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Conformational Studies of 2-Anilino-Substituted 1,3,2-Oxazaphospholanes

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ABSTRACT

A series of 2-anilino-2-thio-1,3,2-oxazaphospholanes derived from ephedrine has been synthesized and conformationally studied by proton NMR and X-ray crystallography. The NMR data can be interpreted in terms of twist-envelope conformations in which the anilino substituents on phosphorus adopt predominantly equatorial positions. X-ray crystal structures of (2R,4S,5S)-2-anilino-2-thio-3,4-dimethyl-5-phenyl-1,3-2-oxazaphospholane, (2R,4S,5S)-2-(4-fluoroanilino)-2-thio-3, 4-dimethyl-5-phenyl-1, 3, 2-oxazaphospholane, and (2R,4S,5S)-2-(4-methoxyanilino)-2-thio-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane have been carried out, and these compounds adopt envelop, twist-envelope, and twist-envelope conformations, respectively, with the anilino moieties equatorial.

INTRODUCTION

The use of NMR techniques as well as X-ray crystallography for the study of conformational properties of phosphorus-containing heterocycles is currently very active [1]. We have been interested, recently, in the conformational consequences of phosphorus substituents with different stereoelectronic properties in the six-membered 1,3,2-oxazaphosphorinane [2] and the five-membered 1,3,2-oxazaphospholane [3] ring systems.

It is generally observed in these phosphorus heterocycles that small electronegative substituents on phosphorus prefer an *axial* rather than an *equatorial* disposition. This axial preference has been attributed to the anomeric effect [4] in these compounds. Thus, a favorable orbital interaction between the lone pair on ring nitrogen (or ring oxygen) and the phosphorus-substituent antibonding orbital is geometrically possible when the substituent is axial but not when the substituent is equatorial. In order to assess further this stereoelectronic interaction, it was deemed necessary to synthesize phosphorus-containing heterocycles having substituents on phosphorus in which the electronic nature of the substituent can be altered without affecting the steric requirements of that substituent.

In this article, we report the preparation and conformational analysis of a series of five-membered-ring phosphorus heterocycles (1,3,2-oxazaphospholanes), which have *para*-substituted aniline substituents on phosphorus, **1–5**.

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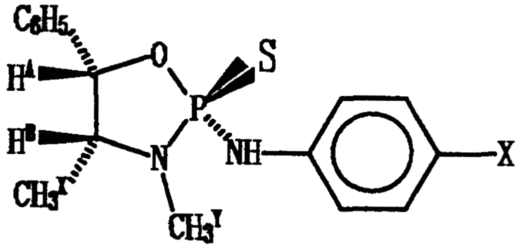
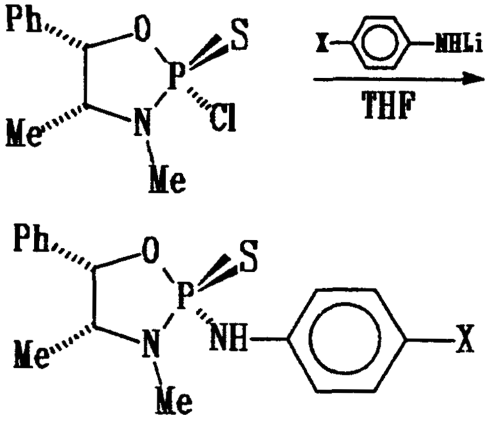


1, X = NMe$_2$ 3, X = F
2, X = OMe 4, X = H
5, X = NO$_2$

RESULTS AND DISCUSSION

Synthesis

The 1,3,2-oxazaphospholanes in this study are conveniently prepared from the 2-chloro-2-thio-1,3,2-oxazaphospholane by reaction with the anion of the corresponding 4-substituted aniline [5]:



This reaction presumably proceeds via retention of configuration at phosphorus [5,6]. In order to confirm the expected stereochemistry of the products, single-crystal structure studies were carried out on 1,3,2-oxazaphospholanes **2**, **3**, and **4**. The X-ray crystal structure of **4** has already been established [7], but we include our structure here for comparison purposes.

NMR Studies

Conformational studies of the 1,3,2-oxazaphospholane ring system have been carried out [3,5,8], and the solution conformational equilibria for this five-membered ring system are conveniently discussed in terms of half-chair (**6**) and twist-envelope (**7** and **8**) forms (Figure 1). The equilibria depend on the stereoelectronic requirements of the substituents on ring carbon, nitrogen, or phosphorus [1,3a]. Note, however, that barriers between conformations are expected to be very low in five-membered-ring heterocyclic systems such as this one.

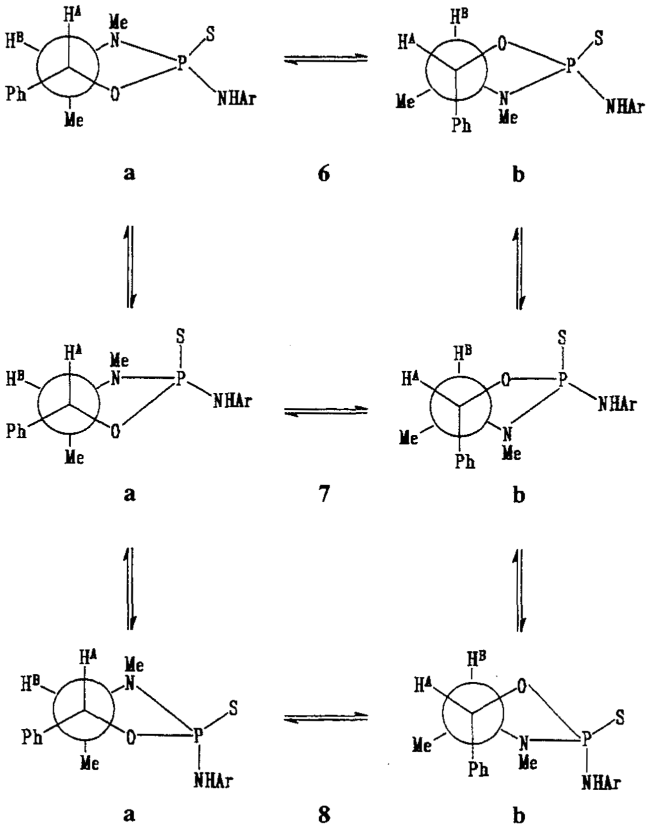


FIGURE 1 Conformational equilibria in 1,3,2-oxazaphospholanes

The ^1H and ^{31}P NMR parameters (coupling constants and chemical shifts) for the 1,3,2-oxazaphospholanes are listed in Table 1. These NMR parameters were obtained at 200 MHz and are essentially first order. The $^3J_{HP}$ vicinal coupling constants for these compounds are consistent for an equilibrium in which the predominant conformation has the methyl group on C(4) axial, H^B equatorial; the phenyl substituent on C(5) equatorial, H^A axial; and the anilino moiety pseudoequatorial, the thiophosphoryl pseudoaxial (conformation **7a**). That is, the H^A–C(5)–O(1)–P(2) dihedral angle is approximately 90°, and J_{AP} is very small; the H^B–C(4)–N(3)–P(2) dihedral angle is about 125°, and J_{BP} is relatively large (ca. 9 Hz). A dihedral angular dependence, $^3J_{PH}$, has been observed in systems containing P–O–C–H and P–N–C–H [1]. Lee and Sarma [9] have determined the Karplus relationship: $^3J_{POCH} = 18.1 \cos^2 \phi_{PH} - 4.8 \cos \phi_{PH}$.

It is useful to analyze the coupling data by considering conformational equilibria such as those

TABLE 1 NMR Data for the 1,3,2-Oxazaphospholanes

Compound	*X*	δ_A	δ_B	δ_X	δ_Y	δ_P	J_{AP}	J_{BP}	J_{AB}	J_{BX}	J_{YP}
1	NMe_2	5.56	3.54	0.28	2.68	78.44	0.5	9.7	6.4	6.5	11.8
2	OMe	5.60	3.58	0.32	2.70	78.17	0.4	9.7	6.7	6.6	12.0
3	F	5.64	3.61	0.41	2.69	77.91	0.5	9.1	6.7	6.6	12.2
4	H	5.67	3.64	0.48	2.69	77.61	0.9	8.4	6.9	6.6	12.3
5	NO_2	5.81	3.82	0.80	2.79	71.11	2.1	9.3	6.8	6.6	7.0

TABLE 2 Crystallographic Data for 1,3,2-Oxazaphospholanes **2–4**

	2	*3*	*4*
Molecular formula	$C_{17}H_{21}PO_2N_2S$	$C_{16}H_{18}PON_2SF$	$C_{16}H_{19}PON_2S$
Formula weight	348.40	336.36	318.37
Crystal color, habit	colorless block	colorless block	colorless block
Crystal dimensions, mm	0.2 × 0.2 × 0.4	0.15 × 0.05 × 0.2	0.3 × 0.3 × 0.5
Crystal system, space group	orthorhombic, $P2_12_12_1$	monoclinic, $P2_1$	orthorhombic, $P2_12_12_1$
Lattice parameters			
a, Å	28.527(1)	27.764(1)	10.9417(6)
b, Å	6.646(1)	6.910(2)	16.758(1)
c, Å	9.783(2)	9.172(2)	9.1763(6)
β (°)	90.0	91.268(7)	90.0
V, $Å^3$	1854.8(7)	1759.3(8)	1682.6(3)
Z	4	4	4
D_{calcd}, g cm^{-3}	1.247	1.270	1.257
F_{000}	736	704	672
μ_λ, cm^{-1}	24.29	25.89	25.87
No. refls. measd.	3304	6098	2916
No. obsd. refls.	897	4753	2629
R	0.035	0.045	0.043
R_w	0.044	0.058	0.059
GoF	2.00	1.97	2.25
Max. peak in final diff. map, $e^-/Å^3$	0.19	0.17	0.22
Min. peak in final diff. map, $e^-/Å^3$	−0.22	−0.28	−0.15

shown in Figure 1. That is, the substituents on C(4) and C(5) preclude eclipsing, and the disposition of the phosphorus end of the ring depends upon the steric and electronic effects of the substituents. Since the steric requirements of phenyl are greater than those of methyl (the conformational energy of phenyl in cyclohexane equilibria is about 3.0 kcal/mol, whereas that of methyl is only 1.7 kcal/mol [10]), conformational equilibria favoring **6a** ⇌ **7a** ⇌ **8a** are more likely than those favoring **6b** ⇌ **7b** ⇌ **8b**. In addition, force-field calculations on the 1,3,2-oxazaphospholane ring system (using the program ALCHEMY II [11]) indicate the half-chair **6a** to be a transition structure between **7a** and **8a** (that is, **6a** does not represent an energy minimum). Thus, a simple equilibrium **7a** ⇌ **8a** can now be envisioned. Since $J_{obsd} = N_{7a} \times J_{7a} + N_{8a} \times J_{8a}$, and since we assume $N_{8a} = 1 - N_{7a}$, then $N_{7a} = (J_{obsd} - J_{8a})/(J_{7a} - J_{8a})$. In order to obtain a rough estimate of the molar fractions of **7a** and **8a** (N_{7a} and N_{8a}), we need to have reasonable values for J_{7a} and J_{8a} (both J_{AP} and J_{BP} for conformers **7a** and **8a**). If we use the geometrical parameters obtained by force-field geometry optimization (ALCHEMY II) of **7a** and **8a**, and the Karplus relationship described by Lee and Sarma [9], then we arrive at the following: For **7a**, H^A–C(5)–O(1)–P(2) = 87.3°, $J_{AP} = 0.0$ Hz; H^B–C(4)–N(3)–P(2) = 126.2°, $J_{BP} = 9.1$ Hz. For **8a**, H^A–C(5)–O(1)–P(2) = 98.2°, $J_{AP} = 1.1$ Hz; H^B–C(4)–N(3)–P(2) = 138.5°, $J_{BP} = 13.7$ Hz. Using these vicinal proton-phosphorus coupling constants, we calculate a **7a**/**8a** ratio of about 80/20 for **1** and **2** and about 100% **7a** for **3**. This model does not seem to work well for **4** and **5**; J_{BP} is too low in **4** and too high in **5**. It may be that population of **7b** is occurring to some extent in these equilibria, serving to increase J_{AP} and to decrease J_{BP} [Note that the ALCHEMY II minimized geometry of **7b** has H^A–C(5)–O(1)–P(2) = 126.6° (leading to $J_{AP} = 9.3$ Hz) and H^B–C(4)–N(3)–P(2) = 107.7° ($J_{BP} = 3.0$ Hz)].

There are additional problems with this **7a** ⇌ **8a** equilibrium analysis. There seems to be, at best, only a very subtle trend in the NMR coupling data with respect to changes in the electronic nature of the anilino substituent on phosphorus. Note that J_{AP} increases slightly for **1** $\simeq$ **2** $\simeq$ **3** $<$ **4** $<$ **5**, and that J_{BP} decreases **1** $\simeq$ **2** $>$ **3** $>$ **4**, but increases again for **5**. If the *endo*-anomeric effect (orbital interaction between the lone pair on endocyclic N and O with the exocyclic P–N antibonding orbital) is important in the conformation of these compounds, then going from strongly electron-donating groups in the order NMe_2 > OMe > F > H should result in *increased* population of **8a** rather than decreased. Electron-withdrawing substituents, X, such as NO_2 should *increase* the *endo*-anomeric effect. This increased *endo*-anomeric effect should manifest itself in increasing population of **8a** at the expense of **7a** (which should increase J_{BP}).

An alternative way of analyzing the coupling data is to imagine a single conformation dominating the equilibria. It may be that conformation **7a** is populated to a very large extent in solution and that the subtle changes in $^3J_{HP}$ reflect subtle geometrical changes in the structure. Thus, if **7a** is populated by compounds **1** or **2** in solution, then the coupling J_{AP} and J_{BP} reflect the torsion angles H^A–C(5)–O(1)–P(2) = 70° and H^B–C(4)–N(3)–P(2) = 128° [Note that these dihedral angles are very close to those found in the X-ray crystal structure of **2** (see subsequent discussion): H^A–C(5)–O(1)–P(2) = 72.4° and H^B–C(4)–N(3)–P(2) = 125.2°]. So, **3** (X = F) and **4** (X = H) would then be seen to have decreasing H^B–C(4)–N(3)–P(2) dihedral angles (a trend that develops as X becomes less electron donating). Note that the H^B–C(4)–N(3)–P(2) dihedral angle is *not* decreased in the crystal structure of **3** as compared to that of **2** (see subsequent discussion). Note also that equilibria between conformer **7a** (that found in the crystal structure of **2**) and the envelope conformation, **9**, found in the crystal structure of **4** (see subsequent discussion) may also be possible.

There is an interesting anomaly in these NMR results. The data for **3** (X = F) do not fall in line according to the expected electronic nature of F. A *para*-fluoro substituent is generally considered to be a net electron-withdrawing substituent (σ_P = 0.15, a positive value indicating an electron-withdrawing group) [12]. The coupling data for **3** fall between those for **2** (X = OMe, $\sigma_P = -0.28$) and **4** (X = H, $\sigma_P = 0.0$). This anomalous trend has also been noted in 2-anilino-2-oxo-1,3,2-oxazaphosphorinanes [13]. That is, to fall between X = H and X = OMe, fluorine must behave as an electron-donating substituent.

It seems evident that, in the conformations of phosphorus heterocycles, a 4-fluoroanilino substituent is net electron donating compared to the anilino substituent itself. Since σ_P values represent a sum of resonance (σ_R) and inductive (σ_I) effects,

$$\sigma_P = A\sigma_R + B\sigma_I$$

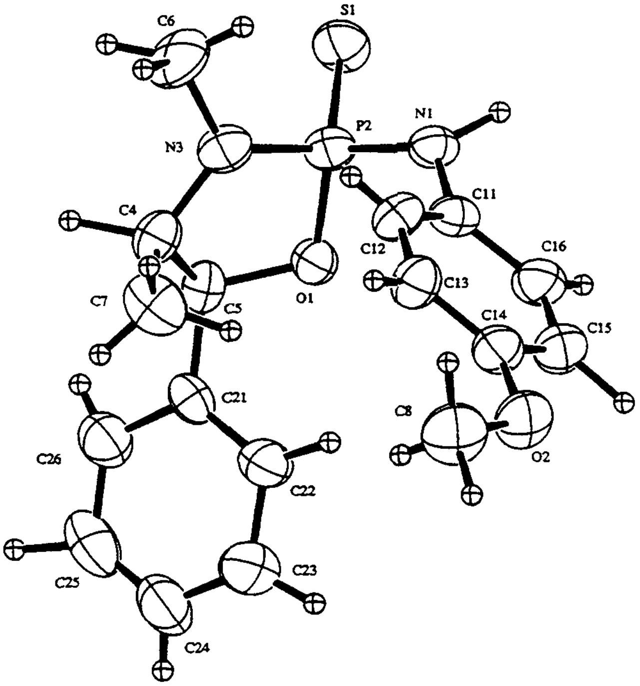


FIGURE 2 ORTEP perspective drawing of oxazaphospholane 2

apparently the coefficients *A* and *B* for the electronic effects of *para* substituents in these conformational studies are not the same as those obtained by correlation with ^{13}C chemical shifts [14] or by other measurements such as chemical reactivities or acidities [12].

The coupling data for **5** (X = NO_2) are different from those of **1–4**. In **5**, J_{AP} is significantly larger (2.1 Hz) than those for **1–4** (all nearly 0 Hz); J_{BP} coupling does not follow the trend established by compounds **1–4**; and J_{YP} is completely different (7 Hz) than those for **1–4** (all about 12 Hz). Apparently, compound **5** (X = NO_2, the only truly electron-withdrawing substituent) behaves in a different manner than do those compounds with electron-donating substituents. It may be that, with an electron-withdrawing group, the *endo*-anomeric effect becomes important enough so that conformation **8a** is predominantly populated rather than **7a**. That is, the predominant conformation of **5** actually has H^A–C(5)–O(1)–P(2) $\simeq$ 104° (thus, $J_{AP} \simeq 2$) and H^B–C(4)–N(3)–P(2) for **5** (X = NO_2) > H^B–C(4)–N(3)–P(2) for **4** (X = H).

Chemical shift trends for compounds **1–4** parallel the coupling trends. Thus, the chemical shifts for H^A, H^B, and H^X increase (shift to lower field) with the decreasing electron-donating ability of X. Note that X = F is a net electron-donating group (δ_A, δ_B, and δ_X for X = F lie between those for X = OMe and X = H). Similarly, ^{31}P chemical shifts decrease (shift to higher field) as X becomes a poorer

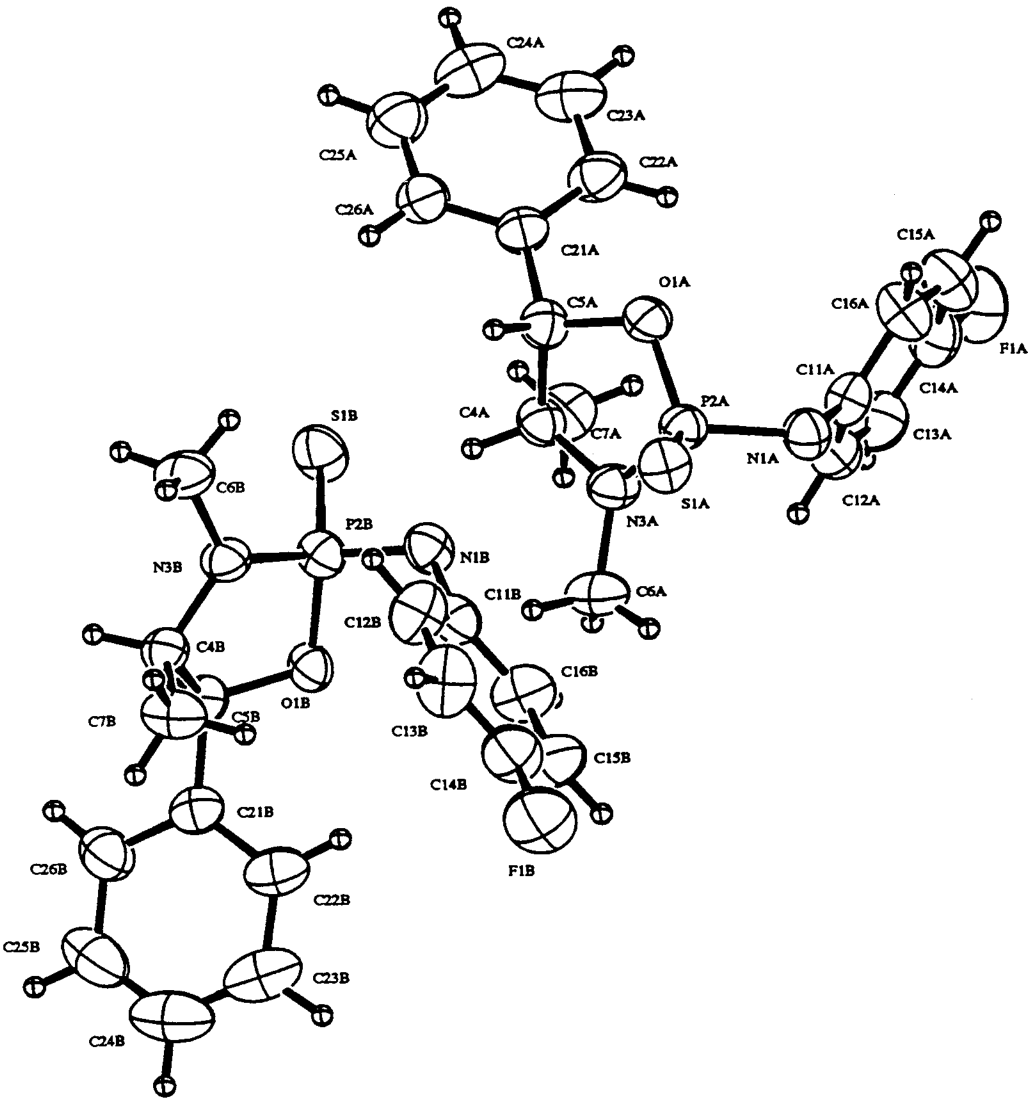


FIGURE 3 ORTEP perspective drawing of oxazaphospholane 3

electron-donating group. Again, δ_P for X = F lies between δ_P for X = OMe and δ_P for X = H, indicating F to be a net electron-donating group. For X = NO_2 (a strongly electron-withdrawing group), the chemical shifts follow the trends established by compounds **1**–**4**, but the differences are much less subtle (e.g., $\Delta\delta_P$ for **1** and **4** = 0.8 ppm, but $\Delta\delta_P$ for **4** and **5** = 6.5 ppm). This may again reflect a conformational shift rather than merely a subtle change in torsional angle.

X-ray Crystal Structure Studies

Single-crystal X-ray structure studies have been carried out on 1,3,2-oxazaphospholanes **2** (X = OMe), **3** (X = F), and **4** (X = H). The crystallographic data for the compounds are listed in Table 2. Final atomic parameters are listed in Tables 3–5, respectively [15]. Selected bond lengths and bond angles are compiled in Table 6, and torsion angles are listed in Table 7. ORTEP perspective drawings of the compounds, including the labeling schemes, are shown in Figures 2–4, respectively. Note that there are two crystallographically independent molecules of **3** in the asymmetric unit.

The conformation adopted by oxazaphospholanes **2** and **3**, in the solid state, can best be described as a twist-envelope in which both the phenyl group on C(5) and the *para*-substituted anilino group on phosphorus are both equatorial, that is, conformation **7a** (Figure 1). The X-ray crystal structure of **4**, on the other hand, indicates that this compound adopts a P-flap envelope with the anilino group equatorial, **9**. The crystal structure of **4** in this study and that determined previously by Bartczak et al. [7] are virtually identical.

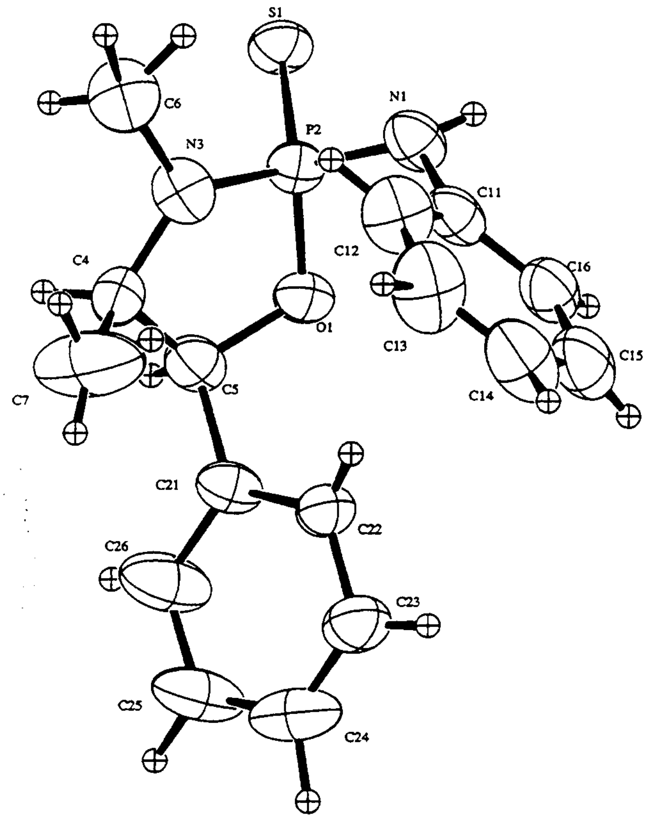


FIGURE 4 ORTEP perspective drawing of oxazaphospholane 4

TABLE 3 Final Atomic Parameters for 1,3,2-Oxazaphospholane **2**

Atom	*x*	*y*	*z*	B_{eq}
P(2)	0.20911(5)	0.3901(2)	0.6673(2)	5.06(8)
S(1)	0.26610(5)	0.5480(3)	0.6739(2)	7.0(1)
O(1)	0.1615(1)	0.5081(6)	0.7026(4)	5.1(2)
O(2)	0.0482(2)	−0.1404(8)	0.3314(5)	7.8(3)
N(1)	0.2028(1)	0.2961(8)	0.5145(5)	5.1(3)
N(3)	0.2016(2)	0.2192(7)	0.7840(5)	5.6(3)
C(4)	0.1623(3)	0.260(1)	0.8793(7)	5.9(4)
C(5)	0.1495(2)	0.479(1)	0.8457(7)	5.1(3)
C(6)	0.2379(4)	0.079(2)	0.828(1)	9.1(6)
C(7)	0.1225(3)	0.108(1)	0.860(1)	8.0(5)
C(8)	0.0333(5)	−0.317(2)	0.401(2)	9.0(7)
C(11)	0.1636(2)	0.179(1)	0.4704(7)	5.0(3)
C(12)	0.1546(2)	−0.008(1)	0.5203(8)	5.7(4)
C(13)	0.1167(3)	−0.119(1)	0.4799(7)	5.9(4)
C(14)	0.0873(2)	−0.043(1)	0.3801(7)	6.1(4)
C(15)	0.0963(2)	0.143(1)	0.3218(8)	6.9(4)
C(16)	0.1343(2)	0.255(1)	0.3655(7)	6.4(4)
C(21)	0.0993(2)	0.5397(9)	0.8694(7)	5.3(3)
C(22)	0.0660(2)	0.517(1)	0.7679(8)	6.7(4)
C(23)	0.0190(3)	0.568(2)	0.795(1)	8.4(5)
C(24)	0.0070(4)	0.642(2)	0.918(1)	9.1(6)
C(25)	0.0384(4)	0.664(1)	1.018(1)	8.8(6)
C(26)	0.0851(3)	0.615(1)	0.9953(8)	7.4(5)

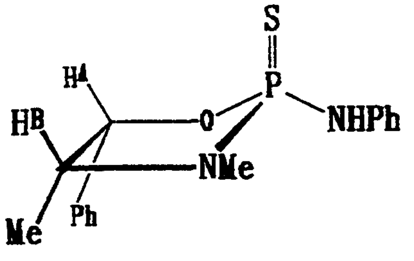
TABLE 4 Final Atomic Parameters for 1,3,2-Oxazaphospholane **3**

Atom	*x*	*y*	*z*	B_{eq}
P(2A)	0.79751(3)	−0.5619(2)	−0.1650(1)	5.34(5)
S(1A)	0.74823(4)	0.5480(3)	0.6739(2)	7.0(1)
O(1A)	0.1615(1)	−0.7613(3)	−0.1669(1)	6.50(6)
F(1A)	0.9388(1)	0.0537(6)	−0.5049(4)	10.6(2)
N(1A)	0.8000(1)	−0.4692(6)	−0.3313(4)	5.9(2)
N(3A)	0.7934(1)	−0.3924(6)	−0.0400(4)	5.7(2)
C(4A)	0.8342(2)	−0.3920(7)	0.0661(5)	5.7(2)
C(5A)	0.8603(2)	−0.5848(8)	0.0351(5)	5.8(2)
C(6A)	0.7487(2)	−0.299(1)	−0.0045(6)	7.7(3)
C(7A)	0.8641(2)	−0.2104(8)	0.0565(6)	7.6(3)
C(11A)	0.8366(2)	−0.3346(7)	−0.3728(5)	5.9(2)
C(12A)	0.8350(2)	−0.1443(8)	−0.3271(6)	6.8(3)
C(13A)	0.8697(2)	−0.0122(8)	−0.3714(7)	7.9(3)
C(14A)	0.9047(2)	−0.074(1)	−0.4627(6)	7.5(3)
C(15A)	0.9080(2)	−0.261(1)	−0.5094(6)	8.1(3)
C(16A)	0.8737(2)	−0.393(1)	−0.4629(6)	7.4(3)
C(21A)	0.9135(1)	−0.5974(7)	0.0678(5)	5.7(2)
C(22A)	0.9470(2)	−0.5321(8)	0.0338(6)	7.1(3)
C(23A)	0.9954(2)	−0.5281(9)	0.008(1)	8.4(3)
C(24A)	1.0090(2)	−0.564(1)	0.1492(8)	8.5(3)
C(25A)	0.9765(2)	−0.626(1)	0.2479(6)	8.8(3)
C(26A)	0.9292(2)	−0.6381(9)	0.2070(5)	7.3(3)
P(2B)	0.71354(4)	−0.7951(2)	0.3308(1)	5.52(5)
S(1B)	0.78050(4)	−0.7225(3)	0.3438(1)	7.45(7)
O(1B)	0.6749(1)	−0.6306(5)	0.3694(3)	5.6(1)
F(1B)	0.51602(9)	−1.0488(7)	−0.0290(4)	11.0(2)
N(1B)	0.7007(1)	−0.8643(6)	0.1625(4)	6.0(2)
N(3B)	0.6934(1)	−0.9520(6)	0.4480(4)	5.5(2)
C(4B)	0.6574(1)	−0.8735(7)	0.5473(5)	5.2(2)
C(5B)	0.6602(1)	−0.6528(7)	0.5196(5)	5.1(2)
C(6B)	0.7169(2)	−1.1337(8)	0.4838(6)	7.3(3)
C(7B)	0.6083(2)	−0.9633(7)	0.5211(7)	6.9(3)
C(11B)	0.6529(2)	−0.9131(8)	0.1154(5)	6.1(2)
C(12B)	0.6328(2)	−1.089(1)	0.1460(6)	8.1(3)
C(13B)	0.5862(2)	−1.135(1)	0.0983(7)	9.1(4)
C(14B)	0.5611(2)	−1.004(1)	−0.0188(7)	8.1(3)
C(15B)	0.5801(2)	−0.829(1)	−0.0155(7)	9.2(4)
C(16B)	0.6262(2)	−0.784(1)	0.0341(6)	8.1(3)
C(21B)	0.6147(1)	−0.5450(7)	0.5465(6)	5.8(2)
C(22B)	0.5810(2)	−0.5090(7)	0.4344(6)	7.2(3)
C(23B)	0.5371(2)	−0.421(1)	0.466(1)	9.3(4)
C(24B)	0.5270(2)	−0.369(1)	0.605(1)	10.4(5)
C(25B)	0.5598(3)	−0.400(1)	0.7133(8)	9.9(4)
C(26B)	0.6042(2)	−0.4860(9)	0.6864(6)	7.8(3)

It is interesting that these very similar compounds adopt somewhat different conformations. Also interesting is the fact that, both in solution and in the solid state, the anilino moiety is found to be equatorial rather than axial as would be expected based upon the anomeric effect, $n[N(3)]-\sigma^*[P-N(1)]$. Indeed, in analogous six-membered-ring 1,3,2-oxazaphosphorinane-2-oxides, para-substituted anilino groups on phosphorus are strongly axial seeking [13].

TABLE 5 Final Atomic Parameters for 1,3,2-Oxazaphospholane **4**

Atom	*x*	*y*	*z*	B_{eq}
P(2)	0.14672(7)	0.06265(4)	0.6686(1)	4.90(4)
S(1)	0.27165(8)	−0.01768(5)	0.6487(1)	6.10(4)
O(1)	0.0102(2)	0.0297(1)	0.6795(3)	5.8(1)
N(1)	0.1742(3)	0.1169(2)	0.8125(4)	6.3(2)
N(3)	0.1210(3)	0.1224(2)	0.5321(4)	6.3(1)
C(4)	0.0099(4)	0.1039(3)	0.4535(5)	7.7(2)
C(5)	−0.0599(4)	0.0426(2)	0.5475(4)	6.2(2)
C(6)	0.2199(5)	0.1644(3)	0.4586(7)	8.4(3)
C(7)	−0.0607(5)	0.1796(6)	0.419(1)	17.8(6)
C(11)	0.0961(3)	0.1807(2)	0.8614(4)	6.1(2)
C(12)	0.0972(5)	0.2519(2)	0.7919(5)	8.1(2)
C(13)	0.0212(7)	0.3128(3)	0.8290(7)	10.4(3)
C(14)	−0.0551(6)	0.3036(4)	0.9420(7)	10.2(4)
C(15)	−0.0572(6)	0.2338(5)	1.0170(7)	9.5(4)
C(16)	0.0187(5)	0.1711(3)	0.9752(5)	7.4(2)
C(21)	−0.1889(3)	0.0650(2)	0.5901(4)	5.8(2)
C(22)	−0.2121(4)	0.1149(2)	0.7075(4)	5.8(2)
C(23)	−0.3309(4)	0.1349(3)	0.7457(5)	7.4(2)
C(24)	−0.4254(4)	0.1062(3)	0.6721(9)	9.3(3)
C(25)	−0.4052(4)	0.0589(4)	0.5537(8)	9.7(3)
C(26)	−0.2878(5)	0.0386(4)	0.513(1)	9.9(4)



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The bond lengths and bond angles in 1,3,2-oxazaphospholanes **2**, **3**, and **4** seem to be completely regular. The thiophosphoryl, P=S, bond is somewhat long, consistent with what has generally been observed when the thiophosphoryl group is axial rather than equatorial. X-ray crystal structures of 1,3,2-dioxa- and 1,3,2-oxazaphosphorinane-2-sulfides indicate equatorial P=S bond lengths to range between 1.89–1.92 Å (average 1.90 Å) [16], while axial P=S bonds are slightly longer, 1.90–1.93 Å (average 1.92 Å) [17]. Similar results are seen in 1,3,2-oxazaphospholanes [7,18]. This slight bond lengthening of the axial P=S group may be attributed to the *endo*-anomeric effect, n[N(3)]–σ^*P=S.

The P(2)–N(1)–C(11) bond angle of 124.9° in **2**, 122.6° and 122.2° in **3**, and 123.7° in **4** indicate sp^2 hybridization at the exocyclic nitrogen. Similarly, the sum of the bond angles about N(3) is 356.4° in **2**, 356.8° and 357.9° in **3**, and 354.9° in **4**, indicating nearly trigonal-planar geometry (sp^2 hybridization) about the *endo* nitrogen as well.

The conformation of the equatorial anilino moiety is such that, not only is the N(1) lone pair in conjunction with the P=S group, but it also allows for an exoanomeric interaction between the N(1) lone pair and the P(2)–N(3) and P(2)–O(1) antibonding orbitals {n[N(1)–σ^*[P–N(3)] and n[N(1)–σ^*[P–O(1)], respectively}. Another interesting feature of the anilino group is that, in both structures, although the exocyclic nitrogen, N(1), is conjugated with the thiophosphoryl group, it is not conjugated with the aryl group. That is, the P(2)–N(1)–C(11)–C(12) torsion angles of −67.5° in **2**, −74.9° and −79.1° in **3**, and −76.5° in **4** indicate the phosphoramide functionality and the aryl group are nearly perpendicular. This lack of conjugation through the exocyclic phosphoramide, insulating the *para*-substituted aryl groups, may be responsible for the nearly absent stereoelectronic effects noted in this series of compounds (see previous discussion).

EXPERIMENTAL

Methods and Materials

Analyses were carried out by either Galbraith Laboratories, Inc. (Knoxville, TN) or by Atlantic Microlab, Inc. (Norcross, GA). Melting points are uncorrected. ^{1}H NMR spectra were obtained at 200 MHz; coupling constants were measured on 100 Hz SW expansions, with 32K database, and 9.044 second acquisition times and are probably accurate to ±0.2 Hz. ^{31}P NMR spectra were taken at 81.015 MHz under proton noise decoupling conditions. Positive ^{31}P chemical shifts are in δ (parts per million) downfield from external 85% H_3PO_4.

(2S,4R,5S)-2-Anilino-2-thio-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane (**4**). *Typical Procedure for the Preparation and Purification of the 1,3,2-Oxazaphospholanes*

A solution of n-butyllithium (1.6 M in hexanes) was slowly added to a solution of aniline (350 mg, 3.82 mmol, freshly distilled from CaH_2) in anhydrous tetrahydrofuran (THF, 20 mL), under dry nitrogen atmosphere, to give a yellow solution. The reaction mixture was stirred at room temperature for 1 hour, after which a solution of (2*R*,4*R*,5*S*)-2-chloro-2-thio-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane (1.0 g, 3.82 mmol) in anhydrous THF (15 mL) was added. The reaction mixture was allowed to stir overnight, the solvents were removed from the reaction mixture, and the residue was chromatographed on a gravity column of florisil eluting with ethyl acetate. The product obtained was further purified by recrystallization from ethyl acetate/pentane to give

TABLE 6 Selected Geometrical Parameters for 1,3,2-Oxazaphospholanes **2**, **3**, and **4**

	Bond Lengths (Å)			
Atoms	**2**	**3A**	**3B**	**4**
P(2)–S(1)	1.936(2)	1.942(2)	1.927(2)	1.931(1)
P(2)–O(1)	1.605(4)	1.592(3)	1.607(3)	1.591(2)
P(2)–N(1)	1.630(5)	1.658(4)	1.647(3)	1.632(3)
P(2)–N(3)	1.625(5)	1.645(4)	1.634(4)	1.627(3)
O(1)–C(5)	1.454(7)	1.470(5)	1.454(5)	1.450(4)
N(1)–C(11)	1.429(7)	1.435(6)	1.427(5)	1.441(5)
N(3)–C(4)	1.482(9)	1.476(5)	1.471(5)	1.447(6)
C(4)–C(5)	1.539(9)	1.546(6)	1.548(6)	1.543(7)

	Bond Angles (°)			
Atoms	**2**	**3A**	**3B**	**4**
S(1)–P(2)–O(1)	116.0(2)	117.4(1)	116.7(1)	115.42(9)
S(1)–P(2)–N(1)	109.3(2)	108.0(1)	108.8(1)	109.4(1)
S(1)–P(2)–N(3)	117.8(2)	116.9(1)	118.4(1)	118.5(2)
O(1)–P(2)–N(1)	106.9(2)	106.6(2)	106.3(2)	108.5(2)
O(1)–P(2)–N(3)	94.5(2)	95.4(2)	94.9(2)	95.9(2)
N(1)–P(2)–N(3)	111.2(3)	111.8(2)	110.8(2)	108.2(2)
P(2)–O(1)–C(5)	110.0(3)	109.9(2)	109.7(3)	113.0(2)
P(2)–N(3)–C(4)	114.5(4)	113.4(3)	114.2(3)	113.3(3)
N(3)–C(4)–C(5)	102.6(5)	103.5(4)	103.0(4)	106.2(3)
P(2)–N(3)–C(6)	124.0(6)	123.3(3)	124.5(3)	121.8(3)
C(4)–N(3)–C(6)	117.9(7)	120.1(4)	119.2(4)	119.8(4)
P(2)–N(1)–C(11)	124.9(4)	122.6(3)	122.2(3)	123.7(3)

TABLE 7 Dihedral Angles (°) in 1,3,2-Oxazaphospholanes **2**, **3**, and **4**

Atoms	**2**	**3A**	**3B**	**4**
N(1)–P(2)–N(3)–C(4)	−119.2(4)	−118.8(3)	−118.4(3)	129.6(3)
S(1)–P(2)–O(1)–C(5)	−96.0(4)	−96.6(3)	−97.4(2)	−106.3(2)
O(1)–P(2)–N(3)–C(4)	−9.1(4)	−8.6(3)	−8.9(3)	−17.9(3)
P(2)–N(3)–C(4)–C(5)	−11.1(6)	−11.6(4)	−11.1(4)	11.0(4)
N(3)–C(4)–C(5)–O(1)	29.1(6)	29.1(4)	29.1(4)	2.1(4)
C(4)–C(5)–O(1)–P(2)	−38.0(6)	−37.5(4)	−37.6(4)	−14.7(3)
C(5)–O(I)–P(2)–N(3)	28.0(4)	27.5(3)	27.8(3)	19.2(2)
P(2)–O(1)–C(5)–C(21)	−164.6(4)	−163.2(3)	−162.9(3)	−141.2(2)
P(2)–N(3)–C(4)–C(7)	112.2(6)	114.7(4)	113.3(4)	136.3(4)
P(2)–O(1)–C(5)–H(A)	72.4	78.6	79.0	107.4
P(2)–N(3)–C(4)–H(B)	−125.2	−126.9	−127.1	−120.4

310 mg (25% yield) of pure **4** as a colorless crystalline solid.

X-ray Crystal Structure of (2S,4R,5S)-2-(4-Methoxyanilino)-2-thio-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane (**2**), *(2S,4R,5S)-2-(4-Fluoroanilino)-2-thio-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane* (**3**), *and (2S,4R,5S)-2-Anilino-2-thio-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane* (**4**)

In each study, a clear colorless crystal suitable for an X-ray crystal structure (grown using the vapor diffusion technique using ethyl acetate and hexane) determination was mounted on a Rigaku AFC5R diffractometer with graphite monochromated Cu K_α radiation and a 12 KW rotating anode generator. Cell constants (Table 2) and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections.

In the crystal structure of **3**, note that the packing resembles $P2_12_12_1$, but we chose to solve the structure in $P2_1$ for the following reasons. (1) We collected data for several crystals, all of which gave β values of 91.3°. (2) We tested the data for Laue group *Pmmm*; it failed. (3) For $h00$, h odd, 6 of 10 reflections were observed with an average $I/\sigma(I)$ of 6; 45/60 of $00l$, l odd were observed with an average $I/\sigma(I)$ of 12.

The data were collected at a temperature of 23° ± 1° using the $\omega - 2\theta$ scan technique to a maximum 2θ value of 120°. The weak reflections [$I < 15.0\sigma(I)$] were rescanned (maximum of four rescans), and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal to detector distance was 600.0 mm.

Empirical absorption corrections, based on azimuthal scans of several reflections, were applied in the cases of compounds **3** and **4**; azimuthal scans of several reflections indicated no need for an absorption correction in **2**. The data were corrected for Lorentz and polarization effects. In **3**, the intensities of three check reflections (measured every 150 reflections) had declined by −26.00%. A linear correction factor was applied to the data to account for this phenomenon.

All three structures were solved by direct methods [19]. The nonhydrogen atoms were refined anisotropically. All hydrogen atoms were located in difference Fourier maps, and their positional and isotropic temperature factors were refined. The final cycle of full-matrix least-squares refinement [20] converged to give the unweighted and weighted agreement factors listed in Table 2.

Neutral atom scattering factors were taken from Cromer and Waber [21]. Anomalous dispersion effects were included in F_C [22]; the values for $\Delta f'$ and $\Delta f''$ were those of Cromer [23]. All calculations were performed using the TEXSAN [24] crystallographic software package of Molecular Structure Corporation.

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