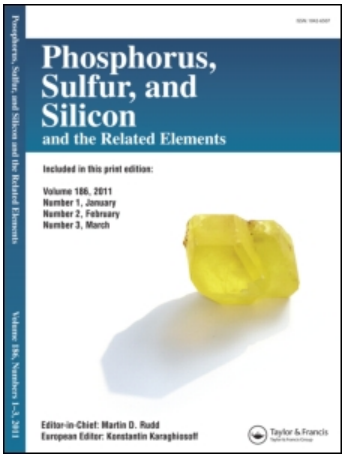

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CONFORMATIONS OF SATURATED SIX-MEMBERED-RING PHOSPHORUS HETEROCYCLES SYNTHESES AND X-RAY CRYSTAL STRUCTURES OF TWO 2-(DIMETHYLAMINO)-2-OXO-3-ARYL-5,5-DIMETHYL-1,3,2-OXAZAPHOSPHORINANES

Wesley G. Bentrude[a]; William N. Setzer[a]; Ahmed A. Kergaye[a]; Victor Ethridge[a]; M. Reza Saadein[a]; Attta M. Arif[a]
[a] Department of Chemistry, The University of Utah, Salt Lake City, Utah

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CONFORMATIONS OF SATURATED SIX-MEMBERED-RING PHOSPHORUS HETEROCYCLES SYNTHESES AND X-RAY CRYSTAL STRUCTURES OF TWO 2-(DIMETHYLAMINO)-2-OXO-3-ARYL-5,5-DIMETHYL-1,3,2-OXAZAPHOSPHORINANES

WESLEY G. BENTRUDE, WILLIAM N. SETZER, AHMED A. KERGAYE, VICTOR ETHRIDGE, M. REZA SAADEIN and ATTA M. ARIF

Department of Chemistry, The University of Utah, Salt Lake City, Utah 84112

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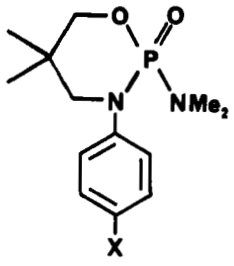
The crystal and molecular structures have been determined for 2-(dimethylamino)-2-oxo-3-(4-fluorophenyl)-5,5-dimethyl-1,3,2-oxazaphosphorinane, **1**, and 2-(dimethylamino)-2-oxo-3-(4-dimethylaminophenyl)-5,5-dimethyl-1,3,2-oxazaphosphorinane, **2**. Compound **1** crystallizes in the monoclinic space group $P2_1/c$ with eight molecules per unit cell (2 crystallographically independent molecules) of dimensions a = 17.251(4) Å, b = 10.822(3) Å, c = 18.075(6) Å, and β = 118.20(2)°. Compound **2** crystallizes in the monoclinic space group $P2_1/a$ with Z = 4, a = 14.148(7) Å, b = 6.907(4) Å, c = 17.210(6) Å, and β = 94.33(3)°. Full-matrix least-squares refinement of these structures converged at R = 0.0469 and R = 0.0581 for **1** and **2**, respectively. Both compounds adopt chair conformations in the solid state with equatorially disposed dimethylamino substituents on phosphorus.

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

INTRODUCTION

The 1,3,2-oxazaphosphorinane ring system is an essential structural feature which renders cyclophosphamide, trophosphamide, and isophosphamide, efficacious anticancer drugs.[1,2] In addition, this heterocyclic ring system affords the opportunity to study the effect on the conformational properties of cyclohexane by replacing ring carbon atoms with various heteroatoms. Although the structural and conformational properties of 1,3,2-oxazaphosphorinanes have been less well investigated than those of the corresponding 1,3,2-dioxaphosphorinanes,[3,4] recent studies have emphasized the special conformational features of the 1,3,2-oxaza rings, including the importance of the nature of R at N(3) on chair-twist equilibria,[5–8] and the relatively small conformational energies of substituents[9,10] on phosphorus in certain 1,3,2-oxazaphosphorinanes.

It is likely that both steric as well as stereoelectronic factors affect the conformational properties of this ring system. The steric effects of aryl substitution at N(3) on the structure and conformation of the 1,3,2-oxazaphosphorinane ring have been demonstrated,[5–7] but the affects of changing the electronic nature of N(3) on conformation or other structural properties have not been probed. In this paper, we present syntheses and single-crystal X-ray structural studies on two 1,3,2-oxazaphosphorinanes with *para*-substituted phenyl substituents on ring nitrogen: 2-(dimethylamino)-2-oxo-3-(4-fluorophenyl)-5,5-dimethyl-1,3,2-oxazaphosphor-



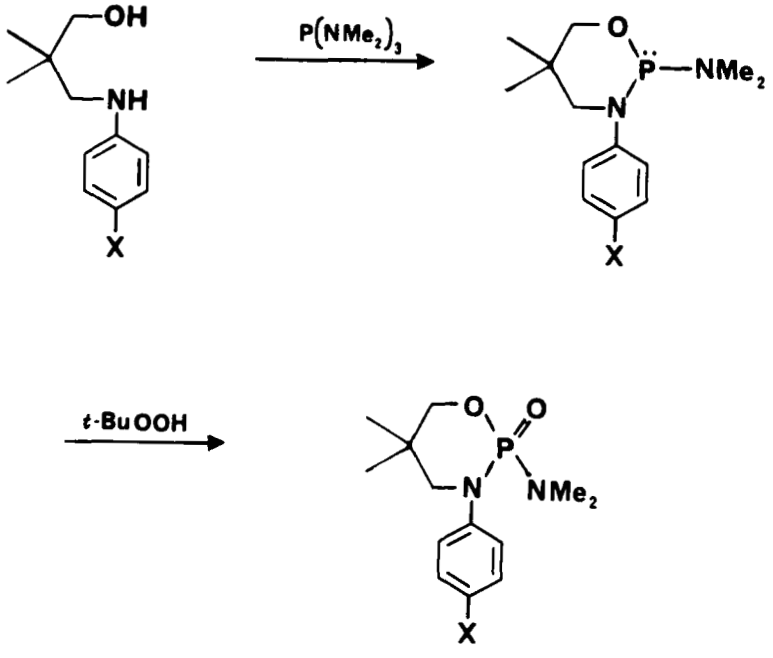
1, X = F

2, X = NMe_2

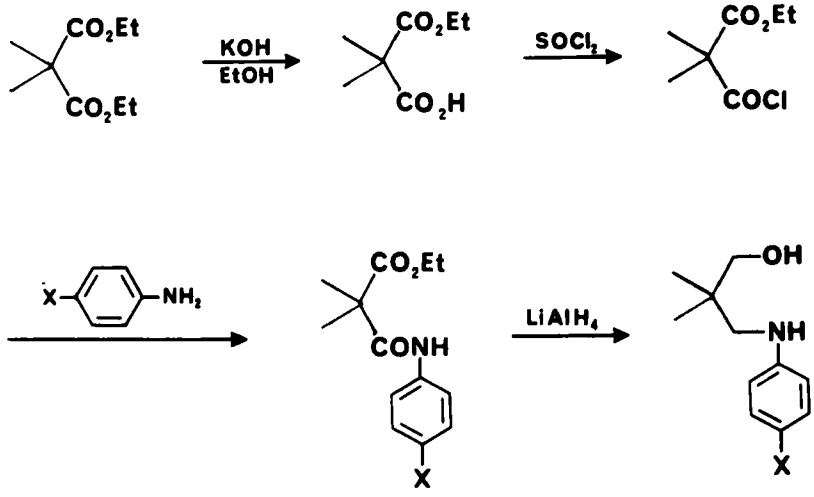
inane, **1**, and 2-(dimethylamino)-2-oxo-3-(4-dimethylaminophenyl)-5,5-dimethyl-1,3,2-oxazaphosphorinane, **2**.

RESULTS AND DISCUSSION

Syntheses. The 1,3,2-oxazaphosphorinanes described in this structural study were prepared by cyclization of the appropriate amino alcohol with hexamethylphosphorous triamide. The resulting trivalent 1,3,2-oxazaphosphorinane was oxidized using *tert*-butylhydroperoxide:



The amino alcohols were prepared from diethyl dimethylmalonate by saponification to the half ester, conversion to the acid chloride, and then reaction with the appropriate substituted aniline to give the corresponding amide ester. The amide ester was then reduced with lithium aluminum hydride to the amino alcohol:



X-ray Structural Studies. The crystal data for **1** and **2** are listed in Table I. The final atomic parameters for the compounds are compiled in Tables II and III, respectively. There are two crystallographically independent molecules in the crystal structure of **1**. Perspective views of these two molecules are shown in Figures

TABLE I

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

Compound	**1**	**2**
Molecular formula	$C_{13}H_{20}N_2O_2FP$	$C_{15}H_{26}N_3O_2P$
Molecular weight	286.29	311.37
Crystal size, mm	0.23x0.21x0.18	0.30x0.30x0.25
Radiation, Å	MoKα (0.71073)	MoKα (0.71073)
Space group	$P2_1/c$	$P2_1/a$
Cell dimensions		
a, Å	17.251(4)	14.148(7)
b, Å	10.822(3)	6.907(4)
c, Å	18.075(6)	17.210(6)
β, deg	118.20(2)	94.33(3)
V Å^3	2973.85	1677.02
Z	8	4
d_{calcd}, g cm^{-1}	1.279	1.233
No. of unique data	4995	2903
No. of observed data	2342	1725
Absorption coeff., mm^{-1}	18.93	16.63
Final residuals		
R	0.0469	0.0581
R_w	0.0481	0.0587

TABLE II
Atomic parameters for compound **1**

Atom	x	y	z	B(Å²)
P(2)	0.43907(8)	0.9190(1)	0.74831(8)	3.65(3)
F(1)	0.6154(2)	0.5542(3)	1.0769(2)	6.3(1)
O(1)	0.3878(2)	1.0468(3)	0.7226(2)	4.63(9)
O(9)	0.4198(2)	0.8384(4)	0.6769(2)	5.6(1)
N(3)	0.4085(2)	0.8687(4)	0.8175(2)	3.5(1)
N(10)	0.5415(2)	0.9565(4)	0.8005(2)	4.2(1)
C(4)	0.3116(3)	0.8691(5)	0.7866(3)	4.3(1)
C(5)	0.2728(3)	0.9982(6)	0.7604(3)	4.9(1)
C(6)	0.2950(3)	1.0472(6)	0.6939(4)	5.7(2)
C(7)	0.1724(4)	0.9879(7)	0.7219(4)	7.7(2)
C(8)	0.3087(4)	1.0843(7)	0.8354(4)	7.8(2)
C(11)	0.5742(3)	1.0343(6)	0.8751(4)	5.6(2)
C(12)	0.6053(4)	0.9197(8)	0.7742(4)	7.8(2)
C(13)	0.4608(3)	0.7836(5)	0.8826(3)	3.1(1)
C(14)	0.4587(3)	0.7910(5)	0.9584(3)	4.0(1)
C(15)	0.5100(3)	0.7113(5)	1.0235(3)	4.3(1)
C(16)	0.5631(3)	0.6289(5)	1.0118(3)	4.4(1)
C(17)	0.5664(3)	0.6188(5)	0.9381(3)	4.7(1)
C(18)	0.5128(3)	0.6968(5)	0.8721(3)	3.9(1)
P(2)′	0.09062(8)	0.8414(1)	0.37226(7)	3.23(3)
F(1)′	0.1782(2)	1.3664(4)	0.5782(2)	7.2(1)
O(1)′	0.1008(2)	0.7701(3)	0.3009(2)	3.77(8)
O(9)′	0.0077(2)	0.8163(4)	0.3727(2)	4.74(9)
N(3)′	0.1083(2)	0.9851(4)	0.3525(2)	3.08(9)
N(10)′	0.1759(2)	0.8032(4)	0.4593(2)	3.8(1)
C(4)′	0.0619(3)	1.0288(5)	0.2645(3)	3.4(1)
C(5)′	0.0766(3)	0.9433(5)	0.2052(3)	3.6(1)
C(6)′	0.0500(3)	0.8130(5)	0.2151(3)	4.4(1)
C(7)′	0.0168(4)	0.9857(5)	0.1150(3)	5.0(2)
C(8)′	0.1728(3)	0.9474(6)	0.2246(3)	4.9(1)
C(11)′	0.2645(3)	0.8144(6)	0.4701(3)	5.4(2)
C(12)′	0.1678(4)	0.7279(6)	0.5220(3)	6.2(2)
C(13)′	0.1263(3)	1.0809(5)	0.4139(3)	3.1(1)
C(14)′	0.0806(3)	1.0897(5)	0.4595(3)	3.6(1)
C(15)′	0.0991(3)	1.1867(5)	0.5162(3)	4.3(1)
C(16)′	0.1612(3)	1.2706(6)	0.5243(3)	4.8(1)
C(17)′	0.2078(3)	1.2639(6)	0.4808(3)	5.1(2)
C(18)′	0.1912(3)	1.1667(5)	0.4256(3)	4.4(1)

1 and 2, along with the labeling schemes. A perspective view of compound **2** with the labeling scheme is shown in Figure 3. Selected bond lengths, bond angles, and torsion angles for the compounds are listed in Table IV.[11]

Both compounds **1** and **2** adopt chair conformations in their crystal structures. The planar dimethylamino substituent on phosphorus is equatorially disposed in both structures. Dimethylamino substituents on phosphorus have been shown to have an axial preference in 1,3,2-oxazaphosphorinanes without substitution at N(3),[9,10] while preferring an equatorial position, as a result of steric interactions, when N(3) has a phenyl substituent.[5-7]

The general structural features of compounds **1** and **2** appear to be completely regular and are comparable to other chair structures of 1,3,2-oxazaphosphorinanes. The ring shows some degree of flattening at the phosphorus end, typical of 1,3,2-

TABLE III

Atomic parameters for compound **2**

Atom	x	y	z	B(Å²)
P(2)	0.19612(9)	0.0721(2)	0.19152(7)	3.12(2)
O(1)	0.2045(2)	0.0836(5)	0.1003(2)	3.49(7)
O(9)	0.1432(2)	0.2324(5)	0.2232(2)	4.37(8)
N(3)	0.3096(3)	0.0493(6)	0.2242(2)	3.20(8)
N(10)	0.1450(3)	−0.1346(6)	0.2037(2)	3.96(9)
N(19)	0.3767(3)	−0.1500(8)	0.5417(2)	5.3(1)
C(4)	0.3766(3)	0.1895(8)	0.1924(3)	3.9(1)
C(5)	0.3709(3)	0.1860(8)	0.1037(3)	3.8(1)
C(6)	0.2704(4)	0.2229(7)	0.0717(3)	3.8(1)
C(7)	0.4050(4)	−0.0106(9)	0.0740(3)	4.9(1)
C(8)	0.4327(4)	0.351(1)	0.0746(3)	6.1(1)
C(11)	0.0569(4)	−0.1520(9)	0.2400(3)	5.4(1)
C(12)	0.1797(4)	−0.3124(8)	0.1697(4)	5.3(1)
C(13)	0.3273(3)	0.0048(7)	0.3053(3)	3.3(1)
C(14)	0.3487(4)	−0.1875(7)	0.3279(3)	3.9(1)
C(15)	0.3656(4)	−0.2362(8)	0.4051(3)	4.3(1)
C(16)	0.3624(3)	−0.1022(8)	0.4647(3)	3.9(1)
C(17)	0.3424(4)	0.0906(8)	0.4411(3)	4.6(1)
C(18)	0.3238(4)	0.1359(8)	0.3634(3)	4.3(1)
C(20)	0.3836(5)	−0.005(1)	0.6018(3)	6.0(2)
C(21)	0.4105(5)	−0.339(1)	0.5644(4)	6.9(2)

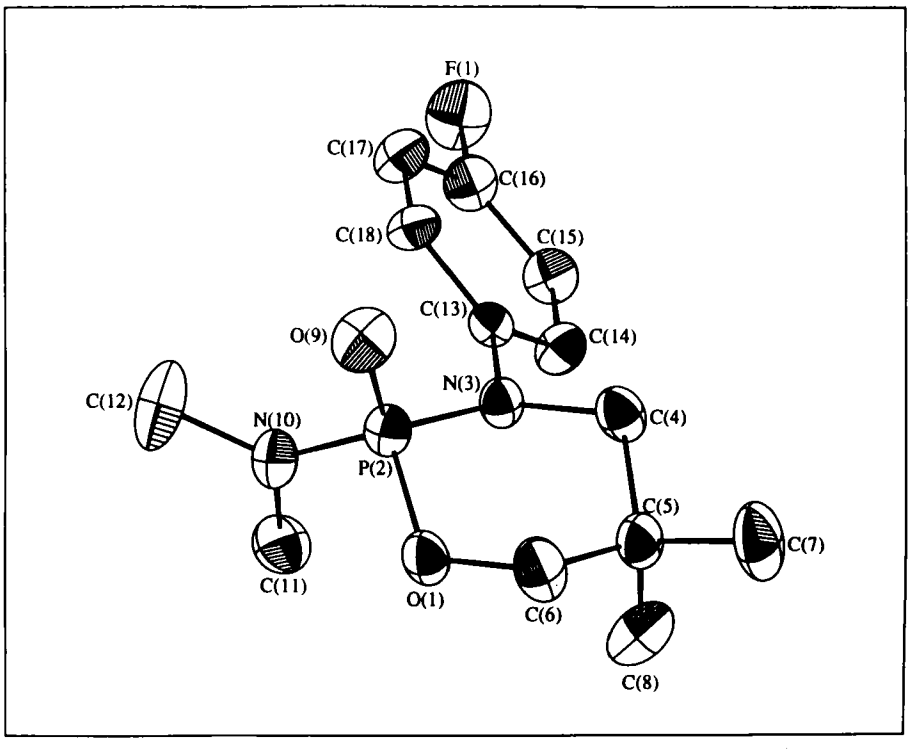
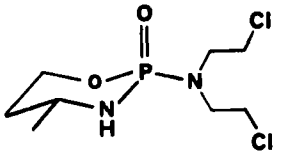


FIGURE 1 ORTEP perspective view of compound **1**.

oxazaphosphorinanes.[12] The angle, ϕ, between the phosphorus flap [the plane defined by O(1), P(2), and N(3)] and the average plane defined by O(1), N(3), C(4), and C(6), is 45.3° and 42.0° for **1** and **1'** (Me_2N, equatorial), about the same as that found for **2** (43.1° Me_2N, equatorial), for 4-methylcyclophosphamide, **3** (43.6°, R_2N, equatorial)[13]; and for 2-(4-dimethylaminoanilino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, **4** (44.2°, ArNH, equatorial).[12] The same angle is considerably smaller for 2-(dimethylamino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, **5** (39.6°, Me_2N, axial).[9] This is consistent with the trend noted in the accompanying paper[12] that ϕ is decreased when an apical substituent (RNH or R_2N) is observed.

In the structures of both **1** and **2**, the dimethylamino substituent on phosphorus is planar. The sum of bond angles about N(10) is 359.9° and 358.2° for the two molecules of **1**, and 358.6° for **2**. The sp^2 hybridization of the dimethylamino group and the coplanarity of the substituent with the phosphoryl group [O(9)—P(2)—N(10)—C(11) = −178.6° for **1**, −176.6° for **1'**, and 1.4° for **2**] allows for conjugation between the Me_2N and P=O groups and/or ring P—N and P—O σ^* bonds.[14] The bond angle sums about N(3), 347.6° to 354.5° indicate some nonplanarity.

The geometrical parameters for **1** and **2** are very similar. The contrasting electronic effects of the *para* substituents on the N(3)-phenyl group are apparently not manifested in the structural features of these compounds. Fluorine is generally considered to be a strong σ-withdrawing group and a π-donating group; dimethylamino serves as a weak σ-withdrawing but a potentially strong π-donating group.[13]



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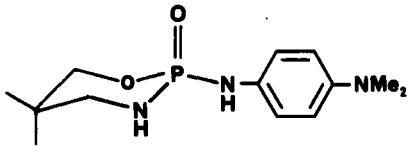

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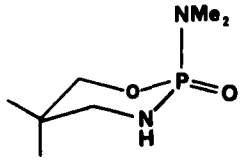

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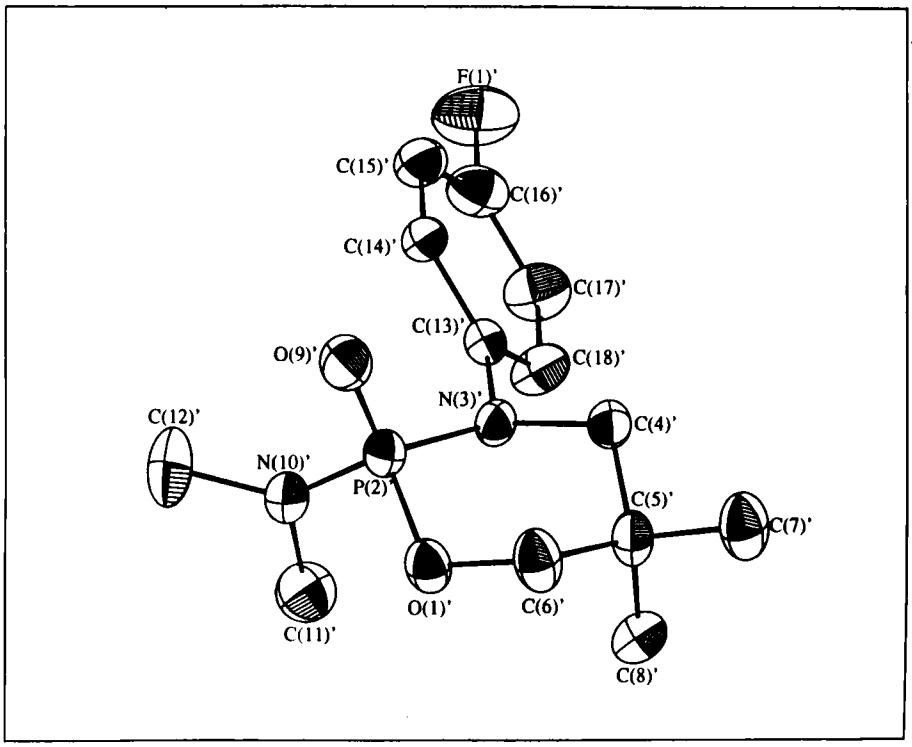


FIGURE 2 ORTEP perspective view of compound **1'**.

There can be little, if any, conjugation between the N(3) lone pair and the aryl substituent; because the P(2)—N(3)—C(13)—C(14) dihedral angles in these compounds ($-148.5°$ in **1**, $-41.7°$ in **1'**, and 100.9° in **2**) preclude π overlap between the phenyl ring and the N(3) lone pair, especially for **2**. Thus, any resonance electronic effects of the *para* substituents with N(3) are "turned off." In such cases, σ values are a reasonable measure of electronic effects. Thus, *para*-fluoro is mildly electron withdrawing ($\sigma_P = 0.15$) and *para*-dimethylamino is electron donating ($\sigma_p = -0.63$).[15]

According to current understanding of the anomeric effect,[16] overlap of the N(3) lone pair with the P—Z σ^* orbital of the axial substituent on phosphorus (in these structures, P=O) should result in a *shortening* of the P(2)—N(3) bond with concomitant *lengthening* of the P(2)—O(9) bond. One might expect, then, that compound **1** containing the *para*-fluoro substituent (inductively electron withdrawing) should experience *less* anomeric stabilization than should compound **2**, with the *para*-dimethylamino substituent (at best, only weakly inductively electron withdrawing and, based on its σ_p value, electron donating). Such a difference is not observed in these crystal structures, however (Table IV).

It seems likely that the change in the anomeric stabilization in question is not great enough in response to the interchange of *para*-fluoro with *para*-dimethylamino to be exhibited as a P—N(3) or P=O bond length change. By comparison, for a series of 1,3,2-dioxaphosphorinanes, **6**, with —OR = 2-nitrophenoxy, 3-nitro-

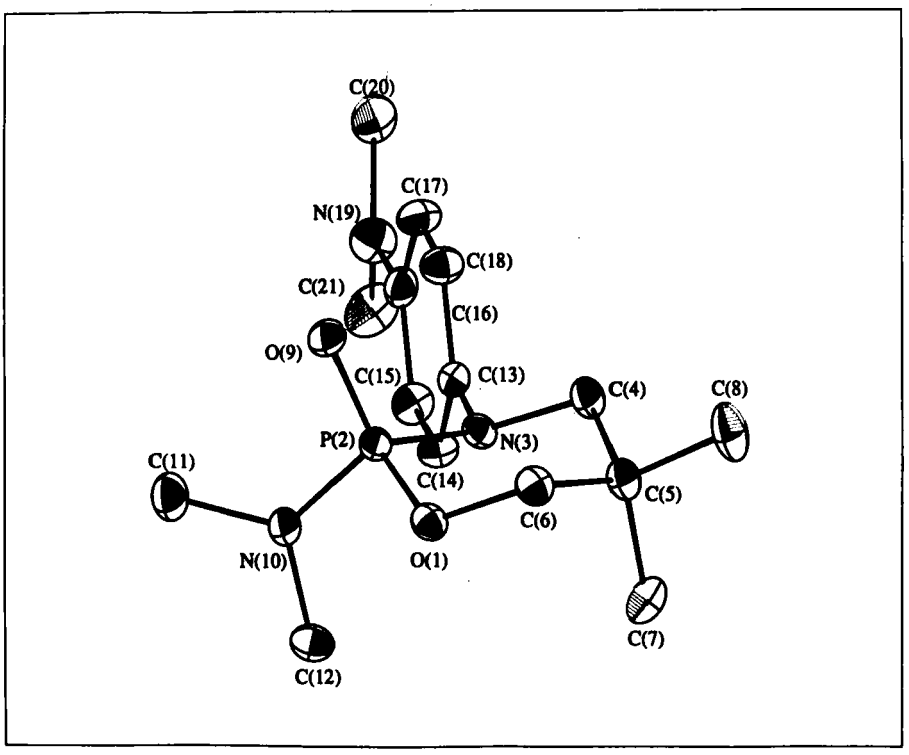
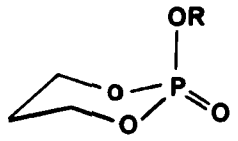


FIGURE 3 ORTEP perspective view of compound **2**.

phenoxy, phenoxy, and for **7** with —OR = methoxy, a range of exocyclic P—OR bondlengths (1.564 Å to 1.597 Å) was noted.[17] However, for the series of aryloxy substituents, the range was only 1.587 Å to 1.597 Å (all three within 2σ error limits of one another), even with the involvement of a strongly electron withdrawing substituent, *para*-nitro (σ_p = 0.81).[15] Similarly, for a series of tetrahydropyranyl acetals with axial —OR, the phenoxy- and 4-chlorophenoxy-substituted compounds showed no experimental differences in the exocyclic, axial C—OR bond lengths or in those of the endocyclic C—O bonds expected to be shortened by such anomeric interactions. Again, NO_2 substituents resulted in a measurable effect on both bond lengths: exocyclic C—OR, phenoxy (1.433(3) Å), 2,5-dinitrophenoxy (1,458(5) Å)[18]; endocyclic C—O, phenoxy (1.405(3) Å), 2,5-dinitrophenoxy (1.383(5) Å). These substituents, for both the 1,3,2-dioxaphosphorinanes and the tetrahydropyranyl acetals, span a much wider range of electronic character than do *p*-F and *p*-NMe_2. We shall attempt to obtain X-ray quality crystals for the analog of **1** and **2** for which X = NO_2.

It should be noted that in the accompanying paper[12] in which an ArNH group is attached exocyclic to phosphorus and the substituent on N(3) is hydrogen, the compounds crystallize in chair conformations with the ArNH group either axial or equatorial depending on the nature of Ar. In those cases, small but significant differences in the lengths of several bonds about phosphorus (including the P=O bond) are found as a function of conformation (ArNH axial or equatorial). Rel-



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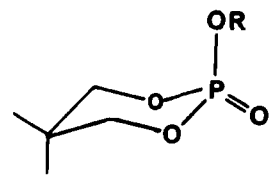

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TABLE IV

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

Atoms	Compound		
	1	**1'**	**2**
P(2)—O(1)	1.588(3)	1.582(3)	1.585(3)
P(2)—O(9)	1.461(3)	1.460(3)	1.465(3)
P(2)—N(3)	1.662(3)	1.656(3)	1.668(3)
P(2)—N(10)	1.613(4)	1.620(3)	1.622(4)
O(1)—C(6)	1.431(5)	1.452(5)	1.452(5)
N(3)—C(4)	1.491(5)	1.481(5)	1.488(6)
C(4)—C(5)	1.524(6)	1.524(5)	1.523(6)
C(5)—C(6)	1.518(6)	1.519(6)	1.508(6)
O(1)—P(2)—N(3)	100.1(2)	100.3(2)	101.4(2)
P(2)—N(3)—C(4)	114.6(3)	118.1(3)	116.0(3)
N(3)—C(4)—C(5)	111.7(4)	112.1(3)	111.9(4)
C(4)—C(5)—C96)	109.2(4)	108.8(3)	109.9(4)
C(5)—C(6)—O(1)	111.7(4)	111.0(3)	112.1(4)
C(6)—O(1)—P(2)	118.8(3)	118.1(3)	117.8(3)
O(1)—P(2)—N(10)	104.9(2)	105.5(2)	103.9(2)
O(1)—P(2)—O(9)	113.5(2)	113.6(2)	114.2(2)
O(2)—P(2)—N(10)	113.3(2)	113.0(2)	111.8(2)
O(2)—P(2)—N(3)	116.7(2)	117.2(2)	116.9(2)
N(3)—P(2)—N(10)	107.0(2)	105.9(2)	107.5(3)
P(2)—N(10)—C(11)	121.6(3)	121.7(3)	122.6(4)
P(2)—N(10)—C(12)	122.1(4)	121.4(3)	121.4(3)
C(11)—N(10)—C(12)	116.2(4)	115.1(4)	115.6(4)
P(2)—N(3)—C(13)	121.9(3)	120.2(2)	116.2(3)
C(4)—N(3)—C(13)	118.0(3)	114.0(3)	115.4(3)
O(1)—P(2)—N(3)—C(4)	51.7(4)	47.0(4)	48.8(4)
P(2)—N(3)—C(4)—C(5)	−58.7(5)	−53.5(5)	−55.2(5)
N(3)—C(4)—C(5)—C(6)	56.8(5)	54.9(5)	55.7(5)
C(4)—C(5)—C(6)—O(1)	−56.2(6)	−58.9(6)	−57.2(5)
C(5)—C(6)—O(1)—P(2)	60.5(6)	63.2(6)	60.2(5)
C(6)—O(1)—P(2)—N(3)	−53.8(4)	−51.8(4)	−51.4(3)
O(9)—P(2)—N(10)—C(11)	−178.6(4)	−176.6(4)	1.4(5)
P(2)—N(3)—C(13)—C(14)	148.5(4)	−41.7(6)	100.9(4)

atively large bond length effects similarly are found for *cis*-2,3-dichloro-1,4-dioxane in which one chlorine is axial and the other equatorial.[19]

An alternative explanation for the lack of variation in comparable bond lengths in **1** and **2** also should be considered. The stabilization resulting from overlap of the Me_2N lone pair with the P(2)—N(3) σ^* orbital (the *exo* anomeric effect) is predicted to be *decreased* by the *p*-NMe_2 substituent because of an increase in the P(2)—N(3) σ^* energy. A resulting *increase* in the P(2)—N(3) bond length could

offset the expected *decrease* arising from the *endo* anomeric interaction and lead to no net change in the P(2)—N(3) bond length. There is, in this connection, no variation between **1** and **2** in the exocyclic P—N(10) bond distance.

Solution ^1H NMR studies of the chair-chair equilibrium for 1,3,2-oxazaphosphorinanes of this type, in which the conformation found here is exchanged for the alternative chair with Me_2N axial, have been carried out[20] for a range of substituents from *p*-NMe_2 to *p*-NO_2. In acetone-d_6, the percentage of conformer with the Me_2N equatorial varies from about 86% (*p*-NMe_2) to about 70% (*p*-NO_2). This decrease amounts to a $\Delta\Delta G°$ of only about 0.6 kcal/mol. Of course, in these equilibria, anomeric effects are potentially operative on both chair conformers and may act in a compensatory way, but it can be noted that the net effect, though real, is relatively small.

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. ^1H NMR spectra were taken on a Varian SC 300 or XL 300 spectrometer operated in the FT mode, or on a Varian VXR 500. ^{31}P NMR spectra were made at 121 MHz on a Varian XL 300 under proton noise decoupling conditions. Positive ^{31}P chemical shifts are in ppm downfield from external 85% H_3PO_4.

Preparation of N-(4-N',N'-Dimethylaminophenyl)-2-carboethoxy-2-methylpropionamide. A mixture of 2-carboethoxy-2-methylpropionic acid[9] (39.2 g, 0.244 mol) and thionyl chloride (20.0 mL, 32.6 g, 0.274 mol) was heated under reflux for 1 h. The reaction mixture was cooled to room temperature, and the excess thionyl chloride removed under reduced pressure. The residue was taken up in diethyl ether (150 mL) and slowly added dropwise to a stirred solution of *N,N*-dimethyl-4-phenylenediamine (65.4 g, 0.480 mol) in diethyl ether (200 mL) at room temperature. The reaction mixture was cooled to −20°C, and the hydrochloride salt filtered off. The filtrate was dried over $MgSO_4$. Evaporation of the ether left a solid which was recrystallized from hexane/THF to give 26.8 g (39.3% yield) of the desired product as a colorless crystalline solid: mp 77–78°C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, CH_3CH_2O, J_{HH} = 7.08 Hz), 1.54 (s, 6H, Me_2C), 2.91 (s, 6H, NMe_2), 4.23 (q, 2H, CH_3CH_2O, J_{HH} = 7.08), 6.71 (d, 2H, C_6H_4, J_{HH} = 8.98), 7.37 (d, 2H, C_6H_4, J_{HH} = 8.79), 8.29 (s, 1H, NH); IR (KBr) 3300 s, 3000–2900 m, 2840 w, 1725 s, 1700 s, 1600 m, 1510 s, 1465 w, 1440 w, 1410 w, 1385 w, 1360 w, 1310 w, 1300 m, 1255 s, 1230 s, 1160 m, 1140 m, 1110 w, 1020 s, 915 w, 825 s, 745 w, 680 w cm^{-1}. Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 65.02; H, 8.03; N, 10.06.

Preparation of N-(4-Fluorophenyl)-2-carboethoxy-2-methylpropionamide. A mixture of 2-carboethoxy-2-methylpropionic acid (26.7 g, 0.167 mol) and thionyl chloride (15.0 mL, 24.5 g, 0.206 mol) was heated under reflux for 1 h. The reaction mixture was cooled to room temperature, and the excess thionyl chloride was removed under reduced pressure. The residue was taken up in diethyl ether (150 mL) and slowly added dropwise to a stirred solution of 4-fluoroaniline (29.6 mL, 34.7 g, 0.312 mol) in diethyl ether (200 mL) at room temperature. The reaction mixture was cooled to −20°C, and the hydrochloride salt filtered off. The filtrate was dried over $MgSO_4$. Evaporation of ether left a solid which was recrystallized from ether/pentane to give 33.4 g (79.0% yield) of the desired product as a pale yellow crystalline solid: mp 59–60°C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, CH_3CH_2O, J_{HH} = 7.14 Hz), 1.54 (s, 6H, Me_2C), 4.24 (q, 2H, CH_3CH_2O, J_{HH} = 7.14), 7.01 (t, 2H, C_6H_4, J_{HH} = 9.09), 7.48 (dd, 2H, C_6H_4, J_{HH} = 9.11 Hz, J_{HF} = 4.82 Hz), 8.71 (s, 1H, NH); IR (KBr) 3260 s, 3210 s, 3160 m, 3060 m, 2990 m, 2940 w, 2880 w, 2810 w, 1730 s, 1655 s, 1615 m, 1550 s, 1460 m, 1405 s, 1390 s, 1360 w, 1310 s, 1300 m, 1210 s, 1170 s, 1155 m, 1140 m, 1090 m, 1020 m, 960 w, 940 w, 915 w, 870 w, 850 w, 830 w, 815 w, 790 w, 750 m, 720 w, 700 m cm^{-1}. Anal. Calcd. for $C_{13}H_{16}NO_3F$: C, 61.65; H, 6.37; N, 5.53; F, 7.50. Found: C, 61.73; H, 6.38; N, 5.52; F, 7.47.

Preparation of N-(4-Fluorophenyl)-2-(hydroxymethyl)-2-methylpropylamine. A solution of *N*-(4-fluorophenyl)-2-carboethoxy-2-methylpropionamide (33.4 g, 0.132 mol) in anhydrous diethyl ether (250 mL) was added dropwise to a rapidly stirred suspension of $LiAlH_4$ (10.0 g, 0.264 mol) in anhydrous diethyl ether (250 mL) at 0°C under argon atmosphere. The reaction mixture was then heated under

gentle reflux for five days under argon. The assembly was cooled to 0°C, stirred and slowly quenched with a mixture of water (19 mL, 1.1 mol) and diethyl ether (150 mL). The reaction mixture was allowed to warm to room temperature while stirring for 1 h. Magnesium sulfate (ca. 30 g) was then added along with a small amount of activated charcoal, and stirring was continued for 0.5 h. The reaction mixture was filtered, and the solids washed with ether (3 × 50 mL). The ether was removed from the filtration under reduced pressure. The residue was fractionally distilled collecting the fraction boiling at 107–109°C/0.1 mm to give 16.7 g (64.1% yield) of the desired product as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 6H, Me_2C), 2.97 (s, 2H, CH_2N), 3.25 (broad s, 2H, NH and OH), 3.45 (s, 2H, CH_2O), 6.57 (d, 2H, C_6H_4, J_{HH} = 9.00 Hz), 6.86 (d, 2H, C_6H_4, J_{HH} = 8.77 Hz); IR (neat film) 3600–3100 broad s, 3045 w, 2960 s, 2880 s, 1850 broad w, 1610 m, 1510 s, 1470 s, 1400 m, 1360 m, 1330–1270 broad m, 1250 m, 1220 s, 1150 m, 1040 s, 890 w, 820 s, 790 w, 745 m cm^{-1}. Anal. Calcd. for $C_{11}H_{14}NOF$: C, 66.98; H, 8.18; N, 7.10; F, 9.63. Found: C, 67.08; H, 8.21; N, 7.07; F, 9.45.

Preparation of N-(4-N',N'-Dimethylaminophenyl)-2-(hydroxymethyl)-2-methylpropylamine. A solution of *N*-(4-*N'*,*N'*-dimethylaminophenyl)-2-carboethoxy-2-methylpropionamide (26.8 g, 96.3 mmol) in anhydrous diethyl ether (250 mL) was added dropwise to a rapidly stirred suspension of $LiAlH_4$ (10.0 g, 0.246 mol) in anhydrous diethyl ether (250 mL) at 0°C under argon atmosphere. The reaction mixture was then heated under gentle reflux for three days. The assembly was cooled to 0°C, stirred and slowly quenched with a mixture of water (19 mL, 1.06 mol) and diethyl ether (150 mL). The reaction mixture was allowed to warm to room temperature while stirring for 1 h. Magnesium sulfate (ca. 30 g) was then added along with a small amount of activated charcoal, and stirring was continued for 0.5 h. The reaction mixture was filtered, and the solids were washed with diethyl ether (3 × 50 mL). The ether was removed from the filtrate under reduced pressure. The residual solid was recrystallized from ethyl acetate/hexane to give 18.7 g (87.6% yield) of the desired product as a colorless crystalline solid: mp 123–124°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 6H, Me_2C), 2.91 (s, 3H, CH_2N and OH), 3.22 (broad s, 1H, NH), 3.63 (s, 2H, CH_2O), 6.70 (d, 2H, C_6H_4, J_{HH} = 8.10 Hz), 7.34 (d, 2H, C_6H_4, J_{HH} = 8.06 Hz); IR (KBr) 3400 broad s, 3240 broad s, 2960 s, 2890 s, 2810 s, 1620 w, 1510 s, 1460 s, 1355 w, 1295 s, 1260 m, 1250 s, 1195 s, 1160 m, 1140 s, 1095 m, 1050 s, 1030 m, 995 m, 930 s, 905 w, 840 w, 810 s, 790 m, 710 m cm^{-1}. Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.33; H, 10.03; N, 12.58.

Preparation of 2-(Dimethylamino)-2-oxo-3-(4-fluorophenyl)-5,5-dimethyl-1,3,2-oxazaphosphorinane, **1**. A solution of *N*-(4-fluorophenyl)-2-(hydroxymethyl)-2-methylpropylamine (5.0 g, 25 mmol) and hexamethylphosphorous triamide (4.6 mL, 4.1 g, 25 mmol) in ethyl acetate (45 mL) and toluene (45 mL) was refluxed for 20 h under argon. The solvents were removed under reduced pressure. The residue was taken up in dichloromethane (50 mL) and cooled in an ice salt bath (−10°C). *tert*-Butylhydroperoxide (8.6 mL, 3.0 *M*, 26 mmol) in toluene was added dropwise to the reaction mixture which was stirred under argon. The solution was allowed to warm to room temperature and was stirred overnight. Solvents were removed *in vacuo* and the crude viscous liquid was fractionally distilled twice (bp 146–148°C/0.05 mm Hg) to give 2.7 g (38% yield) of pure product which crystallized upon standing: mp 63–64°C; ^{1}H NMR (500 MHz, C_6D_6) δ 0.41 (s, 3H, CCH_3), 0.95 (s, 3H, CCH_3), 2.37 (d, 6H, NMe_2, J_{HP} = 9.59 Hz), 2.56 (ddd, 1H, CH_2N), 3.23 (dd, 1H, CH_2N), 3.37 (ddd, 1H, CH_2O), 4.12 (dd, 1H, CH_2O), 6.78 (t, 2H, C_6H_4, J_{HH} = 8.64 Hz), 7.24 (ddd, 2H, C_6H_4, $^3J_{HH}$ = 9.03 Hz, $^4J_{HF}$ = 4.91 Hz, $^4J_{HP}$ = 1.06 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 22.4 (s, CCH_3), 23.2 (s, CCH_3), 32.4 (d, CCH_3, $^3J_{CP}$ = 2.0 Hz), 36.2 (d $PNCH_3$, $^2J_{CP}$ = 4.4 Hz), 63.7 (d, CH_2N, $^2J_{CP}$ = 1.1 Hz), 75.6 (d, CH_2O, $^2J_{CP}$ = 6.1 Hz), 115.9 (d, *m*-C_6H_4, $^2J_{CP}$ = 22.2 Hz), 127.2 (dd, *o*-C_6H_4, $^3J_{CP}$ = 5.2, $^3J_{CF}$ = 8.1 Hz), 151.8 (d, *p*-C_6H_4, $^1J_{CF}$ = 243.1 Hz), 159.5 (s, *ipso*-C_6H_4); ^{31}P NMR (121 MHz, acetone-d_6) δ 10.80; IR (KBr) 2960 m, 2910 m, 2890 m, 2805 w, 1500 s, 1475 m, 1460 m, 1370 m, 1350 w, 1310 m, 1270 (m, P=O), 1210 (s, P=O), 1190 s, 1120 m, 1100 s, 1090 m, 1060 m, 1000 s, 970 m, 890 s, 835 s, 810 s, 780 s, 745 m, 730 w, 720 w, 670 w cm^{-1}. Anal. Calcd. for $C_{13}H_{20}N_2O_2PF$: C, 54.54; H, 7.04; N, 9.79; P, 10.82; F, 6.64. Found: C, 54.60; H, 6.76; N, 9.97; P, 10.85; F, 6.45.

Preparation of 2-(Dimethylamino)-2-oxo-3-(4-dimethylaminophenyl)-5,5-dimethyl-1,3,2-oxazaphosphorinane, **2**. A solution of *N*-(4-*N'*,*N'*-dimethylaminophenyl)-2-(hydroxymethyl)-2-methylpropylamine (5.0 g, 23 mmol) and hexamethylphosphorous triamide (4.1 mL, 3.7 g, 23 mmol) in ethyl acetate (40 mL) and toluene (40 mL) was refluxed for 20 h under argon. The solvents were removed under reduced pressure. The residue was taken up in dichloromethane (50 mL) and cooled to −10°C. *tert*-Butylhydroperoxide (7.3 mL, 3.0 *M*, 22 mmol) in toluene was added dropwise to the reaction mixture which was stirred under argon. The solution was allowed to warm to room temperature and was stirred for 1 h. Solvents were removed *in vacuo* to give 7.6 g of a purplish-white crude solid. A 5.0-g sample of the solid was flash chromatographed on a 25 × 250 mm column of silica gel (Baker, 50 g, 60–200 mesh), eluting with ethyl acetate. Removal of the ethyl acetate *in vacuo* and recrystallization of the solid residue from diethyl ether gave 0.9 g (20% yield) of the desired product as a colorless crystalline

solid: mp 97–98°C; ^{1}H NMR (500 MHz, C_6D_6) δ 0.42 (s, 3H, CCH_3), 1.10 (s, 3H, CCH_3), 2.49 (s, 6H, $C_6H_4NMe_2$), 2.52 (d, 6H, $PNMe_2$, J_{HP} = 9.48 Hz), 2.72 (ddd, 1H, CH_2N), 3.43 (dd, 1H, CH_2N), 3.45 (ddd, 1H, CH_2O), 4.24 (dd, 1H, CH_2O), 6.59 (d, 2H, C_6H_4, J_{HH} = 8.88 Hz), 7.48 (d, 2H, C_6H_4, J_{HH} = 9.05 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 22.6 (s, CCH_3), 23.4 (s, CCH_3), 32.5 (d, CCH_3, $^3J_{CP}$ = 1.8 Hz), 36.5 (d, $PNMe_2$, $^2J_{CP}$ = 4.3 Hz), 40.5 (s, $ArNMe_2$), 64.6 (d, CH_2N, $^2J_{CP}$ = 2.0 Hz), 75.6 (d, CH_2O, $^2J_{CP}$ = 5.9 Hz), 113.6 (d, *m*-C_6H_4, $^4J_{CP}$ = 6.0 Hz), 127.4 (d, *o*-C_6H_4, $^3J_{CP}$ = 5.3 Hz), 135.6 (s, *ipso*-C_6H_4), 148.9 (s, *p*-C_6H_4); ^{31}P NMR (121 MHz, acetone-d_6) δ 11.93; IR (KBr) 2970 s, 2950 s, 2880 s, 2840 s, 1620 s, 1540 s, 1470 m, 1460 m, 1450 m, 1360 m, 1310 m, 1250 (s, P=O), 1220 (s, P=O), 1190 s, 1090 s, 1070 m, 1035 m, 995 s, 960 s, 940 m, 910 m, 890 s, 810 s, 805 s, 780 s, 770 s, 720 s, 660 m, 640 w cm^{-1}. Anal. Calcd. for $C_{15}H_{26}N_3O_2P$: C, 57.86; H, 8.42; N, 13.50; P, 9.95. Found: C, 57.93; H, 8.53; N, 13.55; P, 9.82.

X-ray Single-Crystal Structure Study of **1** *and* **2**. In each study, a clear, colorless crystal, suitable for X-ray diffraction, was mounted on a Syntex $P\bar{1}$ diffractometer equipped with scintillation counter and graphite monochromated MoKα radiation. The automatic centering, indexing, and least-squares routines were carried out on 15 reflections to obtain the cell dimensions which are given in Table I. The data were reduced to F_o and σ (F_o). Lorentz and polarization factors were applied to all reflections. The θ-2θ scan mode over the range $3.0° \leq 2\theta < 46.0°$ for **1** and $2.5° \leq 2\theta \leq 48.0°$ for **2** was used to collect the data, of which those with $I \geq 3\sigma$ (I) were considered observed and were used in the calculations.

Each of the structures was solved by direct methods and refined by full-matrix least-squares techniques.[21] Hydrogen atoms were added to the structures in geometrically ideal positions. The hydrogen atom parameters were not refined in structure **1**, but, except for H(7), were refined isotropically in structure **2**. Refinement converged at $R = \Sigma||F_o| - |F_c||/|F_o| = 0.0469$ and $R_w = \Sigma w^{1/2}|F_o - F_c|/\sigma w^{1/2}|F_o| = 0.0481$ for structure **1**; $R = 0.0581$ and $R_w = 0.0587$ for structure **2**.

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