$-OCH_3$), 3.3 (m, 1, >CHCO–), and 0.65–2.1 (m, 4, cyclopropyl); mass spectrum calcd, 191.09462; found, 191.09425.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.99; H, 6.85; N, 7.39.

Irradiation of the 2-proton multiplet at δ 4.6 resulted in simplification of the lowest field cyclopropyl absorption. Also, saturation of the olefinic signal at 5.95 caused collapse of the broad doublet due to >CHN< and some sharpening of the higher field cyclopropyl region.

B. Longer Reaction Time. When the reaction was carried out as above except that the reaction mixture was left at room temperature for 22 hr prior to treatment with thiophenol and pyridine, the only product found was **46**, 35 mg (30%), in the form of colorless crystals, mp 227.5–228.5°, from methylene chloride: $\nu_{max}^{CHCl_3}$ 1680 and 1725 cm^{-1}; $\delta_{TMS}^{CDCl_3 + DMSO\text{-}d_6}$ 8.6 (br, 1, >NH), 6.15 (dd, J = 4 and 11 Hz, 1, olefinic), 5.5 (t, J = 11 Hz, 1, olefinic), 4.35 (m, 1, >CHN<), 3.5 (d, J = 11 Hz, 1, >CHCO–), and 2.7 (peak partially obscured by DMSO, $-CH_2-$); mass spectrum calcd, 177.07897; found, 177,07865.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.28; N, 7.91. Found: C, 67.27; H, 6.31; N, 7.92.

Hydrolysis of 45. A solution of 20 mg of **45** in 0.3 ml of $CDCl_3$ was placed in an nmr tube and treated with one drop of a solution of perchloric acid in methanol. Scanning of the spectrum within minutes of the acid treatment showed only peaks due to **46**. The solution was washed with water, dried, and evaporated to afford 18 mg (97%) of colorless crystals, mp 226–228°, identical (ir) with the material isolated above.

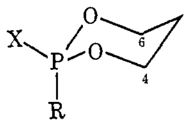
Stereochemistry of Oxidation of Trivalent Phosphorus and Configurational Assignments in 2-Substituted 1,3,2-Dioxaphosphorinanes

J. A. Mosbo[1] and J. G. Verkade*

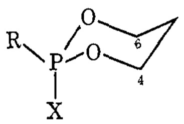
Contribution from the Department of Chemistry, Iowa State University, Ames, Iowa 50010. *Received January 22, 1973*

Abstract: From dipole moment and nmr measurements on the isomeric 2-oxo-2-methoxy-1,3,2-dioxaphosphorinanes VIIIa,b, it is shown that the stereospecific oxidation of the parent compounds IIa,b occurs with retention of configuration at phosphorus. With this information and additional dipole moment and nmr studies carried out on the isomeric 2-oxo-2-dimethylamino-1,3,2-dioxaphosphorinanes VIIa,b, the configurations at phosphorus in these isomers as well as those in the trivalent phosphorus parents Va,b are assigned The equilibrium ratio of Va,b (1:10) shows that in contrast to the 2-methoxy analogs IIa,b the more stable configuration is that wherein the Me_2N group is equatorial. That the same is true for the oxidized analogs VIIa,b relative to VIIIa,b is shown from hydrolysis experiments. The results for the 2-methoxy systems are rationalized on the basis of a modified gauche effect, which in the case of the 2-dimethylamino compounds is dominated by a steric problem incurred by the Me_2N group in its attempt to adopt a preferred rotameric conformation. The analogous stability relationships in the 2-substituted-2-oxo systems are also consistent with a modified gauche effect tempered by steric requirements of the dimethylamino group.

The bulk of the information regarding the preferred stereochemical disposition of phosphorus substituents in chair-form 2-R-1,3,2-dioxaphosphorinanes Ia,b (where X = lone pair and R = halogen, alkoxy, alkyl, phenyl), while not unequivocal nor uncontested,[2] indicates rather strongly that configuration Ia is thermodynamically the more stable one. The axial preference of R has been inferred from dipole moment measurements,[3] nmr couplings and chemical shifts,[4] X-ray structural work on derivatives formed by assumed stereochemical paths,[5] and deductive reasoning concerning the stereochemical course of exchanging one R group for another.[6] Most of the structural knowledge obtained to date on the 2-oxo derivatives of Ia,b (X = O) stems from crystal structure determinations on compounds possessing various R groups (OPh, OH, Br, Ph, Me, NR_2) along with ring substituents in some cases.[5,7] With the apparent exception of R = NR_2,[7f] the phosphoryl oxygen is equatorial in the solid state. The structural behavior of 1,3,2-dioxaphosphorinane systems where X = lone pair or O is complicated in the solution state by the presence of conformational



Ia



Ib

---

[1] National Science Foundation Trainee.

(2) (a) D. Gagnaire, J. B. Robert, and J. Verrier, *Bull. Soc. Chim. Fr.*. 2240 (1967); (b) A. V. Bogat-skii, A. A. Kolesnik, Yu. Yu. Samitov, and T. D. Butova, *J. Gen. Chem. USSR*, 37, 1048 (1967); (c) J. P. Albrand, D. Gagnaire, J. B. Robert, and M. Haemers, *Bull. Soc. Chim. Fr.*, 3496 (1969).

(3) (a) D. W. White, G. K. McEwen, and J. G. Verkade, *Tetrahedron Lett.*, 1905 (1969); (b) C. Bodkin and J. P. Simpson, *J. Chem. Soc. D*, 829 (1969).

(4) (a) W. G. Bentrude, K. C. Yee, R. D. Bertrand, and D. M. Grant, *J. Amer. Chem. Soc.*, **93**, 797 (1971); (b) W. G. Bentrude and J. H. Hargis, *ibid.*, **92**, 7136 (1970); (c) W. G. Bentrude and K. C. Yee, *Tetrahedron Lett.*, 3999 (1970).

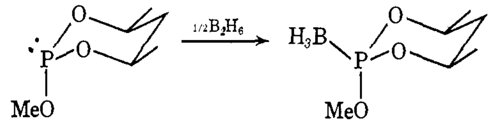
(5) (a) M. G. B. Drew, J. Rodgers, D. W. White, and J. G. Verkade, *J. Chem. Soc. D*, 227 (1971); (b) J. Rodgers, D. W. White, and J. G. Verkade, *J. Chem. Soc. A*, 77 (1971); (c) M. G. B. Drew and J. Rodgers, *Acta Crystallogr., Sect. B*, **28**, 924 (1972); (d) M. Haque, C. N. Caughlan, J. M. Hargis, and W. G. Bentrude, *J. Chem. Soc. A*, 1786 (1970).

(6) D. W. White, R. D. Bertrand, G. K. McEwen, and J. G. Verkade, *J. Amer. Chem. Soc.*, **92**, 7125 (1970).

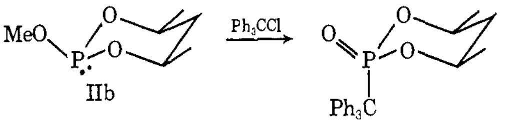
(7) (a) H. J. Geise, *Recl. Trav. Chim. Pays-Bas*, **86**, 362 (1967); (b) M. Haque, C. N. Caughlan, and W. L. Moats, *J. Org. Chem.*, **35**, 1446 (1970); (c) W. Murayama and M. Kainosho, *Bull. Chem. Soc. Jap.*, **42**, 1819 (1969); (d) T. A. Beineke, *Acta Crystallogr.*, **25**, 413 (1969); (e) R. C. G. Killian, J. L. Lawrence, and I. M. Magennis, *Acta Crystallogr., Sect. B*, 27, 189 (1971); (f) W. S. Wadsworth, private communication.

equilibria which have been detected by nmr[3b,4,6,8] and to a lesser extent by ir spectroscopy.[8a,9]

In order to simplify solution configurational assignments in trivalent and pentavalent phosphorus heterocycles of the type represented by Ia,b, we have chosen to study derivatives possessing equatorial methyl groups on C-4 and C-6. These substituents render substantially inaccessible a second chair form to the ring as well as reduce the likelihood of boat and twist-boat conformers. Consequently, the methyl ring substituents engender compounds which are isomeric at phosphorus as in IIa and IIb. While the presence of these isomers was recognized at the time of their original synthesis,[10] their configurational assignments were made on the basis of structural work carried out on the products of reactions 1 and 2 and their probable stereochemical courses.[5a-c]



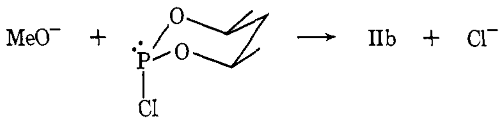
IIa (1)



IIb (2)

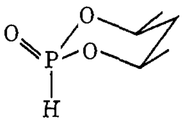
Because IIa is the only isomer formed in an equilibrium-controlled transesterification (eq 3) while IIb is made by an S$_N$2 route (eq 4),[6,10] IIa is the thermodynamically more stable isomer.

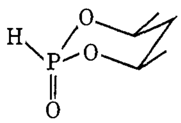
$$P(OMe)_3 + meso\text{-}(HOCHMe)_2CH_2 \rightleftharpoons \text{IIa} \qquad (3)$$



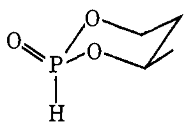
(4)

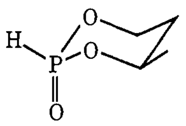
The configurational assignment of IIa,b then allowed the determination of the phosphorus stereochemistry of IIIa,b assuming that the reaction of IIa with HBr proceeds *via* a Michaelis–Arbuzov mechanism.[11]


IIIa

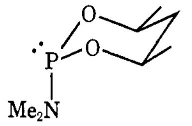

IIIb

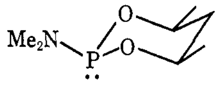
Equilibrium experiments between IIIa and IIIb further show that IIIa is the more stable isomer, $\Delta H°$ being 4.4 kcal/mol and $\Delta G°$ at 40° being 1.6 kcal/mol.[11] A similar conclusion was reached by others for IVa,b on the basis of dipole moment measurements.[12]

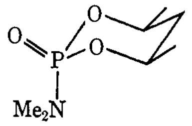

IVa

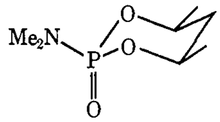

IVb

In a recent preliminary communication,[13] we reported the surprising result that the thermodynamically more stable isomer of V is Vb from dipole moment measurements on VIa,b and nmr measurements (^{31}P and lanthanide induced shifts) on Va,b, VIa,b, and VIIa,b.

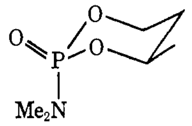

Va

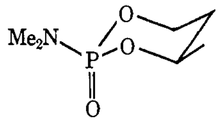

Vb


VIa


VIb

Bentrude and Tan[14] drew parallel conclusions for the isomeric pair of 2-dimethylamino-5-*tert*-butyl-1,3,2-dioxaphosphorinanes.


VIIa


VIIb

Here, we present details of our investigations as well as evidence that VIb is thermodynamically more stable than VIa. A rationale for the relative stabilities of isomers of various 2-substituted-1,3,2-dioxaphosphorinanes in terms of bonding is also advanced. Our configurational assignments at phosphorus in these systems depend to a considerable extent on the assumed retention of configuration at phosphorus when Va and Vb are oxidized with N_2O_4. Experimental evidence is put forth which strongly supports the validity of this assumption.

Experimental Section

***meso*-2,4-Pentanediol.** The synthesis of this compound was performed as reported previously.[6]

2-Chloro-4,6-dimethyl-1,3,2-dioxaphosphorinane. This material was synthesized as reported previously[6] from PCl_3 and meso diol.

2-Dimethylamino-4,6-dimethyl-1,3,2-dioxaphosphorinane (Va,b). These isomers were prepared in *ca.* 10:1 ratio of Vb:Va (see Discussion) by two difference procedures.

(a) A solution of 5.0 g (0.048 mol) of meso diol and 7.8 g (0.048 mol) of trisdimethylaminophosphine was combined and heated at 55° for 3 hr under a nitrogen atmosphere. The temperature was then raised to 65° for 10 hr and then to 85° until no more dimethylamine could be detected leaving the reaction. Rapid heating resulted in formation of considerable quantities of polymer and poor yields of desired compound. The product obtained in about 60% yield was vacuum distilled at 44–46° (2 mm).

---

[8] (a) D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc. B*, 1454 (1971); (b) J. H. Hargis and W. G. Bentrude, *Tetrahedron Lett.*, 5365 (1968); (c) W. G. Bentrude and J. H. Hargis, *J. Chem. Soc. D*, 1113 (1969); (d) W. G. Bentrude and K. C. Yee, *ibid.*, 169 (1972); (e) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc. C*, 752 (1970); (f) A. R. Katritzky, M. R. Nesbit, J. Michalski, Z. Tulimowski, and A. Zwierzak, *J. Chem. Soc. B*, 140 (1970); (g) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc. C*, 2091 (1968).

[9] (a) M. Kainosho, T. Morofushi, and A. Nakamura, *Bull. Chem Soc. Jap.*, 42, 845 (1969); (b) T. H. Siddall and R. N. Wilhite, *Appl. Spectrosc.*, 20, 47 (1966); (c) J. P. Majoral, R. Kraemer, J. Devillers, and J. Navech, *Bull. Soc. Chim. Fr.*, 3917 (1970).

[10] D. Z. Denney and D. B. Denney, *J. Amer. Chem. Soc.*, **88**, 1830 (1966).

[11] J. A. Mosbo and J. G. Verkade, *J. Amer. Chem. Soc.*, **95**, 204 (1973).

[12] (a) E. Y. Nifant'ev, A. A. Borisenko, I. S. Nasonovskii, and E. I. Matrosov, *Dokl. Akad. Nauk SSSR*, **196**, 28 (1971); (b) E. Y. Nifant'ev and A. A. Borisenko, *Tetrahedron Lett.*, 309 (1972).

[13] J. A. Mosbo and J. G. Verkade, *J. Amer. Chem. Soc.*, **94**, 8224 (1972).

[14] W. G. Bentrude and H. W. Tan, *J. Amer. Chem. Soc.*, **94**, 8222 (1972); **95**, 4666 (1973).

(b) Into a solution of 7.8 g (0.046 mol) of the phosphorochloridite and 200 ml of diethyl ether maintained at about −25° was bubbled with stirring an excess of 0.092 mol of dimethylamine gas diluted to about 50% by dry nitrogen. Upon completion, the dimethylamine hydrochloride was removed by filtration under nitrogen, the ether removed under vacuum, and the product vacuum distilled in yields exceeding 60%. Pmr spectra prior to and following the distillation of product indicated a ratio of 10:1 for Vb:Va.

2α-Methoxy-4,6-β,β-dimethyl-1,3,2-dioxaphosphorinane (IIa). This compound was synthesized as described previously.[6]

2β-Methoxy-4,6-β,β-dimethyl-1,3,2-dioxaphosphorinane (IIb). Although the synthesis of this compound described previously[6] results in contamination of the desired product with the stable isomer IIa, we have found that a few minor modifications of that procedure lead to pure IIb. To a stirred solution of phosphorochloridite in diethyl ether maintained at 0° was added dropwise with stirring a solution containing a 5% deficit of the molar amount of methanol and a 5% excess of triethylamine in diethyl ether. After filtration under nitrogen, the ether was removed under vacuum and the product vacuum distilled at ≤25° (0.1–0.3 mm). The temperature of the distillation flask did not exceed 40°. The phosphite obtained in 90% yield can be stored for a month or longer at −78° without substantial conversion to the stable isomer.

2β-Oxo-2α-methoxy-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (Xa) and 2α-Oxo-2β-methoxy-4,6-β,β-dimethyl-1,3,2-dioxaphosphorinane (Xb). The compounds were prepared from the phosphites IIa and IIb, respectively, by oxidation with NO_2 at 0° in CCl_4 solution. The former was purified by recrystallization from diethyl ether (mp 57–58°) and the latter by vacuum distillation, bp 86° (0.2 mm). Both isomers displayed parent peaks of *m/e* 180 in their mass spectra.

2β-Oxo-2α-dimethylamino-4,6-β,β-dimethyl-1,3,2-dioxaphosphorinane (VIa) and 2α-Oxo-2β-dimethylamino-4,6-β,β-dimethyl-1,3,2-dioxaphosphorinane (VIb). These compounds were prepared by two procedures.

(a) The isomers were prepared by NO_2 oxidation of the phosphoramidites Ia,b as described above for the phosphates. This resulted in an isomer ratio of 10:1 for VIb:VIa, the same as the ratio of isomers of the starting material.

(b) A mixture of isomers of VIb:VIa of *ca.* 3:2 ratio was obtained by treatment of IIa with excess *N*-chlorodimethylamine. The amine starting material was prepared in benzene by the procedure of Heasley, Kovacic, and Lange[15] and used without further purification. To a solution of 9.9 g (0.06 mol) of phosphite IIa dissolved in 50 ml of benzene was added dropwise the benzene solution of *N*-chlorodimethylamine with stirring. After addition the solution was stirred for 0.5 hr, then heated to reflux for 0.75 hr; it was found that a repetition of this procedure was necessary to completely react all of the phosphite and to ensure high yields (*ca.* 60%) of the desired product. The benzene was removed under vacuum and the isomers were separated by vacuum distillation employing a platinum spinning band column (bp VIb, 63° (0.1 mm); VIa, 82° (0.1 mm)). The mass spectra of both isomers displayed parent peaks of *m/e* 193.

Compounds of 1,3-Butanediol. These compounds were prepared identically with those of the *meso*-2,4-pentanediol with the exception of 2β-oxo-2α-methoxy-4β-methyl-1,3,2-dioxaphosphorinane (IXa). This compound did not crystallize and was vacuum distilled at 116° (0.25 mm). The boiling points of the other compounds were: 2α-oxo-2β-methoxy-4β-methyl-1,3,2-dioxaphosphorinane (IXb), 86° (0.25 mm); 2β-oxo-2β-dimethylamino-4β-methyl-1,3,2-dioxaphosphorinane (VIIa), 82° (0.25 mm); and 2α-oxo-2β-dimethylamino-4β-methyl-1,3,2-dioxaphosphorinane (VIIb), 66° (0.20 mm). All four compounds exhibited parent peaks in their mass spectra of *m/e* 166 and 179 for the phosphates and phosphoramidates, respectively.

LIS Experiments. Chloroform solutions of VIIa,b, IXa, and tris-(1,1,1,2,2,3,3-heptafluoro-4,6-octanedione)europium(III) (Eu(fod)$_3$) were prepared to be 0.2 *M* in phosphorus solute and 0.1 *M* in Eu(fod)$_3$.

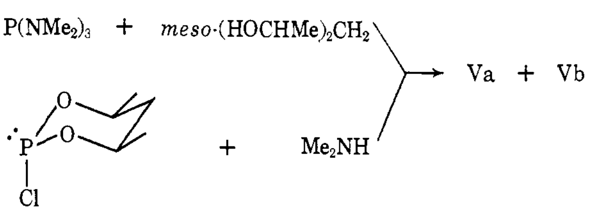
Hydrolysis of VIIa,b. To 0.5 ml of a 1 *M* solution of water in acetonitrile containing one drop of concentrated perchloric acid was added sufficient VIIb to give a 1 *M* solution. A solution of VIIa was similarly prepared and both solutions were placed in a 75° constant-temperature bath. After 1 hr both solutions were *ca.* 30% hydrolyzed as shown by their nmr spectra. However, the spectrum of the sample of VIIa indicated that 33% of the unhydrolyzed phosphoramidate was VIIb; after 2.5 and 5 hr the spectra showed a similar VIIa:VIIb ratio although hydrolysis had progressed. Monitoring the VIIb sample revealed no detectable appearance of VIIa throughout the same period. No further hydrolysis was observed after 5 hr.

Dipole Moments. The instrumentation has been described in detail elsewhere, as is also the treatment of the data.[16] Four solutions of each compound ranging in concentration from about 1 to 10 × 10^{-3} mole fraction in benzene prepared under nitrogen were employed.

Other Instrumentation. Routine pmr spectra were obtained on either a Varian Associates A-60 nmr spectrometer or a Hitachi Perkin-Elmer R20-B spectrometer operating at 60 MHz. Spectra of compounds in the presence of Eu(fod)$_3$ were obtained on a Varian Associates HA-100 nmr spectrometer. ^{31}P chemical shifts were obtained by standard indor techniques employing a Varian Associates HR-60 nmr spectrometer operating at 60 MHz. Mass spectra were provided by an Atlas CH-4 mass spectrometer.

Discussion

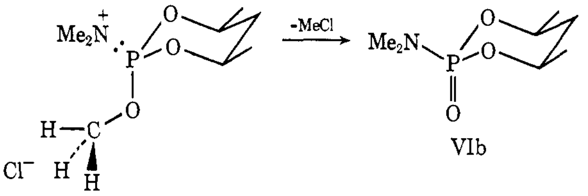
Isomerization of Va,b *vs.* IIa,b. Isomers Va and Vb are produced in essentially the same ratio (1:10) by transesterification (eq 5) and by the reaction of the cyclic phosphorochloridite with excess dimethylamine (eq 6). In contrast to this, the reaction of the diol



(5)

(6)

with P(OMe)$_3$ gives pure IIa while the phosphorochloridite reacts with methanol (in the presence of methoxide) to form only IIb. Thus isomerization of Va and Vb is apparently much more facile under our reaction conditions than that of IIa and IIb, and deductions regarding phosphorus stereochemistry in Va and Vb based on the stereospecificity of reaction 6 are not possible. While the reaction of *N*-chlorodimethylamine with the thermodynamically stable phosphite IIa might have been expected to form VIb owing to the stereospecificity of the Michaelis–Arbuzov reaction (eq 7), isomerization to a *ca.* 3:2 ratio of VIb



VIb

(7)

to VIa rendered stereochemical assignments made on this basis tenuous as well. Because of these difficulties, phosphorus configurational assignments were arrived at from dipole moment, lanthanide induced shift, and ^{31}P chemical shift measurements.

Phosphite Oxidation Stereospecificity. Because most of the measurements reported here were performed on the N_2O_4 oxidation products VIa,b and VIIa,b, which are assumed to form with retention of phosphorus configuration from their trivalent parents, we present first our evidence supporting this assumption. Denney, *et al.*,[17a] pointed out earlier that N_2O_4 oxidizes

---

[15] V. L. Heasley, P. Kovacic, and R. M. Lange, *J. Org. Chem.*, **31**, 3050 (1966).

[16] A. C. Vandenbroucke, R. W. King, and J. G. Verkade, *Rev. Sci. Instrum.*, **39**, 558 (1968).

[17] (a) D. Z. Denney, G. Y. Chen, and D. B. Denney, *J. Amer. Chem. Soc.*, **91**, 6838 (1969); (b) J. Michalski, A. Okruszek, and W. Stec, *J. Chem. Soc. D*, 1495 (1970).

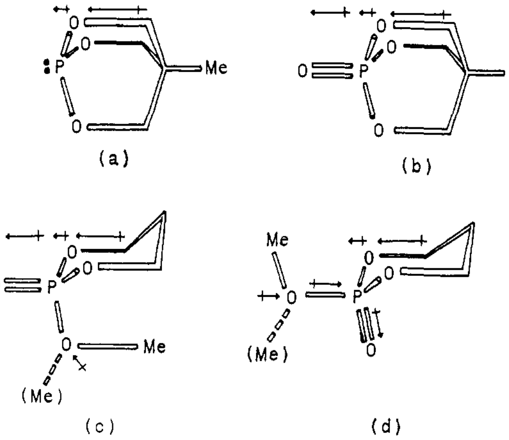
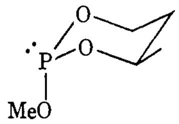
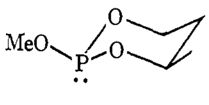


Figure 1. Molecular dipole components in a bicyclic phosphite (a), a bicyclic phosphate (b), and two conformational forms of a monocyclic six-membered ring phosphate (c and d).

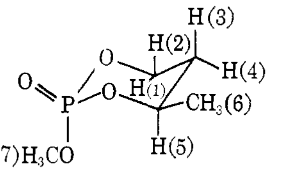
bicyclic phosphites and monocyclic phosphites such as IIa,b with similar ease. Thus it seemed reasonable to suppose that since the former compounds are unable to undergo inversion, it was unnecessary for the latter to do so in order to oxidize. Michalski, *et al.*,[17b] concluded that N_2O_4 oxidation of VIIIa and VIIIb to IXa and IXb, respectively, occurred with retention of phosphorus configuration although acyclic phosphines apparently did not. Because the arguments in the literature were not unequivocal, we sought further experimental evidence. The data discussed below accord well with stereo retentive N_2O_4 oxidation of monocyclic phosphites, thus supporting the earlier postulates.[17]



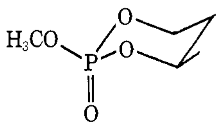
VIIIa



VIIIb

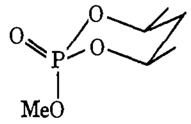


IXa

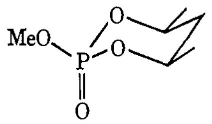


IXb

From our earlier dipole moment work on bicyclic phosphite esters,[13] we were forced to conclude that despite the larger electronegativity of oxygen, the P–O group moment was in the direction of phosphorus as shown in Figure 1a. This anomaly was attributed to constraint of the oxygen lone-pair density to enhance the molecular moment along the C_{3v} axis and π-electron transfer from oxygen to phosphorus. The latter effect is expected to augment in the bicyclic phosphate (Figure 1b). It is seen in Figure 1c that opening the caged phosphate to form a six-membered phosphate would not be expected to alter the molecular moment appreciably except when the methoxy group is in the "extended" position. Even if the extended form of the molecule is predominant, the main component of the molecular dipole will still be roughly along the phosphorus phosphoryl oxygen axis since one C–O bond moment is a comparatively small contribution to the overall moment.[19] Figure 1d shows that a decrease in molecular moment is expected when the configuration at phosphorus is inverted. The conformers shown in Figures 1c and 1d are well represented by isomers Xa and Xb, respectively. The experimental dipole moment of Xa is 6.11 D (Table I) which as expected (if the configuration shown is correct) is less than that of the bicyclic phosphate (7.10 D[20]). In further accord with this hypothesis is the measured moment of Xb which is even less (4.69, Table I).



Xa



Xb

Table I. Dipole Moment Data for 2-R-2-Oxo-4,6-dimethyl-1,3,2-dioxaphosphorinanes[a]

Compd	$\partial\epsilon/\partial X$	$\partial n/\partial X$	P_0	μ
Xa	51.04	−0.126	763	6.11 ± 0.05
Xb	29.98	−0.097	449	4.69 ± 0.05
VIa	46.15	−0.092	689	5.80 ± 0.1
VIb	22.20	−0.123	335	4.05 ± 0.1

[a] μ expressed in debyes, obtained in benzene solution.

Further confirmation for N_2O_4 oxidation of IIa,b with retention of phosphorus configuration comes from the lanthanide induced shift studies on IXa,b. The method of preparation of these isomers is exactly analogous to that of Xa,b from which they differ only in the absence of one ring methyl group. The LIS experiments are more informative for IXa,b than for Xa,b, as is now explained. In the presence of $Eu(fod)_3$, protons are shifted according to the relationship $\Delta\delta = k(3\cos^2\theta - 1)/R^3$.[21] There is good evidence that the phosphoryl oxygen is the preferential complexation site for lanthanides[22] and protons as well.[23] Dreiding models of IXa,b indicate that protons H(1), H(2), and H(5) are of similar distances to the metal for isomer a assuming that the lanthanide complex is located near the phosphoryl oxygen along the P=O axis. In IXb, however, H(1) and H(5) are about the same distance while H(2) is substantially further from the metal complex. Protons H(1) and H(5) are considerably closer to the shift reagent in IXb than in IXa, but H(2) is about the same distance in both isomers. The nmr shifts for these protons in IXa,b (Table II) are entirely in agreement with these considerations, lending further credence to the conclusion that N_2O_4 oxidation

---

(18) A. C. Vandenbroucke, E. J. Boros, and J. G. Verkade, *Inorg. Chem.*, 7, 1469 (1968).

(19) Hybridization changes accompanying angle changes (OPO and POC) as a result of strain release from a bicyclic to a monocyclic phosphate will also affect the molecular dipole but these are not expected to be large enough to be dominant.

(20) T. L. Brown, J. G. Verkade, and T. S. Piper, *J. Phys. Chem.*, 65, 2051 (1961).

(21) Here θ is the angle between the symmetry axis of the complex and the vector from the lanthanide ion to the proton, R is the distance from the proton to the lanthanide ion and k is a collection of constants: B. L. Shapiro, I. R. Hlubucek, and G. R. Sullivan, *J. Amer. Chem. Soc.*, 93, 3281 (1971).

(22) (a) J. L. Burdett and L. L. Burger, *Can. J. Chem.*, 44, 11 (1966); (b) S. C. Goodman and J. G. Verkade, *Inorg. Chem.*, 5, 498 (1966).

(23) L. J. Vande Griend, D. W. White, and J. G. Verkade, *Phosphorus*, 3, 5 (1973).

Table II. ^{1}H Chemical Shift Data for 2-R-2-Oxo-4-methyl-1,3,2-dioxaphosphorinanes in Absence and Presence of Eu(fod)$_3$

Compd	H_1	H_2	H_3	H_4	H_5	H_6	H_7
IXa							
Without Eu(fod)$_3$	4.4	4.4	1.9	1.9	4.4	1.37	3.73
With Eu(fod)$_3$	7.39	6.59	4.28	3.44	7.71	2.67	8.31
$\Delta\delta$	3.0	2.2	2.4	1.5	3.3	1.30	4.58
IXb							
Without Eu(fod)$_3$	4.5	4.5	2.0	2.0	4.5	1.40	3.73
With Eu(fod)$_3$	9.02	6.72	4.60	3.55	9.61	2.77	7.67
$\Delta\delta$	4.5	2.2	2.6	1.6	5.1	1.37	3.94
VIIa							
Without Eu(fod)$_3$	4.3	4.3	1.9	1.9	4.3	1.42	2.65
With Eu(fod)$_3$	6.58	5.92	4.46	3.42	6.58	3.32	5.29
$\Delta\delta$	2.3	1.6	2.6	1.5	2.3	1.90	2.64
VIIb							
Without Eu(fod)$_3$	4.3	4.3	1.8	1.8	4.3	1.33	2.68
With Eu(fod)$_3$	8.93	6.49	4.55	3.15	9.63	2.52	6.41
$\Delta\delta$	4.6	2.2	2.8	1.4	5.3	1.19	3.73

of the parent phosphites (IIa,b) occurs with retention. Recent LIS studies by Yee and Bentrude[24] using a similar phosphate ring system of known geometry involved similar deductive reasoning about the ring structure.

The ^{31}P chemical shifts of VIIIa,b in Table III show that if their configurational assignments are correct, an equatorial P═O leads to a ^{31}P shift which is upfield of the corresponding P═O$_{(ax)}$ isomer. That this is very probably a general phenomenon is indicated by the results of Bentrude and Tan[25] who have found this to be true for a variety of analogous systems.

Table III. ^{1}H and ^{31}P Spectral Parameters of 2-R-4,6-Dimethyl-1,3,2-dioxaphosphoranes and 2-R-2-Oxo-4,6-dimethyl-1,3,2-dioxaphosphoranes

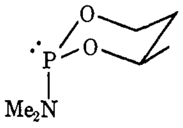
Compd	$\delta_{CCH_3}{}^a$	$^3J_{HCCH_3}$	$^4J_{POCCH_3}$	$\delta_{CH}{}^a$	$\delta_{CH_2}{}^a$	$\delta_{XMe}{}^{a,b}$	$^3J_{PXCH_3}{}^b$	$\delta_{^{31}P}{}^c$
IIa	1.20	6.4		4.2	1.9	3.52	12.0	-129^d
IIb	1.28	6.8		4.2	1.9	3.51	10.8	-133^d
Va	1.21	6.8		4.2	1.9	2.47	8.2	-137
Vb	1.25	6.4		4.2	1.9	2.68	8.8	-141
Xa	1.38	6.2	2.2	4.5	1.8	3.80	11.8	$+7.06$
Xb	1.38	6.2	2.2	4.7	1.8	3.78	10.8	$+4.98$
VIa	1.38	6.2	2.2	4.4	1.8	2.66	11.0	-3.49
VIb	1.33	6.2	2.2	4.6	1.8	2.71	10.0	-6.58

[a] In CDCl$_3$ solution relative to internal TMS. [b] X = N or O. [c] In C$_6$H$_6$ solution relative to external H$_3$PO$_4$. [d] These values were inadvertently interchanged in ref 6.

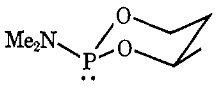
We conclude from the above three lines of evidence, therefore, that phosphite oxidation with N$_2$O$_4$ proceeds with retention of phosphorus configuration.

Configurational Assignments of Va,b and VIa,b. In view of the fact that a P═O bond moment exceeds those of a PNMe$_2$ or POMe group by a factor of at least 2,[26] the determining factor in the magnitude of the molecular moments of VIa,b is the disposition of the P═O link on the ring. The evidence for this was discussed in the previous section for Xa,b, and the similar magnitudes of the dipole moments of VIa and VIb (Table I) strongly suggest that the P═O orientations in VIa and Xa as well as in VIb and Xb are the same.

Strong support for the correctness of these assignments for the isomers VIa,b comes from LIS studies on VIIa,b. The results shown in Table II very nicely parallel those discussed earlier for IXa,b. Noteworthy is our observation that XIa,b displayed no appreciable LIS, and this strengthens the basis for the supposition that lanthanide complexation takes place on the phosphoryl oxygen in VIIa,b and IXa,b.



XIa



XIb

The relative ^{31}P chemical shifts of VIa and VIb in Table III also parallel those for VIIa and VIIb. Since the configurations of the latter are established with substantial certainty in the previous section, the inference of the ^{31}P data is that the configurations of VIa,b are also confirmed as shown. The same is true of the parent pairs IIa,b and Va,b. The ^{31}P data in Table III for these compounds strongly imply that the configurations of Va,b are as shown since the stereochemistries of IIa,b were demonstrated earlier.[5a–c] The same conclusion concerning the relation of ^{31}P shifts to phosphorus stereochemistries has been reached by Bentrude and Tan.[25]

Isomeric Stabilities of II, V, VI, and X. Unlike the situation with IIa,b, wherein no detectable amounts of IIb are present at equilibrium,[6] the equilibrium ratio of Vb to Va is about 10:1 showing that the more stable phosphorus configurations are opposite in the isomeric phosphites and phosphoramidites. That the 10:1 ratio of Vb to Va is very likely the equilibrium ratio is indicated by the observation of this ratio in two different reactions (5 and 6) which were carried out at rather different temperatures and also by the constancy of this ratio after heating the mixture to 120° for 18 hr or on vacuum distillation on a spinning band column.

While six-membered ring phosphates are apparently more stable with an axial OR–equatorial P═O configuration in both the solid state and in solution,[8a] there is growing evidence that the opposite is true when OR is replaced by NR$_2$. In the system XIIa,b, nmr evidence has been put forth[27] suggesting that XIIb is the more stable form in solution when R = Me, although the opposite conclusion was drawn for the

---

(24) K. C. Yee and W. G. Bentrude, *Tetrahedron Lett.*, 2775 (1971).

(25) Unpublished results quoted in ref 5 and private communication from W. G. Bentrude.

(26) C. P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill, New York, N. Y., 1955.

(27) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc. C*, 3033 (1968).

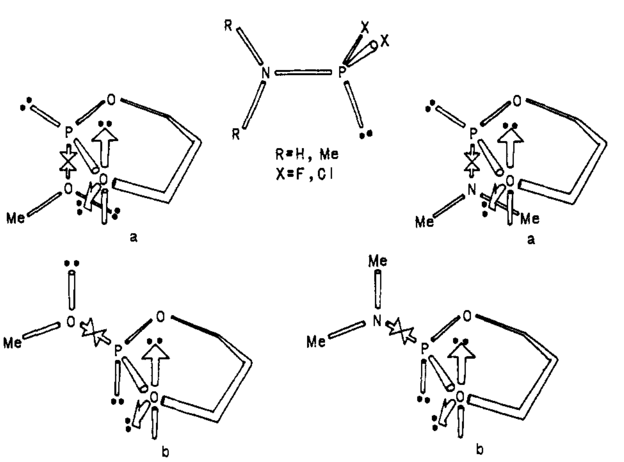
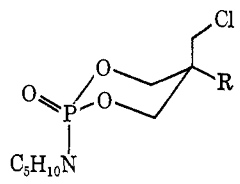
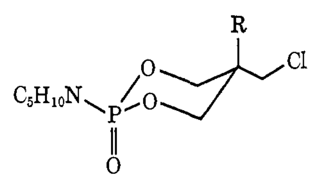


Figure 2. Preferential phosphorus substituent rotamers in some trivalent phosphorus systems. The vectors represent p or hybrid sp orbitals relevant to the gauche effect.

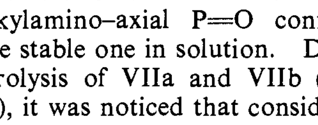


XIIa

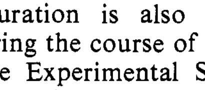


XIIb

same system when R = Et.[28] The only reported solid state structure of this type is that of the potent carcinostat cyclophosphamide (XIII)[29] which indeed does exhibit the equatorial dialkylamino–axial P=O stereochemistry in contrast to the only reported solid-state study of a phosphate (XIV).[7a] The solution evidence



XIII



XIV

is not unequivocal, however, and caution is required in extrapolating solid state structures to solutions because of possible crystal packing effects. We advance here some additional evidence that the equatorial dialkylamino–axial P=O configuration is also the more stable one in solution. During the course of the hydrolysis of VIIa and VIIb (see Experimental Section), it was noticed that considerable isomerization of VIIa to VIIb accompanied hydrolysis of VIIa while no VIIa was detected in the sample of VIIb under the same conditions. The mechanism of hydrolysis in this system warrants further study. It is interesting that vacuum distillation of VIIa,b or XIa,b results in no detectable alteration in isomer ratio.

A Rationale. An interpretation which can be given for the greater thermodynamic stability of axial OMe and equatorial $\mathrm{NMe_2}$ in the trivalent phosphorus heterocycles lies in the gauche effect[30] which has been modified to accommodate electronic changes occurring upon the introduction of a phosphorus atom into the ring system. It is reasonable to suppose that the hybridization around oxygen and nitrogen in OR and $\mathrm{NR_2}$, respectively, is roughly sp^2 when these atoms are attached to phosphorus because the exocyclic POC angle in $\mathrm{MeOP(OCHPh)_2}$ is 117.5°[31] and the nitrogen in $\mathrm{Me_2NPF_2}$,[32] $\mathrm{Me_2NPCl_2}$,[33] and $\mathrm{H_2NPF_2}$[34] possesses a nearly planar configuration. Although no structural data are available for POC angles in six-membered ring trivalent phosphorus compounds, there is no reason to expect it to be very far below 120° in view of the 117.5° exocyclic POC angle mentioned above. Further evidence for this supposition comes from the recent crystal structure determination of *trans*-$\mathrm{P(OCH_2)_3PFe(CO)_3\text{-}P(OCH_2)_3P}$ in which this angle in the $\mathrm{PC_3}$ coordinated polycycle is very nearly 120°.[35] Thus as depicted in Figure 2, the ring oxygens are involved in π bonding to the phosphorus (as shown by shortening of this link compared to the sum of the covalent radii involved[31,35]), and the nonbonding vicinal electron pairs are not quite eclipsed in the a configuration which is the more stable one in the case of the OMe compound. Although the b conformation would be more favorable because of a more gauche relationship between the nonbonding lone pairs, it must be remembered that the electron pair in the p orbital on oxygen is capable of spanning the P–O link in a π-molecular orbital. The electron–electron repulsion resulting from the close proximity of the bottom half of the π MO to the phosphorus lone pair in b could be destabilizing relative to a for the phosphite case.

The rotameric conformations of the OMe and $\mathrm{NMe_2}$ groups shown in the a and b phosphorus stereochemistries in Figure 2 are apparently favored since they have been observed for $\mathrm{Me_2NPF_2}$,[32] $\mathrm{Me_2NPCl_2}$,[33] and $\mathrm{H_2NPF_2}$.[34] A factor in stabilizing this rotameric conformation is the mutual repulsion of both halves of the N–P π MO and the lone-pair density.[36] Despite the flattening of the ring at phosphorus owing to the near 120° POC ring angles, 1–3 steric interactions between one of the nitrogen methyls in a with axial hydrogens may still be responsible for the greater stability of b. In the case of the OMe group, the oxygen lone pair is energetically lower when trans to the phosphorus lone pair than when cis and the oxygen lone pair may even be attracted to the axial protons, the combined effect stabilizing a relative to b.

The greater preference of an *i*-Pr group for the axial position[37] would seem to militate against the above steric argument. It is to be noted, however, that unlike the $\mathrm{NMe_2}$ group which presumably because of N–P π-bonding requirements adopts the rotameric conformation shown in b, the *i*-Pr group can minimize

---

(28) W. S. Wadsworth, *J. Org. Chem.*, **32**, 1603 (1967).

(29) (a) J. C. Clardy, J. A. Mosbo, and J. G. Verkade, *J. Chem. Soc., Chem. Commun.*, 1163 (1972); (b) S. Garcia-Blanco and A. Perales, *Acta Crystallogr., Sect. B*, **28**, 2647 (1972).

(30) S. Wolfe, *Accounts Chem. Res.*, **5**, 102 (1972). In the gauche effect, polar σ-bond pairs and electron pairs tend to assume a gauche relationship.

(31) M. G. Newton, private communication.

(32) E. D. Morris and C. E. Nordman, *Inorg. Chem.*, **8**, 1673 (1969).

(33) J. R. Durig and J. M. Caspar, *J. Phys. Chem.*, **75**, 3837 (1971).

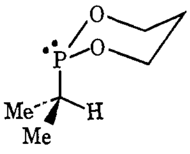
(34) A. H. Brittain, J. E. Smith, P. L. Lee, K. Cohn, and R. H. Schwendeman, *J. Amer. Chem. Soc.*, **93**, 6772 (1971).

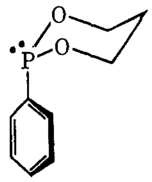
(35) D. A. Allison, J. C. Clardy, and J. G. Verkade, *Inorg. Chem.*, **11**, 2804 (1972).

(36) An inductive effect from $\mathrm{PH_2}$ to nitrogen rather than d orbital participation of phosphorus has been postulated to account for stabilization of the planar nitrogen configuration in $\mathrm{H_2NPH_2}$ (see I. G. Csizmadia, A. H. Cowley, M. W. Taylor, L. M. Tel, and S. Wolfe, *J. Chem. Soc., Chem. Commun.*, 1147 (1972), and references therein). In phosphites and phosphates, however, the phosphorus atom is considerably more electronegative and π bonding appears to be influential; see J. G. Verkade, *Coord. Chem. Rev.*, **9**, 1 (1972/1973).

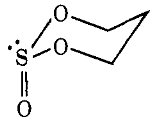
(37) Unpublished results quoted in ref 5.

the 1,3 interactions in order to maximize the gauche effect. The same may be true of the phenyl group[4c] barring conjugation influences sufficiently strong to drive it into the same conformation adopted by an axial NMe_2. Some evidence for the preferred rotameric conformation of the phenyl group as shown is the upfield shift noted for the axial protons on C-4 and C-6[4c,38] brought about by the shielding region of the aromatic ring.

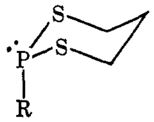




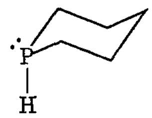
Other systems in which the predominant species is concluded to be that wherein the heteroatom substituent is axial are shown below. All of these cases, along with the trivalent phosphorus systems just discussed, have in common a lone pair as well as an axial substituent on the single heteroatom. It appears that whereas the dioxa and dithia compounds shown could be governed by a modified gauche effect involving π bonding from the chalcogen to the unique heteroatom, the remaining systems are dominated by a more straightforward gauche effect in which the heteroatom lone pair is gauche with respect to two C–H bond pairs. Recently the ratio of axial to equatorial methyl in $MeP(CH_2CH_2)_2CH_2$ was found to be 1.8 at 25° but only 0.50 at $-130°$.[45] The presence of a gauche effect is still indicated, however, by the observation that this ratio in methylcyclohexane is 0.01 at $-110°$[46] wherein the gauche effect cannot operate.



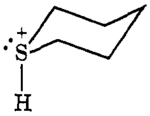
ref 39



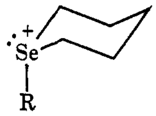
ref 40



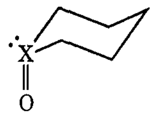
ref 41



ref 42



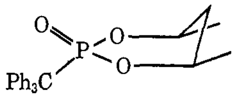
ref 43



X = S, ref 44
X = Se, ref 43

If the gauche effect dominates in pentavalent phosphorus systems, it appears that when a choice is available between a P=O and a P—OR link the lone pair of each of the ring oxygens prefers to be gauche to the latter (*i.e.*, axial P—OR and equatorial P=O). As in the case of a phosphorus lone pair, the more polar P=O bond may prefer to be close to eclipsing the oxygen lone pair (*i.e.*, equatorial P=O) rather than be too close to the bottom halves of the π-molecular orbitals in the ring. The repulsions engendered by an axial P=O could well be increased by the greater π density present in the P=O bond as well as its greater polarity compared to that in the P—OR link. The rotameric preference of the Me_2N group shown in b of Figure 2 again leads to syn–axial steric interactions which stabilize the equatorial NMe_2 group in pentavalent phosphorus systems. While a methylamino group does display a greater axial tendency than a dimethylamino substituent, rotation about the P–N bond would bring the N-methyl group into an unfavorable syn–axial conformation.

It should be pointed out that significant loss of preferential stability of the equatorial P=O–axial P—R configuration in six-membered ring phosphonates is evident in solution when the phosphorus substituent is sufficiently large as with triphenyl methyl,[8a] *t*-butyl,[8d] or aralkyl.[8e] This steric problem becomes very evident in the solid-state structure of XV wherein the bulky phosphorus substituent forces the compound to exhibit a "chaise longue" conformation.[5a] Here a ring flip is precluded by the locking effect of the ring methyl groups. Structural evidence exists for the persistence in the pentavalent phosphorus heterocycles of the rotameric conformation of the Me_2N group shown in Figure 2. Thus in XIII the C_2N plane lies very nearly in the NP=O plane in the solid state.[29]



XV

Acknowledgments. The authors thank the National Science Foundation for generous support of this work in the form of a grant to J. G. V. and a Traineeship to J. A. M. Also acknowledged is the National Cancer Institute (National Institutes of Health research Grant No. 13968-01) for a grant to J. G. V. which aided this research.

---

(38) D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Magn. Resonance*, **4**, 123 (1971).

(39) (a) C. H. Green and D. G. Hellier, *J. Chem. Soc., Perkin Trans. 2*, 458 (1972); (b) G. Wood, G. W. Buchanan, and M. H. Miskow, *Can. J. Chem.*, **50**, 521 (1972); (c) P. Albriktsen, *Acta Chem. Scand.*, **25**, 478 (1971); (d) G. Wood, J. M. McIntosh, and M. H. Miskow, *Can. J. Chem.*, **49**, 1202 (1971); (e) W. Wuchespfennig, *Justus Liebigs Ann. Chem.*, **737**, 144 (1970); (f) R. F. M. White, *J. Mol. Struct.*, **6**, 75 (1970); (g) H. F. Van Woerden, H. Cerfontain, C. H. Green, and R. J. Reijerkerk, *Tetrahedron Lett.*, 6107 (1968); (h) J. W. L. Van Oyen, R. C. D. F. Hasenkamp, G. C. Verschoor, and C. Romers, *Acta Crystallogr., Sect. B*, **24**, 1471 (1968); (i) H. F. Van Woerden and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **86**, 341, 353 (1967); (j) C. Altona, H. J. Geise, and C. Romers, *ibid.*, **85**, 1197 (1966).

(40) R. O. Hutchins and B. E. Maryanoff, *J. Amer. Chem. Soc.*, **94**, 3266 (1972).

(41) J. B. Lambert and W. L. Oliver, Jr., *Tetrahedron*, **27**, 4245 (1971).

(42) (a) J. B. Lambert, D. S. Bailey, and C. E. Mixan, *J. Org. Chem.*, **37**, 377 (1972); (b) J. B. Lambert, R. G. Geske, and D. K. Weary, *J. Amer. Chem. Soc.*, **89**, 5921 (1967).

(43) J. B. Lambert, C. E. Mixan, and D. H. Johnson, *Tetrahedron Lett.*, 4335 (1972).

(44) (a) J. B. Lambert and R. G. Geske, *J. Org. Chem.*, **31**, 3429 (1966); (b) C. R. Johnson and D. B. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965); (c) J. C. Martin and J. J. Uebel, *ibid.*, **86**, 2936 (1964).

(45) S. I. Featherman and L. D. Quin, *ibid.*, **95**, 1698 (1973).

(46) F. A. L. Anet, C. H. Bradley, and G. W. Buchanan, *ibid.*, **93**, 258 (1971).