.0	3.0	17.5	2.6				9.6
20	6	cis	Ph	S	C_6D_6	2–3	−10.5	10.5	22.4	7.0	7.0	−11.0	11.0	3.6	3.6	15.0	1.3				12.0
21	6	trans	Ph	S	C_6D_6	2–3	−11.0	11.3	5.0	4.5	26.0	−11.8	11.8	4.5	4.0	24.0	2.4				12.0

[a] In Hz. [b] J_{HP}. [c] Toluene-d_8. [d] H_Y-decoupled. Y proton is that of NH group. [e] Assigned by analogy to H_Y-decoupled cases. [f] From H_C, H_D regions. [g] H_Y region poorly resolved. [h] H_C, H_D regions non first-order. [i] Apparent value from H_X spectrum. [j] From H_B spectrum. [k] H_Y apparently hidden in H_A spectrum. [l] All values from iterative LAOCN3 analysis of 90-MHz spectrum. [m] *m*-dichlorobenzene.

(5) (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.

(6) Egan, W.; Zon, G. *Tetrahedron Lett.* **1976**, 813.

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

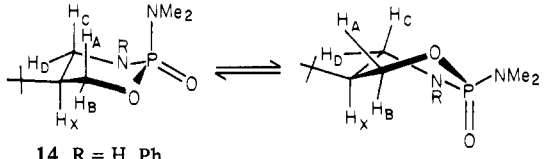
(8) The X-ray structure of *cis*-**4**: Newton, M. G.; Pantaleo, N.; Chandrasekaran, S.; Bentrude, W. G. *Tetrahedron Lett.* **1982**, 1527. A feature of the structure is the pyramidal geometry found about the axial Me_2N attached to the chair-form ring.

(9) This includes compounds described in: (a) Bentrude, W. G.; Hargis, J. H. *Chem. Commun.* **1969**, *1113*. (b) Bentrude, W. G.; Tan, H. W. *J. Am. Chem. Soc.* **1973**, *95*, 4666. (c) Unpublished results from laboratory of W. G. Bentrude.

(10) For an example of such a J_{HCOP} relationship, see: Kung, W.; Marsh, R. E.; Kainosho, M. *J. Am. Chem. Soc.* **1977**, *99*, 5471.

of the three-bond HP couplings through nitrogen depend on the nature of the nitrogen substituent, as shown by values of 22.5 Hz for *trans*-**5** (NPh), 27.8 and 27.4 Hz for *trans*-**3** (NH), 28.5 for *trans*-**6** (NPh), and 33.8–34.8 for *trans*-**4** (NH). This variation may reflect changes in hybridization at nitrogen and the relative electronegativities of H and Ph.

The cis diastereomers of **3** and **4** likewise populate primarily chair conformations, as shown by coupling constant trends parallel to those for *trans*-**3**–**6**. That minor amounts of other conformations are populated, at least by *cis*-**3**, is evidenced by the effects of temperature change on its coupling constants (Table III). This clearly is primarily a chair–twist equilibrium, **14** ⇄ **15**, as over



14, R = H, Ph

15, R = H, Ph

the temperature range (−18 to 97 °C) the decrease in J_{BP} is offset by the increase in J_{AP} while at the same time only small changes in J_{DP} and J_{CP} take place (Table III). As described below, the particular sort of twist conformation populated by *cis*-**5** and *cis*-**6** (and apparently by *cis*-**3** and -**4** in lesser amounts) features J_{AP} and J_{BP} values that are approximately interchanged from those in the chair *but retains* J_{CP} *and* J_{DP} *values of the same relative magnitudes as those in the chair.* A *rough estimate* of the percentage of conformer **14** populated by *cis*-**3** can be made by use of the J_{AP} (2.8 Hz) and J_{BP} (20.7 Hz) values for the cis compound analogous to **3** but with Me_2N replaced by MeO.[9c] This substituent is small and strongly axial seeking and compels populations of nonchair forms to be minimal. Using those values,

$$N(\mathbf{14}) \times J_{AP}(\mathbf{14}) + N(\mathbf{15}) \times J_{AP}(\mathbf{15}) = J_{AP}(\text{obsd}) \quad (1)$$

$$N(\mathbf{15}) = (1 - N(\mathbf{14})) \quad (2)$$

therefore

$$N(\mathbf{14}) = (J_{AP}(\text{obsd}) - J_{AP}(\mathbf{15}))/(J_{AP}(\mathbf{14}) - J_{AP}(\mathbf{15})) \quad (3)$$

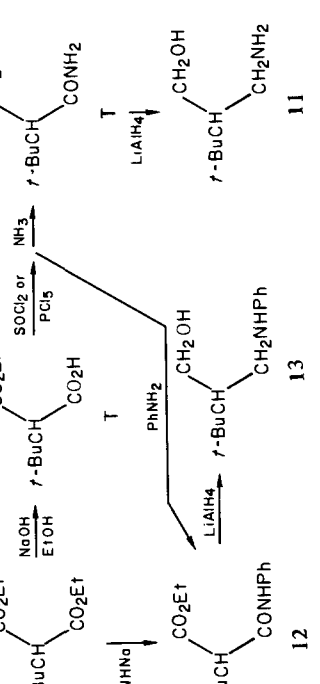
Similarly, for J_{BP}

$$N(\mathbf{14}) = (J_{BP}(\text{obsd}) - J_{BP}(\mathbf{15}))/(J_{BP}(\mathbf{14}) - J_{BP}(\mathbf{15})) \quad (4)$$

assuming that in the twist form they are interchanged, and using eq 1–4 where $N(\mathbf{14})$ and $N(\mathbf{15})$ are mole fractions, one estimates from the values (Table I) for *cis*-**3** at 25 °C (J_{BP} = 16.8 Hz and J_{AP} = 6.5 Hz) that 78–79% of *cis*-**3** is in the chair conformation. (A value of 76% arises if J_{AP} and J_{BP} for *cis*-**5** at −18 °C are used for the twist contributor. (See following discussion concerning *cis*-**5**.) A temperature decrease to −18 °C raises the estimated chair population to 85–92%, depending on which set of J values is used and whether J_{AP} or J_{BP} is being matched. At 97 °C the percentage of chair conformation is lowered to 56–65%. The lack of appreciable contribution of a chair–chair equilibrium is clear from the values of J_{AX} and J_{CX}, which remain high even at 97 °C. J_{AX} and J_{CX} of course would be small in the alternative chair form.

For *cis*-**5** and *cis*-**6** it is obvious from J values that the predominant geometry is far from that of a chair. We were guided in assigning conformation in these cases by the X-ray crystal structure of *cis*-**5** published earlier.[4a] The ORTEP drawing reproduced here (Figure 1) shows the twist conformation of this molecule, which is also illustrated by **15**. Coincidentally, the same conformation, or nearly so, exists both in the crystal and in solution. Characteristic of this structure[4a] is the large $H_AC_6O_1P$ dihedral angle (−158 ± 3°) and large $H_AC_6C_5H_X$ dihedral angle (−153 ± 2°). These angles confer upon the coupling constant pattern the unique combination of large J_{AX} *and* large J_{AP}. *These couplings can never both be large in a chair structure.* J_{BX} (6.5–7.0 Hz) is increased somewhat, as expected for the relatively small H_BCCH_X dihedral angle (−34 ± 3°). The remaining coupling constants for *cis*-**5**, J_{CX}, J_{DX}, J_{CP}, and J_{DP}, fit well if twist structure **15** is primarily populated. The X-ray structure shows that the

Scheme I



12 **13** **11**

Table II. ^{31}P Chemical Shifts for **3**–**6**[a]

compd	^{31}P	solvent	compd	^{31}P	solvent
cis-3	14.6	C_6D_6	*cis*-5	8.5	$CDCl_3$
trans-3	14.7	C_6D_6	*trans*-5	10.9	$CDCl_3$
cis-4	73.2	C_6D_6	*cis*-6	68.2	$CDCl_3$
trans-4	75.2	C_6D_6	*trans*-6	73.7	$CDCl_3$

[a] All values are downfield of 85% H_3PO_4 as external standard. Solutions 5–10% by weight in solute.

Table III. Coupling Constants (Hz) for *cis*-**3** and *cis*-**5** at Various Temperatures

compd	R	X	solvent	concn, %	*T*, °C	J_{AB}[a]	J_{AX}	J_{AP}	J_{BX}	J_{BP}	J_{CD}	J_{CX}	J_{CP}	J_{DX}	J_{DP}	J_{BD}	J_{YC}	J_{YD}	J_{YP}	J_{Me_2N}[b]
cis-3	H	O	C_7D_8[c]	~10	−18	−10.9	11.0	4.2	4.0	18.3	−12.8	11.3	2.3	4.4	24.3	2.2	5.5[e]	7.2	6.4	10.5
cis-3	H	O	C_6D_6[c]	~10	25	−10.8	10.7	6.2	4.7	17.0	−12.6	11.1	2.4	4.4	23.6	2.0	5.2[d]	6.6	6.6	10.8
cis-3	H	O	C_7D_8[c]	~10	97	−10.5	10.0	10.2	5.2	14.3	−12.7	11.2	1.9	5.2	21.4	1.7	4.0[f]	4.1[f]	*g*	10.5
cis-5	Ph	O	MDCB[h]	1-2	−18	−10.5	10.6	19.6	6.0	4.8	−10.5	11.0	1.8	3.4	15.0	1.6				*i*
cis-5	Ph	O	MDCB	1-2	105	−10.4	10.2	17.6	6.7	6.7	−11.3	11.3	3.2	4.0	14.0	1.0				*i*

[a] Coupling constants in Hz. [b] J_{HP} for Me_2N. [c] Toluene-d_8. [d] H_Y decoupled. Y proton is that of NH group. [e] Assigned by analogy to H_Y-decoupled cases. [f] From H_C, H_D spectrum. [g] H_Y hidden by overlap. [h] In *m*-dichlorobenzene. [i] Full spectrum not recorded.

Table IV. Chemical Shifts for 3-6 at 300 MHz, Ambient Probe Temperature (~25 °C)

case	compd	diast	R	X	solvent	concn, %	δ_A	δ_B	δ_C	δ_D	δ_X	$\delta_{t\text{-Bu}}$	δ_R	δ_{Me_2N}
1	3	cis	H	O	C_6D_6	~10	3.82	4.15	2.76	3.16	1.81	0.59	5.54	2.60
2	3	cis	H	O	C_7D_8[b]	2	3.78	4.09	2.72	3.08	1.75	0.60	5.14	2.58
3	3	cis	H	O	$CDCl_3$	~10	3.98	4.34	2.94	3.26	1.88	0.90	5.54	2.69
4	3	cis	H	O	$CDCl_3$	0.1	3.99	4.36	2.97	3.27	1.90	0.89	2.48	2.67
5	3	cis	H	O	Me_2SO-d_6	1	3.88	4.19	2.79	3.07	1.66	0.86	4.67	2.57
6	3	trans	H	O	C_6D_6	1	4.24	3.99	3.14	2.92	1.59	0.56	3.62	2.68
7	3	trans	H	O	C_6D_6	20	4.26	4.04	3.29	3.18	1.66	0.64	4.84	2.71
8	4	cis	H	S	C_6D_6	~10	3.88	4.06	2.76	2.76	1.60	0.58	3.31	2.44
9	4	cis	H	S	C_6D_6	20	4.00	4.19	2.85	3.00	1.77	0.63	3.65	2.45
10	4	cis	H	S	$CDCl_3$	10	4.12	4.32	3.03	3.21	1.87	0.91	a	2.57
11	4	cis	H	S	Me_2SO-d_6	10	4.03	4.19	2.87	3.03	1.65	0.86	5.19	2.41
12	4	trans	H	S	C_6H_6	20	4.46	4.10	3.28	3.01	1.67	0.64	2.62	2.72
13	4	trans	H	S	C_6D_6	10	4.38	3.99	3.16	2.82	1.56	0.60	2.27	2.75
14	4	trans	H	S	C_6D_6	1	4.37	3.94	3.07	2.64	1.51	0.55	1.62	2.72
15	4	trans	H	S	$CDCl_3$	10	4.35	4.20	3.34	3.25	1.79	0.95	2.33	2.85
16	5	cis	Ph	O	C_6D_6	1-2	3.78	4.35	3.27	3.41	2.28	0.53	6.93 (1 H), 7.18 (2 H), 7.41 (2 H)	2.43
17	5	cis	Ph	O	$CDCl_3$	1-2	4.04	4.50	3.49	3.60	2.42	0.94	7.04 (1 H), 7.22 (2 H), 7.34 (2 H)	2.50
18	5	cis[d]	Ph	O	MDCB[c]	1-2	3.91	4.34	3.39	3.49	2.24	0.75	e	2.47
19	5	trans	Ph	O	C_6D_6	1-2	4.38	4.07	3.49	3.37	1.83	0.55	7.01 (1 H), 7.21 (2 H), 7.55 (2 H)	2.48
20	6	cis	Ph	S	C_6D_6	2-3	3.84	4.48	3.31	3.44	2.47	0.54	6.93 (1 H), 7.14 (2 H), 7.36 (2 H)	2.49
21	6	trans	Ph	S	C_6D_6	2-3	4.55	3.86	3.68	3.20	1.85	0.59	6.99 (1 H), 7.16 (2 H), 7.40 (2 H)	2.58

[a] H_Y overlapped with some other protion of the spectrum. [b] Toluene-d_8. [c] *m*-Dichlorobenzene. [d] All values from iterative LAOCN3 analysis at 90 MHz. [e] Obliterated by solvent.

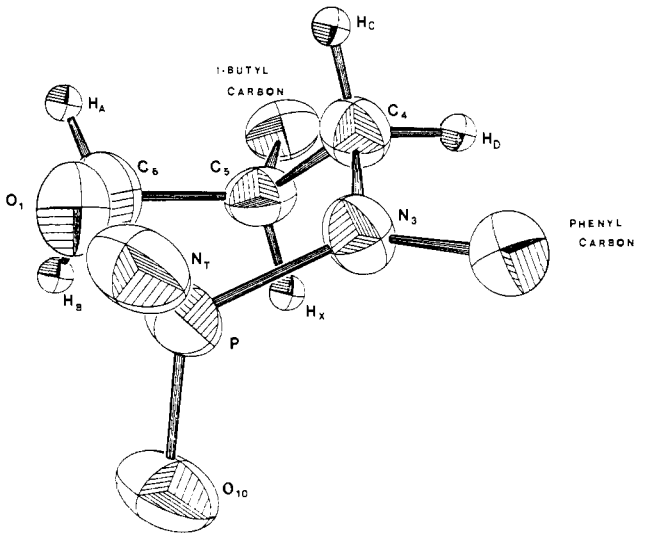


Figure 1. ORTEP drawing of twist *cis*-**5** from X-ray study.

positions of these protons are close to what they would be in a chair-form ring with *tert*-butyl equatorial.[4a] Note that, as expected, large J_{DB} values (2.0–2.5 Hz) are not encountered with the twist conformations since the coplanar W arrangement is absent in the twist conformation, **15**. The coupling constants for *cis*-**6** also fit well those of a twist conformer.

Chemical Shifts. Within the limited number of compounds examined in this study, it appears that certain useful patterns of relative chemical shifts between diastereomers occur, as can be noted from Tables II and IV. The chemical shift of H_A or H_C when these hydrogens are cis to the P=O is *downfield* of its counterpart, either H_B or H_D. The opposite is true when H_A and H_C are trans to the P=O. This same type of correlation is found with the 5-*tert*-butyl-1,3,2-dioxaphosphorinanes[9] and may be a result of the deshielding nature of the P=O. It persists in the oxaza series in spite of the phenyl on nitrogen of **5** and **6** which, because of its own anisotropic properties, could change the relative chemical shifts of H_C and H_D. Also in a given solvent in every case, the methine hydrogen of the cis diastereomer is *downfield* of that for the trans. No reliable differentiation of diastereomers based on the chemical shift of the *tert*-butyl group is evident. The Me_2N chemical shifts are somewhat sensitive to conformation. The resonance of the trans isomer is in each case downfield of that of the cis. Clearly the NH resonances of **3** and **4** vary widely with solvent and solute concentration, as might be expected where intermolecular hydrogen bonding occurs. (See IR results discussed below.) Higher solute concentrations are associated with downfield shifting of this resonance, as is the use of Me_2SO-d_6 as solvent. The highest field NH chemical shifts are found in $CDCl_3$. We are reluctant to attempt to correlate these effects with physical phenomena except to note that in a given solvent, higher solute concentration, and presumably increased intermolecular hydrogen bonding, shifts the NH resonance downfield.

Table V. NH Stretching Frequencies (cm^{-1}) for **3** and **4** in $CDCl_3$

compd	free NH	H-bonded NH
cis-**3**	3420 (0.95)[a]	3235 (0.67)
trans-**3**	3392 (0.98)	3229 (0.68)
cis-**4**	3422 (0.64)	3304 (0.06)
trans-**4**	3371 (1.62)	3249 (0.38)

[a] Numbers in parentheses are absorbances.

Temperature Effects. The temperature effects on the chair–twist equilibrium for *cis*-**3** discussed above, and in particular the decrease in J_{BP} and increase in J_{AP} at higher temperatures (Table III), demonstrate that *the chair conformer is of lower enthalpy*. The opposite is true for *cis*-**5**. As Table III shows, *the twist form of cis*-**5** *is less favored* at higher temperatures as J_{AP} decreases while J_{BP} is increased. Very little **14** is populated by *cis*-**5** at −18 °C. Chemical shift variations as a function of temperature have not been tabulated as they proved to be uninformative.

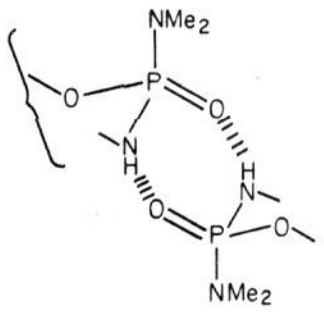
Concentration and Solvent Effects on Coupling Constants and Infrared Bands. Effects of solute concentration and solvent nature were carefully investigated to ascertain whether or not *intermolecular* association might control conformation in the case of *cis*-**4** and especially *cis*-**3**. A particular concern is the possibility that the difference in conformational properties of the NH and NPh compounds could be the result of well-known intermolecular hydrogen bonding effects illustrated by **16**.[7,11] In Table V are

(11) Emsley, J.; Hall, D. "The Chemistry of Phosphorus"; Wiley: New York, 1976.

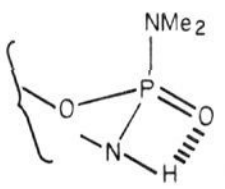
compiled the apparent NH stretching frequencies determined by FT IR on 10% solutions in $CDCl_3$. The free (sharp) and H-bonded (broad) bands are found in the expected regions.[7] Note the relative weakness and smaller frequency shifts of the H-bonded bands of the sulfides.

Dilution to 5% and 1% led in each case to a progressive loss of the H-bonded absorption (compared to the free NH band), which disappeared completely for *trans*-**4** and had absorbance values for *cis*-**3**, *trans*-**3**, and *cis*-**4** of <0.003, <0.008, and <0.001, respectively, at the 1% (10^{-2}–10^{-3} M) level. The 5–10% solutions of *trans*-**4** exhibited a band of unexplained origin at 3436 cm^{-1} not seen with the others. *trans*-**3** had a weak shoulder at about 3400 cm^{-1}.

Most importantly, the J values for *cis*-**3** show virtually no effect of concentration changes in $CDCl_3$ (cases 3 and 4) in the very concentration range in which the degree of intermolecular H bonding is clearly affected. They also fail to respond to solvent changes (cases 1–5, Table I). Thus, one can discount the possibility that the chair conformation for *cis*-**3** with Me_2N axial is the result of *intermolecular* H bonding, e.g., that illustrated by structure **16**. (Me_2SO-d_6 would be especially destructive of such



16



17

interactions.) Likewise, structure **17**[12] cannot account for the conformational difference between *cis*-**3** and *cis*-**5** since there is no evidence of intramolecular H bonding, i.e., no IR band remaining on dilution. The lack of a second free NH band with *cis*-**3** may mean that the band for twist-form *cis*-**3** is at close to the same frequency as that for the chair (peak widths at half-height 20–30 cm^{-1}). Where similar checks on effects of solvent and concentration were made with certain of the other compounds (Table I), no important changes in J values were encountered.

H_Y Couplings. The values of J_{YC}, J_{YD}, and J_{YP}, couplings involving the NH (H_Y), vary considerably from compound to compound and between diastereomers of a given compound. At this time we are unable to interpret these effects. Quite possibly changes in nitrogen hybridization are involved.

Discussion

The most important single conclusion that can be drawn from the above is that the populations of conformations populated by such 1,3,2-oxazaphosphorinane ring systems can be strongly influenced by the nature of the substituent on ring nitrogen (N_3). At least this is true when the group on phosphorus is a relatively bulky one such as Me_2N. Since there seem to be no special stabilizing effects on the chair conformation of the NH compounds, **3** and **4**, one is forced to look for possible stabilization of the twist conformations for *cis*-**5** and *cis*-**6** or destabilization of the chair conformation. It is difficult to imagine a stabilizing effect of a bulkier substituent (Ph vs. H). Thus, we conclude that the phenyl group in some way destabilizes the chair conformation of *cis*-**5** and *cis*-**6**.

Inspection of molecular models and the X-ray crystal structure of *cis*-**4** shows that the axial Me_2N is forced to turn away from the axial hydrogens at carbons 6 and 8.[8] At the same time the phenyl group of *cis*-**5** in the chair conformation encounters steric repulsions between its ortho hydrogens and the equatorial P=O and to a lesser extent the equatorial hydrogen at C_4 unless it moves toward a position in which the nitrogen lone pair is orthogonal

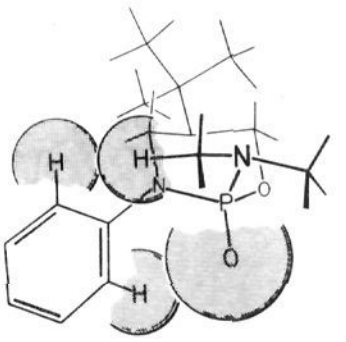
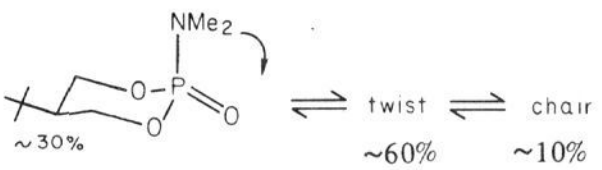


Figure 2. Structure for chair conformation of *cis*-**5** based on Dreiding model. Hemispheres based on approximate atomic radii.

to the lone pairs of the benzene ring. What is also evident, however, is the consequent interaction of the ortho phenyl hydrogen with the Me_2N group. This situation is depicted in Figure 2. We tentatively ascribe the destabilization of the chair conformations of the cis isomers of **5** and **6** to this interaction. In the twist conformation, the Me_2N rotates away from the phenyl and also, as shown in the X-ray study,[4a] is able to assume the conformation in which the trigonal-planar nitrogen system is very nearly coplanar with the P=O bond. (This is the geometry preferred by such systems when they are not sterically restricted.[4a,13]) The phenyl group moves into a position in which an optimal balance of steric repulsions and phenyl–nitrogen conjugative effects is attained (in the crystal about 30° out of the P–N_3–C_4 plane.[4a]) Significantly, a *single* twist conformer is populated. It is one in which the phenyl and Me_2N are moved away from each other, which also minimizes their interaction. On the basis of coupling constants, this same twist conformation is also the one populated to a lesser extent by the NH compounds.

It should be noted that substitution of Ph for H at N_3 (*cis*-**3** vs. *cis*-**5**) changes an equilibrium about 4/1 in favor of the chair (**14**) into one featuring at least 80% of **15** (actually 10–20%, depending on choice of J_{AP} and J_{BP}, etc.; vide supra.). This is a free energy difference ($\Delta\Delta G°$) of 1.6 kcal/mol or more. Restricted rotational entropy may make a significant contribution to the destabilization of **14** for *cis*-**5**.

In comparison to the corresponding 1,3,2-dioxaphosphorinane system, which we earlier estimated[9b] to be about 60% in a twist conformation like **15** and 30% in chair-form **18** [$\Delta G°$(**18** → twist) = −0.4 kcal/mol], a lesser fraction of *cis*-**3** (**14**), i.e., 20%, has been converted to **15** [$\Delta G°$(**14** → **15**) = +0.8 kcal/mol]. Part of this difference (0.4 kcal/mol) comes from the entropy of mixing term (RT ln 2) which favors the twist structure in the 1,3,2-dioxaphosphorinane system since two enantiomers form in the process **18** → twist. This would bring the expected equilibrium constant for **15**/**14**, based on **18**, down from 2 to a value of 1 [$\Delta G°$(**14** → **15**) = 0], but it still leaves 0.8 kcal of unfavorable enthalpy with which to be concerned.



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The conversion of **14** to **15** or of **18** to the corresponding twist structure involves two components, eq 5. One is a *favorable*

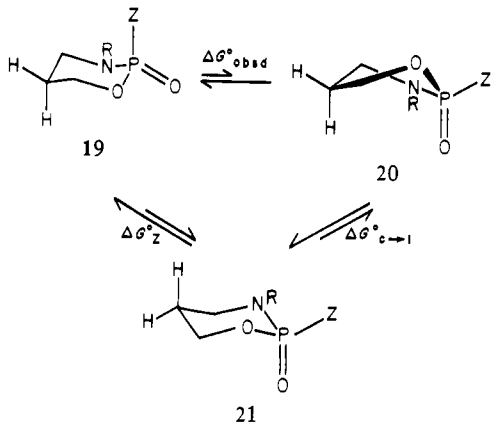
$$\Delta G°_{obsd} = \Delta G°_{Me_2N}(ax \rightarrow eq) + \Delta G°_{c\rightarrow t} \qquad (5)$$

reorientation of the phosphorus end of the molecule in which the P=O and Me_2N switch axial and equatorial positions on the ring, $\Delta G°_{Me_2N}(ax \rightarrow eq)$. This component is illustrated by the isom-

(12) The possibility that such bonding occurs with certain 4,6-dimethylcyclophosphamide analogues with $N(CH_2CH_2Cl)_2$ fixed axial has been proposed.[7]

(13) Representative of many X-ray crystallographic studies that show this phenomenon with Me_2N attached to the 1,3,2-oxazaphosphorinane ring are: Karle, I. L.; Karle, J. M.; Egan, W.; Zon. G.; Brandt, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 4803. Clardy, J. C.; Mosby, J. A.; Verkade, J. G. *Phosphorus Relat. Group V Elem.* **1974**, *4*, 151. Perales, A.; Garcia-Blanco, S. *Acta Crystallogr., Sect. B* **1977**, *B33*, 1939. Camerman, A.; Smith, H. W.; Camerman, N. *Ibid.* **1977**, *B33*, 678. Sternglanz, H.; Einspahr, H. M.; Bugg, C. E. *J. Am. Chem. Soc.* **1974**, *96*, 4014.

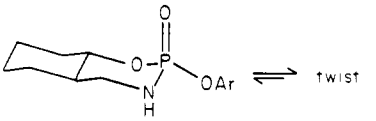
Scheme II



19 20 21

erization **19** → **21** (Z = Me_2N) in Scheme II. The other is the *unfavorable* chair to twist interconversion (**21** to **20** in the 1,3,2-oxazaphosphorinanes), $\Delta G°_{c\rightarrow t}$. How much each of these terms contribute to this difference is difficult to define precisely at this time. From inspection of Dreiding models, it is clear that because of ring flattening by the trigonal-planar ring nitrogen ($P-N_3-C_4$ angle, 119°)[4a] and the increased P–N bond length compared to the P–O endocyclic bond length, the distance between the axial Me_2N and the axial hydrogen at C_4 of the 1,3,2-oxaza rings is increased compared to what it is in the 1,3,2-dioxa compounds. This could result in a less favorable $\Delta G°_{Me_2N}$(ax → eq) term. On the other hand, the lengthened P–N bond compared to the P–O bond in the 1,3,2-oxaza system might decrease cross-ring torsional interactions and lower $\Delta G°_{c\rightarrow t}$. An estimate of $\Delta G°_{c\rightarrow t}$ can be made as follows.

For cyclophosphamide itself, a chair–chair equilibrium has been postulated.[6,7] Using the previously reported time-averaged couplings[7] for this molecule in $CDCl_3$ of J_{AP} = 4.7 Hz and J_{BP} = 17.7 Hz and the assumed interchangeability of the J_{AP} and J_{BP} values between the two chair forms, one can estimate the mole fraction of each chair present. For values of J_{AP} and J_{BP} we employed those used earlier (from the cis MeO derivative corresponding to *cis*-**3**) of 20.7 and 2.8 Hz in order to estimate an 83–89% population of the predominant chair conformation, presumably[7] that with Mu, i.e., $N(CH_2CH_2Cl)_2$, equatorial. Again the percentage depends on whether J_{AP} or J_{BP} is being calculated. This estimate is in good agreement with the value of 86% (6/1 ratio) reported previously and amounts to −1 kcal for $\Delta G°_{Mu}$(ax → eq) for the Mu substituent. If this value is applied to the equilibrium **14** → **15** (or that involving **19**–**21**), then $\Delta G°_{c\rightarrow t}$ is about 1.8 kcal/mol as derived from eq 5: $[\Delta G°_{c\rightarrow t} = -\Delta G°_{Mu}(ax \rightarrow eq) + \Delta G°_{obsd} = -(-1) + 0.8]$. This is somewhat higher than the value of 1 kcal/mol or less estimated for pentavalent 1,3,2-dioxaphosphorinane[9] and 1,3,2-dithiaphosphorinanes systems[14] *but nonetheless much below* $\Delta G°_{c\rightarrow t}$(25 °C) *for either cyclohexane (4–5 kcal/mol)*[15] *or 1,3-dioxane (8 kcal/mol)*.[16] (If the above-mentioned differences in $\Delta S°$ are considered, $\Delta H°_{c\rightarrow t}$ for the 1,3,2-oxaza and 1,3,2-dioxa rings are more nearly the same.) One therefore expects twist conformations which place C_5 opposite pseudoaxial phosphoryl oxygen in twist structures such as **15** and **20** to be energetically quite accessible. *The 1.8 kcal/mol figure for* $\Delta G°_{c\rightarrow t}$ *likely represents a maximum* value since Me_2N should be, if anything, slightly smaller than Mu. Population of a twist conformation also has been demonstrated for the trans-fused-ring system **22** in which the driving force is the reorientation of the ArO into a pseudoaxial position.[17]



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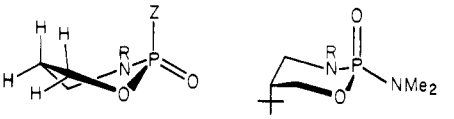
It needs to be carefully pointed out that *there are two distinct chair to twist conformational changes*. The one involved in the above discussion corresponds to the process **21** → **20**, both structures having phosphoryl oxygen axial or pseudoaxial. A second chair to twist isomerization is **19** → **23**. $\Delta G°$ for this process is likely to vary with the steric size of Z and may be larger than that for **21** → **20** to which we have assigned low values in the 1,3,2-dioxa- and -oxazaphosphorinanes.

Noteworthy is the failure of any of the cis isomers to undergo measurable chair–chair equilibration to place the *tert*-butyl axial, structure **24**. Evidently $\Delta G°$ for chair → twist (**21** → **20**) is less



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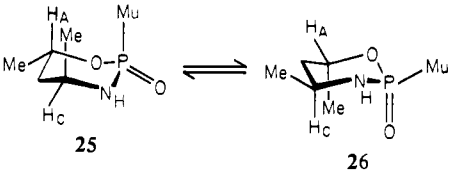
than $\Delta G°$ for placing the *tert*-butyl axial, $\Delta G°_{eq\rightarrow ax}$(*t*-Bu). The latter has a value of 1.4–1.8 kcal/mol in 1,3-dioxanes[18] and trimethylene sulfites[19] and could be similarly low when a *tert*-butyl is placed axial opposite one nitrogen and one oxygen. However, the effect of substituent R (H or Ph) on $\Delta G°_{eq\rightarrow ax}$(*t*-Bu) is unknown and might raise its value above 2 kcal/mol. In any event, rather than populate **24**, *cis*-**3** and *cis*-**5** adopt conformations **14** and **15** with *t*-Bu equatorial or pseudoequatorial. This is in keeping with the relatively low $\Delta G°_{c\rightarrow t}$(**21** → **20**) discussed above, regardless of its precise value.

The chair conformations found for *trans*-**3**–**6** are in accord with the relatively large size of the Me_2N[3] and with the conformations populated by *trans*-**18**.[9b] With smaller Z on phosphorus, depopulation of the diequatorially substituted chair can be observed for the *trans*-1,3,2-oxazaphosphorinanes.[9c]

Our results show, however, that in the absence of substituents larger than hydrogen on N_3 the Me_2N group is not so large that it cannot be forced axial in the presence of another sterically biasing substituent on the ring, as, for example, the 5-*tert*-butyl in *cis*-**3** and *cis*-**4**. There is even the possibility, as discussed earlier, that the Me_2N in the 1,3,2-oxaza system may be sterically somewhat smaller than it is in the 1,3,2-dioxa ring based on considerations of models and X-ray structures showing increased intramolecular distances. Therefore, concerning the substituted cyclophosphamides **7** and **8**, it seems quite reasonable that a conformational equilibria should be found. Moreover, it is most probable that the diastereomer with more equal populations of conformers should be **7** (J_{AP} = 15.3 Hz[7]), i.e., equilibrium **25** ⇄ **26**. In **25** the methyl next to ring nitrogen is 1,3-synaxial to the



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Mu. By contrast conformer **27** of diastereomer **8** places the methyl next to ring oxygen axial and in closer proximity to the Mu than is the methyl in **25**. Conformers **25** and **27** are both thereby depopulated. Though the effect of the axial methyl in **25** and **27**

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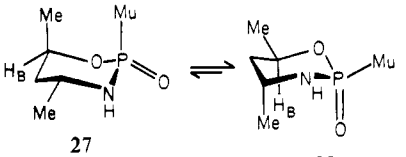
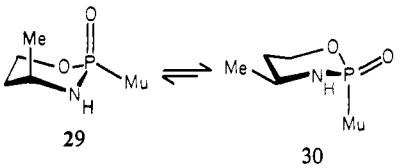
is the same, i.e., the shifting of the equilibria **25** ⇄ **26** and **27** ⇄ **28** toward the right, the latter equilibrium should exhibit a higher population of the conformer on the right. The reported[7] J_{BP} value of 2.4 Hz indeed shows the **27** ⇄ **28** equilibrium to be strongly biased to the right.



In similar fashion probable structural assignments for the 4-methyl-substituted cyclophosphamides[2a,c] can be made and equilibria discussed. Clearly the cis diastereomer should be confined to a single chair conformation with both groups equatorial. For the trans diastereomer it is likely that the equilibrium **29** ⇄ **30** pertains.[2a] The destabilization of the axial Mu in **30**



will be at least partially offset by the axial methyl in **29**, which will displace the equilibrium toward the Mu-axial conformer to a greater extent than in cyclophosphamide itself. It is our view that with *trans*-6-methylcyclophosphamide the Mu-axial conformer analogous to **30** should be even more favored.

Finally, in reference to IR studies referred to in the introduction to this paper, we believe on the basis of our work that the postulation[5] for symmetrically 5,5-disubstituted **1** with Z = alkylNH or PhNH that when R = alkyl or Ph, a chair conformation with amino group equatorial is highly populated may indeed be correct. However, since such a Z is much smaller than Mu, there could be, in our opinion, a reasonably large and perhaps predominant percentage of the alternative chair conformation populated in such cases. (See cyclophosphamide itself.[7]) It is most unlikely that conformations of such molecules with Z = PhO should be, as claimed,[5] strongly perturbed by change in ring nitrogen substituent from R = H (P=O axial) to R = Ph, Me (P=O equatorial). Thus in work to be published later on compounds analogous to **3–6** but with Z = MeO, we find no influence of the nature of R on conformational equilibria.[9c] The P=O IR stretching frequency shifts observed[5] on changing the substituent on ring nitrogen are quite likely entirely unrelated to configuration at phosphorus. We have found this same IR shift to occur in comparing *trans*-**3** to *trans*-**5**,[9c] both of which clearly have the P=O axial in solution. (See above discussion of their ^{1}H NMR spectral parameters.) The intrinsic effect of a substituent change on IR frequency independent of P=O orientation must be considered in these cases. Uncertainties accompanying the use of P=O stretching frequencies to assign configuration at phosphorus in 1,3,2-oxazaphosphorinanes have been noted previously.[7]

Experimental Section

Materials. All solvents and materials were reagent grade or better and were used as received or purified as required. $CHCl_3$ was purified free of EtOH for IR studies. Reactions involving trivalent phosphorus were routinely run under an atmosphere of nitrogen or argon. Elemental analyses were done by Galbraith Laboratories, Knoxville, TN. Melting points are uncorrected. Gas chromatography was routinely performed on an HP 5830 thermal conductivity instrument using silanized 3–4% QF-1 on 80/100 Gas-Chrom Q in 0.25-in. glass columns.

Spectroscopy. ^{1}H NMR spectra were run in the FT mode on a Varian SC 300 instrument at 300 MHz, 32K data base, 3000-Hz SW, 5.459-s acquisition times. Coupling constants were taken from inspection of 100-Hz expansions of the H_A/H_B, H_C/H_D, and H_X spectra and are probably accurate to ±0.2 Hz. The spectrum of *cis*-**5** was also measured at 90 MHz (Varian EM 390, CW mode) and iteratively analyzed with the LAOCN3 program. Coupling constants were assigned by decoupling H_X in all cases to distinguish, e.g., J_{AP} from J_{AX}. In key instances H_Y (i.e., NH) was irradiated to allow correct assignments of couplings to that proton. ^{31}P measurements were made at 32.2 MHz with a Varian FT-80 spectrometer under proton noise decoupling conditions. FT infrared spectra were determined on a Nicolet FT-IR Model 7199 spectrometer with 0.1-mm cells.

Diethyl Isopropylidenemalonate. Diethyl isopropylidenemalonate was synthesized according to a literature[20] procedure in 48% yield [bp 120–125 °C (18 mm); lit. bp 111–113 °C (9 mm)] and was converted[18a] to diethyl *tert*-butylmalonate in 68% yield [bp 107–108 °C (13 mm); lit.[18a] bp 109–114 °C (17 mm)].

2-Carbethoxy-3,3-dimethylbutyric Acid (9). Solid potassium hydroxide (15 g, 0.231 mol) was added to diethyl *tert*-butylmalonate (50.0 g, 0.231 mol) dissolved in 120 mL of absolute ethanol followed by a 3-h reflux. The reaction mixture was then cooled to room temperature. Ethanol was removed by rotary evaporation, and the solid residue was dissolved in ~150 mL of water. Ether extraction (3 × 100 mL) recovered the starting material. The water layer was acidified with 10% HCl, and an oil separated out. This heterogeneous mixture was extracted with ether (3 × 100 mL), and the dried ($MgSO_4$) combined ether layers were removed by rotary evaporation to leave 38 g of an oily residue, 93% yield based on the reacted diethyl *tert*-butylmalonate; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.17 (9 H, s, $(CH_3)_3C$), 1.30 (3 H, t, $CO_2CH_2CH_3$), 3.30 (1 H, s, methine H), 4.23 (2 H, q, $CO_2CH_2CH_3$), 9.9 (1 H, s, CO_2H). Half-ester **9** was used without further purification.

2-Carbethoxy-3,3-dimethylbutyramide (10). A mixture of 2-carbethoxy-3,3-dimethylbutyric acid (**9**, 80 g, 0.42 mol) and thionyl chloride (60 g, 0.50 mol) was heated under reflux for 1.5 h. After the reaction was cooled to room temperature, the excess thionyl chloride was removed under reduced pressure. Anhydrous ether (1500 mL) was added to the remaining residue, and anhydrous ammonia was passed into the solution until no more precipitate formed. The precipitate was filtered off and washed with ether (3 × 50 mL). The combined ether solutions were dried ($MgSO_4$) and rotary evaporated to leave a crystalline residue that was recrystallized from absolute ethanol–pentane to obtain pure amide ester **10**: 22 g (29% yield), mp 103–104 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.08 (9 H, s, *t*-Bu), 1.25 (3 H, t, CH_3CH_2O, J = 7 Hz), 3.08 (1 H, s, methine H), 4.18 (2 H, q, CH_3CH_2O, J = 7 Hz), 6.10 (<1 H, br s, NH or OH), 6.95 (<1 H, br s, NH or OH). Improved yields were obtained by use of PCl_5.

2-(Hydroxymethyl)-3,3-dimethylbutylamine (11). A solution of **10** (9.2 g, 0.051 mol) in anhydrous THF (70 mL) was added over a 1-h period to a stirred slurry of lithium aluminum hydride (5.6 g, 0.15 mol) in anhydrous THF (80 mL). After 2 days of reflux, the reaction mixture was cooled and then hydrolyzed by the addition of 7 mL of water followed by 54 mL of 15% NaOH solution and another 18 mL of water. The resulting mixture was stirred for an hour. The ether layer was separated, and the remaining aqueous layer was extracted with ether (3 × 150 mL). The combined ether layers were dried ($MgSO_4$), filtered, and rotary evaporated to leave a residue, which on distillation at reduced pressure gave **11**, an oil; 3.10 g (48% yield), bp 92–93 °C (1.75 mm). Workup of reductions run on a 5-g scale by simply adding at 0 °C a 3-mol excess of H_2O to quench remaining $LiAlH_4$ gave pure amine alcohol in 75% yield. The use of base on the large-scale reactions avoided occasional gum formation; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.82 (9 H, s, *t*-Bu), 1.20–1.63 (1 H, m, methine H), 2.20 (1 H, s, OH), 2.42–2.83 (2 H, m, CH_2NH_2), 3.05–3.40 (2 H, m, CH_2OH). Anal. Calcd for $C_7H_{17}ON$: C, 64.12; H, 12.98. Found: C, 64.24; H, 12.76.

***N*-Phenyl-2-carbethoxy-3,3-dimethylbutyramide (12).** Under conditions of vigorous stirring were mixed aniline (47 g, 0.50 mol), small pieces of sodium (3.0 g, 0.13 mol), and copper powder (0.50 g). Mild heating resulted in an effervescent reaction. Another 8.5 g of sodium was added over a 2-h period. After further heating for 5 h, 0.5 g of aniline was added, and heating was continued for another 0.5 h. The reaction mixture was cooled to room temperature. To it was added a quantity of diethyl *tert*-butylmalonate (108 g, 0.502 mol). Gentle heating initiated a vigorous reaction. About 60 mL of dry toluene was added followed by 3 h of gentle heating. To the cooled reaction mixture was added cautiously 500 mL of ice water. Acidification with 420 mL of 12% HCl yielded a black, oily mass, which was then ether extracted. Removal of the $MgSO_4$-dried ether and addition of 20 mL of EtOH led in 2 days to the crystallization of several grams of the diamide byproduct. The filtrate was concentrated and vacuum distilled at 143–145 °C (1 mm) to afford 87 g (66% crude yield) of nearly pure monoamide **12**, which crystallized overnight, mp 63–65 °C. Recrystallization from EtOH/H_2O of 200 mg of this material gave 150 mg of colorless crystals: mp 67–69 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 9.05 (1 H, br s, NH), 7.0–7.8 (5 H, m, aromatic), 4.18 (2 H, q, CH_3CH_2O, J_{HH} = 7 Hz), 3.20 (1 H, s, methine H), 1.27 (3 H, t, CH_3CH_2O, J_{HH} = 7 Hz), 1.93 (9 H, s, *t*-Bu). Anal.

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Calcd for $C_{15}H_{21}ON_3$: C, 68.44; H, 7.98; N, 5.32. Found: C, 68.50; H, 8.31; N, 5.55. Compound **12** was also synthesized via the acid chloride and aniline according to the preparation of **10**.

***N*-Phenyl-2-(hydroxymethyl)-3,3-dimethylbutylamine (13).** Compound **12** (85 g, 0.32 mol) in 150 mL of ether was added over 1.5 h to a stirred mixture of $LiAlH_4$ (25 g, 0.65 mol) in 60 mL of ether cooled to 10 °C. After 6 h at room temperature and 90 h at reflux, the mixture was worked up by successively adding 25 mL of H_2O (1.5-h period), a solution of 75 g of NaOH in 110 mL of H_2O, another 20 mL of H_2O, and again 75 g of NaOH in 110 mL of H_2O. The ether layer was separated and the aqueous mixture extracted with ether. Evaporation of the combined dried ether layers gave 60 g of crude product **13**. Distillation yielded 46 g (69%) of 99.8% pure amino alcohol (GLC), **13**, bp 135–138 °C (1 mm). Reductions on a 5-g scale could be worked up by simply quenching the $LiAlH_4$ by the addition at 0 °C of a 3-mol excess of H_2O to give 95% yields of pure amine alcohol: ^1H NMR (90 MHz, $CDCl_3$) δ 0.95 (9 H, s, *t*-Bu), 1.30–1.80 (1 H, m, methine H), 3.35 (2 H, br s, OH and NH, D_2O exchange confirmed), 2.80–3.35 (2 H, m, CH_2NH), 3.50–4.08 (2 H, m, CH_2OH), 6.45–6.85 (3 H, m, aromatic), 6.95–7.30 (2 H, m, aromatic); 99.8% pure by GLC. Anal. Calcd for $C_{13}H_{21}ON$: C, 75.32; H, 10.21; N, 6.76. Found: C, 74.95; H, 10.39; N, 6.75.

***cis*- and *trans*-2-(Dimethylamino)-2-oxo-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane (3).** A modification of a procedure[21] for preparation of cyclophosphamide was used. A solution of Me_2NPOCl_2[22] (3.8 g, 0.024 mol) in 34 mL of ethyl acetate was added over a 15-min period to a stirred solution of 2-(hydroxymethyl)-3,3-dimethylbutylamine (**11**) (3.1 g, 0.024 mol) and triethylamine (4.8 g, 0.48 mol) in 21 mL of ethyl acetate cooled to 5 °C. After the reaction mixture was stirred at room temperature for 48 h, the triethylamine hydrochloride was filtered off. The viscous oil remaining from evaporation of the solvent was short-path vacuum distilled to give 5.0 g (95% crude yield) of a mixture of solid diastereomers of **3** in 41/59 (cis/trans) ratio (GLC). *trans*-**3** crystallized in 95% diastereomeric purity from ethyl acetate, mp 121–123 °C. Elution column chromatography of 0.50 g of crude product (SiO_2) gave pure *cis*-**3**, 0.12 g, mp 102–104 °C, using ethyl acetate as eluting solvent, and also a pure mixture of both diastereomers (0.30 g) used for quantitative elemental analysis. Anal. Calcd for $C_9H_{21}N_2O_2P$: C, 49.08; H, 9.61; P, 14.06. Found: C, 49.09; H, 9.78; P, 14.02.

***cis*- and *trans*-2-(Dimethylamino)-2-thio-5-*tert*-butyl-1,3,2λ^5-dioxaphosphorinane (4).** Into 56 mL of ether at 0 °C were added dropwise and simultaneously a solution of $PSCl_3$ (2.6 g, 0.015 mol) in 26 mL of ether and a solution of 2-(hydroxymethyl)-3,3-dimethylbutylamine, **11** (2.0 g, 0.015 mol), and triethylamine (3.1 g, 0.030 mol) also in 26 mL of ether. On completion of the addition, stirring was continued at room temperature for 4 h. The amine hydrochloride was removed by filtration and the ether by rotary evaporation. The residue was redissolved in 30 mL of dry ether. Anhydrous Me_2NH was passed through the solution until no more precipitate was generated. Filtration of the reaction mixture and ether evaporation left solid product **4**, 3.6 g (100% crude yield), containing both diastereomers in 41/59 (cis/trans) ratio (GLC). Separation of the diastereomers was effected by open column elution chromatography with hexane mixed with increasing amounts of $CHCl_3$ as eluting solvent. From a 1.5-g mixture were obtained 50 mg of *cis*-**4** (mp 112–113 °C) and also 55 mg of *trans*-**4** (mp 105–106 °C) along with 100 mg of a mixture of the two, all better than 99% pure by GLC. Quantitative elemental analysis was done on the mixture. Anal. Calcd for $C_9H_{21}N_2OPS$: C, 45.74; H, 8.96; P, 13.11. Found: C, 45.68; H, 8.99; P, 12.90.

***cis*- and *trans*-2-(Dimethylamino)-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane.** A solution of hexamethylphosphorous triamide (5.0 g, 0.024 mol) and amino alcohol **13** (4.0 g, 0.024 mol) in toluene (40 mL) and ethyl acetate (40 mL) was refluxed for 6 h, after which the solvent was removed under vacuum to afford 6.6 g of a colorless liquid. Distillation gave 4.2 g (62%) of the desired trivalent product, bp 165–166 °C (3 mm), 99% pure by GLC. Two signals were present in the ^{31}P NMR spectrum (C_6D_6) at δ 136.3 (cis, 75%) and 138.3 (trans, 25%). ^1H NMR (90 MHz, $CDCl_3$): δ 0.85, 0.90 (3 H, s, *tert*-butyl), 1.60–2.05 (1 H, m, methine H), 2.65, 2.55 (6 H, d, J = 7.5 Hz, Me_2N ratio 23/77), 3.45–3.65 (2 H, m, NCH_2), 3.70–4.15 (2 H, m, OCH_2), 6.70–7.33 (5 H, m, C_6H_5).

***cis*- and *trans*-2-(Dimethylamino)-2-oxo-3-phenyl-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane (5).** The above product (3.3 g, 0.011 mol) in 40 mL of CH_2Cl_2 at −35 °C was oxidized by dropwise addition of 9.1 mL of a 3% solution of N_2O_4 in CH_2Cl_2. The mixture was warmed slowly to 32 °C. Solvent removal left 3.0 g of a yellow solid, crude **5**. GLC analysis showed only about 4% of unreacted trivalent material along with the product oxides in 75/25 (cis/trans) ratio. On solution in 10 mL of benzene and cooling to about 10 °C, 850 mg (2 crops) of crystalline *cis*-**5**, mp 165–166 °C, was obtained; ^{31}P NMR ($CDCl_3$) δ +8.5. Anal. Calcd for $C_{15}H_{25}N_2O_2P$: C, 60.82; H, 8.45; P, 10.46. Found: C, 60.49; H, 8.62; P, 10.75.

Chromatography on a gravity column (SiO_2) packed and eluted with Et_2O separated a 3.0-g mixture of **5** similar to the above into 1.3 g of the major isomer (*cis*-**5**) and, after recrystallization, 0.3 g of the minor one (*trans*-**5**); mp 125–126 °C from ether; ^{31}P NMR ($CDCl_3$) δ +10.9. Anal. Calcd for $C_{15}H_{25}N_2O_2P$: C, 60.82; H, 8.45; P, 10.46. Found: C, 60.66; H, 8.57; P, 10.50.

In an alternative route to **5**, **2-chloro-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane** was prepared by addition of a solution of amino alcohol **13** (12 g, 0.058 mol) and Et_3N (15 g, 0.15 mol) in 50 mL of ether dropwise and simultaneously with a solution of PCl_3 (8.0 g, 0.058 mol) in 50 mL of ether to 100 mL of ether stirred and cooled to about 10 °C. Following the addition, the reaction mixture was stirred for 1.5 h at ice-bath temperature and for another 2 h at room temperature. Removal of the solid amine hydrochloride and ether followed by vacuum distillation (bp 155–158 °C (1.3 mm)) gave an oil: 9.5 g (61%); ~90% pure by ^{31}P NMR ($CDCl_3$) δ +148.7; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.92 (9H, s, *t*-Bu), 1.75–2.15 (1 H, m, methine H), 3.05–3.87 (2 H, m, CH_2NPh), 4.00–4.46 (2 H, m, OCH_2), 7.0–7.4 (5 H, m, C_6H_5).

By a procedure parallel to that for preparation of **4**, a reaction involving Me_2NH and the above trivalent chloro compound gave trivalent **2-(dimethylamino)-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane** in 10/90 cis/trans ratio (^{31}P NMR). Oxidation by N_2O_4 in CH_2Cl_2 yielded trans-rich **5** from which *trans*-**5** was easily separated by elution chromatography.

***cis*- and *trans*-2-(Dimethylamino)-2-thio-3-phenyl-1,3,2λ^5-oxazaphosphorinane (6).** The above trivalent precursor (0.14 g, 0.50 mmol) of diastereomer ratio 75/25 (cis/trans) was dissolved in 5 mL of benzene and to it was added S_8 (0.016 g, 0.50 mmol) over a period of 5 min. After the mixture was heated at 40 °C for 40 min, GLC showed the reaction to be complete with product sulfide **6** in cis/trans ratio of 77/23.

Elution column chromatography (SiO_2) of 500 mg of crude **6**, cis/trans ratio 60/40, using as eluting solvents pentane, 99/1 pentane–ether, and 98/2 pentane–ether afforded 100 mg of the GLC-pure *trans*-**6**, mp 94–95 °C. Nearly pure *cis*-6 from chromatography (200 mg) was recrystallized from ether and then benzene to give 100 mg of colorless crystals, mp 145–145.5 °C. An 80/20 mixture of diastereomers was used for elemental analysis. Anal. Calcd for $C_{15}H_{25}N_2OPS$: C, 57.70; H, 8.00; P, 9.92. Found: C, 57.74; H, 8.17; P, 9.91.

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Registry No. 3, isomer 1, 77815-22-6; **3**, isomer 2, 77815-23-7; **4**, isomer 1, 82757-16-2; **4**, isomer 2, 83096-33-7; **5**, isomer 1, 70219-43-1; **5**, isomer 2, 70219-44-2; **6**, isomer 1, 83096-34-8; **6**, isomer 2, 83096-35-9; **9**, 83096-36-0; **10**, 83096-37-1; **11**, 15521-17-2; **12**, 83096-38-2; **13**, 83096-39-3; *cis*-2-(dimethylamino)-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorane, 83096-40-6; *trans*-2-(dimethylamino)-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorane, 83096-41-7; 2-chloro-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorane, 83096-42-8; diethyl *tert*-butylmalonate, 759-24-0.

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