Geometrical Isomerism in 4-Phosphorinanols[1]

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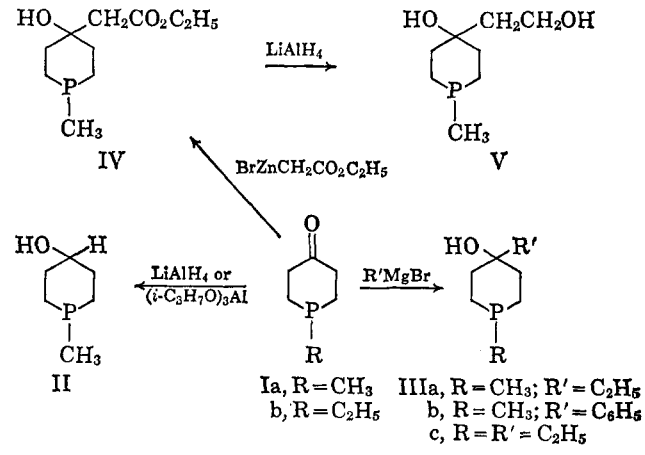
Abstract: Condensation of P-alkyl 4-phosphorinanones with Grignard or Reformatsky reagents gave tertiary phosphorinanols which, because of configurational stability of trivalent phosphorus, exist as *cis–trans* isomers. Reduction of 1-methylphosphorinanone with lithium aluminum hydride or aluminum isopropoxide gave the *cis–trans* secondary alcohol. Two of the tertiary alcohols have been separated by distillation into the stable geometric isomers; others have been indicated by their proton magnetic resonance spectra or gas chromatographic behavior also to exhibit the isomerism. The secondary alcohol isomers have not yet been found to be separable, but the isomerism is indicated on the pmr spectrum by the presence of two P-CH_3 doublets. For P-methyl tertiary alcohols, it is tentatively proposed that the isomer with the more downfield P-CH_3 doublet, which has the smaller coupling constant, has a *cis* relation of P-CH_3 (predominantly equatorial) and 4-OH (predominantly axial). The *trans* isomer is believed to differ by having predominantly axial P-CH_3. For the secondary alcohol, where 4-OH is predominantly equatorial, the *cis* isomer is believed to have axial P-CH_3. These suggestions are supported by the infrared spectra, which indicate the same conformation for the C–O group in a pair of isomers.

Horner and co-workers have demonstrated configurational stability for trivalent phosphorus in acyclic phosphines by synthesizing optically active derivatives,[3] and other groups have found evidence from proton magnetic resonance (pmr) spectra for the presence of geometric isomers in substituted cyclic phosphites (1,3,2-dioxaphospholanes[4] and 1,3,2-dioxaphosphorinanes)[5] and cyclic amides (1,3,2-diazaphospholanes).[6] Recently, we reported geometrical isomerism in two types of cyclic phosphines: the six-membered ring 1-methyl-4-ethyl-4-phosphorinanol (IIa),[7] and the five-membered ring 1,2-dimethyl-3-phospholene.[8] In each case the *cis* and *trans* isomers were separated by preparative gas chromatography, and in the former case by fractionation on a spinning-band column. The purpose of this paper is to demonstrate the common occurrence of geometrical isomerism among the 4-phosphorinanols, and to propose an assignment of *cis* and *trans* forms from consideration of their spectral properties. The convention is used in this paper that *cis* refers to the relation of the 4-hydroxyl and P substituent in both tertiary (revising an earlier suggestion[7]) and secondary alcohols.

The alcohols (Table I) utilized in this study were prepared from 4-phosphorinanones by the reactions illustrated in Scheme I. Ketone Ib has been previously reported;[9] Ia was prepared by a similar procedure. The reactivity of the carbonyl group was normal, and in general the reactions proceeded in good yield.

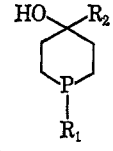
The conformation of heterocyclic phosphines has not previously been studied. However, it has been

Scheme I



pointed out that six-membered heterocyclic systems should bear a conformational resemblance to cyclo-

Table I. 4-Phosphorinanols



R_1	R_2	Bp, °C (mm)	Yield, %
CH_3	H	65 (0.5)	64
CH_3	C_2H_5	45–62 (0.2)	56
CH_3	C_6H_5	110–18 (0.1)	83
CH_3	$CH_2CO_2C_2H_5$	75–90 (0.15)	47[a]
CH_3	CH_2CH_2OH	107–20 (0.15)	69
C_2H_5	C_2H_5	47–63 (0.1)	62

[a] Yield based on ketone actually consumed in Reformatsky reaction.

hexane,[10] and thianes (thiacyclohexanes), which are of current interest, have been expressed by the usual chair

(1) Supported by Research Grant CA-05507, National Cancer Institute, U. S. Public Health Service. Taken from the Ph.D. dissertation of H. E. Shook, Jr., 1966.

(2) To whom inquiries may be directed.

(3) L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffman, and P. Beck, *Tetrahedron Letters*, 161 (1961); L. Horner, *Pure Appl. Chem.*, 9, 225 (1964).

(4) H. Goldwhite, *Chem. Ind.* (London), 494 (1964).

(5) D. Z. Denney and D. B. Denney, *J. Am. Chem. Soc.*, 88, 1830 (1966).

(6) E. W. Abel and R. P. Bush, *J. Organometal. Chem.* (Amsterdam), 3, 245 (1965).

(7) L. D. Quin and H. E. Shook, Jr., *Tetrahedron Letters*, 2193 (1965).

(8) L. D. Quin, J. P. Gratz, and R. E. Montgomery, *ibid.*, 2187 (1965).

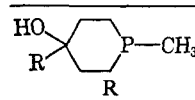
(9) R. P. Welcher, G. A. Johnson, and V. P. Wystrach, *J. Am. Chem. Soc.*, 82, 4437 (1960).

(10) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 243.

formula with axial and equatorial substituents.[11] However, in expressing conformations for cycles containing second-row elements, it must be remembered that bond lengths and bond angles differ from those of first-row elements, and distortions of cyclohexane geometry are to be expected. For phosphorus, the bond to carbon is about 0.33 A longer than the carbon–carbon bond, and bond angles may lie between the limits 90° (p^3) and 109° 28′ (sp^3 hybridization). While very few data are available on bond angles in phosphines,[12] it would appear that a value around 100° may be used for discussion. Framework molecular models (Prentice-Hall, Inc.), with slight modification, permit the construction of phosphorinanes containing this bond angle; some observations of significance in the discussion to follow emerge from examination of the models. First, in the conformation resembling the cyclohexane chair, widening of the ring at the C–P–C position increases puckering at the 4-carbon; an axial substituent thereon is tipped slightly toward the ring, possibly increasing the interaction with axial protons. Also an equatorial substituent on phosphorus is elevated above the familiar equatorial position of cyclohexane. The dihedral angle between the equatorial P substituent and an axial 2-proton is approximated from the model to be only about 38°. A boat (flexible) form has also been considered for the phosphorinanes. On converting a chair with an equatorial P substituent to a boat, a severe flagpole–bowsprit interaction develops; this is, of course, not the case with a chair having an axial P substituent. However, in both forms, strong interactions, approaching those in cyclohexane, prevail between substituents on the 2–3 and 5–6 carbons. Since there seems to be no obvious preference for this conformation, the structures in this paper are written as chairs, but no implication of a fixed conformation is made by this choice.

The alcohols derived from reactions of 1-methyl-4-phosphorinanone (Scheme I) possess a feature believed to be of value in arriving at tentative configurational assignments. It is well known that a pmr spatial interaction effect of a hydroxyl group on methyl resonances exists in ring compounds.[13] Thus, when a methyl group is *cis* to a hydroxyl group, the methyl resonance occurs downfield from its position in a *trans* orientation. The effect is most pronounced when these ring substituents are near each other, but is still observable for 1,4 substitution. In the 4-phosphorinanols, if phosphorus bond angles are about 100°, equatorial P-methyl and axial 4-hydroxy are both tipped toward the ring, and the spacing between them is similar to that in carbocyclic systems. We have observed consistently a difference in P-CH_3 signals for benzene solutions of isomeric 1-methyl-4-phosphorinanol derivatives; we have tentatively attributed this to the spatial interaction effect, and have made use of the effect in proposing assignments of *cis–trans* structures (Table II). The chemical shift differences for the methyl signals of the *cis* and *trans* isomers of the 1-methyl-4-phosphorinanols are in the range 0.01–0.06 ppm (Table II). The magnitude of the effect is not unlike that observed in the 4-methylcyclohexanol (0.024 ppm) and 10-methyldecalol-2 families (0.026 ppm).[13a] The *cis–trans* assignments[14] are consistent with other data (*vide infra*), but future work on this system should be directed toward providing chemical proof for them. In this connection, the point will be made that the substituent on phosphorus appears to occupy predominantly an axial position in one geometric isomer, and an equatorial position in the other; the possibility has not been ruled out that the methyl signals appear at different field because of shielding effects associated with their orientation, independently of the presence of hydroxyl. A study of other phosphorinane isomer pairs lacking a hydroxyl substituent may lead to clarification of this matter.

Table II. P-Methyl Pmr Data[a]



R	*cis*[b] δ	*cis*[b] J_{PCH}	*trans* δ	*trans* J_{PCH}
C_2H_5	0.95[c]	2.5	0.91[c]	3.8
C_6H_5	0.93[d]	2.0	0.92[d]	4.0
$CH_2CO_2C_2H_5$[e]	0.93	2.0	0.89	3.5
CH_2CH_2OH[f]	0.95	2.5	0.90	3.0
H[g]	0.91	3.5	0.85	2.5

[a] Chemical shifts, δ, are given in ppm to low field relative to internal tetramethylsilane and are taken as the midpoint of the P-methyl doublet. Coupling constants, J_{PCH}, are given in cps. [b] *cis* refers to relationship of hydroxyl and methyl. [c] 180 mg in 0.5 ml of benzene. [d] 100 mg in 0.5 ml of benzene. [e] 220 mg of a mixture of both isomers in 0.5 ml of benzene. [f] 200 mg of a mixture of both isomers in 0.5 ml of benzene. [g] 130 mg of a mixture of both isomers in 0.5 ml of benzene.

Tertiary Phosphorinanols. The preparation (Scheme I) and separation by fractional distillation of the *cis* and *trans* isomers of 1-methyl-4-ethyl-4-phosphorinanol (IIIa) have been announced previously.[7] The isomers were also separated by preparative-scale gas chromatography. They showed P-CH_3 signals at different field (Table II) and formed isomeric benzyl perchlorate salts. Gas chromatography of the mixture resulting from the Grignard preparation of the isomers showed the *cis*:*trans* ratio to be 1.3:1. Few data are available on the stereochemistry of Grignard reaction with cyclohexanones; the *cis* isomer was, however, also seen to be formed predominantly from 4-*t*-butylcyclohexanone and methylmagnesium chloride or bromide.[15]

The C–O stretching bands in the infrared spectra of the separated *cis* and *trans* isomers of IIIa appear at 1100 and 1105 cm^{-1}, respectively. A similar frequency (1117 cm^{-1}) has been reported for C–O stretching in 1-methylcyclohexanol.[16] The similarity in the C–O bands of the IIIa isomers suggests that they have the same configuration at the 4 position, since it is well known that substantial differences exist between bands for axial and equatorial C–O.[17a] Furthermore, among substituted cyclohexanols, alkyl groups are known to have

(11) (a) C. Johnson and C. McCants, Jr., *J. Am. Chem. Soc.*, **87**, 5404 (1965), and earlier papers; (b) J. C. Martin and J. J. Uebel, *ibid.*, **86**, 2936 (1964).

(12) R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press Inc., New York, N. Y., 1965, Chapter 2.

(13) (a) J. I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961); (b) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, J. Okamoto, and K. Tsuda, *Chem. Pharm. Bull. (Tokyo)*, **10**, 338 (1962); (c) P. S. Wharton and T. I. Bair, *J. Org. Chem.*, **30**, 1681 (1965); (d) H. O. House and B. A. Tefertiller, *ibid.*, **31**, 1068 (1966).

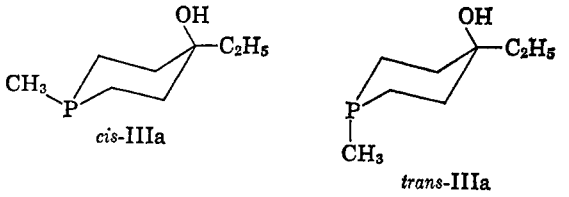
(14) Following the convention for cyclohexanols, the *cis* form is designated as that with a *cis* relationship of the P-CH_3 and 4-OH groups. It is felt this designation is preferable to the opposite, used earlier.[7]

(15) W. J. Houlihan, *J. Org. Chem.*, **27**, 3860 (1962).

(16) H. H. Zeiss and M. Tsutsui, *J. Am. Chem. Soc.*, **75**, 897 (1953).

(17) M. Hanack, "Conformation Theory," Academic Press Inc., New York, N. Y., 1965: (a) p 98; (b) p 112.

a stronger preference for the equatorial position.[17b] The suggestion may then be made that both *cis* and *trans* IIIa have an axial hydroxyl group. These structures imply that conformational effects at phosphorus are less important than those at the 4 position in establishing a preferred conformation for these compounds.

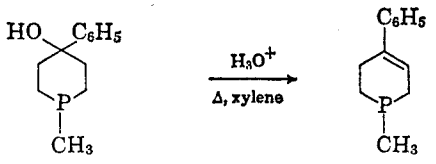


cis-IIIa *trans*-IIIa

1,4-Diethyl-4-phosphorinanol (IIIc) was prepared by reacting ethylmagnesium bromide with ketone Ib. Gas chromatography again showed the existence of two isomers of the alcohol, formed in approximately equal amounts. No attempt was made to separate these isomers. The isomer mixture had a C–O stretching band at 1110 cm^{-1}.

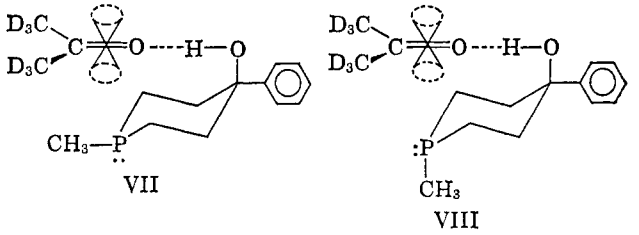
Reaction of 1-methyl-4-phosphorinanone (Ia) with phenylmagnesium bromide gave 1-methyl-4-phenyl-4-phosphorinanol (IIIb) as a mixture of isomers in approximately equal amounts (by gas chromatography). The alcohol isomers were separated by fractional distillation on a spinning-band column. Some dehydration accompanied the preparation of IIIb, as seen by the appearance of a gas chromatographic peak attributed to compound VI. This compound, 1-methyl-4-phenyl-1,2,5,6-tetrahydrophosphorin, was prepared separately by acid-catalyzed dehydration of the alcohol mixture (Scheme II). The following data were obtained from the ultraviolet spectrum: λ_{max} 242 mμ (log ε 3.99). The following data have been reported for the related phenylcyclohexene: λ_{max} 247 mμ (log ε 4.079).[18] The formation of VI from both alcohols may be taken as evidence for the assignment of the alcohols as geometric isomers. The separated alcohols also gave isomeric benzyl perchlorate salts.

Scheme II



cis- and *trans*-IIIb VI

In a chair conformation, both isomers of alcohol IIIb should prefer to have the bulky phenyl group in an equatorial position.[19] This infers that the P-methyl group is axial in the *trans* isomer. The pmr spectra of the separated isomers, run on benzene solutions of the same concentration, show as in IIIa that the methyl groups are indeed in slightly different environments (Table II). A pmr solvent effect was noted for alcohol IIIb which tends further to confirm the configurational assignments. The *cis* isomer, dissolved in CD_3COCD_3, has its P-methyl doublet (J_{PCH} = 2.0 cps) centered at 1.05 ppm, while it is at 0.93 ppm in benzene; the *trans* isomer has this doublet (J_{PCH} = 4.0 cps) centered at 1.13 ppm in acetone and at 0.92 ppm in benzene. The signals are thus reversed from the positions noted in benzene. This can be explained by considering the complex VII to be formed by a molecule of the *cis* isomer undergoing hydrogen bonding[20] to a molecule of CD_3COCD_3. The π-electron cloud of the carbonyl group will prefer to stay as far away as possible from the π-electron cloud of the phenyl ring. This brings the equatorial P-methyl group of the *cis* isomer into the shielding cone of the carbonyl group.[21] The resonance of the equatorial methyl in complex VII thus appears at higher field than that of the axial methyl of complex VIII.



A Reformatsky reaction on ketone Ia gave 1-methyl-4-carbethoxy-4-phosphorinanol (IV), the only tertiary alcohol isomer mixture of this study which, to this time, has not been resolved by gas chromatography. The pmr spectrum, however, did show that isomers had been formed (Table II). Lithium aluminum hydride reduction of the carbethoxy group of IV gave a mixture of the isomeric 1-methyl-4-(2-hydroxyethyl)-4-phosphorinanols (V), which is resolvable by gas chromatography. No attempt was made to separate the isomers of IV and V.

Preliminary attempts to study the thermally induced equilibration of *cis* and *trans* isomers have been partially hampered by an accompanying dehydration; such studies will more profitably be made on systems lacking the tertiary hydroxyl, and are to be undertaken. However, an indication of a fair degree of configurational stability for IIIa was obtained from the observation that refluxing a sample containing 70% *trans* and 30% *cis* in benzene (64 hr) or toluene (28 hr) produced no change in the isomer ratio.

1-Methyl-4-phosphorinanol. Lithium aluminum hydride (LAH) and Meerwein–Ponndorf–Verley (MPV) reductions of 4-phosphorinanones have been reported previously.[22] By either method, compound Ia gave 1-methyl-4-phosphorinanol (II) as a mixture of *cis* and *trans* isomers as seen by the presence of two P-CH_3 signals in the pmr spectrum (Figure 1) run in benzene.[23] The *cis* isomer has its P-CH_3 doublet (J_{PCH} = 3.5 cps) centered at 0.91 ppm, and the *trans* isomer has this doublet (J_{PCH} = 2.5 cps) centered at 0.85 ppm. In the neat liquid or in dimethyl sulfoxide solution, only one doublet was observed. Under conditions so far used, gas chromatography has given only one peak. The

(18) A. C. Cope, F. S. Fawcett, and G. Munn, *J. Am. Chem. Soc.*, **72**, 3399 (1950).

(19) E. W. Garbisch, Jr., and D. B. Patterson, *ibid.*, **85**, 3228 (1963).

(20) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, Chapter 6.

(21) (a) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, Chapter 4; (b) A. D. Cross and I. T. Harrison, *J. Am. Chem. Soc.*, **85**, 3223 (1963).

(22) R. P. Welcher and N. E. Day, *J. Org. Chem.*, **27**, 1824 (1962); R. P. Welcher, U. S. Patent, 3,105,096 (Sept 24, 1963).

(23) The ^{31}P nmr spectrum of this sample (neat) also provides evidence for the presence of the isomers. Two broad signals (about equal in area) appear at 61.0 and 55.3 ppm relative to external 85% phosphoric acid. Details on these and other ^{31}P spectra will be published later. Mr. Stephen Dale is thanked for preparing this spectrum.

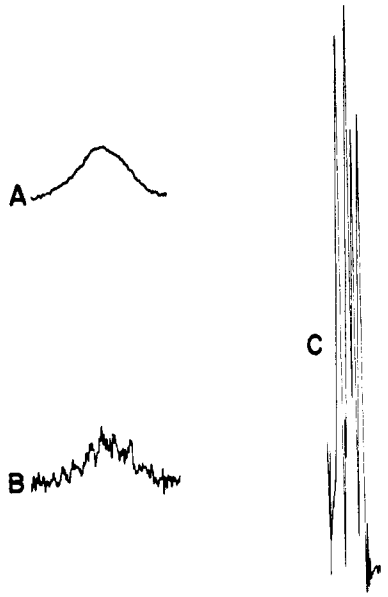


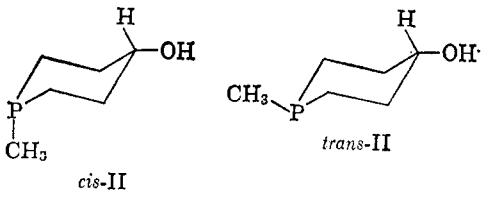
Figure 1. Some features of the pmr spectrum of 1-methyl-4-phosphorinanol (II): A, carbinol proton, neat; B, carbinol proton, benzene solution; C, P-CH_3 doublets, benzene solution.

infrared spectrum of II shows only one strong band attributable to C–O stretching (1035 cm^{-1}); this suggests, as for the tertiary alcohol IIIa, that both isomers have the same configuration at the 4 position, presumably with equatorial hydroxyl. For cyclohexanol itself, a difference in the C–O stretching frequency for axial and equatorial hydroxyl groups has been observed.[24]

In rigid ring systems, or systems having a preferred conformation, carbinol proton signals appear at different field depending on axial or equatorial character; furthermore, axial protons are characterized by broad peaks, while equatorial protons generally give sharper peaks.[11b,25] It is significant that only one signal for a carbinol proton appears in the spectrum of the mixture of isomers of II; the appearance (Figure 1) of the signal suggests that it is not the result of coincidence of two different signals. This conclusion is consistent with the observation of a single C–O stretching band in the infrared spectrum. The broadness of the peak, 18 cps at half-height (W_H), is indicative of axial orientation of the carbinol proton. From these considerations, the suggestion may be made that the *cis* and *trans* isomers of II differ in having the methyl on phosphorus axially or equatorially disposed, respectively. This suggestion receives support from the values for the geminal (PCH) coupling constant of the methyl group, as discussed in the last section of this paper. These assignments again imply that steric factors about the phosphorus atom are less important than those about the 4-carbon in controlling the conformation of the ring. A mobile equilibrium with other conformations must, of course, be considered for these structures.

(24) R. A. Pickering and C. C. Price, *J. Am. Chem. Soc.*, **80**, 4931 (1958).

(25) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 4; (b) C. Y. Chen and R. J. W. Le Fèvre, *Tetrahedron Letters*, 737 (1965); (c) H. Feltkamp and N. C. Franklin, *Tetrahedron*, **21**, 1541 (1965); (d) J. I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961); (e) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958).



cis-II *trans*-II

The ratio of isomers from either LAH or MPV reduction of ketone Ia was estimated from the P-methyl doublet peak heights to be approximately 1:1. These results are in contrast to those reported for 4-methylcyclohexanone, the carbon analog of 1-methyl-4-phosphorinanone (Ia); LAH reduction gave 19% *cis* and 81% *trans*,[26] while MPV reduction gave 33% *cis* and 67% *trans*.[27] It is, in fact, unusual for LAH and MPV reductions of cyclohexanones to provide the same amounts of isomeric alcohols. The distribution of isomers from hydride reductions of cyclic ketones has been discussed in terms of two effects, "steric approach control" and "product development control."[28,29] The latter effect, leading to the most stable (*trans*) isomer, should hold for reduction of an unhindered carbonyl as in Ia. That approximately equal amounts of each isomer are obtained in the two reductions performed may indicate that the two isomers, even though one contains an axial P-methyl group, are of similar energy. Alternatively, the basic phosphorus atom may form complexes with the reducing agents, permitting intramolecular hydride transfer equally to each face of the carbonyl group. The product composition from a reduction with a system where complexes cannot be formed (*e.g.*, sodium in alcohol) would be helpful in exploring this matter further.

PCH Coupling Constants. The bond hybridization of phosphines is thought to be variable between p^3 and sp^3. A study of the data in Table II indicates that, if the *cis–trans* assignments are correct, the larger geminal coupling constant is associated with an axial P-methyl group. This suggests that the axial P-methyl bond has more s character than the equatorial bond, based on the proposal by Hendrickson, *et al.*,[30] that an increase in the s character of the P–C bond generally results in an increase in the geminal coupling constant.[31] Coskran and Verkade have employed this concept in explaining the unusually large J_{PCH} of 9.3 cps for 2,6,7-trioxa-1,4-diphosphabicyclo[2.2.2]octane.[32] They suggested that the C–P–C bond angle is near the tetrahedral value (requiring sp^3 bond hybridization) in this bicyclic structure in order to minimize strain, and that

(26) D. S. Noyce and D. B. Denney, *ibid.*, **72**, 5743 (1950).

(27) L. M. Jackman, A. K. Macbeth, and J. A. Mills, *J. Chem. Soc.*, 2641 (1949).

(28) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(29) J. Richer [*J. Org. Chem.*, **30**, 324 (1965)] has recently questioned the theory of product development control. He states that a steric concept is sufficient to explain the stereochemical results of hydride reductions of cyclic ketones. The equatorial hydrogens of the carbons flanking the carbonyl group are in the "plane" of the carbonyl; the axial hydrogens are "perpendicular" to this plane and hinder attack from the equatorial side. Therefore, more *trans* isomer should result from a preferred axial attack of hydride, and not necessarily from product stability.

(30) J. B. Hendrickson, M. L. Maddox, J. J. Sims, and H. D. Kaesz, *Tetrahedron*, **20**, 449 (1964).

(31) Some exceptions to this generalization have been reported: C. E. Griffin and M. Gordon, *J. Organometal. Chem.* (Amsterdam), **3**, 414 (1965); J. F. Nixon and R. Schmutzler, *Spectrochim. Acta*, **23**, 565 (1966).

(32) K. J. Coskran and J. G. Verkade, *Inorg. Chem.*, **4**, 1655 (1965).

the large coupling constant is a consequence of this greater degree of s character. Similar reasoning may be applied to the derivatives of the 1-methyl-4-phosphorinanols to explain the difference in the geminal coupling constant of the methyl group. Thus, phosphorus bearing an axial methyl may have somewhat greater bond angles, and thus more s character in order to minimize 1,3-nonbonded interaction. Models clearly indicate that 1,3 interactions of an axial P-methyl are diminished as the bond angle approaches the tetrahedral value.

As pointed out earlier, it is felt that chair conformations are probably more energetically favored than the boat for these isomers. The observed difference in the $P\text{-}CH_3$ coupling constants for the isomers appears consistent with this view; it is the *trans* isomer that would more likely assume a boat conformation (with equatorial $P\text{-}CH_3$), yet its coupling constant reflects increased, rather than decreased, steric interaction relative to the *cis* isomer.

It may be noted in Table II that the tertiary alcohols assigned the *cis* configuration have the smaller J_{PCH}, while the secondary alcohol II of *cis* configuration has the larger J_{PCH}. Conformational preferences at the 4 position are held responsible for this effect. The hydroxyl group of both isomers of II is thought to prefer the equatorial position, while in the tertiary alcohols it is thought to prefer the axial position in both isomers. For II, the *cis* isomer would have an axial methyl, while for the tertiary alcohols the *cis* isomer would have an equatorial methyl.

Experimental Section

General. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Triangle Chemical Laboratories, Inc., Chapel Hill, N. C. Melting points were taken in capillary tubes on a Mel-Temp apparatus and are corrected. All boiling points are uncorrected. Infrared spectra were run on either the Perkin-Elmer 137 or 237 recording spectrophotometer. Proton magnetic resonance spectra were obtained using a Varian Associates A-60 spectrometer with, unless otherwise noted, an internal tetramethylsilane (TMS) reference. All reactions of trivalent phosphorus compounds were run in a nitrogen atmosphere. 1-Ethyl-4-phosphorinanone (Ib) was prepared by a published method.[9] Bis(2-cyanoethyl)methylphosphine was prepared by the method of Grayson, Keough, and Johnson.[33]

1-Methyl-4-phosphorinanone (Ia). A solution of bis(2-cyanoethyl)methylphosphine (44.7 g, 0.29 mole) in dry toluene (200 ml) was added dropwise over a 3-hr period to a refluxing mixture of potassium *t*-butoxide (50.0 g, 0.44 mole) in dry toluene (1.5 l.). After refluxing and stirring for 15 hr, the mixture was allowed to cool. Glacial acetic acid (100 ml) was added, and stirring was continued for 1 hr. Toluene was then distilled under slightly reduced pressure, leaving a yellow solid. Hydrochloric acid (250 ml, 6 *N*) was added, and the solution was refluxed for 13 hr. An additional quantity of hydrochloric acid (250 ml, 6 *N*) was added, and the solution was refluxed for 24 hr. The cooled acidic solution was made basic with cold, 10 *N* sodium hydroxide and extracted with three 250-ml portions of ether. Removal of ether on a rotary evaporator and vacuum distillation of the residue gave 21.6 g (57.4%) of 1-methyl-4-phosphorinanone, bp 55–57° (1.2 mm) [lit.[7] bp 57–58° (0.7 mm)]. The infrared spectrum (neat) showed carbonyl absorption at 1710 cm^{-1}. The pmr spectrum, run on a benzene solution, showed a P-methyl doublet (J_{PCH} = 3.2 cps) centered at 0.76 ppm.

1-Methyl-4-phosphorinanol (II). A. By Lithium Aluminum Hydride Reduction of Ia. A solution of 1-methyl-4-phosphorinanone (Ia) (8.9 g, 68.4 mmoles) in 75 ml of tetrahydrofuran (THF) was added over a 45-min period at room temperature to a slurry of LAH (5.6 g, 140 mmoles) in THF (500 ml). After heating and stirring for 2 hr at 50°, the reaction mixture was cooled in an ice bath; cold water (100 ml) was added very slowly to destroy excess LAH. After stirring for 12 hr, a saturated sodium sulfate solution (100 ml) was added, and the mixture was extracted with three 250-ml portions of ether. Removal of solvent on a rotary evaporator and vacuum distillation of the residue gave 5.8 g (64.4%) of a mixture of the *cis* and *trans* isomers of 1-methyl-4-phosphorinanol, bp 65° (0.5 mm).

Anal. Calcd for $C_6H_{13}OP$: C, 54.54; H, 9.92; P, 23.44. Found: C, 54.49; H, 9.86; P, 23.36.

The infrared spectrum (neat) showed a broad absorption at 3350 cm^{-1}, assigned to O–H stretching, and a strong band at 1035 cm^{-1}, assigned to C–O stretching. The pmr spectrum, run on a benzene solution, showed an axial carbinol proton (multiplet) centered at 3.47 ppm, methylene protons at 1.0–2.5 ppm (multiplet), and $P\text{-}CH_3$ protons centered at 0.91 (doublet, J_{PCH} = 3.5 cps, assigned to this *cis* isomer), and at 0.85 ppm (doublet, J_{PCH} = 2.5 cps, assigned to the *trans* isomer).

B. By Meerwein–Ponndorf–Verley Reduction of Ia. 1-Methyl-4-phosphorinanone (Ia) (5.4 g, 41.4 mmoles) was treated with aluminum isopropoxide (15.5 g, 76 mmoles) in dry isopropyl alcohol (180 ml). Vacuum distillation of the product gave 3.5 g (63.3%) of a mixture of the *cis* and *trans* isomers of 1-methyl-4-phosphorinanol, bp 62–63° (0.5 mm).

A mixture of phosphonium salts was obtained by quaternizing 1-methyl-4-phosphorinanol with benzyl bromide. An analytical sample crystallized once from methanol–ethyl acetate as white needles, mp 222–225°.

Anal. Calcd for $C_{13}H_{20}BrOP$: C, 51.50; H, 6.65; P, 10.22. Found: C, 51.69; H, 6.63; P, 10.36.

Other analytically pure samples from various crystallizations had melting points of 231–233, 203–206, and 185–195°; apparently different mixtures of *cis* and *trans* isomers were obtained. The pmr spectra in trifluoroacetic acid solution for all mixtures were similar, and only one P-methyl doublet was present.

1-Methyl-4-ethyl-4-phosphorinanol (IIIa). To the Grignard reagent prepared by adding ethyl bromide (17.4 g, 0.16 mole) in anhydrous ether (60 ml) to magnesium (4.1 g, 0.17 g-atom) covered by 80 ml of anhydrous ether was added slowly with cooling 11.0 g (0.0808 mole) of 1-methyl-4-phosphorinanone (Ia) in anhydrous ether (60 ml). After the addition was completed, the reaction mixture was refluxed for 9 hr. After cooling, water (30 ml) and a 25% ammonium chloride solution (100 ml) were added. The ether and aqueous layers were separated, and the aqueous layer was extracted with two 200-ml portions of benzene. Removal of solvent on a rotary evaporator and vacuum distillation of the residue gave 6.9 g (51.2%) of a mixture of the *cis* and *trans* isomers of 1-methyl-4-ethyl-4-phosphorinanol, bp 56–55° (0.25 mm) [lit.[7] bp 45–62° (0.2 mm)].

Gas chromatography (gc) on a 1 m × 8 mm column of polypropylene glycol on 30–60 Chromosorb P, 1:3, at 168° showed a trace of unchanged ketone Ia. The retention times at 70 cc of helium per minute for the *cis* and *trans* isomers of 1-methyl-4-ethyl-4-phosphorinanol were 6.8 and 8.0 min, respectively (area of *cis*:*trans*, 1.3). Several distillations through a spinning-band column gave the *cis* [bp 62° (0.55 mm)] and *trans* [bp 68–69° (0.6 mm)] isomers. The isomers were also separated by preparative scale gc (5 ft × 3/8 in. column of 20% Carbowax 20 M on 60–80 Chromosorb P at 170°). Data for the benzyl perchlorate salts of each isomer have been published.[7]

1,4-Diethyl-4-phosphorinanol (IIIc). The procedure was similar to that used for the preparation of 1-methyl-4-ethyl-4-phosphorinanol (IIIa). 1-Ethyl-4-phosphorinanone (Ib) (10.3 g, 0.07 mole) in anhydrous ether (50 ml) was added to the Grignard reagent prepared by adding ethyl bromide (16.3 g, 0.15 mole) in anhydrous ether (60 ml) to magnesium (3.9 g, 0.16 g-atom) covered by 70 ml of anhydrous ether. Vacuum distillation of the product gave 7.7 g (61.5%) of a mixture of the *cis* and *trans* isomers of 1,4-diethyl-4-phosphorinanol, bp 47–63° (0.1 mm).

The infrared spectrum (neat) showed a broad absorption at 3400 cm^{-1}, assigned to the O–H stretching vibration, and a strong band at 1110 cm^{-1}, assigned to the C–O stretching vibration. Carbonyl absorption from a trace of unchanged ketone Ib was also evident.

The mixture of alcohol isomers was quaternized with benzyl bromide, and bromide was exchanged for perchlorate by dissolving the phosphonium salt in water and adding excess 35% perchloric acid. The analytical sample of the benzyl perchlorate salt was crystallized from water–methanol, mp 139°.

(33) M. Grayson, P. Keough, and G. Johnson, *J. Am. Chem. Soc.*, **81**, 4803 (1959).

Anal. Calcd for $C_{16}H_{26}ClO_5P$: C, 52.67; H, 7.18; P, 8.48. Found: C, 52.72; H, 7.37; P, 8.41.

1-Methyl-4-phenyl-4-phosphorinanol (IIIb). To the Grignard reagent prepared by adding bromobenzene (27.3 g, 174 mmoles) in anhydrous ether (50 ml) to magnesium (4.2 g, 174 mg-atoms) covered by 50 ml of anhydrous ether was added slowly with cooling 1-methyl-4-phosphorinanone (Ia) (11.3 g, 87 mmoles) in anhydrous ether (100 ml). After the addition was completed, the mixture was refluxed for 2.5 hr. After cooling, water (40 ml) and a 25% ammonium chloride solution (150 ml) were added to the mixture, which was then stirred for 1 hr and allowed to stand for 8 hr. The ether and aqueous layers were separated, and the aqueous layer was extracted with two 100-ml portions of ether. The combined ether extracts were extracted with three 100-ml portions of a cold 5% (by weight) hydrochloric acid solution. The acidic solution was made basic with cold sodium hydroxide, and the basic solution was extracted with three 200-ml portions of ether. Removal of ether on a rotary evaporator and vacuum distillation of the residue gave a small forerun (0.4 g) of unchanged ketone Ia and 15.0 g (82.8%) of a mixture of the *cis* and *trans* isomers of 1-methyl-4-phenyl-4-phosphorinanol, bp 110–118° (0.1 mm).

Gc (5 ft × 0.25 in. column of 20% silicone oil SF 96 on 60–80 Chromosorb P at 220°) showed a trace of unchanged ketone Ia and a trace of the unsaturated compound VI. The retention times at 100 cc of helium per minute for the *cis* and *trans* isomers of the alcohol were 6.8 and 8.1 min, respectively. Fractionation of the isomer mixture was performed with a spinning-band column. Product fractions were: (A) bp 102–110° (0.2 mm), predominantly *cis* isomer; (B) bp 112–114° (0.2 mm), 40% *cis* and 60% *trans* (by gc); and (C) bp 114–116° (0.2 mm), predominantly *trans* isomer. In another preparation the *cis* isomer precipitated from a mixture of isomers after standing for 2 weeks and had mp 92–100°.

The infrared spectrum (KBr pellet) of the *cis* isomer showed a broad absorption at 3325 cm^{-1}, assigned to the O–H stretching vibration, and a band at 1045 cm^{-1}, assigned to the C–O stretching vibration. The pmr spectrum, run on a solution of 63 mg in 0.5 ml of CD_3COCD_3, showed phenyl protons at 7.1–7.7 ppm (multiplet), methylene protons at 1.2–2.3 ppm (multiplet), and P–CH_3 protons (doublet, J_{PCH} = 2.0 cps) centered at 1.05 ppm. The *cis* isomer was quaternized with benzyl bromide, and bromide was exchanged for perchlorate. The analytical sample of the benzyl perchlorate salt crystallized from water–methanol as prisms, mp 228–229°.

Anal. Calcd for $C_{19}H_{24}ClO_5P$: C, 57.22; H, 6.06; P, 7.77. Found: C, 57.14; H, 6.21; P, 7.81.

The infrared spectrum (neat) of the *trans* isomer contained a broad band at 3400 cm^{-1}, assigned to the O–H stretching vibration, and a band at 1045 cm^{-1}, assigned to the C–O stretching vibration. The pmr spectrum, run on a solution of 71 mg in 0.5 ml of CD_3COCD_3, showed phenyl protons at 7.2–7.8 ppm (multiplet), methylene protons at 1.2–2.4 ppm (multiplet), and P-CH_3 protons (doublet, J_{PCH} = 4.0 cps) centered at 1.13 ppm. The *trans* isomer was quaternized with benzyl bromide, and bromide was exchanged for perchlorate. The analytical sample of the benzyl perchlorate salt crystallized from water–methanol as plates, mp 215–217°.

Anal. Calcd for $C_{19}H_{24}ClO_5P$: C, 57.22; H, 6.06; P, 7.77. Found: C, 57.06; H, 6.18; P, 7.85.

1-Methyl-4-carbethoxymethyl-4-phosphorinanol (IV). The Reformatsky reagent was prepared by reacting ethyl bromoacetate (61.8 g, 0.37 mole) with zinc (58.8 g, 0.9 g-atom) in 75 ml of dry benzene and 75 ml of dry ether, prior to adding dropwise with vigorous stirring 1-methyl-4-phosphorinanone (Ia) (26.6 g, 0.204 mole) in 80 ml of ether–benzene, 1:1 v/v. A yellow precipitate formed, and a slightly exothermic reaction occurred. After the addition, the reaction mixture was refluxed for 2.5 hr. Glacial acetic acid was then added with stirring and cooling. After stirring for 1 hr, the liquid was decanted. The residue was dissolved in 7 *N* hydrochloric acid (125 ml), and this solution was decanted from excess zinc. The two acid solutions were combined, brought to pH 9 with concentrated ammonium hydroxide, and extracted with three 250-ml portions of benzene. Removal of solvent on a rotary evaporator and vacuum distillation through a Vigreux column (150 × 10 mm) gave a forerun (8.7 g) of unchanged ketone Ia and a second fraction, bp 75–109° (0.9–2.5 mm). The second fraction was redistilled and gave a forerun of unchanged ketone Ia (3.5 g) and 11.2 g (46.8% yield based on ketone consumed) of a mixture of the *cis* and *trans* isomers of 1-methyl-4-carbethoxymethyl-4-phosphorinanol, bp 75–90° (0.15 mm).

The infrared spectrum (neat) contained a broad band at 3500 cm^{-1}, assigned to the O–H stretching frequency, and a strong band at 1725 cm^{-1}, assigned to ester carbonyl. The pmr spectrum (in ppm), run on a solution containing 0.22 g in 0.5 ml of benzene, showed OCH_2CH_3 protons (quartet, J = 7.5 cps) centered at 3.95, OCH_2CH_3 protons (triplet, J = 7.5 cps) centered at 1.02, CH_2CO protons (singlet) at 2.75, ring methylene protons at 1.2–2.2 (multiplet), and P-CH_3 protons centered at 0.93 (doublet, J_{PCH} = 2.0 cps, assigned to the *cis* isomer) and 0.89 ppm (doublet, J_{PCH} = 3.5 cps, assigned to the *trans* isomer).

The benzyl bromide salt was precipitated as an oil by quaternizing a mixture of the alcohol isomers with benzyl bromide. The benzyl tetraphenylboride salt was formed by adding a hot solution of sodium tetraphenylboron in absolute ethanol to a hot solution of the benzyl bromide salt. The analytical sample was crystallized from absolute ethanol as plates, mp 145.5–146.5°.

Anal. Calcd for $C_{41}H_{46}BO_3P$: C, 78.34; H, 7.38; P, 4.93. Found: C, 78.47; H, 7.40; P, 5.05.

1-Methyl-4-(2-hydroxyethyl)-4-phosphorinanol (V). To a suspension of LAH (6 g, 0.15 mole) in anhydrous ether (200 ml) was added with cooling 1-methyl-4-carbethoxymethyl-4-phosphorinanol (IV) (10.3 g, 0.05 mole) in anhydrous ether (100 ml). After refluxing for 1 hr, excess LAH was destroyed by the slow addition of wet ether (100 ml) and then cold water (100 ml). Stirring was continued for 1 hr. A 5% sodium sulfate solution (200 ml) was added, and the aqueous phase was separated from the ether layer. The aqueous phase was extracted with two 200-ml portions of ether. Removal of ether on a rotary evaporator and vacuum distillation of the residue gave 5.7 g (69.2%) of a mixture of the *cis* and *trans* isomers of 1-methyl-4-(2-hydroxyethyl)-4-phosphorinanol, bp 107–120° (0.15 mm).

The infrared spectrum (neat) contained a broad absorption at 3350 cm^{-1}, assigned to the O–H stretching vibration, and a band at 1060 cm^{-1}, assigned to the C–O stretching vibration. No C=O absorption was present. The pmr spectrum (in ppm), run on a solution of 0.2 g in 0.5 ml of benzene, showed CH_2OH protons at 3.5–4.0 (multiplet), methylene protons at 1.0–2.2 (multiplet), and P–CH_3 protons centered at 0.95 (doublet, J_{PCH} = 2.5 cps, assigned to the *cis* isomer) and 0.90 (doublet, J_{PCH} = 3.0 cps, assigned to the *trans* isomer). The pmr spectrum, run on a solution prepared by dissolving 0.4 g of diol (V) in 0.3 ml of CD_3COCD_3 containing one drop of D_2O, showed CH_2CH_2OH protons (triplet, J = 6.5 cps) centered at 3.95 ppm.

A mixture of phosphonium salts was obtained by quaternizing a mixture of both isomers of diol V with benzyl bromide. Bromide was then exchanged for the tetraphenylboride anion. The analytical sample was crystallized from ethanol–methanol as plates, mp 169.5–171°.

Anal. Calcd for $C_{39}H_{44}BO_2P$: C, 79.86; H, 7.56; P, 5.28. Found: C, 79.79; H, 7.48; P, 5.25.

1-Methyl-4-phenyl-1,2,5,6-tetrahydrophosphorin (VI). To a solution of *cis*- and *trans*-1-methyl-4-phenyl-4-phosphorinanol (IIIb) (1 g, 4.8 mmoles) in xylene (25 ml) was added two drops of concentrated hydrochloric acid, and the mixture was refluxed for 19 hr. The xylene solution was shaken with a 5% sodium hydrogen carbonate solution (25 ml), and the organic layer was separated from the aqueous layer. The organic phase was then washed with water (25 ml). Removal of solvent on a rotary evaporator and vacuum distillation of the residue gave 0.44 g (48.3%) of 1-methyl-4-phenyl-1,2,5,6-tetrahydrophosphorin, bp 84–85° (0.1 mm), λ_{max}^{EtOH} 242 mμ (log ε 3.99).

The infrared spectrum showed bands at 3025, 1645, and 845 cm^{-1} assigned to the trisubstituted double bond. The pmr spectrum (in ppm), run on a deuteriochloroform solution, showed phenyl protons (singlet) at 7.27, vinyl proton at 5.8–6.2 (broad unresolved peak), methylene protons at 1.3–2.8 (multiplet), and P-CH_3 protons (doublet, J_{PCH} = 3.0 cps) centered at 1.08.

An analytical sample of the benzyl bromide salt of 1-methyl-4-phenyl-1,2,5,6-tetrahydrophosphorin was crystallized from methanol–ethyl acetate as plates, mp 222–223°.

Anal. Calcd for $C_{19}H_{22}BrP$: C, 63.17; H, 6.14; P, 8.57. Found: C, 63.71; H, 6.39; P, 8.85.

In another preparation, the analytical sample had mp 225–228°. *Anal.* Found: C, 63.57, 63.71; H, 6.67, 6.39.