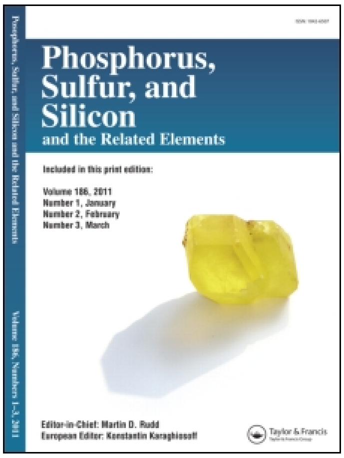

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SOLID-STATE CONFORMATIONS OF FIVE MEMBERED RING PHOSPHORUS HETEROCYCLES: X-RAY CRYSTAL STRUCTURES OF THREE 1,3,2-OXAZAPHOSPHOLANES

William N. Setzer[a]; Barry G. Black[a]; John L. Hubbard[b]
[a] Department of Chemistry, The University of Alabama in Huntsville, Huntsville, Alabama [b] Department of Chemistry, The University of Vermont, Burlington, Vermont

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SOLID-STATE CONFORMATIONS OF FIVE-MEMBERED RING PHOSPHORUS HETEROCYCLES: X-RAY CRYSTAL STRUCTURES OF THREE 1,3,2-OXAZAPHOSPHOLANES

WILLIAM N. SETZER and BARRY G. BLACK
Department of Chemistry, The University of Alabama in Huntsville, Huntsville, Alabama 35899

and

JOHN L. HUBBARD
Department of Chemistry, The University of Vermont, Burlington, Vermont 05405

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Single-crystal X-ray structural determinations have been made on (2*S*,4*R*,5*R*)-2-phenoxy-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane, **1**; (2*S*,4*R*,5*R*)-2-(dimethylamino)-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane, **2**; and (2*S*,4*R*,5*S*)-2-phenoxy-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane, **3**. The solid-state conformations adopted by these materials are P(2) half-chair, envelope C(4), and P(2) half-chair, respectively.

Key words: Oxazaphospholane; conformation structure; X-ray crystal; ephedrine; pseudoephedrine.

INTRODUCTION

The five membered ring is conformationally the most important ring system in chemistry after the six-membered ring. The conformational properties of cyclopentane and substituted cyclopentanes,[2] and saturated five-membered ring heterocycles[3] have been reviewed. Conformational analyses of these ring systems are usually discussed in terms of *envelope* (C_s) and *half-chair* (C_2) conformations.

We have been interested in the conformational consequences of phosphorus substituents in phosphorus heterocycles. Recently we have studied, using NMR, the conformational properties of a series of 1,3,2-oxazaphospholanes derived from ephedrine and pseudoephedrine.[4] The 1,3,2-oxazaphospholanes were prepared by reaction of either ephedrine or pseudoephedrine with the appropriate $ZP(O)Cl_2$ reagent. The resulting diastereomers were separated by liquid chromatography. In order to confirm our stereochemical assignments and to provide additional structural and conformational information on this heterocyclic system, it was deemed necessary to undertake single-crystal X-ray studies of some of these compounds. This paper reports the X-ray crystal structures of three of these heterocycles: (2*S*,4*R*,5*R*)-2-phenoxy-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane, **1**; (2*S*,4*R*,5*R*)-2-(dimentylamino)-2-oxo-3,4-dimethyl-5-

phenyl-1,3,2-oxazaphospholane, **2**; and (2*S*,4*R*,5*S*)-2-phenoxy-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane, **3**.

RESULTS AND DISCUSSION

The crystal data for **1**, **2**, and **3** are listed in Table I. The final atomic parameters for the compounds are compiled in Tables II, III, and IV, respectively. Perspective views of molecules **1**, **2**, and **3** are given in Figures 1, 2, and 3, along with the labeling schemes. Selected bond lengths, bond angles, and torsion angles for the compounds are listed in Table V.[5]

X-ray crystal structures of similar compounds, **4–7**, derived from ephedrine have been reported by Bartczak and coworkers.[6–9] The endocyclic bond lengths and bond angles for compounds **1–3** are comparable to those reported for **4–7**. The P(2)–O(2) bond lengths of 1.46 Å, 1.47 Å, and 1.45 Å, for **1–3**, respectively, are typical for phosphoryl P═O double bonds.[10]

The geometry at the phosphorus atom in each of the compounds, as expected, is a distorted tetrahedron. In compound **1**, the sum of the angles about the endocyclic nitrogen, N(3), is 359°, indicating a planar sp^2 nitrogen. The nitrogen in 3 is nearly planar ($\Sigma = 355°$). In compound **2**, however, the sum of the angles about N(3) is only 345°, intermediate between ideal sp^3 and sp^2 hybridization

TABLE I

Crystal data for 1,3,2-oxazaphospholanes **1**, **2** and **3**

Compound	**1**	**2**	**3**
Molecular formula	$C_{16}H_{18}NO_3P$	$C_{12}H_{19}N_2O_2P$	$C_{16}H_{18}NO_3P$
Molecular weight	303.3	254.3	303.3
Color, habit	colorless prism	colorless plate	colorless prism
Size, mm	0.25 × 0.20 × 0.25	0.08 × 0.20 × 0.25	0.15 × 0.20 × 0.25
Space group	$P2_12_12_1$ (No. 19)	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions			
a, A	9.719 (3)	10.768 (6)	9.702 (3)
b, A	10.480 (3)	10.993 (3)	10.722 (3)
c, A	15.389 (5)	11.431 (6)	15.319 (5)
V, A^3	1567.4 (8)	1353.1 (11)	1593.5 (8)
Z	4	4	4
d_{calcd}, g/cm^3	1.29	1.25	1.26
$F(000)$, e^-	640	544	920
No. of unique data	1211	1045	1231
No. of observed data	852	650	783
Absorption coeff. (μ_λ), cm^{-1}	1.78	1.90	1.75
Final residuals			
R	0.0817	0.0963	0.1033
R_w	0.0429	0.1253	0.0642
Weighting scheme, w	$1/[\sigma^2(F)+0.0001F^2]$	$1/[\sigma^2(F)+0.0159F^2]$	$1/[\sigma(F)+0.0003F^2]$
GOF	1.30	0.80	1.43
Largest diff. peak, e^-A^{-3}	0.42	0.49	0.46
Largest diff. hole, e^-A^{-3}	−0.39	−0.41	−0.49

TABLE II

Final atomic parameters for 1,3,2-Oxazaphospholane **1**

Atomic coordinates (×10⁴) and equivalent isotropic displacement coefficients (Å² × 10³)

	x	*y*	*z*	*U*(eq)
P (2)	−1626 (3)	−7959 (3)	−9351 (2)	45 (1)
O (3)	−2900 (7)	−7632 (6)	−8735 (5)	47 (3)
O (2)	−1560 (8)	−6954 (6)	−10011 (4)	63 (3)
O (1)	−1892 (7)	−9401 (5)	−9638 (4)	40 (3)
N (3)	−237 (9)	−8225 (7)	−8809 (5)	53 (4)
C (5)	−683 (11)	−10207 (9)	−9448 (6)	37 (4)
C (4)	45 (11)	−9601 (10)	−8661 (6)	43 (4)
C (3)	1555 (9)	−9951 (9)	−8643 (7)	67 (5)
C (2)	568 (12)	−7250 (9)	−8367 (7)	82 (6)
C (12)	−2238 (12)	−11813 (10)	−8785 (7)	50 (5)
C (13)	−2672 (10)	−13047 (11)	−8625 (7)	54 (5)
C (14)	−1938 (14)	−14037 (11)	−9018 (8)	69 (6)
C (15)	−852 (18)	−13818 (11)	−9510 (9)	100 (8)
C (16)	−444 (13)	−12566 (12)	−9676 (7)	74 (5)
C (11)	−1144 (12)	−11558 (10)	−9313 (7)	43 (4)
C (22)	−4508 (11)	−9206 (10)	−8282 (7)	50 (5)
C (23)	−4957 (14)	−10100 (11)	−7647 (8)	62 (5)
C (24)	−4253 (14)	−10269 (12)	−6890 (8)	67 (6)
C (25)	−3125 (13)	−9514 (12)	−6731 (6)	64 (6)
C (26)	−2635 (12)	−8607 (10)	−7321 (8)	56 (5)
C (21)	−3371 (13)	−8481 (10)	−8092 (7)	43 (4)

Equivalent isotropic *U* defined as one third of the trace of the orthogonalized U_{ij} tensor.

TABLE III

Final atomic parameters for 1,3,2-Oxazaphospholane **2**

Atomic coordinates (×10⁴) and equivalent isotropic displacement coefficients (Å² × 10³)

	x	*y*	*z*	*U*(eq)
O (1)	−3182 (16)	−9313 (12)	−6590 (12)	62 (6)
P (2)	−1976 (5)	−9371 (4)	−5804 (4)	41 (2)
N (3)	−1833 (14)	−10905 (12)	−5846 (14)	44 (5)
C (4)	−3101 (19)	−11421 (17)	−6121 (16)	32 (7)
C (5)	−3645 (16)	−10490 (16)	−6943 (16)	34 (6)
O (2)	−2107 (14)	−8768 (12)	−4662 (11)	62 (5)
C (6)	−646 (23)	−9206 (21)	−7755 (18)	75 (10)
N (1)	−846 (14)	−8818 (14)	−6502 (15)	43 (6)
C (2)	−1042 (20)	−11438 (18)	−4955 (18)	63 (9)
C (1)	−2919 (20)	−12696 (15)	−6681 (18)	58 (8)
C (3)	−81 (19)	−7849 (18)	−6096 (19)	71 (9)
C (12)	−5847 (28)	−11193 (21)	−7650 (19)	80 (11)
C (13)	−7108 (22)	−11151 (23)	−7454 (27)	87 (12)
C (14)	−7608 (29)	−10567 (24)	−6533 (27)	95 (13)
C (15)	−6924 (28)	−9974 (20)	−5816 (22)	79 (10)
C (16)	−5644 (19)	−9938 (21)	−5922 (20)	63 (9)
C (11)	−5054 (19)	−10542 (16)	−6847 (14)	39 (6)

Equivalent isotropic *U* defined as one third of the trace of the orthogonalized U_{ij} tensor.

TABLE IV

Final atomic parameters for 1,3,2-Oxazaphospholane **3**

Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients (Å $\times 10^3$)

	x	*y*	*z*	*U*(eq)
P (2)	1133 (6)	4155 (4)	9283 (4)	50 (2)
C (5)	522 (17)	6338 (13)	9641 (10)	45 (6)
C (4)	−672 (13)	5843 (13)	9083 (10)	41 (6)
C (3)	−640 (17)	6284 (13)	8131 (9)	73 (8)
C (2)	−1538 (16)	3594 (15)	8803 (12)	86 (10)
O (2)	1896 (12)	3524 (9)	8597 (8)	77 (6)
O(1)	1665 (9)	5495 (8)	9480 (7)	51 (5)
N (3)	−479 (14)	4473 (10)	9166 (9)	54 (6)
O (3)	1351 (12)	3328 (10)	10117 (7)	55 (5)
C (22)	−150 (20)	3043 (15)	11297 (13)	52 (8)
C (23)	−585 (19)	3265 (16)	12131 (14)	60 (8)
C (24)	142 (25)	4099 (23)	12625 (12)	81 (11)
C (25)	1298 (26)	4721 (18)	12295 (16)	90 (12)
C (26)	1661 (19)	4502 (16)	11437 (15)	62 (9)
C (21)	996 (23)	3642 (16)	10940 (14)	67 (9)
C (12)	117 (18)	8665 (15)	9848 (10)	63 (8)
C (13)	533 (20)	9905 (13)	9635 (10)	55 (8)
C (14)	1656 (18)	10196 (15)	9124 (10)	48 (7)
C (15)	2362 (17)	9209 (18)	8756 (10)	62 (8)
C (16)	2032 (16)	7981 (14)	8930 (10)	39 (6)
C (11)	931 (16)	7704 (14)	9472 (10)	37 (6)

Equivalent isotropic *U* defined as one third of the trace of the orthogonalized U_{ij} tensor.

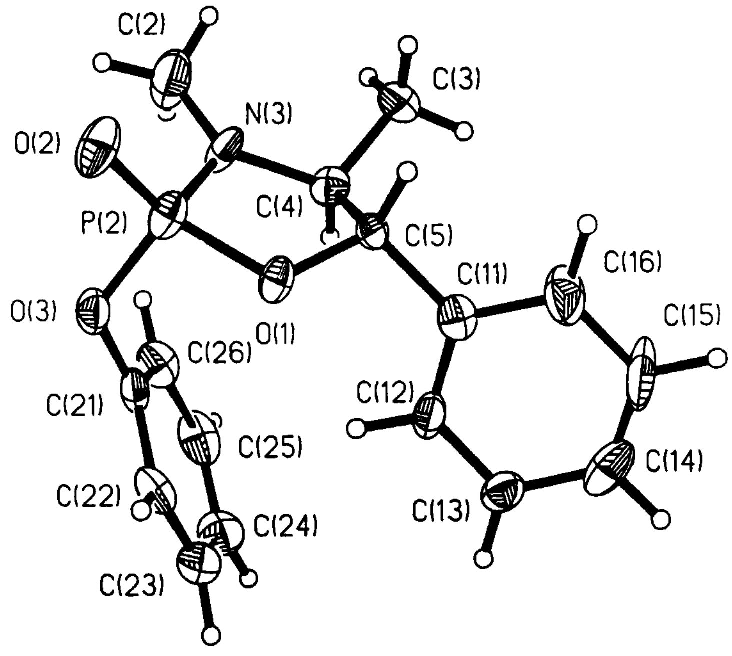


FIGURE 1 ORTEP perspective view of 1,3,2-oxazaphospholane **1**.

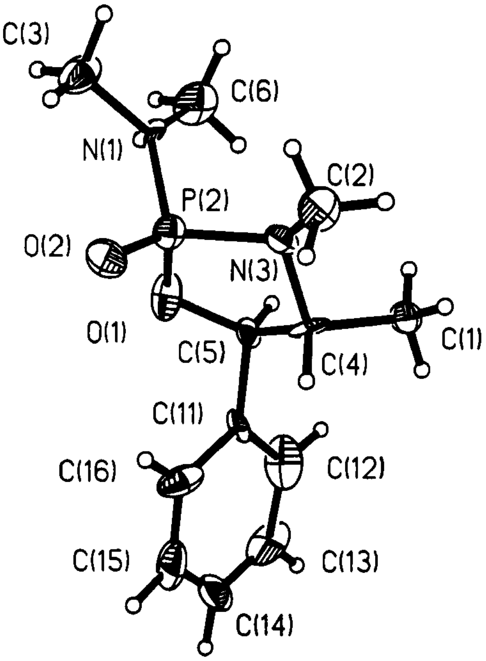


FIGURE 2 ORTEP perspective view of 1,3,2-oxazaphospholane **2**.

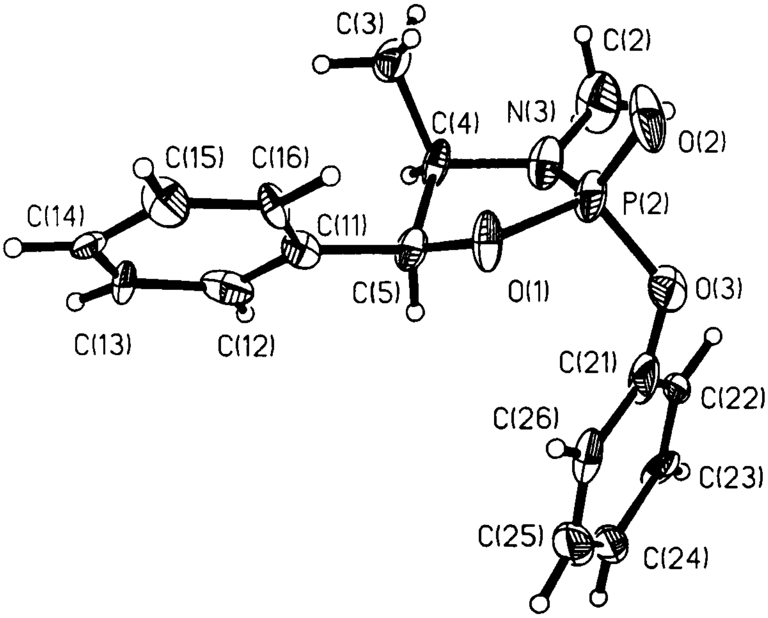


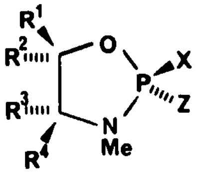
FIGURE 3 ORTEP perspective view of 1,3,2-oxazaphospholane **3**.

TABLE V

Selected bond lengths (Å), bond angles (deg), and torsion angles (deg) for 1,3,2-Oxazaphospholanes **1**, **2**, and **3**

Atoms	Compound **1**	 **2**	 **3**
P(2)-O(2)	1.463 (7)	1.470 (13)	1.454 (13)
P(2)-O(1)	1.595 (6)	1.580 (17)	1.554 (10)
P(2)-N(3)	1.611 (9)	1.693 (14)	1.612 (15)
O(1)-C(5)	1.477 (12)	1.445 (22)	1.454 (18)
N(3)-C(4)	1.486 (13)	1.512 (25)	1.487 (18)
C(4)-C(5)	1.540 (14)	1.509 (26)	1.533 (21)
P(2)-O(3)	1.598 (7)	—	1.569 (12)
P(2)-N(1)	—	1.577 (16)	—
O(1)-P(2)-N(3)	96.6 (4)	95.7 (7)	98.3 (6)
P(2)-N(3)-C(4)	113.7 (7)	107.3 (11)	110.1 (9)
N(3)-C(4)-C(5)	101.2 (8)	103.0 (14)	101.4 (11)
C(4)-C(5)-O(1)	106.6 (7)	107.5 (15)	105.4 (11)
C(5)-O(1)-P(2)	111.0 (5)	113.9 (11)	110.9 (8)
O(1)-P(2)-N(3)-C(4)	-10.8 (9)	-23.2 (13)	-13.3 (12)
P(2)-N(3)-C(4)-C(5)	27.2 (11)	35.4 (15)	31.0 (14)
N(3)-C(4)-C(5)-O(1)	-33.0 (11)	-33.8 (16)	-37.3 (14)
C(4)-C(5)-O(1)-P(2)	28.7 (10)	19.4 (16)	31.1 (14)
C(5)-O(1)-P(2)-N(3)	-11.2 (7)	2.3 (13)	-11.2 (12)

geometries.



	R^1	R^2	R^3	R^4	X	Z
1:	Ph	H	Me	H	OPh	O
2:	Ph	H	Me	H	O	NMe_2
3:	H	Ph	Me	H	OPh	O
4:	Ph	H	H	Me	Cl	S
5:	Ph	H	H	Me	S	Cl
6:	Ph	H	H	Me	NHPh	S
7:	Ph	H	H	Me	SMe	O

The conformation of compound **1** adopted in the crystal structure can best be described as a half-chair with approximate pseudo C_2 symmetry through the phosphorus atom. The methyl group at C(4) and the phenyl group at C(5) are both pseudoequatorial in this conformation. The solid-state conformation of compound **3** is also best described as a P(2) half-chair but with the C(4)-methyl group pseudoaxial and the C(5)-phenyl group pseudoequatorial.

It is interesting that compounds **1** and **3** adopt conformations such that the phenoxy substituent is *not* pseudoaxial. Owing to the anomeric effect,[11] small electronegative substituents on phosphorus in six-membered-ring phosphorus heterocycles (1,3,2-dioxa- and 1,3,2-oxazaphosphorinanes) are axial seeking.[12] Such a conformational preference has been noted in solution conformational analysis of 1,3,2-oxazaphospholanes[4] and it is curious that the axial-seeking nature of the phenoxy group on phosphorus is not reflected in these crystal structures. The similarity in bond lengths between the endocyclic P(2)–O(1) and the exocyclic P(2)–O(3) is additional evidence *against* the anomeric effect in the observed solid-state conformations for **1** and **3**. Note that the solid-state conformations of **4**,[6] **5**,[7] and **6**[8] are such that the chloro or anilino substituents are also *not* pseudoaxial.

Interestingly, the O(1)–P(2)–O(3)–C(21) dihedral angle in **1** is 44°, placing the phenyl group of the phosphorus substituent directly over the plane of the heterocyclic ring. This conformation about the P(2)–O(3) bond may serve not only to avoid lone pair/lone pair interactions between O(3) and O(1) or N(3) but also positions the O(3) lone pairs in a more favorable antiperiplanar arrangement to both the P(2)–O(1) bond and the P(2)–N(3) bond—the *exo*-anomeric effect.[11] The conformational preference of the phenoxy substituent over the plane of the heterocycle is at the expense of possibly increased 1,3-steric interactions between the phenoxy substituent and the C(5)-phenyl group.

The conformation about the P(2)–O(3) bond in compound **3** is the same as that found in **1** [O(1)–P(2)–O(3)–C(21) = 50°]. This is the analogous conformation adopted by the anilino group in **6**.[8] The P(2)–O(3)–C(21) bond angles for **1** and **3** are 122° and 126°, respectively, indicating possible sp^2 hybridization and conjugation with the phosphoryl group.

Compound **2** adopts, in the crystalline state, an envelope conformation with a C(4) flap. In this conformation, the C(4)-methyl substituent, the C(5)-phenyl substituent, and the P(2)-dimethylamino substituent are all pseudoequatorial. The sum of the bond angles around exocyclic N(1) is 359°, indicating planar sp^2 hybridization. This dimethylamino group is nearly coplanar with the phosphoryl P=O group [O(2)–P(2)–N(1)–C(3) = 2°] allowing for conjugation between them. Additional evidence for this conjugation is found in the relatively short P(2)–N(1) bond of 1.58Å, compared to the endocyclic P(2)–N(3) bond length of 1.69Å. Note that in compound **6**, the exocyclic and endocyclic P–N bond lengths are 1.65Å and 1.64Å, respectively.[8] The conformation adopted by the dimethylamino substituent places C(6) of that group over the plane of the heterocycle. Steric repulsions between this group and the C(4)-methyl group may be responsible for the envelope C(4) conformation of the heterocyclic ring.

EXPERIMENTAL

The preparation of compounds **1**, **2**, and **3** have been described elsewhere.[4] In all cases, clear colorless crystals suitable for X-ray diffraction were obtained by vapor diffusion of hexane into a solution of each compound in ethyl acetate.

In each study, a relatively small, colorless crystal was fixed vertically in a glass capillary with silicone grease and mounted on a Nicolet *R3m*/V auto diffractometer equipped with a scintillation counter and Mo Kα radiation ($\lambda = 0.71073$ Å) with graphite monochromator. Unfortunately, larger crystals were badly twinned, thus limiting significant data to $2\theta \leq 35°$. The indexing of 20 reflections with 2θ between 15° and 25° gave a primitive orthorhombic cell. Axial photographs confirmed symmetry down each of the axes. The space group $P2_12_12_1$ was determined from the systematic absences present in the data. No empirical absorption correlation was applied. The automatic centering, indexing, and least-squares routines were carried out to obtain the cell dimensions which are given in Table I. For each structure, the θ–2θ data collection method over the range $3.0° \le 2\theta \le 45.0°$ was used to collect the data of which those with $F \ge 2\sigma(F)$ were considered observed and were used in the calculations. The data were collected using variable scan speeds (3.0 to 15.0 deg/min) at ambient temperatures (22°C). In each case, two standard reflections were monitored every 48 reflections and none of the crystals showed evidence of decomposition during data collection.

Each structure was solved using direct methods (SHELXTL PLUS, MicroVAX II) and refined by full-matrix least-squares techniques. Non-hydrogen atoms were located in subsequent difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in geometrically ideal positions (C—H = 0.96A; $U_H = 0.080$) and not refined.

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