alkyne were observed to coalesce. ^{13}C assignments for **1** are based on a comparison of $^{13}C\{^1H\}$ spectra with gated decoupled spectra and are consistent with the $^1J_{CH}$ couplings, with the long-range coupling[24] in gated spectra, and with the relative intensities of the resonances. Chemical shift differences for the aromatic carbons parallel those observed for **2**. The chemical shifts of the acetylenic carbons are similar to those reported for the analogous hexyne complex.[9b]

The absence of obviously unfavorable intramolecular interligand nonbonding interactions in crystalline **2** would argue against the difference in $\Delta G^{\ddagger}$ for alkyne rotation in **1** and **2** being due to steric factors such as strain relief in **2** and suggests that electronic effects must be considered. The small drop in $\nu(C{\equiv}C)$ (1650 cm^{-1}, as compared with 1675 cm^{-1}[27] for **1**) suggests that there is increased π-back-donation to ligand π^*-orbitals in the more electron-rich **2**, but the absence of structural differences between **1** and **2** indicates that the ground-state differences are not marked. If, however, π-back-bonding is a more significant component of the alkyne–metal interactions in the transition state for rotation[28] than in the ground state, the higher charge density on the metal in **2** may lead to a lower energy transition state for rotation in **2**.

(27) This work.
(28) This transition state would have the geometry of a highly distorted quadrilaterally capped trigonal prism if the potential energy curve for rotation approximates a single maximum function.

Conclusion

The reduction of $[W(PhC{\equiv}CPh)_3CO]$ (**1**) to give what is suggested to be $[W(PhC{\equiv}CPh)_3]^{2-}$ shows that anionic transition-metal complexes with alkyne ligands may be more readily accessible than had been generally assumed. Subsequent reaction of the intermediate anion with Ph_3SnCl confirms that such species will react readily with electrophiles and suggests that they could prove to be useful intermediates in the synthesis of a range of unusual organometallic complexes. Further work is continuing in these laboratories on the development of the chemistry of alkyne complexes of tungsten.

Acknowledgment. We thank the National Science Foundation (Grant CHE 80-16162) for supporting this work. The Nicolet R3 diffractometer and Bruker WM-300 NMR spectrometer were purchased with the aid of grants to Harvard University from the National Science Foundation.

Registry No. $W(PhC{\equiv}CPh)_3CO$, 12120-72-8; $[W(PhC{\equiv}CPh)_3SnPh_3]NEt_4$, 88635-91-0; $[W(PhC{\equiv}CPh)_3SnPh_3]Li$, 88635-92-1.

Supplementary Material Available: Tables of observed and calculated structure factors and of atomic thermal parameters (28 pages). Ordering information is given on any current masthead page.

Conformations of Saturated Six-Membered Ring Phosphorus Heterocycles. Axial, Nonplanar Dimethylamino Group of 5,5-Dimethyl-2-(dimethylamino)-2-oxo-1,3,2-oxazaphosphorinane As Determined by X-ray Crystallography. ^1H NMR and IR Spectroscopic Analysis of Conformation in Solution

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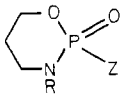
Abstract: The title compound (**7**) crystallized in space group *Pbca* with a = 7.409 (2) Å, b = 12.180 (2) Å, c = 21.912 (4) Å, Z = 8, R = 0.061, R_w = 0.075. The molecule adopts a chair conformation with the 2-dimethylamino substituent axial. The sum of the bond angles about the exocyclic $Me_2N(2)$ (349.3 (13)°) shows a considerable deviation from planarity. The exocyclic P–N(2) bond length is unusually long (1.644 (5) Å). The molecules are intermolecularly hydrogen bonded in chains by way of the N(3)H and phosphoryl oxygen. From ^1H NMR measurements at 300 MHz along with IR results, it is concluded that the same chair conformation is the predominant one populated in solution, by contrast to the known corresponding 1,3,2-dioxaphosphorinane for which Me_2N is equatorial. It is concluded that the dimethylamino group is an effectively smaller substituent (lower axial conformational energy) in the 1,3,2-oxazaphosphorinane ring and in that system is also smaller than the mustard moeity $N(CH_2CH_2Cl)_2$. Intermolecular hydrogen bonding can play a secondary role in determining conformation. The P–N(2) bond lengthening and pyramidal N(2) are attributed to the nonoptimal conformation about the P–N bond required for the axial Me_2N to avoid potential 1,3-syn-axial repulsive steric interactions with the axial hydrogens at C4 and C6.

The 1,3,2-oxazaphosphorinane ring system is of basic interest with regard to an understanding of the effects of heteroatom substitution on the conformational properties of saturated six-membered rings. Moreover, the clinically useful anticancer drugs[2] cyclophosphamide (**1**), isophosphamide (**2**), and trophosphamide (**3**) all contain the 1,3,2-oxazaphosphorinane ring. Cyclophosphamide itself is known to undergo equilibration between alternative chair conformations in solution (**4** ⇄ **5**, Z = $N(CH_2CH_2Cl)_2$; R = H)[3] however, no systematic study of the effect



1, R = H; Z = $N(CH_2CH_2Cl)_2$
2, R = CH_2CH_2Cl; Z = $N(CH_2CH_2Cl)_2$
3, R = CH_2CH_2Cl; Z = $NHCH_2CH_2Cl$

(1) (a) University of Massachusetts. (b) University of Utah.
(2) Hill, D. L. "A Review of Cyclophosphamide", Thomas, C. C.; Springville, IL, 1975.

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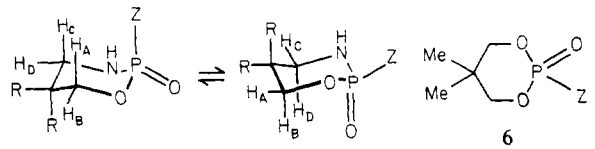
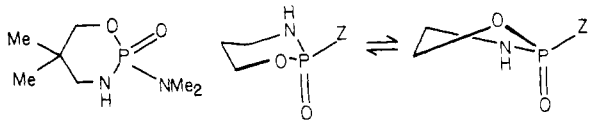


4 5 6

of changing the steric and/or electronic properties of the substituent Z on phosphorus on such an equilibrium, **4** ⇄ **5** (R = H), has been made.[4,5] Indeed the 1,3,2-oxazaphosphorinanes have been much less well studied than have the corresponding 1,3,2-dioxaphosphorinanes, e.g., **6**, which themselves have conformational features[6] that are very different from those of cyclohexane itself and other heterocycles such as 1,3-dioxanes. One expects that the greater length of the P–N bond, compared to P–O, in such rings and the presence of a substituent other than hydrogen on the ring nitrogen should result in important differences in the conformational properties of 1,3,2-oxazaphosphorinanes compared to those of 1,3,2-dioxaphosphorinanes.

In this regard, the remarkable influence of the steric size of the substituent on the ring nitrogen on the conformational energy of a Me_2N substituent on phosphorus in the 1,3,2-oxazaphosphorinane system was noted in an earlier report.[7] This is an important conformational feature obviously absent in 1,3,2-dioxaphosphorinanes. In the present paper, crystallographic, ^1H NMR, and IR results are reported from which it is concluded that the steric size (conformational energy) of the Me_2N in **7**, a



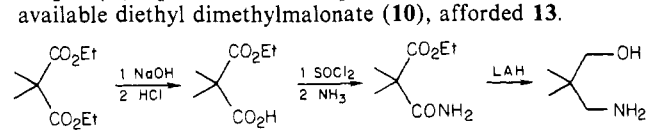
7 8 9

1,3,2-oxazaphosphorinane with the ring nitrogen unsubstituted, is effectively smaller than it is in **6**, the 1,3,2-dioxa counterpart. Thus the Me_2N of **7** is axial in the crystal and predominantly so in solution as well, i.e., structure **4** (R = Me, Z = Me_2N). Furthermore, the X-ray structure of **7** reveals that the axial Me_2N is nonplanar about nitrogen in contrast to the trigonal-planar geometry found in related systems in which the Me_2N is equatorial. In addition the P–N bond appears to be abnormally long. These effects are assigned to loss of optimal geometry about the exocyclic P–N bond involving the axial Me_2N.

The estimation of the equilibrium constant for **5**/**4** (R = Me, Z = Me_2N) reported here allows a better determination of the free energy change associated with the chair–twist equilibrium **9**/**8**. Thus $\Delta G°$ (chair → twist) is probably 1 kcal/mol or less, even lower than the close to 2 kcal/mol value estimated previously[7] on the assumption that the **4** ⇄ **5** equilibrium favors **5**.

Results

Synthesis. The compound of interest, **7**, was prepared in a straightforward manner by reaction of amino alcohol **13** with $Me_2NP(O)Cl_2$. A series of steps, **10** → **13**, based on readily available diethyl dimethylmalonate (**10**), afforded **13**.



10 11 12 13

X-ray Structure. An ORTEP perspective drawing of **7**, along with the labeling scheme, is shown in Figure 1. Atomic coordinates

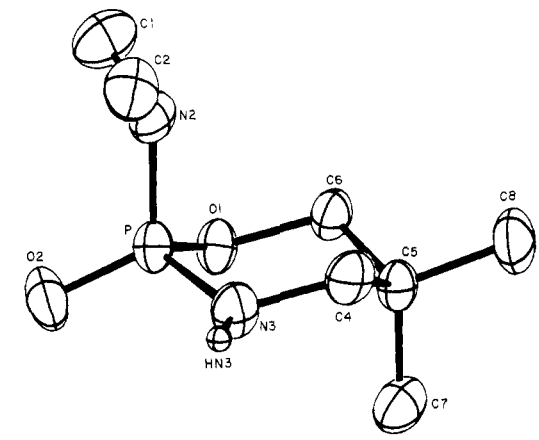


Figure 1. ORTEP plot of $(Me_2C_3H_4ONH)(Me_2N)PO$ (**7**) with thermal ellipsoids at the 50% probability level. Hydrogen atoms, except for HN(3), have been omitted for purposes of clarity.

Table I. Atomic Coordinates in Crystalline $(Me_2C_3H_4ONH)(Me_2N)PO$ (**7**)[a]

atom type[b]	coordinates		
	10^4x	10^4y	10^4z
P	5950 (2)	3835 (1)	3377 (1)
O(1)	5915 (5)	3513 (3)	4078 (2)
O(2)	7495 (6)	3318 (3)	3075 (2)
N(2)	5947 (6)	5184 (4)	3395 (2)
N(3)	3988 (7)	3444 (4)	3125 (2)
C(1)	7397 (10)	5733 (5)	3735 (3)
C(2)	5403 (9)	5776 (5)	2845 (3)
C(4)	2392 (9)	3722 (5)	3488 (2)
C(5)	2598 (8)	3316 (5)	4144 (2)
C(6)	4296 (7)	3797 (5)	4421 (3)
C(7)	2644 (9)	2059 (5)	4169 (3)
C(8)	985 (9)	3723 (5)	4519 (3)
HN(3)	3683 (100)	3341 (58)	2757 (34)

[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 $(Me_2C_3H_4ONH)(Me_2N)PO$ (**7**)[a]

Bond Lengths			
P-O(1)	1.584 (4)	N(1)-C(4)	1.465 (7)
P-O(2)	1.465 (4)	C(4)-C(5)	1.526 (7)
P-N(3)	1.626 (5)	C(5)-O(6)	1.515 (7)
P-N(2)	1.644 (5)	C(6)-O(3)	1.458 (6)
N(2)-C(2)	1.461 (7)	N(3)-HN(3)	0.85 (7)
N(2)-C(1)	1.469 (8)	HN(3)···O(2)	2.03 (7)
Bond Angles			
O(1)-P-O(2)	110.2 (2)	P-N(3)-HN(3)	127 (5)
O(1)-P-N(3)	104.0 (2)	O(4)-N(3)-HN(3)	110 (5)
O(1)-P-N(2)	103.0 (2)	P-N(3)-C(4)	118.0 (4)
O(2)-P-N(2)	116.2 (3)	N(3)-C(4)-C(5)	110.8 (5)
O(2)-P-N(3)	114.8 (3)	C(6)-C(5)-C(4)	109.6 (5)
N(3)-P-N(2)	107.4 (3)	C(5)-C(6)-O(1)	112.6 (4)
P-N(2)-C(2)	118.3 (4)	P-O(3)-C(6)	117.1 (3)
P-N(2)-C(1)	117.7 (4)	P-O(2)···HN(3)	138 (2)
C(1)-N(2)-C(2)	113.3 (5)	N(3)-HN(3)···O(2)	167 (7)

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

(3) (a) White, D. W.; Gibbs, D. E.; Verkade, J. G. *J. Am. Chem. Soc.* **1979**, *101*, 1937. (b) Egan, W.; Zon, G. *Tetrahedron Lett.* **1976**, 813.

(4) Certain examples of molecules of this type with R = H, alkyl, or Ph and Z mostly = ArO or RNH have been studied.[5] However, the favored conformations in these studies were not, in our estimation, always well assigned although the ^1H NMR parameters were carefully determined.

(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) (a) The conformational properties of 1,3,2-dioxaphosphorinanes have been comprehensively reviewed by: Maryanoff, B. E.; Hutchins, K. O.; Maryanoff, C. A. *Top. Phosphorus Chem.* **1979**, *11*, 187. For an earlier review, see: Verkade, J. G. *Phosphorus Sulfur* **1976**, *2*, 251. (b) An interesting contrast in a boat dioxaphosphorianane and a twist oxazaphosphorinane conformation was reported recently: Day, R. O.; Bentrude, W. G.; Yee, K. C.; Setzer, W. N.; Deiters, J. A.; Holmes, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 103. Bentrude, W. G.; Day, R. O.; Holmes, J. M.; Quin, G. S.; Setzer, W. N.; Sopchik, A. E.; Holmes, R. R. *Ibid.* **1984**, *106*, 106.

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

Table III. Ring Dihedral Angles for $(Me_2C_3H_4ONH)(Me_2N)PO$ (7)

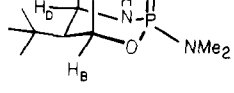
bond	angles, deg
O(1)-P	−46.0
P-N(3)	+45.9
N(3)-C(4)	−54.3
C(4)-C(5)	+56.8
C(5)-C(6)	−58.4
C(6)-O(1)	+56.5

for non-hydrogen atoms appear in Table I, and important bond lengths and angles are given in Table II. 1,3,2-Oxazaphosphorinane **7** is in the chair conformation with the dimethylamino group in the axial position. The atoms O(1), N(3), C(4), and C(6) are coplanar to within ±0.003 Å. The dihedral angle between this four-atom plane and the plane defined by P, O(1), and N(3) is 39.6°, while that between the plane defined by C(4), C(5), and C(6) and the same four-atom plane is 51.7°. In Table III are given the ring torsional angles, which also show the ring to be quite chairlike but with considerable flattening at the phosphorus end.

The geometry about the dimethylamino nitrogen atom, N(2), deviates considerably from planarity, the sum of the bond angles about N(2) being 349.3 (13)° compared to the tetrahedral sum of 328.4° or the planar sum of 360°. The P–N(2) bond length of 1.644 (5) Å is unusually long for an exocyclic dimethylamino group (see discussion below). It is interesting, as well, to compare it to the shorter endocyclic P–N(3) bond of 1.626 (5) Å.

There is evidence of NH···O=P intermolecular hydrogen bonding which results in chains of ring units in the lattice for **7**. The distance between HN(3) and O(2) for a glide-related molecule is 2.03 (7) Å as compared to the van der Waals sum of 2.6 Å.[8]

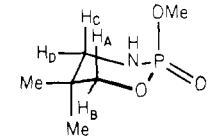
Solution Conformation of 7. The solution conformation of **7** was studied by high-field (300 MHz) ^1H NMR analysis along with IR spectroscopy. The NMR data for **7** and the structurally related compound, *trans*-5-*tert*-butyl-2-oxo-2-(dimethylamino)-1,3,2-oxazaphosphorinane (**14**)[7] appear in Table IV. The



14

proton–proton and proton–phosphorus coupling constants allow definitive conformational assignments to be made, since both $^3J_{HH}$ and $^3J_{HP}$ vary as a function of dihedral angle according to Karplus-like relationships.[9] Spectral parameters for **7** were determined at various concentrations and in different solvents as well to ascertain the roles of intramolecular H-bonding and solvent properties in controlling conformation.

It is clear from the data of Table IV that for **7** a *predominance* of one chair conformation is present in benzene (10% concentration). Thus J_{BP} (14.5 Hz) > J_{AP} (8.6 Hz), and J_{DP}(17.4 Hz) > J_{CP} (10.0 Hz). However, these differences are much greater for **14** which appears to be almost entirely in one conformation. The sums of $J_{AP} + J_{BP}$ for **7** and **14**, nonetheless, are nearly the same, as for those for $J_{CP} + J_{DP}$ as would be expected if $J_{AP}(ax) = J_{BP}(ax)$, $J_{AP}(eq) = J_{BP}(eq)$, $J_{CP}(ax) = J_{DP}(ax)$, and $J_{CP}(eq) = J_{DP}(eq)$. The cross-ring coupling constants, $^4J_{BD}$ for **7** and **14** of 1.8 and 2.0 Hz (C_6D_6), respectively, are sizeable because of the W arrangement of the equatorial hydrogens B and D in the conformation primarily populated. An estimate of the equilibrium **4** ⇄ **5** for **7** can be gained from a consideration of the time-averaged coupling constants. The 1,3,2-oxazaphosphorinane **15**, in benzene, is nearly entirely in one conformation, presumably that shown, because of the axial-seeking nature of the small electronegative methoxy group on phosphorus.[10] The values of J_{AP} (~1



15

Hz) and J_{BP} (21.0 Hz) for **15**,[11] therefore, provide reasonable estimates for the axial and equatorial hydrogen–phosphorus coupling constants for protons A and B of **4** and **5**. If one uses these numbers and expressions 1–4, it is readily estimated that 62–67% of one of the two conformations, **4** and **5**, is populated in the 10% solutions in C_6D_6. (N(4) and N(5) refer to mole fractions of the respective conformers.) By use of J_{CP} and J_{DP} for **7** and equations analogous to (1)–(4), a similar estimate of the population of the major conformer in the equilibrium **4** ⇄ **5**, 65–66%, is made.

$$N(4)J_{AP}(4) + N(5)J_{AP}(5) = J_{AP}(\text{obsd}) \quad (1)$$

$$N(5) = 1 - N(4) \quad (2)$$

therefore

$$N(4) = [J_{AP}(\text{obsd}) - J_{AP}(5)]/[J_{AP}(4) - J_{AP}(5)] \quad (3)$$

similarly, for J_{BP}

$$N(4) = [J_{BP}(\text{obsd}) - J_{BP}(5)]/[J_{BP}(4) - J_{BP}(5)] \quad (4)$$

The assignment of structure **4** rather than **5** to the major conformer is based upon IR spectroscopic analysis (Table V). The P=O stretching frequencies of certain 1,3,2-oxazaphosphorinanes have been correlated roughly with the axial or equatorial orientation of the phosphoryl oxygen.[12] *So long as the other substituents on phosphorus are the same*, the equatorial P=O normally has a higher stretching frequency than does the axial P=O.[5a,11] This correlation has been quite firmly established with 2-oxo-1,3,2-dioxaphosphorinanes.[6] As noted from Table V, the P=O stretching frequency of **7** is about 17 cm^{-1} greater than that of **14** in the solid phase and 15 cm^{-1} greater in solution in CCl_4. In $CDCl_3$ two peaks are present that appear to be assignable to the more intense equatorial (1229 cm^{-1}) and to the weaker axial (1212 cm^{-1}) absorptions. In further, yet unpublished, work,[11] we demonstrated a monotonic decrease in J_{BP} and J_{DP} and increase in J_{AP} and J_{CP} as the R_2N group size (Z of **4** and **5**) was systematically increased in the series of Me_2N, Et_2N, i-Pr_2N. This result is consistent with the above assignments to structures **4** and **5**.

Discussion

Conformation of 7 in Solution. The dimethylamino group on the phosphorus atom of 2-oxo- and 2-thio-1,3,2-dioxaphosphorinanes is a relatively large group sterically (conformational energy). It clearly has a strong preference for the equatorial position.[6] The equilibrium for **6** analogous to **4** ⇄ **5** in benzene features 85–90% of the conformer with Me_2N *equatorial*.[13] Therefore, the above results, which show a preference of the Me_2N of **7** for the *axial* position both in the crystal and in several solvents, mean that the *dimethylamino group is effectively a smaller substituent when attached to the phosphorus of a 2-oxo-1,3,2-oxazaphosphorinane that is unsubstituted at the ring nitrogen.* Hydrogen bonding between molecules of **7** in solution only secondarily affects the equilibrium **4** ⇄ **5**. Thus, progressive dilution from 10% to 1% in two solvents (Table IV) and addition of Me_2SO-d_6 to C_6D_6 solutions caused only small changes in hydrogen–phosphorus coupling constants. In $CDCl_3$ at 0.1% concentration, the intermolecular H-bonded NH stretching vibration

(8) Pauling, L. "The Nature of the Chemical Bond", 3rd ed.; Cornell University Press: Ithaca, NY, 1960; p 260.

(9) 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.

(10) This is well established for 2-oxo-1,3,2-oxazaphosphorinanes[6a] probably as the result of n–σ^* overlap between lone pair electrons on oxygen and the axial P–OCH_3 σ^* orbital. Because of the minimal steric bulk of the MeO, it is conceivable that it could be equatorial.

(11) Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G., unpublished work from this laboratory. Manuscript in preparation.

(12) Kinas, R.; Pankiewicz, K.; Stec, W. J.; Farmer, P. B.; Foster, A. B.; Jarman, M. J. *J. Org. Chem.* **1977**, *42*, 1650.

(13) Majoral, J. P.; Navech, J. *Bull. Soc. Chim. Fr.* **1971**, 95. Majoral, J.-P.; Bergonhou, C.; Navech, J. *Ibid.* **1973**, 3146.

Table IV. ^{1}H NMR Parameters for 7 and 14 at 300 MHz[a]

compd	solvent	concn, %[d]	δ[b] H_A	H_B	H_C	H_D	coupling constants, Hz J_{AB}	J_{AP}	J_{BP}	J_{BD}	J_{CD}	J_{CP}	J_{DP}
7	C_6D_6	10	3.54	3.69	2.64	2.83	−10.5	8.6	14.5	1.8	−12.6	10.0	17.8
7	C_6D_6	1	3.49	3.70	2.56	2.78	−10.8	9.6	13.6	1.8	−12.6	[c]	16.8
7	$CDCl_3$	10	3.78	3.92	2.86	2.97	−11.0	9.3	13.9	1.6	−12.7	12.0	16.2
7	$CDCl_3$	1	3.78	3.96	2.86	3.00	−11.1	10.0	13.1	1.4	−12.5	12.5	15.1
7	$CDCl_3$[f]	0.1	3.75	3.95	2.83	2.98	−11.4	10.7	12.7	1.2	−12.7	~12.5	14.2
7	C_6D_6-Me_2SO-d_6 (1:1)	1	3.65	3.75	2.72	2.81	−10.7	8.7	14.1	1.7	−12.4	10.5	16.6
14[e]	C_6D_6	1	4.24	3.99	3.14	2.92	−11.0	4.0	20.8	2.4	−11.0	5.4	22.0

[a] Ambient temperature, 26 °C. [b] ppm downfield from internal Me_4Si. δ and J values for the 5- and 5′-methyl groups and the Me_2N measured in $CDCl_3$ at 90 MHz are in the Experimental Section. [c] Obscured by Me_2N peak. [d] Weight/volume. [e] Values from ref 7. [f] Accuracy of couplings reduced by low signal/noise broadening at 0.1% concentration.

Table V. IR P=O Stretching Frequencies of 1,3,2-Oxazaphosphorinanes

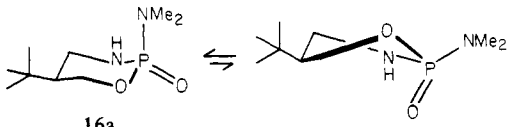
compd	frequency, cm^{-1} KBr	CCl_4	$CDCl_3$
7	1217	1235	1229.[a] 1212
14	1200	1220	1215

[a] More intense peak.

in the IR is virtually eliminated, but the population of **4** is still over 50%. Solvent polarity also is shown by the data of Table IV to have little or no effect on the **4** ⇄ **5** equilibrium.

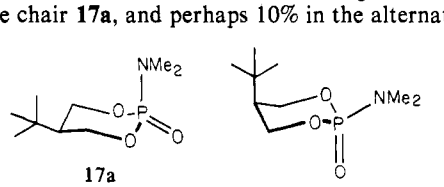
Though it is difficult to completely dissect all of the intra- and intermolecular interactions that contribute to the relative energies of various conformers of these two ring systems, at least part of the difference in conformational behavior may stem from the greater length of the endocyclic P–N bond compared to that of a P–O bond. This can result in a flattening of the ring about phosphorus and in turn an increase in the distance between the axial hydrogens on carbons 4 and 6 and the Me_2N on phosphorus, reducing 1,3-syn–axial repulsions and decreasing the effective steric size of Me_2N. This effect is clearly evident in comparisons of the N2-axial hydrogen internuclear distances of 2.874 (C(4) proton) and 2.714 Å (C(6) proton).

In an earlier study,[7] it was shown that *cis*-2-oxo-2-dimethylamino-5-*tert*-butyl-1,3,2-oxazaphosphorinane (**16**), exists predominantly in the chair conformation, **16a**. The twist conformer,



16a 16b

16b, was only about 25% populated. By contrast, in similar solvents, molecules of the corresponding 1,3,2-dioxaphosphorinane are about 60% in the twist conformation analogous to **16b**, about 30% in the chair **17a**, and perhaps 10% in the alternative chair



17a 17b

conformation with 5-*tert*-butyl axial, **17b**.[14] Whether the difference as to the extent of population of a twist conformation in the two ring systems was a result of decreased effective size of the Me_2N in the 1,3,2-oxazaphosphorinane series or a greater reluctance of that system to undergo the conversion to the twist conformation was not apparent. Indeed, the present results show the former to be true.

Moreover, it now may be readily shown, by using the approach outlined in detail in the earlier paper,[7] that the interconversion **8** ⇄ **9** costs less than 1 kcal/mol ($\Delta G°_{c\rightarrow t}$). Thus the free energy change to convert a chair conformation such as **8** with P=O axial into the twist conformation with P=O pseudoaxial (**9**) is *at least as low as it is for the corresponding 1,3,2-dioxaphosphorinane ring.*[15] The previous estimate for $\Delta G°_{c\rightarrow t}$ of 1.8 kcal/mol was made using the apparent ratio of **5**/**4** for Z = $N(CH_2CH_2Cl)$, i.e., the cyclophosphamide (**1**) case,[3a] in which the Z group is preferentialy equatorial (**5**/**4** ≃ 6[3a]), as an estimate of the steric size of Me_2N. The surprising difference in the effective steric sizes of the mustard and dimethylamino substituents on phosphorus may mean that factors other than 1,3-syn–axial van der Waals repulsions, perhaps electronic and stereoelectronic ones, also are important in determining effective steric size in these rings. A full discussion of the dissection that allows the value of $\Delta G°_{c\rightarrow t}$ for **8** → **9** (Z = Me_2N) to be established, as well as consideration of both steric and electronic effects on effective steric size, will be given in a later paper.[11]

X-ray Crystal Structure of 7. The structures of the 1,3,2-oxazaphosphorinanes **7**, **18**,[16] and *trans*-4-phenylcyclophosphamide[17] (Ph and mustard groups trans) provide the only examples of either 1,3,2-dioxa- or 1,3,2-oxazaphosphorinanes with an R_2N axial. The *trans*-4-phenylcyclophosphamide is conformationally biased by the 4-phenyl substituent. Otherwise, the $N(CH_2CH_2Cl)_2$ is equatorial as in the crystals of **1**,[18] **2**,[19] and **3**[20] as well as in those of 4-peroxy-,[21] 4-keto-,[22] and 4-hydroperoxycyclophosphamide.[23] Also equatorial are the piperidinyl group of **19**[24] and the Me_2N of **20**[25] (pseudoequatorial in a twist conformation). The results for **7** and **18** along with the ^{1}H NMR findings for **7** are consistent with the reduced effective steric size of the Me_2N when attached to phosphorus of a 1,3,2-oxazaphosphorinane system with an unsubstituted ring nitrogen rather than to a 1,3,2-dioxaphosphorinane ring. They also support further the view that Me_2N

(14) Bentrude, W. G.; Tan, H. W. *J. Am. Chem. Soc.* **1973**, *95*, 4666.

(15) The analogous chair → twist conformation has $\Delta G°$ of 1 kcal/mol or less. See ref 14. Also: Bentrude, W. G.; Hargis, J. H. *Chem. Commun.* **1969**, 1113. Bentrude, W. G.; Yee, K. C. *J. Chem. Soc., Chem. Commun.* **1972**, 169. Mosbo, J. A. *Org. Magn. Reson.* **1978**, *6*, 281.

(16) Newton, M. G.; Panteleo, N.; Bentrude, W. G.; Chandrasekaran, S. *Tetrahedron Lett.* **1982**, 1527.

(17) Boyd, V. L.; Zon, G.; Himes, V. L.; Stalick, J. K.; Mighell, A. D.; Secot, H. V. *J. Med. Chem.* **1980**, *23*, 372.

(18) Karle, I. L.; Karle, J. M.; Egan, W.; Zon, G.; Brandt, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 4803. Adamaik, D. A.; Saenger, W.; Kinas, R.; Stec, W. J. *Z. Naturforsch., C* **1977**, *32c*, 672. Clardy, J. C.; Mosbo, J. A.; Verkade, J. G. *Phosphorus Relat. Group V Elem.* **1974**, *4*, 151. Garcia-Blanco, S.; Perales, A. *Acta Crystallogr., Sect. B* **1972**, *28*, 2647.

(19) Brassfield, H. A.; Jacobson, R. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1975**, *97*, 4143. Perales, A.; Garcia-Blanco, S. *Acta Crystallogr., Sect. B* **1977**, *B33*, 1935.

(20) Camerman, A.; Smith, H. W.; Camerman, N. *Cancer Treat. Rep.* **1976**, *60*, 517. Brassfield, H. A.; Clardy, J. C.; Verkade, J. G. *Cryst. Struct. Commun.* **1976**, *5*, 417. Perales, A.; Garcia-Blanco, S. *Acta Crystallogr. Sect. B* **1977**, *B33*, 1939.

(21) Sternglanz, H.; Einspahr, H. M.; Bugg, C. E. *J. Am. Chem. Soc.* **1974**, *96*, 4014.

(22) Camerman, N.; Camerman, A. *J. Am. Chem. Soc.* **1973**, *95*, 5038.

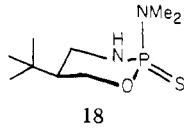
(23) Camerman, A.; Smith, H. W.; Camerman, N. *Acta Crystallogr., Sect. B* **1977**, *B33*, 678.

(24) Wagner, R. E.; Jensen, W.; Wadsworth, W.; Johnson, Q. *Acta Crystallogr., Sect. B* **1973**, *B29*, 2160.

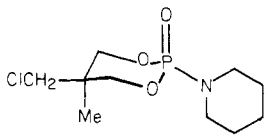
(25) Bajwa, G. S.; Bentrude, W. G.; Pantaleo, N. S.; Newton, M. G.; Hargis, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1602. And unpublished bond-length data.

as a 1,3,2-oxazaphosphorinane substitutent is smaller than is $N(CH_2CH_2Cl)_2$.

The 2-thio compound **18** was reported[16] to have a pyramidal configuration about the nitrogen of the axial Me_2N (bond angle sum of 345°). However, since it had also been reported that the



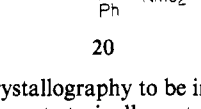
18



19

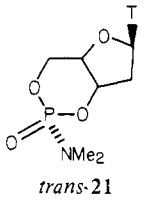
$N(CH_2CH_2Cl)_2$ of *trans*-4-phenylcyclophosphamide is nearly planar about the mustard nitrogen,[17] it was suggested[16] that the nature of the X atom of P=X might influence the degree of planarity about nitrogen for an axial R_2N. *The above results show that this is not an important factor where R_2N is Me_2N.*

The P–N bond length of the axial Me_2N of **7**, 1.644 (5) Å, is shorter than that of the P=S compound, **18**, 1.661 (2) Å (i.e., a difference of 3.16σ).[26] However, it seems more highly significant that the bonds are both *longer* than the 1.622 (3) Å *pseudoequatorial* P–NMe_2 bond of **20** (a difference of 3.77σ),[26] which

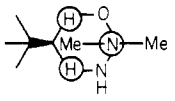


20

was found by X-ray crystallography to be in a twist conformation in the crystal.[25] When not sterically restricted, R_2N and P=X prefer a geometry with *trigonal planarity* about nitrogen and *coplanarity* between the P=X and the R_2N groups.[17-25,27,28] In six-membered rings this is always found for R_2N attached equatorially or pseudoequatorially to the tetracoordinate phosphorus atom of a 1,3,2-dioxa- or 1,3,2-oxazaphosphorinane, i.e., for **1**,[18] **2**,[19] **3**,[20] **18**,[16] **20**,[25] 4-keto,[22] 4-peroxy-,[21] *cis*-, and *trans*-4-hydroperoxycyclophosphamide,[23] **19**,[24] and *trans*-**21**.[29] The bond



trans-21



22

shortening and planar $R_2N/P{=}X$ geometry have been ascribed to π-bonding effects involving an interaction of the nitrogen p-orbital with either a phosphorus d orbital[30,31] or a phosphorus-substituent σ^* orbital.[28,32]

In **7** (and also **18**), however, such an optimal geometry is highly disfavored energetically because the resultant plane of the Me_2N group would bisect the ring and bring one of the methyl groups into close contact with the axial hydrogens at C(4) and C(6) (structure **21**) resulting in repulsive steric interactions. In the structure of Figure 1, the Me_2N and P=O are essentially orthogonal. *Optimal geometry about the P–N bond is lost leading to P–N bond lengthening and loss of planarity about nitrogen.* Changes in bond lengths and nitrogen planarity as a function of P–N torsional angle have previously been observed in the X-ray crystal structures of the noncyclic trimorpholino-, tripiperidino-, and tris(dimethylamino)phosphine selenides.[27] A deviation from planarity about nitrogen has been observed in $Me_2NP(O)Ph_2$.[33] Long P–N bonds occur as well in *trans*-2-(*tert*-butylamino)-2-seleno-4-methyl-1,3,2-dioxaphosphorinanes[34] and in 5,5-dimethyl-2-oxo-2-(phenylamino)-1,3,2-dioxaphosphorinane,[35] both of which have axial alkylamino groups. However, *the combination of both of these effects in cyclic molecules is seen for the first time with **7** and **18**.*

Finally, it is worth noting two other bond length comparisons. As mentioned earlier, the axial Me_2N of **18** is longer than that of **7**. This may reflect the difference in electronegativities of oxygen and sulfur in P=S and P=O. More electronegative substituents on phosphorus have previously been pointed out as being bond shortening.[28] The relatively shorter length of the endocyclic P–N(3) of **7**, 1.626 (5) Å, is consistent with the fact that the $CH_2N(3)H/P{=}O$ bonding system is close to coplanar in **7** as the result of the P=O being equatorial. The same ordering of the endocyclic (1.632 (2) Å) and exocyclic (1.661 (2) Å) P–N bonds was seen for **18**.[16] Although the phenyl substituent may have some effect, it seems significant that by contrast for **20**[25] the exocyclic P–N (1.622 (3) Å) is shorter than the endocyclic one (1.661 (2) Å). The latter is considerably longer than the endocyclic P–N bonds of either **7** or **18**.

Experimental Section

Methods and Materials. Analyses were carried out by Atlantic Microlab, Inc., Atlanta, GA, and Galbraith Laboratories, Inc., Knoxville, TN. Melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 298 spectrophotometer. ^1H 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 were measured at 300 MHz on 100-SW 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 ppm downfield from external 85% H_3PO_4. The mass spectrometer used was a VG Micromass 7070 Double Focusing High Resolution instrument with VG Data System 2000 in the EI mode, direct inlet sampling. FT-IR work was done on a Nicollet 7199 instrument.

X-ray Single-Crystal Structure Study of 7. Clear colorless crystals of **7** were obtained by vapor diffusion mixing of a solution of the compound in ethyl acetate with pentane. A well-formed crystal, sealed in a thin-walled glass capillary as a precaution against moisture sensitivity, was mounted on an Enraf-Nonius CAD4 diffractometer equipped with graphite-monochromated Mo Kα radiation ($\lambda(K\alpha_1) = 0.70930$, $\lambda(K\alpha_2) = 0.71359$ Å) at an ambient temperature of 23 ± 2 °C. The details of the experimental and computational procedures have been described previously.[36]

A colorless crystal was used, 0.18 × 0.29 × 0.35 mm, space group *Pbca* [D_{2h}^{15}, No. 61],[37] $a = 7.409$ (2) Å, $b = 12.180$ (2) Å, $c = 21.912$ (4) Å, $Z = 8$, and $\mu_{MoK\alpha} = 0.250$ mm^{-1}. 1735 independent reflections ($+h$, $+k$, $+l$) were measured by using the θ–2θ scan mode for $2° \leq 2\theta_{MoK\alpha} \leq 50°$. No corrections were made for absorption.

The structure was solved using a combination of direct methods (MULTAN) and Fourier difference techniques and was refined by full-matrix least squares.[38] The 12 independent non-hydrogen atoms were refined anisotropically. Coordinates for the 17 independent hydrogen atoms were obtained by a combination of difference Fourier techniques and calculation. Only the coordinates of HN(3), initially obtained from a difference Fourier, were refined. Calculated H atom coordinates were updated as refinement converged so that the final C–H bond lengths were 0.98 Å. Isotropic thermal parameters were fixed at 5 Å^2 for all H atoms. The final agreement factors[39] were $R = 0.061$ and

(26) Stout, G. H.; Jensen, L. H. "X-ray Structure Determination", Macmillan: New York, 1968; p 419–421. These differences correspond to >99% and probability >99.9%, respectively, that the bond lengths are different.
(27) Romming, C.; Songstad, *Acta Crystallogr., Sect A* **1979**, *A33*, 187.
(28) Paxton, K.; Hamor, T. A. *J. Chem. Soc., Dalton Trans.* **1978**, 647.
(29) Newton, M. G.; Pantaleo, N. S.; Bajwa, G. S.; Bentrude, W. G. *Tetrahedron Lett.* **1977**, 4457.
(30) Craig, D. P.; Paddock, N. L. *J. Chem. Soc.* **1962**, 4118. Paddock, N. L. *Quart. Rev.* **1964**, *18*, 168.
(31) Cowley, A. H.; Dewar, M. J. S.; Jackson, W. R.; Jennings, W. B. *J. Am. Chem. Soc.* **1970**, *92*, 5206.
(32) Burdon, J.; Hotchkiss, J. C.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 2*, **1976**, 1052.
(33) Mazur-ul-Haque; Caughlan, C. N. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1101.
(34) Bartczak, T. J.; Christensen, A.; Kinas, R.; Stec, W. J. *Cryst. Struct. Commun.* **1976**, *5*, 21.
(35) Cameron, T. S.; Goldecki, Z.; Karolak-Wojeichonska, J. *Acta Crystallogr., Sect. B* **1976**, *B32*, 492.
(36) Sau, A. C.; Day, R. O.; Holmes, R. R. *Inorg. Chem.* **1981**, *20*, 3076.
(37) "International Tables for X-ray Crystallography"; Kynoch Press: Birmingham, England, 1969; Vol. I, p 150.
(38) 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 37, Vol. IV, 1974, pp 72–98. Real and imaginary dispersion corrections for O and P were taken from the same source, pp 149–150.

R_w = 0.075 for the 1055 reflections having $I \geq 2\sigma(I)$.

2-(Dimethylamino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane (7). A solution of $Me_2NP(O)Cl_2$[40] (9.72 g, 60 mmol) in anhydrous ethyl acetate (25 mL) was added slowly to a rapidly stirred solution of 2-(hydroxymethyl)-2-methylpropylamine (6.19 g, 60 mmol) and triethylamine (15.9 mL, 12.1 g, 120 mmol) in anhydrous ethyl acetate (100 mL), cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 5 days. The triethylamine hydrochloride was filtered off and the solvents removed from the filtrate to give 7.80 g of the crude product. A 2.73-g sample of the product so obtained was distilled from bulb to bulb with an air-bath temperature of 145 °C at 0.50 torr to give 1.31 g (35% yield) of 2-(dimethylamino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane (**7**) as a colorless crystalline solid: mp 110–111 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.94 (s, 3 H, CCH_3), 1.06 (s, 3 H, CCH_3), 2.73 (d, J_{HP} = 12 Hz, 6 H, Me_2N), 2.8–3.1 (m, 2 H, CH_2N), 3.7–4.1 (m, 2 H, CH_2O); ^{31}P NMR (CD_3COCD_3) δ 11.76; IR (KBr) 3240, 2960, 2880, 1475, 1387, 1324, 1303, 1284, 1217 (s, P=O), 1180, 1090, 1038, 1005, 975, 957, 870, 807, 783, 688 cm^{-1}; mass spectrum, *m/e* 192 (38%, M^+), 137 (100%), 108 (32%), 107 (17%). Anal. Calcd for $C_7H_{17}N_2O_2P$: C, 43.74; H, 8.92; P, 16.11. Found: C, 43.63; H, 8.96;, P, 16.09.

2-Carboethoxy-2-methylpropionic Acid (11). Diethyl dimethylmalonate (**10**) (100 g, 0.515 mol) was added to a solution of potassium hydroxide (34.0 g, 0.515 mol) in ethanol (250 mL). The reaction mixture was refluxed for 4 h, and the ethanol was removed by rotary evaporation. The residue was taken up in water and washed with ethyl ether (3 × 100 mL). The aqueous phase was acidified at 0 °C with 10% aqueous HCl and extracted with ether (3 × 100 mL). The ether layers were combined and the ether removed by rotary evaporation. Residual H_2O was removed by azeotropic distillation of benzene. The residual solvents were removed in vacuo to give 83.1 g (quantitative yield) of crude 2-carboethoxy-2-methylpropionic acid as a clear colorless liquid, which was used without further purification: ^{1}H NMR (90 MHz, neat) δ 1.20 (t, 3 H, $CO_2CH_2CH_3$), 1.39 (s, 6 H, $C(CH_3)_2$), 4.24 (q, 2 H, $CO_2CH_2CH_3$), 11.80 (s, 1 H, CO_2H); IR (neat film) 3300–3000 (O–H), 2988, 2940, 1755–1695 (C=O), 1470, 1410, 1389, 1368, 1300–1255, 1190–1130, 1027, 862 cm^{-1}.

2-Carboethoxy-2-methylpropionamide (12). A mixture of 2-carboethoxy-2-methylpropionic acid (**11** (83.1 g, 0.515 mol) and thionyl chloride (55 mL, 90 g, 0.75 mol) was refluxed for 1 h. The excess thionyl chloride was removed in vacuo, and the yellow residue was taken up in ethyl ether (500 mL). Anhydrous ammonia was bubbled through the reaction mixture at room temperature until no more precipitate formed. The reaction mixture was filtered and the filtrate washed with water (3 × 150 mL). The ether layer was dried over anhydrous $MgSO_4$. Evaporation of the ether left a pale yellow crystalline solid, which was recrystallized from ether/pentane to give 21.3 g (25.9% yield) of 2-carboethoxy-2-methylpropionamide (**12**) as a colorless crystalline solid: mp 65–66 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3 H, $CO_2CH_2CH_3$), 1.45 (s, 6 H, $(CH_3)_2C$), 4.20 (q, 2 H, $CO_2CH_2CH_3$), 6.60 (broad, 2 H, NH_2); IR (KBr) 3400 (s, N–H), 3320, 3200, 2990, 1717 (s), 1690, 1670 (s), 1635, 1470, 1460, 1446, 1402, 1390, 1370, 1362, 1300, 1268, 1190, 1160, 1150, 1114, 1030. Anal. Calcd for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.76; H, 8.27; N, 8.80.

2-(Hydroxymethyl)-2-methylpropylamine (13). A solution of 2-carboethoxy-2-methylpropionamide (**12**) (15.6 g, 100 mmol) in anhydrous ethyl ether (300 mL) was added slowly to a rapidly stirred suspension of lithium aluminum hydride (11.4 g, 300 mmol) in ethyl ether (300 mL). The reaction mixture was heated at gentle reflux for 24 h. The reaction mixture was then cooled to 0 °C and quenched with a mixture of ethyl ether (300 mL) and water (24.9 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Anhydrous magnesium sulfate (ca. 40 g) was added and stirring continued for 15 min. The reaction mixture was filtered and the solids washed with ethyl ether (4×). The ether was removed from the filtrate by rotary evaporation. The residue was distilled from bulb to bulb with an air-bath temperature of 45 °C at 0.05 torr to give 8.45 g (81.9% yield) of 2-hydroxymethyl-2-methylpropylamine as a colorless crystalline solid: mp 98–100 °C (lit.[41] mp 98–100 °C); ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.87 (s, 6 H, $C(CH_3)_2$), 2.70 (s, 2 H CH_2NH_2), 2.97 (s, 2 H, CH_2OH), 3.48 (s, 2 H, CH_2NH_2); IR (neat film) 3500–3000 (O–H, N–H), 2950, 2870, 1600, 1475, 1392, 1364, 1140, 1053 (s), 963–940 cm^{-1}.

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Registry No. **7**, 88946-46-7; **10**, 1619-62-1; **11**, 5471-77-2; **12**, 81891-82-9; **13**, 26734-09-8; $Me_2NP(O)Cl_2$, 677-43-0.

Supplementary Material Available: Thermal parameters (Table A), fixed hydrogen atom parameters (Table B), and a listing of observed and calculated structure factor amplitudes for **7** (6 pages). Ordering information is given on any current masthead page.

(39) $R = \sum||F_o| - |F_c||/\sum|F_o|$, $R_w = \{\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2\}^{1/2}$.
(40) Walsh, E. N.; Toy, A. D. F. *Inorg. Synth.* **1963**, *7*, 69.
(41) Cook, M. J.; Jones, R. A. Y.; Katritzky, A. R.; Manas, M. M.; Richards, A. C.; Sparrow, A. J.; Trepanier, D. L. *J. Chem. Soc., Perkin Trans. 2* **1973**, 325.