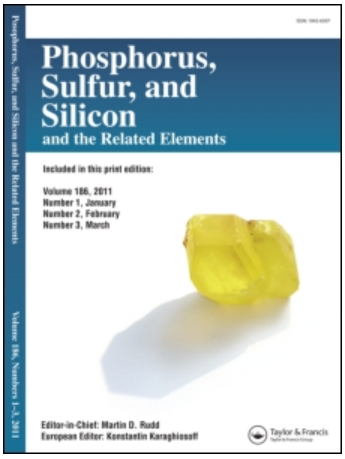



**Phosphorus, Sulfur, and Silicon and the Related Elements**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

# CRYSTAL AND MOLECULAR STRUCTURE OF 2-OXO-BIS(2-β-CHLOROETHYLAMINO)-4,6-DIMETHYL-1,3,2-OXAZAPHOSPHORINANE: AN ANALOGUE OF CYCLOPHOSPHAMIDE

L. E. Carpenter Ii[a]; D. Powell[a]; R. A. Jacobson[a]; J. G. Verkade[a]
[a] Gilman Hall and the Ames Laboratory of the DOE, Iowa State University, Ames, Iowa

**To cite this Article** Carpenter Ii, L. E. , Powell, D. , Jacobson, R. A. and Verkade, J. G.(1982) 'CRYSTAL AND MOLECULAR STRUCTURE OF 2-OXO-BIS(2-β-CHLOROETHYLAMINO)-4,6-DIMETHYL-1,3,2-OXAZAPHOSPHORINANE: AN ANALOGUE OF CYCLOPHOSPHAMIDE', Phosphorus, Sulfur, and Silicon and the Related Elements, 12: 3, 287 — 293
**To link to this Article: DOI:** 10.1080/03086648208078961
**URL:** http://dx.doi.org/10.1080/03086648208078961

*Phosphorus and Sulfur*, 1982, Vol. 12, pp. 287–293
0308-664X/82/1203–0287/$06.50/0



# CRYSTAL AND MOLECULAR STRUCTURE OF 2-OXO-BIS(2-β-CHLOROETHYLAMINO)-4,6-DIMETHYL-1,3,2-OXAZAPHOSPHORINANE: AN ANALOGUE OF CYCLOPHOSPHAMIDE

L. E. CARPENTER II, D. POWELL, R. A. JACOBSON and J. G. VERKADE*

*Gilman Hall and the Ames Laboratory of the DOE,*
*Iowa State University, Ames, Iowa 50011*

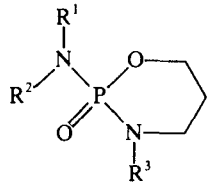
(*Received May 29, 1981; in final form October 25, 1981*)

The isomer of the title compound chosen for determination of its crystal and molecular structure by x-ray means has been found to possess an axial mustard group and an equatorial phosphoryl oxygen. This contrasts the phosphorus stereochemistry in cyclophosphamide in which these groups are interchanged. As a consequence of forcing the mustard group into the axial position in the title compound, the $C_2N$ plane of this moiety is positioned such that neither of the pendant $ClCH_2CH_2$ groups are under the ring. The rotomeric conformation of this group differs from that in cyclophosphamide wherein the mustard $C_2N$ plane is perpendicular to the OPN plane in the ring.



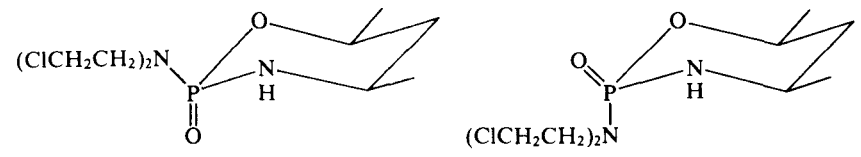
## INTRODUCTION

Phosphamides of the type **1–4** are very effective antitumor agents.[1] In order to gain insight into the metabolic pathways taken by these systems, a large number of studies have been directed at understanding their stereochemical behavior in the solid



| | | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|
| **1** | cyclophosphamide | $CH_2CH_2Cl$ | $CH_2CH_2Cl$ | H |
| **2** | isophosphamide | $CH_2CH_2Cl$ | H | $CH_2CH_2Cl$ |
| **3** | triphosphamide | $CH_2CH_2Cl$ | $CH_2CH_2Cl$ | $CH_2CH_2Cl$ |
| **4** | sulfophosphamide | $CH_2CH_2OSO_2Me$ | H | $CH_2CH_2Cl$ |

state and in solution.[1-6] As part of the latter investigations on cyclophosphamide (**1**), we compared several solution spectroscopic properties of **5a** and **5b** which are rigid analogues of the chair forms of **1** and concluded that **1** tends to exist in a chair



**5a** **5b**

conformer having an axial O=P group.[6] A key assumption in that study was the stereochemistry at phosphorus as shown for **5a** and **5b**. At that time, only prelimi-

* Author to whom all correspondence should be addressed.

nary results for the stereochemistry of **5b** determined by x-ray diffraction were available and we report here the completed crystal and molecular determination.

## EXPERIMENTAL

Compound **5b** was prepared as described earlier[6] and recrystallized from ethyl acetate/Skelly B. A crystal (~0.3 mm × 0.1 mm × 0.1 mm) was removed from a cluster of needles and mounted on a glass fiber. The crystal was found to be monoclinic with $a = 11.11(2)$, $b = 7.808(3)$, $c = 16.88(3)$Å and $\beta = 105.3(3)°$ with four molecules per unit cell. A density of 1.29 g/cm$^3$ was calculated based on a unit cell volume of 1413(2)Å.$^3$ Systematic extinctions ($0k0$, $k = 2n + 1$; $h\,l$, $h + l = 2n + 1$) indicated space group $P_{2_1/n}$ which was confirmed by subsequent solution and refinement of the structure.

Using an automated four-circle diffractometer, designed and built in the Ames Laboratory, equipped with scintillation counter and interfaced to a PDP-15 computer, data were collected at room temperature with graphite-monochromated Mo $K_\alpha$ radiation ($\lambda = 0.70954$Å) employing a procedure previously described.[7] Four octants were examined within a sphere $2\theta < 45°$ yielding 4284 measured intensities. During data collection the intensities of three standard reflections were monitored every 75 reflections to check for instrument and crystal stability. Whenever a significant drop in the intensity of one or more reflections was observed, all three of the reflections were relocated and their integrated intensities redetermined. A 25% decay in standard intensities was found when data collection was completed. All intensities were corrected for decay through a least squares fitting of a third order polynomial to the measured standard intensity sum as a function of reflection count. After decay correction, the corrections for Lorentz-polarization effects and averaging of equivalent data yielded 1359 observed reflections

TABLE I

Final atomic and positional parameters

| | *x* | *y* | *z* |
|---|---|---|---|
| $Cl_1$ | 0.0509(3) | 0.2555(4) | 0.4654(2) |
| $Cl_2$ | −0.1697(5) | 0.8356(8) | 0.2653(5) |
| P | 0.1017(2) | 0.5531(2) | 0.2006(1) |
| N1 | 0.0604(6) | 0.5866(8) | 0.2866(4) |
| N2 | 0.1039(6) | 0.3482(8) | 0.1855(4) |
| O1 | 0.2185(5) | 0.6442(8) | 0.2017(3) |
| O2 | −0.0050(5) | 0.6227(6) | 0.1267(3) |
| C1 | −0.1224(8) | 0.525(1) | 0.1055(6) |
| C2 | −0.0081(8) | 0.250(1) | 0.1424(5) |
| C3 | −0.0953(9) | 0.353(1) | 0.0763(5) |
| C4 | −0.2102(9) | 0.629(1) | 0.0393(7) |
| C5 | 0.041(1) | 0.083(1) | 0.1092(6) |
| C6 | 0.016(1) | 0.455(1) | 0.3365(6) |
| C7 | 0.117(1) | 0.394(1) | 0.4015(7) |
| C8 | 0.074(1) | 0.762(1) | 0.3239(7) |
| C9 | −0.027(2) | 0.867(2) | 0.309(1) |
| H—$C_1$ | −0.1562 | 0.5343 | 0.164 |
| H—$C_2$ | −0.0468 | 0.2156 | 0.180 |
| H1—$C_3$ | −0.0312 | 0.3562 | 0.022 |
| H2—$C_3$ | −0.1562 | 0.2656 | 0.039 |
| H1—$C_4$ | −0.2406 | 0.7656 | 0.063 |
| H2—$C_4$ | 0.8310 | 0.6560 | −0.028 |
| H3—$C_4$ | 0.7029 | 0.5940 | 0.023 |
| H1—$C_5$ | 0.1090 | 0.0310 | 0.164 |
| H2—$C_5$ | −0.0218 | 0.0053 | 0.071 |
| H3—$C_5$ | 0.0000 | 0.1090 | 0.094 |
| H1—$C_6$ | −0.0781 | 0.5156 | 0.352 |
| H2—$C_6$ | −0.0156 | 0.3906 | 0.297 |
| H1—$C_7$ | 0.1406 | 0.5187 | 0.438 |
| H1—$C_8$ | 0.1093 | 0.8281 | 0.273 |
| H1—$C_9$ | −0.0937 | 1.0031 | 0.320 |
| H—$N_2$ | 0.156 | 0.328 | 0.219 |

TABLE II

Final thermal parameters[a]

| | $\beta(1,1)$ | $\beta(2,2)$ | $\beta(3,3)$ | $\beta(1,2)$ | $\beta(1,3)$ | $\beta(2,3)$ |
|---|---|---|---|---|---|---|
| $Cl_1$ | 0.0253(5) | 0.048(1) | 0.0081(1) | 0.0063(5) | 0.0061(2) | 0.0084(3) |
| $Cl_2$ | 0.0262(7) | 0.077(2) | 0.0291(7) | 0.015(1) | 0.0066(6) | −0.016(1) |
| P | 0.0112(2) | 0.0174(4) | 0.0042(1) | −0.0005(2) | 0.0012(1) | −0.0002(1) |
| $N_1$ | 0.0149(8) | 0.019(1) | 0.0051(3) | −0.0022(9) | 0.0039(4) | −0.0007(5) |
| $N_2$ | 0.0112(7) | 0.016(1) | 0.0048(3) | −0.0015(8) | 0.0014(4) | −0.0016(5) |
| $O_1$ | 0.0104(6) | 0.027(1) | 0.0064(3) | −0.0052(8) | 0.0018(3) | −0.0019(5) |
| $O_2$ | 0.0116(6) | 0.020(1) | 0.0053(2) | −0.0002(7) | 0.0001(3) | 0.0018(4) |
| $C_1$ | 0.010(1) | 0.032(2) | 0.0055(4) | −0.002(1) | −0.0002(5) | 0.0022(9) |
| $C_2$ | 0.015(1) | 0.020(1) | 0.0045(4) | −0.003(1) | 0.0029(6) | −0.0012(7) |
| $C_3$ | 0.014(1) | 0.026(2) | 0.0043(4) | −0.004(1) | −0.0000(5) | 0.0006(8) |
| $C_4$ | 0.010(1) | 0.039(3) | 0.0088(7) | 0.000(1) | −0.0001(7) | 0.005(1) |
| $C_5$ | 0.024(1) | 0.024(2) | 0.0072(6) | −0.003(1) | −0.0004(8) | −0.0054(9) |
| $C_6$ | 0.017(1) | 0.030(2) | 0.0055(5) | −0.000(1) | 0.0015(7) | −0.0021(9) |
| $C_7$ | 0.019(1) | 0.037(3) | 0.0063(5) | 0.001(1) | 0.0015(8) | 0.001(1) |
| $C_8$ | 0.023(1) | 0.024(2) | 0.0096(7) | −0.001(1) | 0.006(1) | 0.001(1) |
| $C_9$ | 0.035(3) | 0.041(4) | 0.022(2) | 0.003(3) | −0.004(2) | −0.006(2) |

[a] The $\beta_{ij}$ are defined by: $T = \exp\{-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})\}$. The isotropic temperature factors for all hydrogen atoms were set equal to 5.0 Å.[2]

($F_0 \geq 3\sigma F_0$). Due to the small size of $\mu$ (5.4 $cm^{-1}$), no absorption correction was deemed necessary. Lattice constants were obtained by a least squares refinement of the precise $\pm 2\theta$ ($|2\theta| > 25°$) measurements of 12 strong independent reflections.

The program MULTAN[8] was used to locate the position of the phosphorus atom. The remaining non-hydrogen atomic positions were subsequently obtained from electron density maps.[7] Anisotropic refine-

TABLE III

Intramolecular bond distances (Å) and angles (°)

| | | | |
|---|---|---|---|
| P—$O_1$ | 1.475(6) | $C_6$—$H_1C_6$ | 1.23 |
| P—$O_2$ | 1.573(7) | $C_6$—$H_2C_6$ | 0.84 |
| P—$N_1$ | 1.654(8) | $C_7$—$H_1C_7$ | 1.14 |
| P—$N_2$ | 1.621(9) | $C_8$—$H_1C_8$ | 1.15 |
| $N_2$—$C_2$ | 1.48(1) | $C_9$—$H_1C_9$ | 1.33 |
| $O_2$—$C_1$ | 1.47(1) | $O_1$—P—$O_2$ | 108.63(37) |
| $C_1$—$C_3$ | 1.48(1) | $O_1$—P—$N_2$ | 115.35(39) |
| $C_1$—$C_4$ | 1.51(1) | $O_1$—P—$N_1$ | 111.05(39) |
| $C_2$—$C_3$ | 1.50(1) | $N_1$—P—$N_2$ | 108.25(35) |
| $C_2$—$C_5$ | 1.57(1) | $N_1$—P—$O_2$ | 108.39(36) |
| $N_1$—$C_6$ | 1.49(1) | $N_2$—P—$O_2$ | 104.82(31) |
| $N_1$—$C_8$ | 1.50(1) | P—$N_1$—$C_6$ | 126.55(58) |
| $C_6$—$C_7$ | 1.43(1) | P—$N_1$—$C_8$ | 119.51(65) |
| $C_8$—$C_9$ | 1.35(2) | P—$N_2$—$C_2$ | 122.91(53) |
| $C_7$—$Cl_1$ | 1.81(1) | P—$O_2$—$C_1$ | 116.59(52) |
| $C_9$—$Cl_2$ | 1.58(2) | $N_2$—$C_2$—$C_3$ | 112.41(70) |
| | | $N_2$—$C_2$—$C_5$ | 106.22(72) |
| | | $O_2$—$C_1$—$C_3$ | 107.74(75) |
| | | $O_2$—$C_1$—$C_4$ | 105.00(71) |
| | | $C_1$—$C_3$—$C_2$ | 112.59(70) |
| | | $C_5$—$C_2$—$C_3$ | 113.29(71) |
| | | $C_4$—$C_1$—$C_3$ | 112.80(77) |
| | | $C_6$—$N_1$—$C_8$ | 113.83(78) |
| | | $N_1$—$C_6$—$C_7$ | 110.70(86) |
| | | $N_1$—$C_8$—$C_9$ | 119.16(1.01) |
| | | $C_6$—$C_7$—$C_{11}$ | 107.24(80) |
| | | $C_8$—$C_9$—$C_{12}$ | 132.08(1.22) |

TABLE IV

Torsional[a] and interplanar angles (°)

| | | | |
|---|---|---|---|
| $O_1$—P—$N_2$—$C_1$ | −148.4 | $O_2$—P—$N_2$ to $C_1$—$O_2$—$N_2$—$C_2$ | 31.8 |
| $O_1$—P—$O_2$—$C_1$ | 168.4 | $C_1$—$C_3$—$C_2$ to $C_1$—$O_2$—$N_2$—$C_2$ | 51.9 |
| P—$N_2$—$C_2$—$C_3$ | 32.8 | $O_2$—$N_2$—$C_2$ to $C_1$—$O_2$—$N_2$ | 14.9 |
| P—$O_2$—$C_1$—$C_3$ | −64.9 | $O_2$—$N_2$—$C_2$ to $C_1$—$O_2$—$N_2$—$C_2$ | 8.7 |
| $C_6$—$N_1$—P—$N_2$ | −7.8 | $C_2$—$N_2$—$O_2$ to $C_1$—$O_2$—$N_2$—$C_2$ | 8.6 |
| $C_6$—$N_1$—P—$O_2$ | 105.6 | $O_2$—P—$N_2$ to $O_2$—$N_2$—$C_2$ | 24.3 |
| $C_8$—$N_1$—P—$N_2$ | 168.5 | $O_2$—P—$N_2$ to $C_2$—$N_2$—$O_2$ | 39.0 |
| $C_8$—$N_1$—P—$O_2$ | −78.4 | | |

[a] The angle a-b-c-d is positive when the angle is clockwise as viewed down the b to c axis and minus when this angle is counterclockwise.

ment of these parameters by full matrix least squares techniques[9] led to a conventional $R$ factor of 0.134 and a weighted $R_\omega$ factor 0.161. The positions of the hydrogen atoms were located from an electron density difference map. Anisotropic refinement then gave a conventional $R$ factor of 0.106 and a weighted $R_\omega$ factor of 0.128. Large thermal motion of $Cl_2$ and $C_8$ precluded achievement of lower $R$ and $R_\omega$ values. However, the distance between $Cl_2$ and $C_8$ is in the expected range and is close to that between $Cl_1$ and $C_6$. The calculated and observed structure factors, final atomic and positional parameters, final thermal parameters, intramolecular bond distances and angles, and torsional and interplanar angles appear in Tables I, II, III and IV, respectively.

## DISCUSSION

From Figure 1 it is seen that the solid phase structure **5b** possesses the same stereochemistry as that assigned to it on the basis of earlier solution studies.[6] In 2-*R*-2-oxo-1,3,2-dioxaphosphorinane systems there is a marked tendency for conformers with equatorial dialkylamino *R* groups to dominate in solution, whereas this dominance is less pronounced when *R* is an alkylamino function.[1] These observations are reflected in the solid phase for *R* = piperidino and anilino which are found to be equatorial and axial, respectively.[1] In 2-*R*-2-oxo-1,3,2-oxazaphosphorinanes, the situation is not quite as straightforward. The proclivity of the $(ClCH_2CH_2)_2N$ group of **1** to be equatorial in solution[6] is realized in the solid phase structure.[1] The sim-

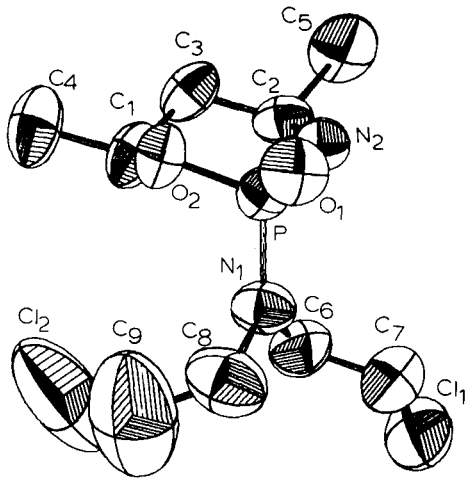
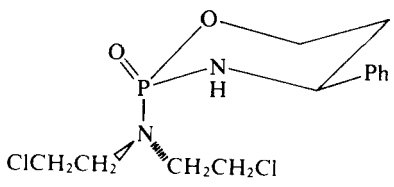


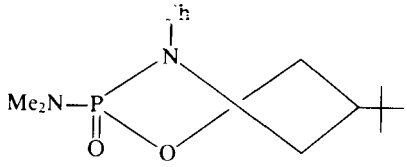

FIGURE 1 Computer-generated drawing of **5b**.[15]

ilarity of **3** to **1** coupled with the finding that the $(ClCH_2CH_2)_2N$ group is equatorial in the solid phase for **3**[1] suggests that **3** also exists mainly in this conformation in solution. Unexpectedly, however, the $ClCH_2CH_2NH$ group in racemic **2** is equatorial in the solid phase,[1a] whereas it has recently been found in the x-ray structural determination of the S(−) enantiomer[5] to be axial. Apparently the predilection of the $ClCH_2CH_2NH$ group for a particular stereochemistry is not very strong and this is probably also the case in solution.

Biasing the ring with ring carbon substituents as in **5b, 6** and **7** produces some interesting consequences. The overriding tendency for the methyl, phenyl and *t*-butyl

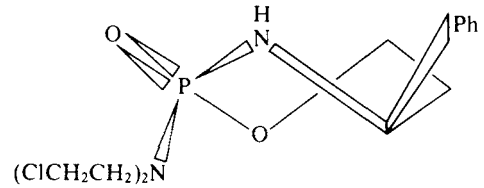



**6**

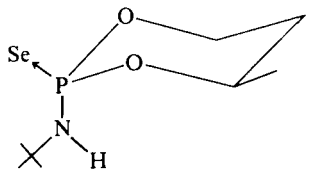



**7**

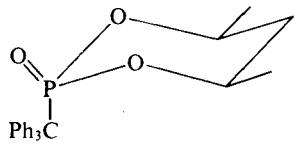
groups to be equatorial in these compounds forces the $(ClCH_2CH_2)_2N$ substituent to adopt a relatively unfavorable axial stereochemistry in **5b** and **6**.[10] This problem appears to be alleviated in **7** by the adoption of a twist-boat conformation which allows the $Me_2N$ group to be pseudo equatorial.[4] Although a similar option appears to exist for **6** as shown below, a twist-boat conformation for **5b** would place one methyl group in a sterically unfavorable pseudo axial position.




Forcing bulky phosphorus substituents into the axial position in chair-form phosphorinane rings as in **5b, 6, 8**[11] and **9**[1] has given rise to two principal compen-




**8**




**9**

sating conformational changes. In the equatorial position of **1–3,** the $C_2N$ plane of the mustard group is nearly perpendicular to the OPN plane of the ring.[1,13] This phenomenon also occurs in acyclic systems of the type $O{=}PX_2(NMe_2)$.[12] In **5b** and **6,** the $C_2N$ plane of the mustard group rotates in order to prevent a $ClCH_2CH_2$ moiety from interacting with axial hydrogens under the ring. The same is true for the HNC plane in **8**.[14] In **9** the more bulky $Ph_3C$ group lacks the proper symmetry to exercise this choice, and instead causes the ring to flatten to a "chaise longue" conformation. Thus the angle between the OPO and $(OC)_2$ planes of the ring is 3.7° in **9** whereas in other 2-*R*-2-oxo-1,3,2-dioxaphosphorinanes where *R* is non-bulky, this angle ranges from 33.5 to 40°.[1] In **5b** this angle is ca. 32°.

The tendency for the exocyclic nitrogen to possess a planar geometry when equatorial in phosphamides is well documented.[1b] Apparently this is also the case when the nitrogen substituent is axial as shown from Figure 1 for **5b** and as is suggested from the depiction in Ref. 5 of the structure of the S(−) enantiomer of **2**. In both structures this plane is not perpendicular to the ring OPN plane as is the case when the exocyclic N substituent is equatorial. Thus in structure **5b** the exocyclic $NC_2$ plane and the PN(endocyclic) bond make an angle of 7.8° and a similar conformation appears to be adopted by the exocyclic NHC moiety of the S(−) enantiomer of **2** in the solid state.[5] Syn-1,3-diaxial interactions may be too severe in structures such as **5b** for stabilization of the electronically favored conformation in which the exocyclic $NC_2$ plane is perpendicular to the ring NPO plane.

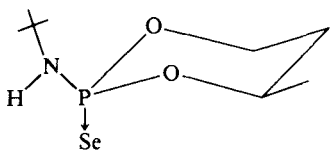
ACKNOWLEDGMENT

The authors are grateful to the National Science Foundation for a grant and to the DOE for financial support of this research.

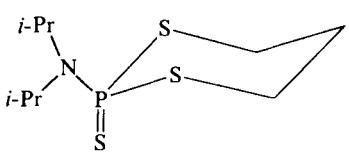


REFERENCES

1. See (a) K. Pankiewicz, R. Kinas, W. J. Stec, A. B. Foster, M. Jarman, J. M. S. Van Maanen, *J. Am. Chem. Soc.*, **101,** 7712, (1979), (b) A. E. Wroblewski, S. M. Socol, A. Okruszek, J. G. Verkade, *Inorg. Chem.*, **19,** 3713 (1980).
2. See B. E. Maryanoff, R. O. Hutchins and C. A. Maryanoff, in *Topics in Stereochemistry*, N. L. Allinger and E. L. Eliel, Eds., Vol. 11, John Wiley and Sons, Inc., New York, New York, 1979, p. 187 for a recent review of the area.
3. W. Egan, G. Govil, N. Sharpless and G. Zon, private communication.
4. G. Bajwa, W. Bentrude, N. Pantaleo, M. Newton and J. Hargis, *J. Am. Chem. Soc.*, **101,** 1602 (1979).
5. D. A. Adamiak, M. Gdaniec, K. Pankiewicz and W. J. Stec, *Angew. Chem., Int. Ed.*, **19,** 549 (1980).
6. D. W. White, D. E. Gibbs and J. G. Verkade, *J. Am. Chem. Soc.*, **101**(8), 1937 (1979).
7. F. Takosagawa and R. A. Jacobson, *Acta Crystallog.*, B34, 213 (1978).
8. P. M. Main, M. M. Woolfson and G. Germain, MULTAN: A Computer Program for the Automatic Determination of Crystal Structures, Department of Physics, University of York, York, England, (1971).
9. R. L. Lapp and R. A. Jacobson, ALLS, A Generalized Crystallographic Least Squares Program U.S. Department of Energy Report IS-4708-UC-4, Ames Laboratory, DOE, Iowa State University, Ames, Iowa 50010.
10. V. L. Boyd, G. Zon, V. L. Himes, J. K. Stalick, A. D. Mighall and H. V. Secor, *J. Med. Chem.*, **23,** 372 (1980).
11. T. J. Bartczak, A. Christensen, R. Kinas and W. J. Stec, *Cryst. Struct. Comm.*, **5,** 21 (1976).
12. J. G. Verkade, *Phosphorus and Sulfur*, **2,** 251 (1975).
13. This geometry is also closely realized in the related systems **10** (T. J. Bartczak, A. Christensen, R. Kinas and W. J. Stec, *Cryst. Struct. Comm.*, **4,** 701 (1975)) and **11** (A. Grand, J. B. Robert and A. Filhol, *Acta Crystallogr.*, **B33,** 1526 (1977)).

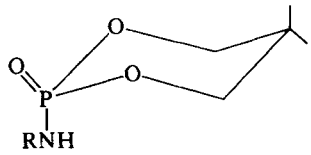



**10**




**11**

14. It should be noted that a CNH moiety has a considerable tendency to be axial despite the absence of an equatorial group on the ring. Thus not only the S(−) enantiomer of **2** is consistent with this no-




**12** R = HC(O)
**13** R = Ph

tion but the same is true for compounds **12** (T. S. Cameron and J. Karolak-Wojciechowska, *Acta Crystallogr.*, **B33,** 2342 (1977) and **13** (T. S. Cameron, Z. Galdecki and J. Karolak-Wojciechowska, *Acta Crystallogr.*, **B32,** 492 (1976). In all three cases, however, the plane defined by the nitrogen and its pendant atoms is twisted away from coplanarity with the O=P—N plane suggesting the presence of prohibitively large syn-1,3-diaxal interactions even with the N—H hydrogen.

15. C. A. Johnson, ORTEP-II, A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations, U.S. Atomic Energy Commission Report ORNYL-3794, Second Revision with Supplemental Instructions, Oak Ridge National Laboratory, Oak Ridge, Tenn., (1971).