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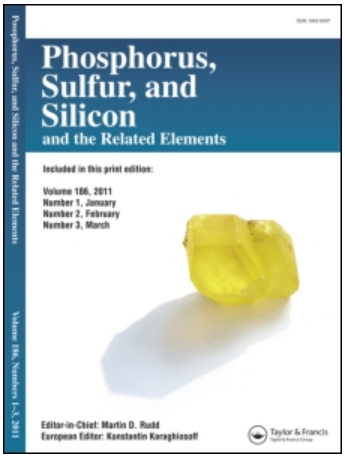

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CONFORMATIONS OF SATURATED SIX-MEMBERED-RING PHOSPHORUS HETEROCYCLES. SYNTHESES AND X-RAY CRYSTAL STRUCTURES OF THREE 2-ANILINO-2-OXO-5,5-DIMETHYL-1,3,2-OXAZAPHOSPHORINANES

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CONFORMATIONS OF SATURATED SIX-MEMBERED-RING PHOSPHORUS HETEROCYCLES. SYNTHESES AND X-RAY CRYSTAL STRUCTURES OF THREE 2-ANILINO-2-OXO-5,5-DIMETHYL-1,3,2-OXAZAPHOSPHORINANES

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Single-crystal X-ray structural determinations have been made on 2-anilino-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, **1**; 2-(4-fluoroanilino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, **2**; and 2-(4-dimethylaminoanilino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, **3**. Compounds **1** and **2** are isostructural and crystallize in the monoclinic space group $P2_1/c$ with four molecules per unit cell. The cell dimensions for **1** are: a = 12.234(4) Å, b = 8.891(3) Å, c = 12.152(4) Å, and B = 110.77(4)°. The cell dimensions for **2** are: a = 12.505(1) Å, b = 8.919(1) Å, c = 12.211(1) Å, and B = 109.14(1)°. Compound **3** crystallizes in the monoclinic space group $P2_1/n$ with four molecules per unit cell of dimensions a = 6.321(2) Å, b = 19.963(3) Å, c = 12.236(2) Å, and B = 104.89(4)°. Full-matrix least-squares refinement for each of the structures led to conventional R factors of 5.1% for **1**, 4.9% for **2**, and 9.5% for **3**. The conformation adopted by **1** and **2** is the chair conformation with the anilino substituent axial. Compound **3** adopts the alternative chair conformation with an equatorially disposed anilino substituent. Structural variations are found which can be attributed to the operation of *exo* and *endo* anomeric effects.

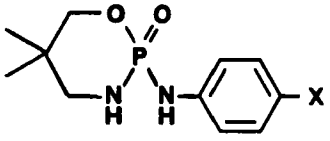
Key words: Oxazaphosphorinane; phosphorus; heterocycle; conformation; X-ray crystal structure; anomeric effect.

INTRODUCTION

We have been interested in the general question of the effect of replacing ring carbon atoms of the cyclohexane ring system by heteroatoms (P, O, S, N, etc.). Heteroatom replacement results in (a) alteration of bond lengths and bond angles within the ring, (b) replacement of ring hydrogen atoms by heteroatom lone pairs, and (c) introduction of bond and molecular dipoles, all of which can have profound effects on the conformational preferences of the six-membered ring. The 1,3,2-oxazaphosphorinane ring system is of special interest because the clinically useful anticancer drugs[1] cyclophosphamide, isophosphamide, and trophosphamide all possess this heterocyclic ring system. We have found the conformational behavior of 1,3,2-oxazaphosphorinanes to be very different from that of cyclohexanes. For

example, 2-oxo-1,3,2-oxazaphosphorinanes are able to adopt twist conformations with relative ease,[2,3] and there is a small axial preference of a dimethylamino substituent on phosphorus when the substituent on ring nitrogen is hydrogen.[4,5] We have found, also, a progressive increase in the conformational free energies of dialkylamino substituents on phosphorus, $Me_2N < Et_2N < (ClCH_2CH_2)_2N <$ *i*-Pr_2N.[4] The conformational energies of phosphorus substituents in this heterocyclic ring system can be attributed to both steric and electronic effects.

In order to isolate and assess systematically the importance of changes in electronic properties of phosphorus substituents, we have synthesized a series of anilino-substituted 1,3,2-oxazaphosphorinanes with various *para* substituents on the anilino moiety. Thus, we can change the electronic nature of the phosphorus substituent without changing the steric requirements. Single-crystal X-ray structural studies were undertaken to examine the structural ramifications of these electronic substitutions. In this paper we report the syntheses and X-ray crystal structures of three anilino-substituted phosphorus heterocycles: 2-anilino-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, **1**; 2-(4-fluoroanilino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, **2**; and 2-(4-dimethylaminoanilino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, **3**. Significant differences in ring conformation and key bond lengths are found.



1, X = H

2, X = F

3, X = NMe_2

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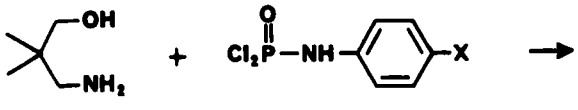
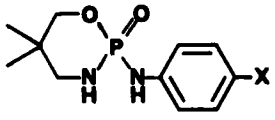
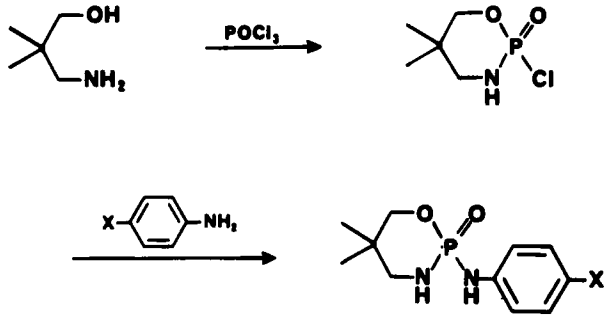
RESULTS AND DISCUSSION

Syntheses. Compounds **1** and **3** were each prepared by cyclization of 2-(hydroxymethyl)-2-methylpropylamine and the appropriate phosphoramidic dichloride:





Compound **2** was prepared by cyclization with phosphorus oxychloride followed by reaction with the appropriate aniline:



X-ray Crystal Structures. 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.[6]

Compounds **1** and **2** are isomorphous and adopt, in the crystal, chair conformations with the anilino substituent axial. Compound **3**, on the other hand, adopts the alternative chair conformation with the anilino group equatorial—a very unexpected result. An axial preference of the anilino group is presumably due to the anomeric effect in this heterocyclic ring system[7] and this effect is generally observed for small electronegative substituents on phosphorus in 1,3,2-dioxaphosphorinanes as well as 1,3,2-oxazaphosphorinanes.[8] Thus, the anilino group is axial in the X-ray crystal structure of 5,5-dimethyl-2-anilino-2-oxo-1,3,2-dioxaphosphorinane.[9] Differences in crystal packing may be responsible for the conformational differences in **1** and **2** vs. **3**. The fortuitous difference in the conformations of **1** and **2** compared to **3**, however, presents a unique opportunity to compare structural parameters of

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TABLE I

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

Compound	**1**	**2**	**3**
Molecular formula	$C_{11}H_{17}N_2O_2P$	$C_{11}H_{16}N_2O_2FP$	$C_{13}H_{22}N_3O_2P$
Molecular weight	240.24	258.23	283.312
Crystal size, mm	0.3 × 0.2 × 0.4	0.3 × 0.3 ×0.3	0.3 × 0.3 × 0.5
Diffractometer	CAD-4	CAD-4	CAD-4
Radiation, Å	MoKα (0.71073)	CuKα (1.54178)	MoKα (0.71073)
Space group	$P2_1/c$	$P2_1/c$	$P2_1/n$
Cell dimensions			
a, Å	12.234(4)	12.505(1)	6.321(2)
b, Å	8.891(3)	8.919(1)	19.962(3)
c, Å	12.152(4)	12.211(1)	12.236(2)
β, deg	110.77(4)	109.14(1)	104.89(4)
V, Å^3	1235.9	1286.6	1492.2
Z	4	4	4
Absorption coeff. (μ), mm^{-1}	0.215	1.719	0.192
Final R	0.051	0.049	0.095

TABLE II

Atomic parameters for compound **1**

Atom	x	y	z	B(Å²)
P(2)	0.47502(4)	0.33741(6)	0.34413(4)	3.138(9)
O(1)	0.3649(1)	0.2985(2)	0.2324(1)	3.59(3)
O(2)	0.5022(1)	0.4993(2)	0.3545(1)	3.90(3)
N(1)	0.5762(2)	0.2361(2)	0.3200(2)	3.98(4)
N(3)	0.4477(2)	0.2754(2)	0.4569(2)	4.05(4)
C(4)	0.3746(2)	0.1404(3)	0.4444(2)	4.26(5)
C(5)	0.2612(2)	0.1494(3)	0.3373(2)	3.75(4)
C(6)	0.2930(2)	0.1659(3)	0.2288(2)	3.81(4)
C(7)	0.1855(2)	0.2805(3)	0.3493(2)	5.49(6)
C(8)	0.1938(2)	0.0021(3)	0.3252(3)	5.64(6)
C(1)′	0.6976(2)	0.2410(2)	0.3817(2)	3.59(4)
C(2)′	0.7479(2)	0.3358(3)	0.4767(2)	4.48(5)
C(3)′	0.8676(2)	0.3393(3)	0.5316(3)	5.61(7)
C(4)′	0.9386(2)	0.2484(4)	0.4937(3)	5.90(7)
C(5)′	0.8891(2)	0.1535(4)	0.4013(3)	5.65(6)
C(6)′	0.7687(2)	0.1479(3)	0.3449(2)	4.52(5)
HN(1)	0.554	0.174	0.265	4.0
HN(3)	0.455	0.334	0.517	4.0

TABLE III

Atomic parameters for compound **2**

Atom	x	y	z	1000 *U*
P(2)	0.02631(3)	0.65878(5)	0.15668(3)	40.6(2)
O(1)	0.13214(9)	0.6976(1)	0.26522(9)	29.8(6)
O(2)	0.00022(9)	0.4975(1)	0.14626(9)	44.6(6)
N(1)	0.0732(1)	0.2587(2)	0.3172(1)	45.9(8)
N(3)	0.0541(1)	0.7219(2)	0.0448(1)	59.2(8)
C(4)	0.1238(2)	0.8570(2)	0.0553(2)	49.5(10)
C(5)	0.2334(1)	0.8488(2)	0.1596(1)	45.0(9)
C(6)	0.2012(1)	0.8310(2)	0.2683(1)	43.6(9)
C(7)	0.3076(2)	0.7198(3)	0.1469(3)	59.1(15)
C(8)	0.2973(3)	−0.0027(3)	0.1707(3)	63.8(18)
C(1)′	0.1901(1)	0.2558(2)	0.3785(1)	45.2(8)
C(2)′	0.2370(2)	0.1603(2)	0.4714(2)	49.4(10)
C(3)′	0.3536(2)	0.3414(3)	0.0268(2)	55.9(10)
C(4)′	0.4195(2)	0.2525(3)	0.4897(2)	56.1(10)
C(5)′	0.3766(2)	0.3489(3)	0.3999(2)	55.5(12)
C(6)′	0.2608(2)	0.3504(2)	0.3441(2)	49.7(10)
F(1)′	0.46612(9)	0.7489(2)	0.4545(1)	74.7(8)
HN(1)	−0.054(1)	0.820(2)	0.233(2)	67(6)
HN(3)	0.047(1)	0.662(2)	−0.013(2)	63(6)

2-oxo-1,3,2-oxazaphosphorinanes which differ primarily in the axial or equatorial placement of the P═O and NHAr groups attached to phosphorus. Although the substituents on the axial NHPh moiety differ in **1** (X = H) and **2** (X = F), the structural parameters of **1** and **2**, as will be seen, are essentially the same, being unaffected by the *para*-fluoro substituent in **2**. The potentially electron donating *p*-NMe_2 of **3** may add a small electronic pertubation to the system (see comments below). However, its effect is unlikely to be a major factor in the effects noted which we assign primarily to the change in phosphorus configuration in **1** and **2** vs. **3**.

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TABLE IV
Atomic parameters for compound **3**

Atom	x	y	z	B(Å²)
P(2)	0.3015(5)	0.0174(1)	0.6331(2)	2.98(5)
O(1)	0.428(1)	0.0580(4)	0.7416(5)	3.9(2)
O(2)	0.290(1)	0.0537(3)	0.5260(5)	2.5(2)
N(1)	0.436(1)	−0.0520(4)	0.6303(7)	3.6(2)
N(3)	0.074(1)	−0.0010(4)	0.6634(6)	3.2(2)
C(4)	−0.042(2)	0.0489(6)	0.7170(9)	5.0(3)
C(5)	0.121(2)	0.0796(6)	0.8200(9)	4.5(3)
C(6)	0.309(2)	0.1108(6)	0.7870(9)	4.9(3)
C(7)	0.189(3)	0.0236(9)	0.914(1)	8.1(4)
C(8)	−0.014(3)	0.1352(8)	0.868(1)	8.1(5)
C(1)′	0.507(2)	−0.1039(5)	0.7138(7)	3.0(2)
C(2)′	0.365(2)	−0.1255(5)	0.7794(8)	3.8(3)
C(3)′	0.427(2)	−0.1804(5)	0.8554(9)	4.0(2)
C(4)′	0.627(2)	−0.2131(5)	0.8611(9)	4.1(3)
C(5)′	0.764(2)	−0.1896(6)	0.7954(9)	4.7(3)
C(6)′	0.695(2)	−0.1338(6)	0.7227(9)	4.3(3)
N(1)′	0.687(2)	−0.2707(5)	0.9312(8)	5.2(2)
C(7)′	0.560(2)	−0.2866(6)	1.011(1)	6.1(3)
C(8)′	0.898(2)	−0.2991(7)	0.950(1)	6.4(4)
HN(1)	0.542	−0.041	0.653	5.0
HN(3)	−0.013	−0.016	0.604	5.0

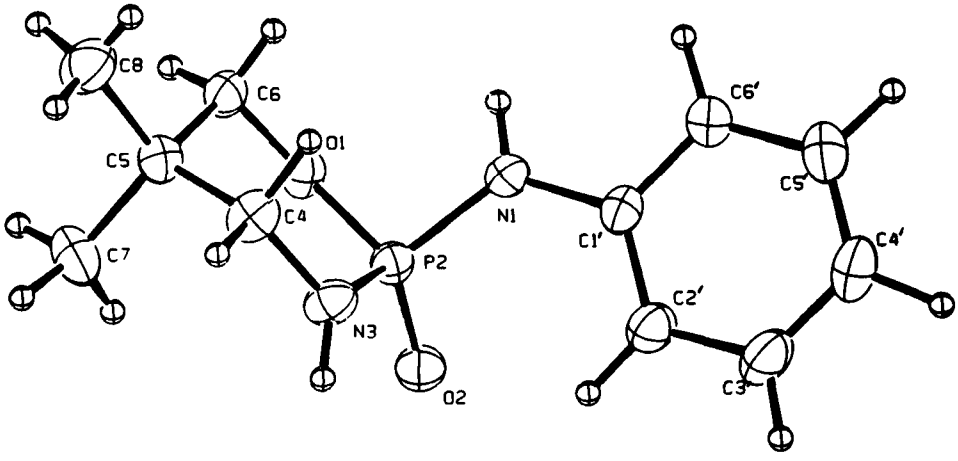

FIGURE 1 ORTEP perspective view of 1,3,2-oxazaphosphorinane **1**.

The gross structural features of **1**, **2**, and **3** are comparable to other structures of 1,3,2-oxazaphosphorinanes having amino substituents on phosphorus and adopting chair conformations.[10–13] The phosphorus end of the heterocycle is somewhat flattened in the 1,3,2-oxazaphosphorinanes. Such flattening has also been observed in 1,3,2-dioxaphosphorinanes.[14] Interestingly, the six-membered ring is more flattened in **1** and **2** than in **3**. Thus, the angle between the O(1)—P(2)—N(3) flap and the O(1)—N(3)—C(4)—C(6) average plane, ϕ, is 31.3° in **1** and 31.6° in **2**, but 44.2° in **3**. Note that the analogous flap angle in the structurally similar compound, 2-anilino-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane, is 34°.[9] The anilino

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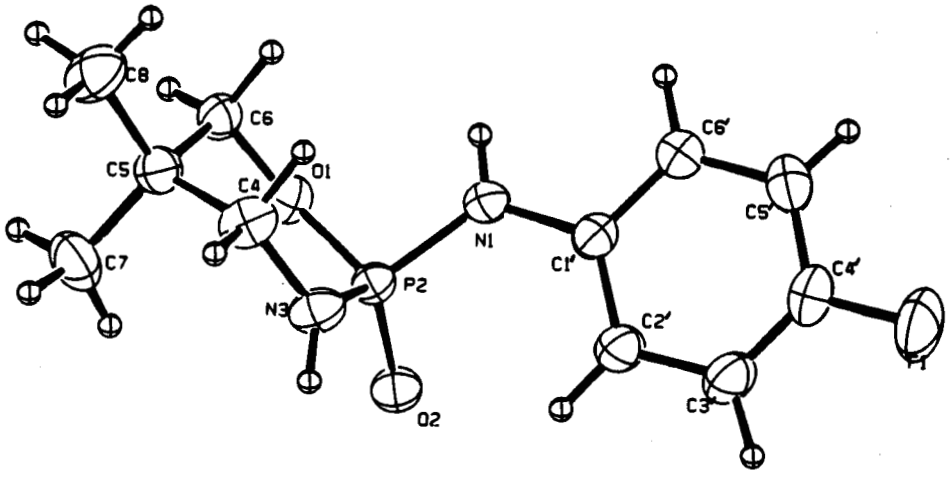

FIGURE 2 ORTEP perspective view of 1,3,2-oxazaphosphorinane **2**.

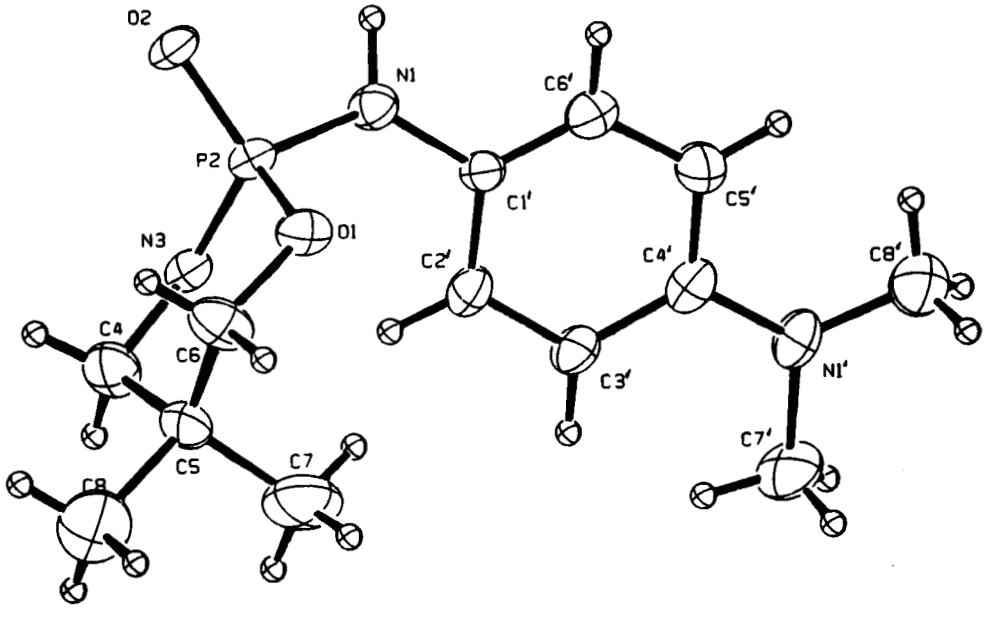

FIGURE 3 ORTEP perspective view of 1,3,2-oxazaphosphorinane **3**.

group is axial in this compound. The 2-(dimethylamino)-2-oxo-3-aryl-5,5-dimethyl-1,3,2-oxazaphosphorinanes, described in the accompanying paper,[15] have the Me_2N group equatorial and show values of ϕ ranging 42–45°. The increased flattening for the chair with the axial anilino group perhaps may be attributed to the increased steric demand of that group compared to the phosphoryl. X-ray crystal structures of *cis*- and *trans*-2-(*t*-butylamino)-2-seleno-4-methyl-1,3,2-dioxaphosphorinane show analogous trends. The structure with the axial *t*-butylamino group has a phosphorus

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TABLE V

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

Atoms	Compounds		
	1	**2**	**3**
P(2)—O(1)	1.5746(9)	1.5741(9)	1.587(3)
P(2)—O(2)	1.4725(9)	1.472(1)	1.484(3)
P(2)—N(1)	1.639(1)	1.645(2)	1.629(4)
P(2)—N(3)	1.619(1)	1.618(2)	1.615(4)
O(1)—C(6)	1.463(2)	1.463(2)	1.483(6)
N(3)—C(4)	1.473(2)	1.468(3)	1.486(6)
C(4)—C(5)	1.530(2)	1.536(2)	1.533(7)
C(5)—C(6)	1.509(2)	1.517(3)	1.419(7)
N(1)—C(1)′	1.408(2)	1.407(2)	1.443(6)
O(1)—P(2)—N(3)	106.54(5)	106.30(7)	102.2(2)
P(2)—N(3)—C(4)	119.37(9)	119.8(1)	121.2(3)
N(3)—C(4)—C(5)	112.3(1)	112.1(1)	109.2(4)
C(4)—C(5)—C(6)	108.2(1)	108.0(2)	110.9(5)
C(5)—C(6)—O(1)	113.0(2)	112.7(1)	108.7(4)
C(6)—O(1)—P(2)	121.65(8)	121.77(9)	118.8(3)
O(1)—P(2)—N(1)	101.20(5)	101.44(7)	107.4(2)
O(1)—P(2)—O(2)	112.74(5)	112.91(6)	112.9(2)
O(2)—P(2)—N(1)	112.97(6)	112.72(8)	107.8(2)
O(2)—P(2)—N(3)	111.64(6)	111.73(8)	117.9(2)
N(1)—P(2)—N(3)	111.14(7)	111.13(8)	108.1(2)
P(2)—N(1)—C(1)′	127.6(1)	127.4(1)	131.5(3)
P(2)—N(1)—HN(1)	117(1)	117(1)	101(5)
C(1)′—N(1)—HN(1)	115(1)	115(1)	82(6)
P(2)—N(3)—HN(3)	121(2)	118(1)	108(3)
C(4)—N(3)—HN(3)	117(2)	119(1)	109(3)
O(1)—P(2)—N(3)—C(4)	31.7(2)	32.1(2)	42.0(8)
P(2)—N(3)—C(4)—C(5)	−49.2(3)	−49.3(2)	−50.1(11)
N(3)—C(4)—C(5)—C(6)	59.8(2)	59.5(2)	57.3(12)
C(4)—C(5)—C(6)—O(1)	−58.3(2)	−58.3(2)	−62.4(12)
C(5)—C(6)—O(1)—P(2)	47.4(2)	47.8(2)	60.5(10)
C(6)—O(1)—P(2)—N(3)	−30.8(2)	−31.2(1)	−46.3(8)
O(2)—P(2)—N(1)—C(1)′	49.3(2)	51.0(2)	175.8(9)
P(2)—N(1)—C(1)′—C(2)′	1.2(3)	1.5(3)	41.0(13)

flap angle, ϕ, of 37°[16] whereas the equatorially disposed *t*-butylamino group results in a flap angle of 44°.[17]

The geometry around the phosphorus atom in each of these compounds, as expected, is a distorted tetrahedron. Although the P(2)—O(2) bond lengths are typical for phosphoryl P=O double bonds, it is worth noting that P(2)—O(2) is somewhat longer (1.484 Å) in compound **3** than those in **1** or **2** (1.473 Å and 1.472 Å, respectively). In addition, P(2)—O(1) is longer in **3** (1.587 Å) than in **1** or **2** (1.575 Å and 1.574 Å, respectively) while P(2)—N(1) is shorter in **3** than those in **1** and **2** (1.629 Å, 1.639 Å, and 1.645 Å, respectively). For the P(2)—O(2) and P(2)—O(1) bonds, these differences are beyond 2.7σ (>99% confidence level). For the P(2)—N(1) bonds, the differences (**1** vs. **3**, e.g.) exceed 2σ (95% confidence level).[18]

All of these bond length results are consistent with the *endo* anomeric effect[7] in this heterocyclic system. That is, the conformation with the axial anilino group on

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phosphorus shows a lengthening of the exocyclic P—N bond with concomitant shortening of the endocyclic P—O bond. An axial disposition of the phosphoryl substituent, on the other hand, results in a lengthening of the phosphoryl P=O bond. Curiously, the endocyclic P(2)—N(3) bonds, in this study, are all equal within experimental error. (See further comment on this finding below.) The P(2)—O(1) bond length responds in such a way as to suggest its involvement in *endo* anomeric interactions may be greater in **1** and **2** than in **3**.

The P(2)—N(1)—C(1)′—C(2)′ dihedral angles for compounds **1** and **2** are small (1.2° and 1.5°, respectively) indicating essential coplanarity and suggesting conjugation between the aryl group and the N(1) nitrogen lone pair. Additional structural evidence in support of such conjugation are the relatively short N(1)—C(1)′ bonds (1.408 Å in **1** and 1.407 Å in **2**) and the sp^2 hybridization of N(1) (sum of bond angles around N(1) for **1** = 360°, sum around N(1) for **2** = 359°) in these compounds. This conjugation is not observed in compound **3**. Thus, P(2)—N(1)—C(1)′—C(2)′ = 41.0° (*not* coplanar), and N(1)—C(1)′ = 1.443 Å (relatively long).

The above results illustrate for the first time for 2-oxo-1,3,2-oxazaphosphorinanes the lengthening of an axial P—N bond *without accompanying pyramidalization at nitrogen*. Closely similar structural details have been noted for the axial anilino group in the corresponding 2-anilino-2-oxo-[9] and 2-seleno-5,5-dimethyl-1,3,2-dioxaphosphorinanes[19] (sum of bond angles about nitrogen, 354° and 359°). The phenyl ring, as noted earlier, is not properly oriented to optimize conjugation with the lone pair of N(1) of **3**. The lack of such an interaction, however, would not necessarily be expected to result in *nonplanarity* about nitrogen for this equatorial, substituted-anilino group. Thus, equatorial dialkylamino groups are normally *planar* in 2-oxo-1,3,2-dioxa- and 2-oxo-1,3,2-oxazaphosphorinanes, presumably to optimize interactions between the exocyclic amino nitrogen and the orbitals and other substituents about phosphorus, and have decreased P—N bond lengths. Furthermore, the P=O bond is usually coplanar with the trigonal planar exocyclic nitrogen and orthogonal to the nitrogen lone pair. (See Reference 5 for a discussion of these effects.) In the structure of **3**, the dihedral angle O(2)—P(2)—N(1)—C(1)′ is 175.8°. Since the position of the HN(1) did not refine well, we are unwilling to say for certain whether N(1) is pyramidal or planar in **3**. But if it is pyramidal, the N lone pair is then in position for overlap with the back lobe of the endocyclic P(2)—N(3) σ^* orbital. This *exo* anomeric interaction (structure **4**) could potentially lead to a lengthened P(2)—N(3) distance in **3** which, however, is not observed [P(2)—N(3) bond distances, 1.615–1.619 Å for **1–3**]. This may be because the *endo* and *exo* anomeric effects involving the P(2)—N(3) bond offset one another. In this regard, as shown in **5**, the dihedral angle O(2)—P(2)—N(1)—C(1′) is about 50° in both **1** (49.3°) and **2** (51.0°). In this conformation the relatively small NH(1) is placed over the 1,3,2-oxazaphosphorinane ring. The aryl ring is coplanar with the P(2)—N(1) bond. Furthermore, the N(1) lone pair is properly oriented for maximal overlap with the P(2)—N(3) σ^* orbital potentially leading to N(3)—P(2) bond lengthening. This may offset the shortening of that bond by the above-described *endo* anomeric interaction of the N(3) lone pair with the apical P(2)—N(1) σ^* orbital.

If the geometry about N(1) is planar instead of the pyramidal arrangement shown in **4**, partial overlap with both the P(2)—N(3) and P(2)—O(1) σ^* orbitals will

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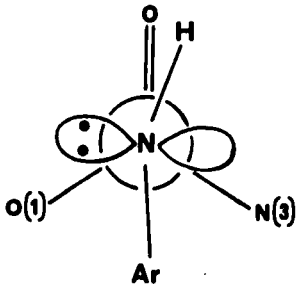
occur. Again a compensatory *exo* anomeric lengthening of the P(2)—N(3) bond would result. In structures **4** and **5**, *exo* and *endo* anomeric effects involving the P(2)—N(1) and P(2)—N(3) σ^* orbitals and nitrogen lone pairs work in opposite directions. It is not possible to say which of the four effects is dominant, but nonetheless a net *lengthening* of the axial P(2)—N(1) bond is observed for **1** and **2** compared to the equatorial one in **3**. At the same time the P(2)—N(3) bond lengths remain unperturbed. This same interplay of interactions of the P(2)—N(1) σ^* orbital with the O(1) lone pair gives a net *shortening* of the P(2)—O(1) bond in **1** and **2**.



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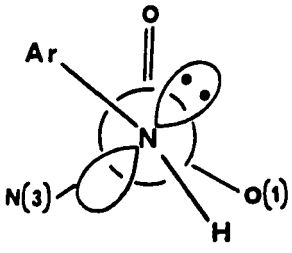

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EXPERIMENTAL

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. ^{1}H NMR spectra were taken on a Varian SC 300 spectrometer operated in the FT mode, or on a Varian EM 390 CW instrument. ^{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 using direct inlet sampling.

Phenylphosphoramidic Dichloride. A solution of phosphorus oxychloride (5.12 mL, 55.0 mmol) in anhydrous dichloromethane (40 mL) was slowly added, under dry nitrogen atmosphere, to a solution of freshly distilled aniline (10.0 mL, 110 mmol) in anhydrous dichloromethane (30 mL). The reaction mixture was stirred at room temperature for three days, the aniline hydrochloride filtered off, and the solvent removed from the filtrate under reduced pressure. The residual solid was recrystallized twice from CH_2Cl_2/pentane to give 8.31 g (78.4% yield) phenylphosphoramidic dichloride as a colorless crystalline solid: mp 86–88°C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.2 (m, aromatic); ^{31}P NMR ($CDCl_3$) δ 8.45; IR (5% $CDCl_3$) 3360, 3150 (s, b, N—H), 2968, 2892, 1600, 1493, 1300, 1256 (s, P=O), 1224, 1033, 1005, 973 cm^{-1}; mass spectrum (EI) m/e 211 (62%), 209 (M^+, 100%), 175 (23%), 173 (84%), 138 (42%), 92 (69%), 91 (48%), 65 (99%). Anal. Calcd. for $C_6H_5PONCl_2$: C, 34.31; H, 2.89; N, 6.67; Cl, 33.76; P, 14.75. Found: C, 34.07; H, 2.82; N, 6.53; Cl, 34.00; P, 14.51.

2-Anilino-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, **1**. A solution of phenylphosphoramidic dichloride (4.32 g, 20.6 mmol) in anhydrous ethyl acetate (100 mL) was added slowly to a rapidly stirred solution of 2-(hydroxymethyl)-2-methylpropylamine (2.13 g, 20.6 mmol), anhydrous triethylamine (5.46 mL, 41.2 mmol), and anhydrous ethyl acetate (200 mL). The reaction mixture was stirred for five days. The triethylamine hydrochloride which had formed was filtered off and the solvent removed from the filtrate under reduced pressure to give 760 mg of a pale yellow solid. The crude solid was recrystallized twice from ethyl acetate to give 584 mg (11.8% yield) 2-anilino-2-oxo-5,5-dimethyl-1,3,2-oxazaphos-

phorinane as a colorless crystalline solid: mp 223–223°C; ^{1}H NMR (90 MHz, acetone-d_6) δ 0.80 (s, 3H, CCH_3), 1.18 (s, 3H, CCH_3), 2.5–4.6 (m, 4H, —NCH_2—, —OCH_2—), 6.5–7.5 (m, 5H aromatic); ^{31}P NMR (acetone-d_6) δ 0.16; IR (KBr) 3280 (s, b, N—H), 3210 (s, b, N—H), 2965, 1607, 1502, 1469, 1297, 1202 (s, P=O), 1087, 1028, 994, 953, 936, 852, 740, 686 cm^{-1}; mass spectrum (EI) m/e 240 (M^+, 100%), 185 (62%), 184 (99%), 155 (48%), 93 (18%). Anal. Calcd. for $C_{11}H_{17}N_2O_2P$: C, 54.99; H, 7.13; N, 11.66; P, 12.89. Found: C, 54.88; H, 7.24; N, 11.43; P, 13.08.

2-(4-Fluoroanilino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, **2.** A solution of $POCl_3$ (2.37 g, 15.6 mmol) in anhydrous tetrahydrofuran (diluted to a total volume of 25 mL) and a solution of 2-(hydroxymethyl)-2-methylpropylamine (2.0 g, 19.4 mmol) and anhydrous triethylamine (3.1 g, 30.7 mmol) in anhydrous tetrahydrofuran (diluted to a total volume of 25 mL) were added slowly and simultaneously, via a syringe drive pump, under argon atmosphere, to cooled (0°C), rapidly stirred tetrahydrofuran (100 mL). The reaction mixture was stirred at 0°C for 1.5 h and for an additional 10 h at room temperature. A solution of 4-fluoroaniline (1.73 g, 15.6 mmol) and triethylamine (1.6 g, 15.8 mmol) was added to the reaction mixture and stirring was continued for 2 days. The triethylamine hydrochloride was filtered off and the solvent removed from the filtrate *in vacuo*. The residue was recrystallized from EtOH/EtOAc/heptane to give 1.27 g (31.5% yield) of the desired product as a colorless crystalline solid: mp 234–235°C; ^{1}H NMR (90 MHz, acetone-d_6) δ 0.79 (s, 3H, CCH_3), 1.14 (s, 3H, CCH_3), 2.57–4.06 (m, 4H, —CH_2N—, —CH_2O—), 6.77–7.17 (m, 4H, aromatic); ^{31}P NMR (acetone-d_6) δ 2.59; IR (KBr) 3278 (s, N—H), 3200 (s, N—H), 2960, 2865, 1501 (s), 1469, 1407, 1388, 1310, 1299, 1287, 1220 (s, P=O), 1198 (s, P=O), 1155, 1084, 1036, 994, 950, 937, 855, 820, 773 cm^{-1}; mass spectrum m/e 258 (M^+, 49%), 202 (32%), 201 (50%), 173 (56%), 166 (11%), 134 (24%), 111 (40%), 110 (22%), 109 (11%), 106 (13%), 84 (16%), 83 (21%), 70 (11%), 56 (11%), 55 (11%), 44 (16%), 41 (22%), 40 (100%). Anal. Calcd. for $C_{11}H_{16}N_2O_2PF$: C, 51.16; H, 6.25; N, 10.85; P, 11.82. Found: C, 50.98; H, 6.07; N, 10.81; P, 11.64.

2-(4-Dimethylaminoanilino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, **3.** Phosphorus oxychloride (1.87 mL, 20.0 mmol) was added slowly to a solution of freshly distilled *N,N*-dimethyl-4-phenylenediamine (2.72 g, 20.0 mmol), anhydrous triethylamine (2.79 mL, 20.0 mmol), and anhydrous ethyl acetate (400 mL). The reaction mixture was stirred at room temperature for two days. The reaction mixture was heated to gentle reflux and a solution of freshly distilled 2-(hydroxymethyl)-2-methylpropylamine (2.06 g, 20.0 mmol), anhydrous triethylamine (4.58 mL, 40.0 mmol), and anhydrous ethyl acetate (200 mL) was slowly added. Reflux was continued for five days. The triethylamine hydrochloride was filtered off and the solvent removed from the filtrate under reduced pressure leaving 3.67 g brown residual oil. A 680-mg sample of the crude oil so obtained was chromatographed by MPLC on silica gel, eluting with EtOAc/EtOH (80:20) to give 160 mg (15.2% yield) 2-(4-dimethylaminoanilino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane as a colorless crystalline solid which was recrystallized from ethyl acetate: mp 199–200°C; ^{1}H NMR (300 MHz, acetone-d_6 δ 0.75 (s, 3H, CCH_3), 1.07 (s, 3H, CCH_3), 2.72 (s, 6H, $N(CH_3)_2$), 2.80 (m, 1H, —NCH_2—), 2.96 (m, 1H, —NCH_2—), 3.73 (m, 1H, —OCH_2—), 3.90 (m, 1H, —OCH_2—), 4.18 (s, 2H, NH), 6.65 (d, J = 8.8 Hz, 2H, aromatic), 6.92 (d, J = 8.8 Hz, 2H, aromatic); ^{31}P NMR (acetone-d_6) δ 4.28; IR (KBr) 3220–3130 (s, b, N—H), 2955, 2875, 1516 (s), 1480, 1442, 1389, 1347, 1323, 1285, 1244, 1218, 1173 (s, P=O), 1080, 1025, 1000 (s), 985, 945, 920, 859, 809, 788 cm^{-1}; mass spectrum (EI) m/e 283 (M^+, 76%), 198 (100%), 136 (15%), 135 (80%), 134 (18%), 119 (11%). Anal. Calcd. for $C_{13}H_{22}N_3O_2P$: C, 55.11; H, 7.83; N, 14.84; P, 10.93. Found: C, 55.16; H, 7.68; N, 14.92; P, 11.07).

X-ray Single-Crystal Structure Studies of **1** *and* **3**.[20] In each study, a well formed crystal was mounted on an Enraf-Nonius CAD-4 diffractometer equipped with scintillation counter and graphite monochromated MoKα radiation (λ = 0.71073 Å). For each structure the θ–2θ data collection method was used to collect the data. Each structure was solved using direct methods (MULTAN[21]) and refined by full-matrix least-squares techniques. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in geometrically ideal positions, except for HN(1) and HN(3) which were located from electron density difference maps, and were not refined.

X-ray Single-Crystal Structure Study of **2**.[22] A well formed crystal of the compound was mounted on an Enraf-Nonius and CAD-4 diffractometer equipped with scintillation counter and CuKα radiation (λ = 1.54178 Å). Intensities were corrected for absorption, Lorentz, and polarization effects. The structure was solved by direct methods (MULTAN[21]) and refined by full-matrix least-squares techniques. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located in difference Fouriers and were refined isotropically.

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