((2-Methyl-2-penten-3-yl)oxy)trimethylsilane was prepared by method B from 2-methyl-3-pentanone (0.050 mol), triethylamine (0.12 mol), and trimethylsilyl chloride (0.065 mol) in 125 mL of DMF. The products were isolated by preparative gas chromatography (see above). One major product was the desired ((2-methyl-2-penten-3-yl)oxy)trimethylsilane and was collected. ^{1}H NMR (C_6D_6): δ 0.35 (9 H, s), 1.26 (3 H, t), 1.75 (3 H, s), 1.88 (3 H, s), 2.29 (2 H, q). The other two products were identified by NMR as (((*Z*)- and (*E*)-2-methyl-3-penten-3-yl)oxy)trimethylsilane.

Product Ratios in Kinetic Enolate Formation. The base solution was prepared from (8.25–8.70) × 10^{-4} mol of amine and (7.5–8.70) × 10^{-4} mol of butyllithium in 5.0 mL of THF or DME and stirred for 30 min at 0 °C. When HMPA was used, an amount equivalent to the base (7.5 × 10^{-4} mol) was added, and the solution stirred a further 15 min at 0 °C. The ketone solution was prepared by dissolving (2.5–2.9) × 10^{-4} mol of ketone in 1.0 mL of THF or DME. All reactions were carried out in a 25-mL Schlenk tube fitted with a 14-mm rubber septum and equipped with a 6-mm magnetic stirring bar. Nitrogen was introduced by a syringe needle and vented to a mineral oil bubbler by another syringe needle. The base solution was stirred at the desired temperature for at least 15 min, and the ketone solution added dropwise over 5–10 min. The mixture was stirred for up to 15 min and quenched with trimethylsilyl chloride ((8.7–9.0) × 10^{-4} mol). The composition of the trimethylsilyl enol ether mixture was determined by gas chromatography. For the products from 3-methyl-2-butanone a 12 ft × 0.125 in. column of 10% SF-96 on Chromosorb W-AW-DMCS, 60–80 mesh, was used. The flow rate was 30 mL min^{-1} at 65 psi of helium. Column, injector, and detector temperatures were 55, 100, and 100 °C, respectively. Typical elution times were 15.5 min for ((3-methyl-1-buten-2-yl)oxy)trimethylsilane and 25 min for ((3-methyl-2-buten-2-yl)oxy)trimethylsilane. For the products from 2-methyl-3-pentanone a J & W Scientific DB-1 (cross-linked silicone) 30 m × 0.53 mm i.d. fused silica capillary column was used. The column flow rate was 8.0 mL min^{-1} at 60 psi of He, and the detector make-up flow rate was 22 mL min^{-1} at 60 psi of He. The column, injector, and detector temperatures were 35, 100, and 150 °C, respectively. Typical elution times were 28.5 min for ((*E*)-2-methyl-3-penten-3-yl)oxy)trimethylsilane, 35.0 min for the *Z* isomer, and 39.0 min for ((2-methyl-2-penten-3-yl)oxy)trimethylsilane. *m*-Xylene (elution time 17.0 min, response factor 1.409 ± 0.019 by weight) was used as an internal standard.

Control Experiments. That the enolates do not equilibrate was shown by two sets of experiments. First, the product ratios were the same whether the reactions mixtures were quenched just after completion of addition (<1 min) or up to 15 min later. Second, equilibration among regioisomers should introduce protium into the deuterated positions of the enolates and hence into the trimethylsilyl ethers derived from them. None was detected by ^{1}H NMR. The percent yields of trimethylsilyl ethers measured by internal standard are high (90.7 ± 5.9%) and independent of quench time. The compositions and yields of the trimethylsilyl enol ether mixtures remained constant for at least 24 h.

Registry No. 1, 565-69-5; 2 (TMS deriv), 19980-42-8; 3 (TMS deriv), 19980-41-7; 4 (TMS deriv), 19980-40-6; D_2, 7782-39-0; 2-methylpropionaldehyde, 78-84-2; 2-(2-propyl)-1,3-dithiane, 6007-25-6; propionaldehyde, 123-38-6; 2-ethyl-1,3-dithiane, 6007-23-4; isoamyl acetate, 123-92-2; ethanol-*1,1-d*$_2$, 1859-09-2; acetone, 67-64-1; 2-propanol-*2-d*, 3972-26-7; ethyl-*1,1-d*$_2$ iodide, 3652-82-2; 2-propyl-*2-d* iodide, 95927-03-0; methyl-*1,1,1-d*$_3$ iodide, 865-50-9; 2-(2-propyl)-2-(methyl-*1,1,1-d*$_3$)-1,3-dithiane, 119336-34-4; 2-(2-propyl)-2-(ethyl-*1,1-d*$_2$)-1,3-dithiane, 119336-35-5; 2-ethyl-2-(2-propyl-*2-d*)-1,3-dithiane, 119336-36-6; 3-methyl-2-butanone-*1,1,1-d*$_3$, 52809-75-3; 4-methyl-3-pentanone-*2,2-d*$_2$, 83682-04-6; 2-methyl-3-pentanone-*2-d*, 83682-03-5; (3-methyl-1-buten-2-yl-oxy)trimethylsilane, 17510-45-1; 3-methyl-2-butanone, 563-80-4; (3-methyl-2-buten-2-yloxy)trimethylsilane, 17510-44-0.

Conformational Analysis of 1,3,2-Oxazaphospholanes Derived from Ephedrine and Pseudoephedrine[1]

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A series of 1,3,2-oxazaphospholanes has been prepared and studied conformationally by ^{1}H NMR spectroscopy at 200 MHz. The NMR data are best interpreted in terms of conformational equilibria involving twist-envelope and half-chair conformations. The conformational preferences are such that small electronegative substituents (such as phenoxy) on phosphorus prefer a pseudoaxial position, whereas bulky phosphorus substituents prefer pseudoequatorial positions in these equilibria. These stereoelectronic effects generally result in twist-envelope conformations for these five-membered ring heterocycles to be favored over half-chair conformations. X-ray crystallographic analyses have been done on (2*S*,4*R*,5*R*)-2-phenoxy-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane (**3**), (2*S*,4*R*,5*R*)-2-(dimethylamino)-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane (**6**), and (2*S*,4*R*,5*S*)-2-phenoxy-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane (**9**). These X-ray crystal structures confirm our stereochemical assignments for these materials and support the conformational conclusions from the NMR studies.

Introduction

The five-membered ring, the most important ring in chemistry after the six-membered ring, has been extensively studied conformationally. The conformational properties of cyclopentane and substituted cyclopentanes[3] and saturated five-membered ring heterocycles[4] have been reviewed. Conformational analyses of these ring systems are usually discussed in terms of *envelope* (C_s) and *half-chair* (C_2) conformations.

(1) This work was presented in part at the 194th National Meeting of the American Chemical Society, New Orleans, LA, August 30–September 4, 1987; paper number ORGN-24.

(2) American Chemical Society Petroleum Research Fund Undergraduate Scholar, 1986–1988.

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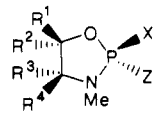
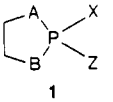
Chart I



2	R^1 = Ph	R^2 = H	R^3 = Me	R^4 = H	X = O	Z = OPh
3	R^1 = Ph	R^2 = H	R^3 = Me	R^4 = H	X = OPh	Z = O
4	R^1 = Ph	R^2 = H	R^3 = Me	R^4 = H	X = O	Z = Ph
5	R^1 = Ph	R^2 = H	R^3 = Me	R^4 = H	X = Ph	Z = O
6	R^1 = Ph	R^2 = H	R^3 = Me	R^4 = H	X = O	Z = NMe_2
7	R^1 = Ph	R^2 = H	R^3 = Me	R^4 = H	X = NMe_2	Z = O
8	R^1 = H	R^2 = Ph	R^3 = Me	R^4 = H	X = O	Z = OPh
9	R^1 = H	R^2 = Ph	R^3 = Me	R^4 = H	X = OPh	Z = O
10	R^1 = H	R^2 = Ph	R^3 = Me	R^4 = H	X = O	Z = Ph
11	R^1 = H	R^2 = Ph	R^3 = Me	R^4 = H	X = Ph	Z = O
12	R^1 = H	R^2 = Ph	R^3 = Me	R^4 = H	X = O	Z = NMe_2
13	R^1 = H	R^2 = Ph	R^3 = Me	R^4 = H	X = NMe_2	Z = O

Conformational analyses using NMR techniques, particularly vicinal proton–phosphorus coupling constants, have been widely utilized in the study of six-membered ring phosphorus heterocycles.[5] Our research group has been interested in extending conformational studies to five-membered ring phosphorus heterocycles (phospholanes, **1**), more specifically, to examine the conformational properties of the 1,3,2-oxazaphospholane system (**1**, A = O, B = NR). Although five-membered rings are less well defined conformationally than six-membered rings, such systems can be conformationally biased by substitution at the ring carbon. Both the 1,3,2-dioxaphospholane ring system[6] and the 1,3,2-oxazaphospholane ring system[7] have been studied conformationally.

NMR studies of a number of 1,3,2-oxazaphospholanes have been undertaken, including some derivatives of ephedrine[8,9] and pseudoephedrine.[9] 1,3,2-Oxazaphospholanes derived from ephedrine have been utilized as chiral intermediates in the stereospecific syntheses of ^{16}O-, ^{17}O-, and ^{18}O-labeled phosphates and thiophosphates,[10] labeled aryl phosphates,[11] and phosphinous tungsten complexes[12] and have been prepared as a method for the determination of enantiomeric purities of alcohols and amines using ^{31}P NMR.[13]



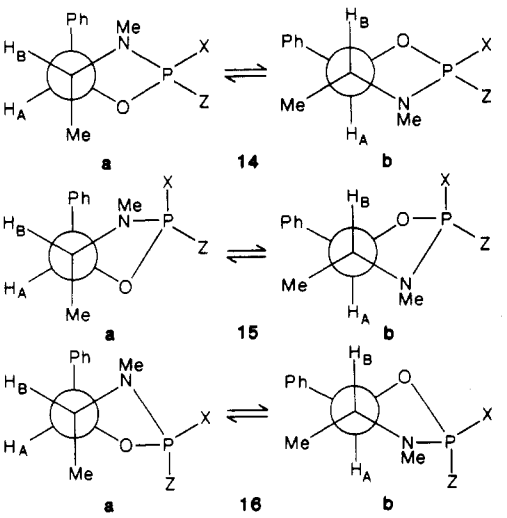
1

This paper presents the synthesis and conformational properties of a series of 1,3,2-oxazaphospholanes (**2–13**) derived from ephedrine and pseudoephedrine (Chart I).

Table I. NMR Data for 1,3,2-Oxazaphospholanes

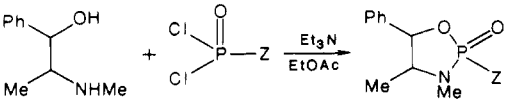
compd	δ_A	δ_B	$\delta_{^{31}P}$	J_{AB}	J_{AP}	J_{BP}
2	4.41	2.91	16.04	8.2	1.6	2.8
3	4.53	2.97	13.94	8.9	2.5	<0.2
4	4.60	3.11	30.44	8.6	2.8	<0.2
5	4.88	3.05	29.15	8.9	<0.2	~0.6
6	4.47	3.00	28.78	8.8	3.0	<0.2
7	4.74	2.87	24.55	9.0	<0.2	~0.3
8	5.32	2.99	14.46	6.2	1.3	18.5
9	5.03	3.00	13.80	6.3	4.6	10.6
10	5.98	3.86	28.03	6.5	<0.2	10.7
11	5.63	3.79	29.16	6.3	4.7	14.4
12	5.61	3.18	25.83	6.8	<0.2	8.9
13	5.12	2.98	25.63	6.2	3.1	18.3

Chart II



Results and Discussion

The 1,3,2-oxazaphospholanes are conveniently prepared by reaction of either (1*S*,2*R*)-(+)-ephedrine or (1*R*,2*R*)-(−)-pseudoephedrine with the appropriate $ZP(O)Cl_2$ reagent. The two diastereomers that resulted from each of the cyclizations were separated by preparative HPLC on silica gel. The stereochemical assignments at phosphorus (relationship of Z to ring Ph) were made on the basis of relative chemical shifts of the ring protons (protons cis to the phosphoryl oxygen tend to be deshielded[14]).



The ^1H and ^{31}P NMR parameters (coupling constants and chemical shifts) for the 1,3,2-oxazaphospholanes are

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listed in Table I. These NMR parameters were obtained at 200 MHz and are essentially first order. Five-membered ring heterocycles such as 1,3,2-dioxa- and 1,3,2-oxazaphospholanes are conveniently discussed in terms of half-chair (**14**) and twist-envelope (**15** and **16**) forms. The equilibria depend on the stereoelectronic requirements of the substituents at carbon or phosphorus.[5] That is, the NMR data do not reflect simple half-chair/half-chair equilibria of the type **14a–14b**. In the 1,3,2-oxazaphospholanes derived from pseudoephedrine (compounds **2–7**), the $^3J_{HH}$ couplings, J_{AB}, indicate equilibria between two conformational manifolds. One of these conformational manifolds would place H_A and H_B in pseudoequatorial positions (gauche with respect to each other), as in **14a**, **15a**, or **16a**, while the other places H_A and H_B in pseudoaxial positions (anti with respect to each other), as in **14b**, **15b**, or **16b** (Chart II).

From the NMR data it is possible to calculate an approximate ratio of these conformational types, with H_A and H_B anti and with H_A and H_B gauche. For the anti and gauche conformations, it is clear that

$$N(\text{anti}) \times J_{AB}(\text{anti}) + N(\text{gauche}) \times J_{AB}(\text{gauche}) = J_{AB}(\text{obsd})$$

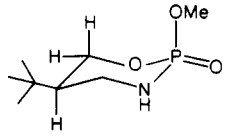
and

$$N(\text{gauche}) = 1 - N(\text{anti})$$

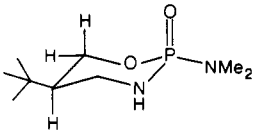
Therefore

$$N(\text{anti}) = [J_{AB}(\text{obsd}) - J_{AB}(\text{gauche})]/[J_{AB}(\text{anti}) - J_{AB}(\text{gauche})]$$

To obtain rough estimates of molar fractions of the anti and gauche conformations [N(anti) and N(gauche)], one need only have reasonable values for J_{AB} for the conformation with H_A and H_B anti and for the conformation with H_A and H_B gauche. As a reasonable model, we use the six-membered ring, 1,3,2-oxazaphosphorinane, system which is conformationally locked (e.g., compounds **17**[14c] and **18**[14b]). Values of J_{AB} = 11.0 Hz for H_A and H_B anti and J_{AB} = 4.0 Hz for H_A and H_B gauche were used. Note,

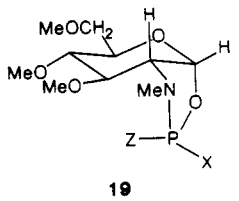


17

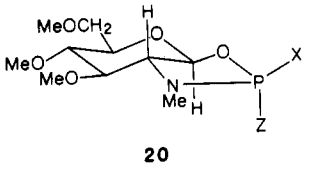


18

however, that $^3J_{HH}$ couplings for the cis-fused oxazaphospholane compounds **19**, where the protons are held in a rigid gauche arrangement by the cis ring fusion, are about 4.8 Hz (range from 4.5 to 5.0 Hz), while the analogous trans-fused compounds **20**, with the protons held rigidly anti by the trans ring fusion, have $^3J_{HH}$ of about 7.1 Hz (range from 6.5 to 7.7 Hz).[7g]



19

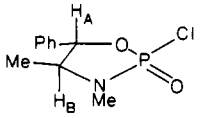


20

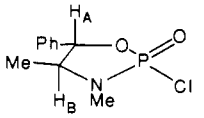
For compound **2**, we calculate an anti/gauche ratio of 60/40. Note that this equilibrium is not simply a half-chair/half-chair equilibrium. In a half-chair/half-chair equilibrium (**14a–14b**), one would expect $J_{AP} \simeq J_{BP}$ because the dihedral angle P–O–C–H_A is approximately equal to the dihedral angle P–N–C–H_B, and these dihedral angles are both about 160° and 90°, respectively, for **14a** and **14b**.[15] The NMR data for compound **2** reveal that $J_{AP} < J_{BP}$, which indicate that the equilibrium is better described as a twist-envelope/twist-envelope type, **16a–16b**, with the phenoxy substituent in a pseudoaxial disposition (i.e., $J_{AP} < J_{BP}$ indicates that ∠P–O–C–H_A < ∠P–N–C–H_B). One may account for this observed conformational equilibrium in terms of either steric or stereoelectronic arguments. The steric interactions between the phenyl substituent at C(5) and the phosphoryl flap would be expected to be greater than the steric interactions between the methyl substituent at C(4) and the phosphoryl flap of the five-membered ring. In addition, the phenoxy substituent has been shown to be axial-seeking in six-membered rings (1,3,2-dioxa-[16], 1,3,2-oxaza-[17], and 1,3,2-diazaphosphorinanes[18]), presumably due to the anomeric effect.[19]

Devillers and Navech[9] have reported NMR data in apparent conflict with ours. Thus these workers report J_{AP} = 2.2 Hz and J_{BP} = 0 Hz for compound **2** (i.e., $J_{AP} > J_{BP}$). We believe this difference is due to a misassignment of the stereochemistry and that the structure corresponding to the NMR data reported by Devillers and Navech is actually compound **3** and not compound **2** (note that the NMR data are very similar to our data for compound **3**). We believe that the stereochemical assignments for compounds **21** and **22**, reported by Devillers and Navech, are also in error. Compound **21** was reported to have vicinal proton–phosphorus couplings of J_{AP} = 3 Hz and J_{BP} = 0 Hz. However, like alkoxy substituents on phosphorus, halogen substituents are known to be axial-seeking, and so the NMR data reported are better accommodated by compound **22** rather than **21**.

In order to confirm our stereochemical assignments for compounds **2** and **3**, a single-crystal X-ray structural analysis was undertaken on compound **3**. The results of this study[20] confirm our assignment of stereochemistry and resolves the conflicting NMR interpretation.



21



22

In compound **3** the anti conformation is preferred over the gauche by a 70/30 ratio.[15] The NMR data for compound **3** show, however, that $J_{AP} > J_{BP}$, consistent with equilibria involving twist-envelope forms **15a–15b**.[15] In an equilibrium of this type, steric arguments do not account for the preference of the phenoxy substituent to be pseudoaxial. That is, the phenoxy substituent in this

(15) Note that there are some potential sources of uncertainty in these interpretations: (1) The conformationally locked six-membered-ring compounds **17** and **18** used as models are *not* ideal and may not reflect analogous coupling values in five-membered rings. (2) Although the Newman projection structures **14–16** and **23–25** are drawn showing C(4)–C(5) completely staggered, the NMR data provide no evidence as to the degree of stagger in these compounds. (3) The vicinal couplings between proton and phosphorus are not necessary the same whether through oxygen or through methyl-usubstituted nitrogen, although $\sum J_{POCH} \simeq \sum J_{PONH}$ for 1,3,2-dioxaphospholanes and 1,3-dimethyl-1,3,2-diazaphospholanes, respectively (see ref 6a). (4) Because of the relatively small values of the coupling constants obtained for these compounds and the inherent errors in measuring them (±0.2 Hz), there are appreciably large uncertainties in the mole ratio calculations.

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(20) The complete X-ray structural analysis of this compound will be reported elsewhere; *Phosphorus Sulfur*, accepted for publication.

compound prefers to be pseudoaxial in spite of increased steric interactions with the phenyl substituent at C(5). Such a conformational preference has been observed in 1,3,2-dioxaphospholanes **1**, (A = B = O, X = OPh, Z = O)[6a] and 1,3,2-oxazaphospholanes **1** (A = O, B = NMe, X = OPh, Z = O).[7a] The conformational preference must be due, then, to the anomeric effect in this five-membered ring system. Interestingly, the solid-state conformation adopted by **3** is half-chair **14b** rather than twist-envelope **15b**, the preferred conformation in solution.[20]

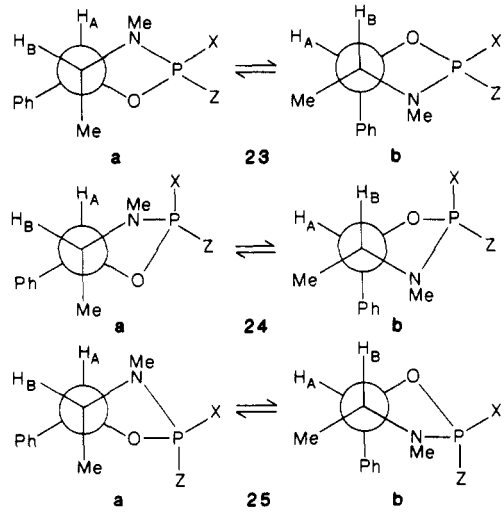
Compound **4** shows $J_{AP} > J_{BP}$, which supports twist-envelope conformations **15a–15b**, with the phenyl group on phosphorus preferentially pseudoequatorial. The magnitude of J_{AB} shows a preference of **15b** over **15a** in a 66/34 ratio. In compound **5** the relatively large value of J_{AB} indicates a preference of the anti geometrical arrangement of H_A and H_B over the gauche (70/30). Interestingly, the values of J_{AP} and J_{BP} are both approximately zero, indicating a half-chair conformation. That is, $J_{AP} \simeq J_{BP} \simeq 0$, which implies an equilibrium between conformations **14a** and **14b** with **14b** predominating. It is not clear why the phenyl substituent on phosphorus in compound **4** is apparently sterically bulky, preferring a pseudoequatorial position, but in compound **5** prefers to be neither axial nor equatorial.[15]

Compound **6** has the relatively sterically demanding NMe_2 substituent[21] cis to the methyl group at C(4) and trans to the C(5) phenyl substituent. One would expect, therefore, a conformational equilibrium involving twist-envelopes of the type **15a–15b**, with a preference for **15b**. The NMR data do in fact support such an equilibrium. Thus, $J_{AP} > J_{BP}$, indicating twist-envelope **15**, while the large value of J_{AB} indicates a preference of **15b** over **15a** (68/32). Note that J_{AP} for **6** is larger than J_{AP} for **4**, which would indicate the dimethylamino substituent on phosphorus to be sterically more demanding than the phenyl group in this heterocyclic system. Compound **7**, on the other hand, has the NMe_2 substituent trans to the methyl group and cis to the phenyl group. The steric demands of the dimethylamino group should result in equilibrating twist-envelopes **16** for compound **17** but the NMR data do not really support this: $J_{AP} \simeq J_{BP} \simeq 0$, indicating equilibrating half-chair conformations **14a–14b**, as was the case for compound **5**. The proton–proton coupling, J_{AB}, is large, thus **14b**/**14a** = 71/29, but, again, it is not at all clear why the dimethylamino group is not as equatorial seeking in diastereomer **7** as it is in diastereomer **6**.

A single-crystal X-ray structure of compound **6**[20] shows that this material adopts twist-envelope conformation **15b** in the solid state. That is, the C(4)-methyl substituent, the C(5)-phenyl substituent, and the P(2)-dimethylamino substituent are all pseudoequatorial, in complete agreement with the NMR interpretation of the preferred conformation in solution. The solid-state structure might best be described as an envelope conformation with a C(4) flap.

In the ephedrine derivatives **8–13**, the vicinal proton–proton couplings between C(4)-H and C(5)-H (i.e., J_{AB}) provides little conformational information. Thus J_{AB} ranges from 6.3 to 6.8 Hz (averaging 6.4 Hz), indicative of a predominantly gauche geometrical arrangement of these two protons in each of the ephedrine derivatives. These

Chart III



data provide no information as to whether H_A or H_B is preferentially axial. Presumably, the greater steric demands of the phenyl group over the methyl group[21] would favor the **23a–24a–25a** conformational manifold (with the C(5) phenyl group equatorial and H_A axial) over **23b–24b–25b**[15] (Chart III).

As was the case with the pseudoephedrine derivatives, the ephedrine derivatives do not show simple half-chair/half-chair equilibria of the type **23a–23b**. Looking first at the compounds with the phenoxy substituents on phosphorus, **8** and **9**, the NMR data for **8** show that $J_{AP} \ll J_{BP}$, which is consistent with H_A axial and H_B equatorial. The data for **9** also show $J_{AP} < J_{BP}$, but by not so great a difference (J_{AP} and J_{BP} = 1.3 and 18.5 Hz, respectively, in **8** and only 4.6 and 10.6 Hz in **9**). These NMR data may be interpreted such that the dihedral angle P–O–C–H_B is larger (more anti) in **8** than in **9**, while P–O–C–H_A in **8** is closer to 90° than that in **9**. This would mean that the preferred conformation for **8** is twist-envelope form **25a** while the preferred conformation for **9** is twist-envelope **24a**. Thus, in the 1,3,2-oxazaphospholane ring system derived from ephedrine, the phenoxy substituent on phosphorus is axial-seeking, just as it is in the pseudoephedrine derivatives. Note that, again, our stereochemical assignments for **8** and **9** are in apparent conflict with those of Devillers and Navech[9] but in agreement with those of Cooper and co-workers.[8a]

An X-ray crystal structure determination of compound **9** confirms our stereochemical assignment for this material.[20] The conformation adopted by compound **9** in the solid state is best described as half-chair **23a**, with pseudoaxial C(4)-methyl substituent and pseudoequatorial C(5)-phenyl substituent.

The ephedrine compounds with the sterically demanding dimethylamino substituent on phosphorus, **12** and **13**, may be analyzed analogously. Thus J_{BP} for **12** is smaller than J_{BP} for **13**, indicating that the dihedral angle P–O–C–H_B in **13** is greater than that in **12**. In addition, J_{AP} = 0 in **12**, whereas J_{AP} = 3.1 Hz in **13**, indicating dihedral angles of about 90° and 120°, respectively, for **12** and **13**.[22] These data indicate the preferred conformation for **12** to be **24a** and for **13** to be **25a**. That is, not surprisingly, the dimethylamino group on phosphorus is equatorial seeking.

The NMR data for **10** (phenyl substituent on phosphorus, cis stereochemistry with respect to the C(4)-methyl

(21) The conformational energy in cyclohexane equilibria for a methyl group is about 1.7 kcal/mol and about 3.0 kcal/mol for a phenyl group. The conformational energy for a dimethylamino substituent is about 2.1 kcal/mol. Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199. In 2-substituted-1,3,2-dioxaphosphorinanes, however, dimethylamino has been found to be more sterically demanding than phenyl. Majoral, J. P.; Bergounhou, C.; Navech, J.; Maria, P. C.; Elegant, L.; Azzaro, M. *Bull. Soc. Chim. Fr.* **1973**, 3142.

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and C(5)-phenyl substituents) are very similar to those for **12**. The P–O–C–H_A dihedral angle is about 90° (i.e., J_{AP} = 0), while P–O–C–H_B is between 120° and 180°. That is, the preferred conformation is **24a**, presumably due to steric interactions resulting from the all-cis arrangement of the substituents. Compound **11**, on the other hand, shows a vicinal coupling, J_{BP} = 14.4 Hz, which is intermediate between that for the phenoxy analogue **9** (J_{BP} = 10.6 Hz) and the dimethylamino analogue **13** (J_{BP} = 18.3 Hz). We interpret these data in terms of a preferred half-chair conformation, **23a**, for compound **11** rather than a twist-envelope conformation.

Conclusions

In the five-membered (1,3,2-oxazaphospholane) rings examined in this work, the relatively small, electronegative phenoxy substituent on phosphorus was found to prefer an axial disposition in the equilibria involved. Indeed, this conformational preference has been observed in other 1,3,2-oxazaphospholanes[7a,8a] as well as in six-membered ring phosphorus hetercycles.[5] The axial-seeking nature of small electronegative substituents on phosphorus can be rationalized in terms of favorable orbital interactions of the lone pairs on the ring heteroatoms with the phosphorus substituent antibonding orbital. Such an orbital interaction is possible only when the phosphorus substituent is axial.

Note that the anomeric effect in such a system should result in increased bonding between ring nitrogen and phosphorus and decreased bonding between the axial phosphorus substituent and phosphorus. There is NMR evidence in support of this interaction. Other things being equal, an increase in bond order should cause an increase in coupling. We can examine the coupling constants between phosphorus and the N(3)-CH_3 protons as a function of conformational preference. Compounds **2** and **3** (phenoxy substituents, axial preference, anomeric effect turned on) have $^3J_{PH}$–(P–N–C–H) 2.5 Hz greater than the analogous couplings for **6** and **7** (dimethylamino substituents, equatorial preference, anomeric effect turned off).

In compound **8**, in which the phenoxy substituent on phosphorus, the methyl group on C(4), and the phenyl group on C(5) are all cis, steric interactions would be expected to reduce the population of **25a** somewhat with respect to **23a**, if not **24a** (i.e., less population of axial phenoxy, less anomeric effect), and $^3J_{PH}$(P–N–C–H) = 10.0 Hz. Compound **9**, on the other hand, would not experience such severe steric interactions and the conformation **24a** with axial phenoxy should be increased (greater anomeric effect) and $^3J_{PH}$ (P–N–C–H) = 10.4 Hz.

Although there are some uncertainties in the methods and caution should be used in the interpretation,[15] it is apparent from these results, the NMR solution study, and the X-ray structural work that the conformations of 1,3,2-oxazaphospholanes are not simple half-chair or envelope forms. The steric and electronic requirements of substituents on this ring system generally result in twist-envelope conformations and the relative preference of one conformation over others can be inferred.

Experimental Section

Methods and Materials. Analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN. Melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 1330 spectrophotometer. ^{1}H NMR spectra were obtained on an IBM/Bruker AF 200 spectrometer, operated in the FT mode. Coupling constants were measured at 200-MHz on 100-Hz SW expansions, 32K data base, 9.044-s acquisition times and are probably accurate to ±0.2 Hz. ^{31}P NMR spectra were made at 81.015 MHz on an IBM/Bruker AF 200 spectrometer under proton noise decoupling conditions. Positive ^{31}P chemical shifts are in δ (parts per million) downfield from external 85% H_3PO_4. Diastereomeric products were separated on an ISCO Model 2300 HPLC equipped with an ISCO Model UA-5 UV detector, ISCO FOXY fraction collector, and a Rainin DYNAMAX silica gel column (21.4 mm i.d. × 25 cm length).

(2*R*,4*R*,5*R*)-2-Phenoxy-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane (2) and (2*S*,4*R*,5*R*)-2-Phenoxy-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane (3). Typical Procedure for the Preparation and Purification of the 1,3,2-Oxazaphospholanes. A mixture of (1*R*,2*R*)-(–)-pseudoephedrine (5.0 g, 0.030 mol), phenyl dichlorophosphate (4.5 mL, 0.030 mol), and triethylamine (8.36 mL, 0.060 mol) in ethyl acetate (300 mL) was stirred at room temperature for 24 h. The triethylamine hydrochloride was filtered off and the solvent removed from the filtrate under reduced pressure to give 10.88 g of a colorless residual solid. A 2.00-g sample of crude product was chromatographed by a gravity column (2.5 × 60 cm) on silica gel, eluting with ethyl acetate (200 mL), to give 1.47 g (87% yield) of a mixture of **2** and **3**. The diastereomers were separated by preparative HPLC on silica gel, eluting with ethyl acetate, to give pure **2** and pure **3** as colorless crystalline solids, which were each recrystallized from ether/pentane. Each of the 1,3,2-oxazaphospholanes synthesized gave consistent ^{1}H NMR and IR spectra and acceptable elemental analyses (C, H, P).

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Registry No. **2**, 119324-17-3; **3**, 119324-18-4; **4**, 119324-19-5; **5**, 119324-20-8; **6**, 119324-21-9; **7**, 119324-22-0; **8**, 21040-32-4; **9**, 21040-33-5; **10**, 119324-23-1; **11**, 119324-24-2; **12**, 119324-25-3; **13**, 119324-26-4; **21**, 28080-18-4; **22**, 31060-12-5; $Cl_2P(O)OPh$, 770-12-7; $Cl_2P(O)Ph$, 824-72-6; $Cl_2P(O)NMe_2$, 677-43-0; (1*S*,2*R*)-(+)-ephedrine, 321-98-2; (1*R*,2*R*)-(–)-pseudoephedrine, 321-97-1.

Supplementary Material Available: Complete experimental details for syntheses of **2–13** and X-ray structural data (final atomic parameters) and ORTEP perspective drawings for **3**, **6**, and **9** (15 pages). Ordering information is given on any current masthead page.