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NON-PLANAR AXIAL Me_2N IN CIS-2-DIMETHYLAMINO-2-THIO-5-t-BUTYL-1,3,2-OXAZAPHOSPHORINANE

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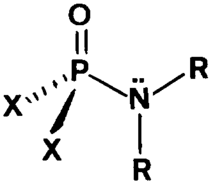
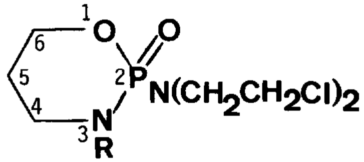
Summary: An X-ray crystallographic study of the title compound shows it to have an axial Me_2N with pyramidal N and a lengthened N-P bond. Conversely, the endocyclic NH-P bond is shortened. The origins of these effects are assigned to specific geometrical relationships of the Me_2N/P=S and NH/P=S groupings imposed by the ring system.

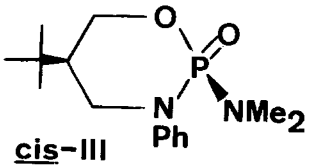
The dialkylamino group, when attached to phosphoryl phosphorus (P=O), generally displays very nearly trigonal planarity about nitrogen and coplanarity of the P=O and R_2N as in I. Typical examples in cyclic systems include X-ray crystallographic structures of: cyclophosphamide, II (R = H);[1] trophosphamide, II (R = CH_2CH_2Cl);[2] 4-ketocyclophosphamide;[3] 4-hydroperoxycyclophosphamide;[4] 4-peroxycyclophosphamide;[5] cis-III (t-Bu and Me_2N cis);[6] trans-IV (Me_2N and thymidyl groups trans);[7] and 2-piperidino-2-oxo-5-methyl-5-chloromethyl-1,3,2-dioxaphosphorinane.[8] In all of these cases, the R_2N is equatorially substituted on a chair-form ring except for III which has, nonetheless, Me_2N pseudoequatorially attached to a twist-form ring. Geometry I apparently reflects optimization of stereoelectronic interactions, perhaps including p-d π bonding.



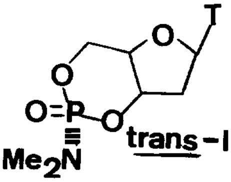
I



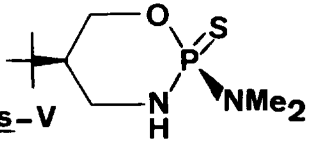
II



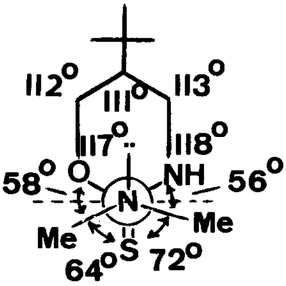
cis-III



trans-IV



cis-V

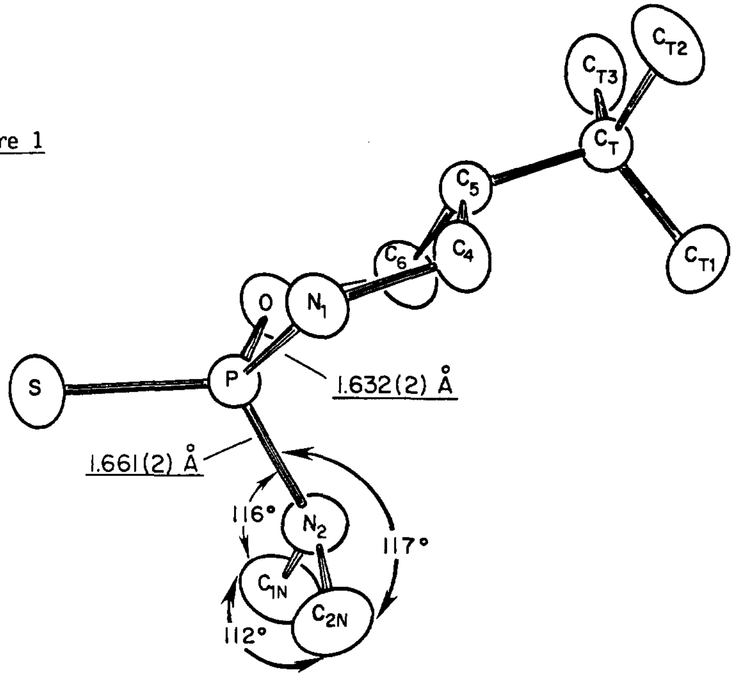


VI

We report here an X-ray crystallographic study of a closely related molecule, *cis*-V. This case represents a test of such P-N bonding ideas in that it has the Me_2N axial where it is not necessarily free to assume the optimal geometry.

Cis-V crystallized in monoclinic space group $P2_1/c$ with a = 9.929(2), b = 12.190(4), c = 10.968(4) Å, and β = 107.32(4)°. In all, 2389 unique non-zero reflections were obtained from measurements on an Enraf-Nonius CAD-4 diffractometer using Cu $K\bar{\alpha}$ radiation and a graphite monochromator. MULTAN direct methods yielded the structure at an R = 5.1% least squares refinement level. An ORTEP diagram of *cis*-V is presented in Figure 1. The respective axial and equatorial positions of the Me_2N and *t*-Bu on the chair-form ring are clearly depicted. The Me_2N is seen to have undergone rotation about the P-N bond so as to minimize 1,3-synaxial steric repulsions with the axial ring hydrogens. The potential for Me_2N/P=S coplanarity and accompanying energetic stabilization is thereby lost. *The obvious result is a pyramidal geometry for the Me_2N.* The bond angles about nitrogen sum to 345°, a significant deviation from planarity.[9] Structure VI is a Newman projection

Figure 1



showing the ring angles and, more importantly, the torsional angles about the P-N_2 bond. Clearly evident is the pyramidal Me_2N geometry. The Me on the NH side of the ring is seen to be rotated 8° away from the P=S bond. This is consistent with the flattening of the ring at N which moves the axial H at C_6 further away from the Me_2N than the one at C_4.

Another important feature of the *cis*-V structure is the *lengthened exocyclic P-N_2 bond* (1.651(2) Å) compared to the values for the 1,3,2-oxazaphosphorinanes listed in Table 1 (average 1.625(2)). In all of the latter, selected because of their relatively low estimated standard deviations, the amine group is equatorial. The longer P-N_2 (exocyclic) bond of *cis*-V apparently

Table 1. Phosphorus-Nitrogen Bond Lengths in 1,3,2-Oxazaphosphorinanes

Compound	P-N Bond Length (Å) Exocyclic	P-N Bond Length (Å) Endocyclic	Ref.
Cyclophosphamide	1.623(5)[a]	1.623(5)[a]	1c
Isophosphamide	1.631(6)	1.651(6)	14
Trophosphamide	1.627(9)	1.656(5)	2
4-Ketocyclophosphamide	1.628(5)	1.668(5)	3
4-Hydroperoxycyclophosphamide	1.624(6)	1.644(6)	4
cis-III	1.622(3)	1.661(2)	6
	avg. 1.625(2)[b]	1.651(6)[b]	

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[a] Estimated standard deviations [b] Standard deviation in average

reflects the lack of P=S/Me_2N coplanarity, as does the pyramidal configuration about N_2 (vide supra).[10,13] The shortening of the equatorial P-N bond appears to be independent of the nature of the other groups bonded to phosphorus as 2-thio-diisopropylamino-1,3,2-dithiaphosphorinane has an exocyclic, equatorial bond length of 1.627(4) Å and features coplanarity of the axial P=S and equatorial $isoPr_2N$ moieties. Similarly, the equatorial, exocyclic P-N bond length of 2-piperidino-2-oxo-5-methyl-5-chloromethyl-1,3,2-dioxaphosphorinane[8] (1.613(6) Å) is in the range of those in Table 1. Furthermore, the endocyclic P-N_1 bond length in cis-V (1.632(2) Å) is shorter than the exocyclic P-N_2 bond (1.661(2)). Since the P=S moiety is equatorial in cis-V, the N_1H and lone pair geometries are optimized with respect to favorable bond-shortening interactions with the P=S and associated groups. Moreover, the value 1.632(2) Å is near the low end of the range of endocyclic P-N bond lengths given in Table 1. (The 4-substituent may perturb these bond lengths, however.) Also notable is the reversal in relative P-N bond lengths in cis-III and 4-ketocyclophosphamide (endo>exo) compared to cis-IV (exo>endo).

Finally, it is obvious that the axial, pyramidal Me_2N in cis-V has likely sacrificed a significant amount of stabilization energy compared to its trigonal-planar, equatorial counterpart. This is in addition to repulsive 1,3-synaxial interactions experienced by the axial Me_2N. Both factors probably contribute to the relatively large steric "size" of Me_2N.[15,16]

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