Configurational Preference of the P-Methyl Group in Some Phosphorinane Derivatives[1]

Louis D. Quin* and Joseph H. Somers

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

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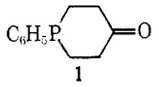
The same isomer mixture (about 55% cis, 45% trans) of 1-methyl-4-phosphorinanol (4) resulted from the reduction of 1-methyl-4-phosphorinanone (3) with seven different systems. The composition was not altered by equilibration techniques. The results were interpreted as indicating a lack of configurational preference of P-CH_3 for equatorial or axial positions and are consistent in this respect with earlier results on 1-methyl-4-substituted phosphorinanols. The observation that the dimethyl ketal of 3 exhibits a single OCH_3 nmr signal is also explainable on this basis; a conformationally biased system should exhibit two signals. *cis,trans*-1-Methyl-4-*tert*-butyl-4-phosphorinanol was prepared by addition of *tert*-butyllithium to 3. The isomer mixture was separated by gas chromatography. The rate of quaternization of these (presumably) conformationally rigid compounds did not differ significantly, indicating little steric influence on the approach of the alkyl group to the axial or equatorial position about phosphorus.

The configurational stability of trivalent phosphorus, first demonstrated in 1961,[2] ensures that C-substituted cyclic tertiary phosphines will exist in cis,trans forms, and isomers of this type were later found to be separable.[3,4] The phosphorinane system[3,5] is of particular interest, for the configurational stability of phosphorus suggests that there could be two structures, with an axial or an equatorial exocyclic P substituent, for whatever conformation the ring adopts. We have established by single-crystal X-ray analysis that the conformation adopted by the ring in 1-phenyl-4-phosphorinanone (1)[6] and its dimethyl ketal (2) is a chair, somewhat flattened relative to cyclohexane by rather low (about 45°) torsion angles about phosphorus.[7] In both compounds, the substituent on phosphorus is directed axially,[8] as is true for the proton on phosphorinane itself (nmr studies).[9]



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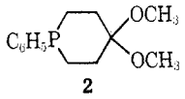
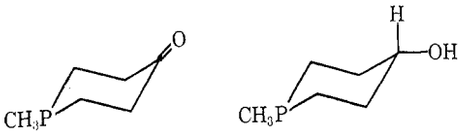


2

In this paper are presented some observations on P-methylphosphorinane derivatives; for this substituent, it has been suggested[5] that little conformational preference is expressed.

Reduction of 1-Methyl-4-phosphorinanone.—Some of our previous work[5] included reduction of the carbonyl of 1-methyl-4-phosphorinanone (3). With either lithium aluminum hydride or aluminum isopropoxide–isopropyl alcohol, the same ratio (55% cis, 45% trans) of isomers of 1-methyl-4-phosphorinanol (4) was obtained. Unlike some tertiary phosphorinanols, the isomers could not be separated by either fractional distillation or gas chromatography, but their presence in the reduction product was indicated by two ^{31}P nmr signals of nearly equal height and by two PCH_3 doublets in the proton nmr spectrum in benzene. The cis structure was assigned to that isomer with downfield PCH_3; both isomers were suggested tentatively from spectral features to differ in configurations at phosphorus, rather than at the carbinol carbon, as is known to be true for 4-methylcyclohexanol. Another point of interest is that reduction of 4-methylcyclohexanone with aluminum isopropoxide–isopropyl alcohol or lithium aluminum hydride has been reported to give different amounts (68 and 75%, respectively) of the thermodynamically more stable *trans*-4-methylcyclohexanol.[10] Our observation that ketone 3 was reduced by both of these reagents to give a nearly 1:1 mixture of 4a and 4b therefore seemed unusual.



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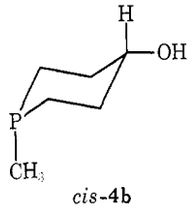
trans-4a



cis-4b

In the present work, we have used four other reducing systems [KBH_4, $NaB(H)(OCH_3)_3$, $LiAl(H)(O\text{-}tert\text{-}Bu)_3$, and $Na\text{–}C_2H_5OH$] on 3 and all gave, within experimental error, the same isomer ratio as before. In addition, an attempt to add *tert*-butylmagnesium chloride to the carbonyl of 3 failed; only reduction occurred, forming the same isomer mixture of 4. The identity of the composition of 4 from the seven reductions cannot be ascribed to a change in the isomer ratio from that formed initially in a reduction to that of the equilibrium value; some of the reducing conditions are not reversible, and equilibration by inversion at phosphorus should occur at higher temperatures[11] than those involved in the reduction procedures. The result with

(1) Supported in part by Public Health Service Research Grant CA-05507, National Cancer Institute. Presented at the Southeastern–Southwestern Regional Meeting of the American Chemical Society, New Orleans, La., Dec 2, 1970. Taken from the Ph.D. Dissertation of J. H. S., Duke University, 1970.

(2) L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann, and P. Beck, *Tetrahedron Lett.*, 161 (1961).

(3) L. D. Quin and H. E. Shook, Jr., *ibid.*, 2193 (1965).

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

(5) H. E. Shook, Jr., and L. D. Quin, *J. Amer. Chem. Soc.*, **89**, 1841 (1967).

(6) A. T. McPhail, J. J. Breen, and L. D. Quin, *ibid.*, **93**, 2574 (1971).

(7) A. T. McPhail, J. J. Breen, J. H. Somers, J. C. H. Steele, Jr., and L. D. Quin, *Chem. Commun.*, 1020 (1971).

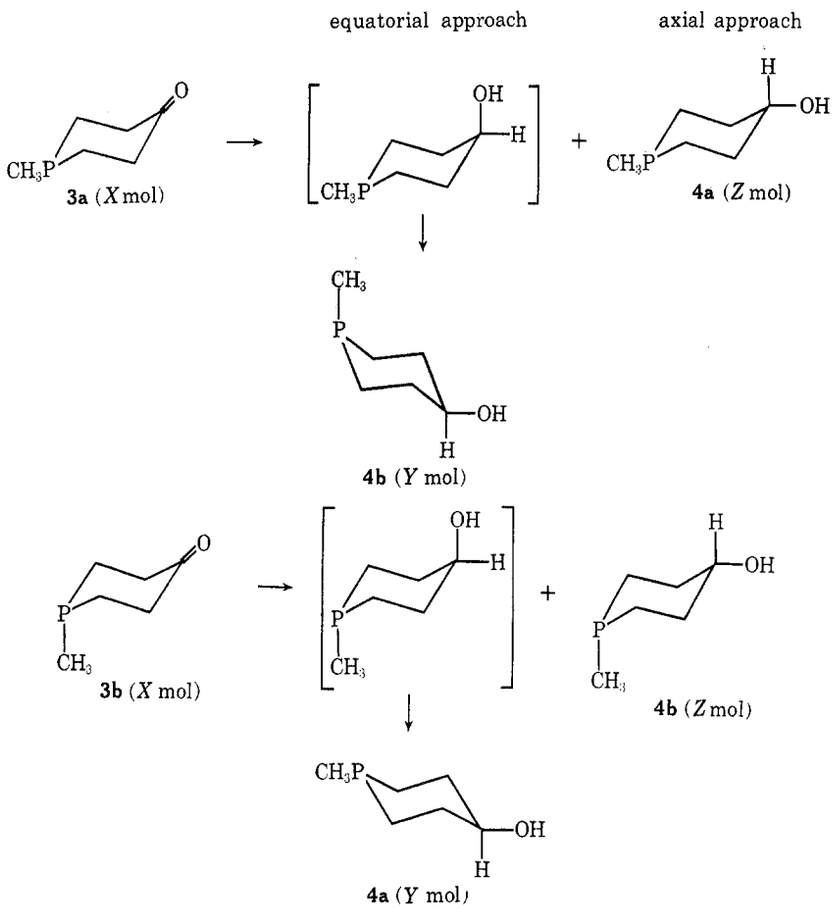
(8) J. P. Albrand, D. Gagnaire, J. Martin, and J. B. Robert, *Bull. Soc. Chim. Fr.*, 40 (1969), have arrived at the opposite conclusion for 1 from nmr studies. Their approach, however, does not seem capable of providing an unequivocal answer.[6]

(9) J. B. Lambert, W. L. Oliver, and G. F. Jackson, *Tetrahedron Lett.*, 2027 (1969).

(10) K. D. Hardy and R. J. Wicker, *J. Amer. Chem. Soc.*, **80**, 640 (1958).

(11) R. D. Baechler and K. Mislow, *ibid.*, **92**, 3090 (1970).

SCHEME I



$Na-C_2H_5OH$ is of particular interest, since in 4-methylcyclohexanone reduction it gives a very high percentage (83%) of trans isomer.[9] Lithium trimethoxyaluminohydride also normally gives a product whose composition reflects the relative stabilities of the isomers.[12]

The formation of nearly 1:1 mixture of *cis,trans*-**4** can be explained if the starting 1-methyl-4-phosphorinanone lacks conformational bias and contains roughly equal amounts of conformers with axial (**3b**) and equatorial (**3a**) PCH_3 at equilibrium. The argument may be developed as follows. (1) Methyl is sterically remote from the carbonyl group; the environment around this group should be similar in both conformations of the ketone. This means that the rates of reduction of *both* conformers by equatorial approach of the reducing agent must be similar, for the two transition states would be of similar energy. For the same reason, the rates of reduction by axial approach should be similar. (2) The extent of equatorial approach of a given reducing agent may not be the same as the extent of axial approach, and relative extents may vary from one reducing agent to another. (3) Initially formed products with axial hydroxyl will undergo ring flipping to the equilibrium composition presumed to be dominated by the conformer with equatorial hydroxyl. Scheme I expresses the result of application of these points to the reduction of an equimolar mixture of the ketone conformers; the total amount of alcohol **4a** formed is seen to equal that of **4b**, independently of the reducing agent used.

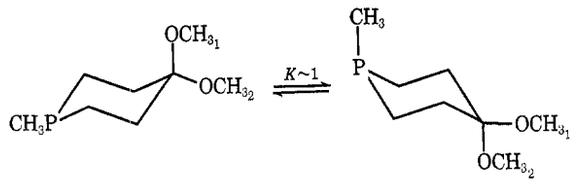
If the postulate of equal-energy conformers for ketone **3** is correct, then the same should be true for the isomers of phosphorinanol **4**, since steric effects on PCH_3 should be similar. Therefore, an equilibrium mixture for **4** should contain equal amounts of each isomer. This is very nearly the composition for **4** resulting from the several reductions of ketone **3**. If the isomers are not of equal energy, then this composition should be capable of modification by equilibration techniques. Equilibration at C-4 with the $AlHCl_2$ system[13] was attempted but no significant change occurred in the isomer ratio of the recovered alcohol. Equilibration by inverting at phosphorus was then attempted; since acyclic optically active phosphines can be racemized at 130°,[11] a temperature of 170° seemed quite adequate for this purpose. However, there was no change in the isomer ratio throughout 18 days, by which time extensive decomposition had occurred. The failure of these equilibration attempts suggests that the reductions of the ketone may have provided the equilibrium mixture in the first place, and provide further indication that axial and equatorial PCH_3 are of similar energy.

The consistency with which *cis*-**4** slightly predominates may be significant. If the structural assignments are correct, it is implied that axial PCH_3 is of slightly lower energy than equatorial. The system would therefore resemble phosphorinane and the *P*-phenyl derivatives **1** and **2** in this sense.

Dimethyl Ketal of 1-Methyl-4-phosphorinanone.—This ketal (**5**) proved of relevance to the conformational argument developed above through its exhibiting a

(12) H. C. Brown and H. R. Deck, *J. Amer. Chem. Soc.*, **87**, 5620 (1965).

(13) E. L. Eliel and M. N. Rerick, *ibid.*, **82**, 1367 (1960).



single sharp methoxy signal, either neat or in nonaromatic solvents, over a wide temperature range (−40 to 100°). This observation is explicable on the basis of the conformational equilibrium not being appreciably biased by PCH_3. This is the situation that holds for the *P*-phenyl ketal **2**; in the crystal, and also apparently in solution, phenyl prefers the axial position,[7] leading to nonequivalence in the OCH_3 groups (3-Hz separation). This behavior is also exhibited by ketals of biased 4-alkyl cyclohexanones.[14,15] While consistent with other data, however, this observation does not *prove* this conformational point, for the possibility must be considered that compensating chemical shift effects produced the apparent singlet. However, it seems unlikely that the effects would exactly compensate over a 140° range, and it is believed that the best explanation is that based on the conformational equilibrium constant being nearly unity.

We have also observed that a significant aromatic solvent effect occurs for ketal **5**; in benzene, for example, two methoxy signals appeared (180.0 and 181.7 Hz), both being upfield relative to the position of a sample measured neat or in nonaromatic solvents (Table I).

Table I

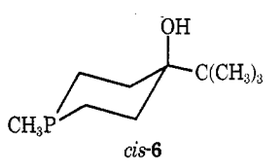
NMR Spectra[a] of 1-Methyl-4,4-dimethoxyphosphorinane (5) in Various Solvents at 35°

Solvent	Wt % 5	—PCH_3 signal— δ	J, Hz	OCH_3 signal, ν, Hz
Neat[b]		0.98	3.0	187.8
Deuterioacetone[b]	30.2	0.98	2.9	186.2
Cyclohexane[c]	16.7	0.91	3.4	194.3
Methanol[c]	21.3	1.03	2.5	190.2
Toluene[b]	14.8	0.86	3.0	178.6, 180.2
Benzene[b]	33.3	1.05	3.2	180.0, 181.7
Pyridine[c]	27.5	0.98	3.1	188.2, 186.9

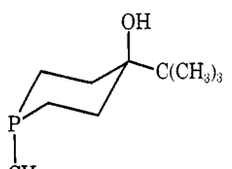
[a] Internal TMS reference. [b] Taken on Varian A-60 spectrometer. [c] Taken on Varian T-60 spectrometer.

The effect is specific for the methyls on oxygen, for the methyl on phosphorus retains its doublet character. Apparently the solvent acts to provide a different shielding environment for each methoxy, possibly through formation of a collision complex. Such complexes with benzene are known for methoxy groups.[16] Since this behavior does not appear to have been recorded for cyclohexanone ketals, we examined the ketal of 4-methylcyclohexanone in benzene, and found the peak separation (2.0 Hz neat) to be increased to 3.4 Hz in benzene. The same was true of the ketal of 4-*tert*-butylcyclohexanone (2.8 Hz separation in deuteriochloroform, 4.1 Hz in benzene). The magnitude of the effect is thus similar (1.3–1.7 Hz) for the two cyclohexanes and for the phosphorinane studied. The presence of a ring substituent is required for the nonequivalence to become detectable, since the ketal of cyclohexanone itself failed to show the effect.

***cis*- and *trans*-1-Methyl-4-*tert*-butyl-4-phosphorinanol.**—This alcohol (**6**) was prepared by adding *tert*-butyllithium to ketone **3**; the isomers were separated by preparative gas chromatography. As has been previously noted for other 1,4-dialkyl-4-phosphorinanols,[5] the isomers differed in the chemical shifts and coupling constants of the PCH_3 group (in benzene, δ 0.89, $J = 4$ Hz; δ 0.95, $J = 2.1$ Hz). These values resemble those reported for related structures,[5] but are of special importance in that they pertain to a system more clearly possessing the 4-alkyl group in the equatorial position in each isomer because of its bulk. The consistency of the values thus places on firmer ground the proposal made previously that, in a cis,trans pair of 1-methyl-4-alkylphosphorinanols, the configurational difference occurs at phosphorus rather than C-4. Cis and trans structures are tentatively assigned[5] to those isomers with the downfield and upfield PCH_3 signal, respectively.[17] They were formed in the ratio 42:58.



cis-**6**



trans-**6**

The availability of this phosphorinane system presumably of fixed ring geometry permitted an investigation of the relative rates of quaternization at phosphorus to determine if a difference existed due to the attacking group approaching an axial (as in *cis*-**6**) or an equatorial (*trans*-**6**) position. Reaction of the separate isomers in kinetic studies with ethyl bromide and the bulkier isobutyl idodide showed semiquantitatively that the rates did not differ significantly. Quaternization of a mixture of the two isomers showed more conclusively that this was the case; with isobutyl bromide or iodide, the ratio of the unreacted isomers of **6** was determined periodically by gas chromatography, and found to remain very nearly constant during the reaction period.

An explanation for the similar reaction rates for *cis*- and *trans*-**6** may be derived from the argument already advanced that isomers of *P*-methylphosphorinanes possess similar energy. The nearly identical reaction rates imply similar activation energies for the two isomers, and therefore that the energies of the two transition states must be nearly the same. That this can be the case is perhaps due to the partial carbon–phosphorus bond of the transition state being of such length as to hold the incoming alkyl substituent away from serious nonbonded interactions in axial approach, thus minimizing energy differences in the two modes of approach.

We have observed that shielding effects on phospho-

(14) E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, **90**, 682 (1968).
(15) D. Tavernier and M. Anteunis, *Bull. Soc. Chim. Belg.*, **76**, 475 (1967).
(16) R. G. Wilson, J. H. Bowie, and D. H. Williams, *Tetrahedron*, **24**, 1407 (1968).
(17) These isomers are solids, and their structure may be conclusively established by X-ray studies, now in progress. The arguments presented in this paper will hold regardless of the correctness of the tentative assignment.

rus differ in *cis*- and *trans*-**6**, as had been noticed previously for *cis*- and *trans*-**4**.[5] In a mixture, that isomer believed to be *cis*-**6** had a ^{31}P chemical shift of 57.7 ppm, while the trans isomer had a value of 67.3 ppm. Hopefully, the acquisition of values for molecular parameters from X-ray studies will make it possible to account for this important effect.

Conclusions

The available data consistently suggest that little energy difference prevails among conformers or isomers of the phosphorinane system which differ in possessing a PCH_3 group in axial or in equatorial position.[18] The phosphorinane system therefore is quite unlike the cyclohexane system, where it is well known that the equatorial disposition for a methyl substituent is highly favored energetically. (Indeed, there may even be a slight preference for axial PCH_3 in the phosphorinanes.) Although bond lengths and angles involving phosphorus are appreciably different from those about carbon, models reveal that an axial P substituent in a chair conformation will still be subject to nonbonded interactions with the axial 3,5 protons. The factor that causes the axial position to be adopted in spite of this cannot be defined at present; London attractive forces have been proposed to explain the axial preference of oxygen in thiane monoxides,[19,20] and may be involved here. The strain introduced by the axial positioning of the substituent could be partially relieved if the external C–P–C angle is increased. This possibility, which implies greater sp^3 character in phosphorus, already has been advanced to account for J_{PCH} being greater for axial than for equatorial PCH_3.[5] Alternatively, the nonbonded interactions associated with an axial substituent could be diminished if in this ring a conformation was adopted which was somewhat flattened at phosphorus; smaller C–P–C–C torsion angles have the effect of removing the P substituent away from the 3,5-diaxial protons. It is expected that X-ray studies on the individual isomers of 1-methyl-4-*tert*-butyl-4-phosphorinanol will reveal structural differences of these or other types.

A similar conformational situation has very recently been encountered in the 1,3,2-dioxaphosphorinane ring; *P*-phenyl[21] as well as *P*-methyl[22] prefer the axial position. The lone pairs on oxygen, along with other bonds, have been mentioned as being involved in interactions with the phosphorus lone pair in these compounds, but finding the same steric result in the phosphorinane ring raises some doubt about this interpretation, at least as far as the oxygen lone pairs are concerned. Clearly, additional experimental work is needed before the unusual conformational preferences of phosphorinanes can be understood.

(18) Another effect has been noted which points to the same conclusion. In substituted (and biased) cyclohexylidene acetic esters and acids, carbonyl exerts a deshielding effect on the equatorial allylic proton of the ring cis to the ester group. In 1-methyl-4-(carbethoxymethylene)phosphorinane *both* protons of the cis allylic position are deshielded. This can be explained if the ring is not conformationally biased by PCH_3. L. D. Quin, J. W. Russell, Jr., R. H. Prince, and H. E. Shook, Jr., *J. Org. Chem.*, **36**, 1495 (1971).

(19) C. R. Johnson and D. B. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(20) N. L. Allinger, J. A. Hirsh, M. A. Miller, and I. J. Tyminski, *ibid.*, **91**, 337 (1969).

(21) W. G. Bentrude and K. C. Yee, *Tetrahedron Lett.*, 3999 (1970).

(22) W. G. Bentrude, K. C. Yee, R. D. Bertrand, and D. M. Grant, *J. Amer. Chem. Soc.*, **93**, 797 (1971).

Experimental Section[23]

Reductions of 1-Methyl-4-phosphorinanone (3).—The product (**4**) of all reductions had the reported[5] boiling point and ^1H and ^{31}P nmr spectra. Product compositions listed in each reduction experiment refer to peak measurements from the ^1H spectra; a few were confirmed by ^{31}P signal measurements. Some measurements were made prior to product distillation; no change in the isomer ratio was detected in the distilled product.

With Sodium and Ethanol.—Freshly cut sodium metal (0.80 g, 0.035 g-atom) in 30 ml of sodium-dried toluene was heated to approximately 100° with vigorous stirring to melt and disperse the sodium. 1-Methyl-4-phosphorinanone[5] (1.50 g, 0.0115 mol) in absolute ethanol (1.6 g, 0.035 mol) was slowly added while maintaining the temperature below 20°. The solution was stirred for 2 hr at 10°. Water (15 ml) was then cautiously added to destroy any excess sodium. The organic layer was extracted with three 40-ml ether portions. Vacuum distillation after solvent removal on a rotary evaporator gave 1.14 g (76%) of 1-methyl-4-phosphorinanol (cis, 54%; trans, 46%).

With Potassium Borohydride.—**3** (2 g, 0.016 mol) in 10 ml of isopropyl alcohol was added dropwise to a refluxing slurry of potassium borohydride (0.54 g, 0.010 mol) in 20 ml of isopropyl alcohol. After refluxing for 3 hr and stirring at room temperature for 12 hr, the mixture was hydrolyzed with 30 ml of 10% KOH. The organic layer was removed, and the aqueous layer was extracted with four 40-ml benzene portions. After removing the solvent from the combined organic layers on a rotary evaporator, the residue was vacuum distilled to give 1.5 g (70%) of **4** (cis, 55%; trans, 45%).

With Sodium Trimethoxyborohydride.—**3** (3 g, 0.023 mol) in 25 ml of tetrahydrofuran was added dropwise to a slurry of sodium trimethoxyborohydride (7.0 g, 0.055 mol) in 250 ml of THF. After a 3-hr reflux period, the solution was cooled to 0° and cautiously hydrolyzed by dropwise addition of 40 ml of 20% NaOH. After stirring at room temperature for 1 hr, the solution was extracted with four 75-ml benzene portions. Removal of the organic solvent on a rotary evaporator followed by vacuum distillation of the residue gave a single fraction (1.7 g) shown by gas chromatography to contain 18% **3** and 82% **4**. The crude product was added to a solution of thiosemicarbazide (2.0 g, 0.022 mol) and sodium acetate (1.0 g) in methyl alcohol and the mixture was refluxed for 2 hr, removing **3** as its crystalline thiosemicarbazone. Rotary evaporation left a gummy solid residue. Water and ether (20 ml each) were added to the residue; the ether layer was separated, and the aqueous layer was extracted with four 20-ml ether portions. The ether was removed on a rotary evaporator, and the residue was distilled to give 0.5 g of **4** (cis, 55%; trans, 45%).

With Lithium Tri-*tert*-butoxyaluminohydride.—**3** (4 g, 0.031 mol) in 40 ml of THF was added dropwise over 30 min to a slurry of lithium tri-*tert*-butoxyaluminohydride (10.9 g, 0.043 mol) in 80 ml of THF. The solution was then refluxed for 2 hr and stirred at room temperature for 8 hr. Water (20 ml) was cautiously added while keeping the temperature at 0°. The solution was stirred overnight and then 20 ml of saturated sodium sulfate solution was added. The mixture was extracted with four 50-ml ether portions. Rotary evaporation, followed by vacuum distillation, gave 2.62 g (64%) of **4** (cis, 56%; trans, 44%).

With *tert*-Butylmagnesium Chloride.—**3** (7 g, 0.054 mol) in 25 ml of ether was added dropwise to 60 ml of 2.7 *M* *tert*-butylmagnesium chloride (0.16 mol) in ether, as obtained from Matheson Coleman, and Bell, East Rutherford, N. J. After refluxing for 7 hr and stirring overnight, the mixture was hydrolyzed at 0° with 50 ml of 25% NH_4Cl. The product was extracted with six 50-ml ether portions, and solvent was then removed. Both nmr and infrared spectra as well as gas chromatography showed a substantial amount (47%) of **3** to be present; this was removed as its thiosemicarbazone as above. Gas chromatography of the recovered product (16% overall yield) showed 5% of **3** still present. No evidence was obtained for addi-

(23) All manipulations of phosphines were conducted in a nitrogen atmosphere. Proton nmr spectra were obtained with a Varian A-60 spectrometer unless otherwise noted and are referenced to internal TMS. Phosphorus nmr spectra were obtained with a Varian V-4300B system at 19.3 MHz with 85% phosphoric acid as reference.

tion of the Grignard reagent to the carbonyl group. The **4** formed contained 52% cis and 48% trans isomers.

Attempted Equilibration of 1-Methyl-4-phosphorinanol with Lithium Aluminum Hydride–Aluminum Chloride.[13]—Anhydrous $AlCl_3$ (3.3 g, 0.025 mol) was placed in a 50-ml erlenmeyer flask connected by Gooch tubing to a 100-ml three-neck flask containing $LiAlH_4$ (0.30 g, 0.0080 mol) in 20 ml of THF. The $AlCl_3$ was added slowly to the flask with vigorous stirring. After the exothermic reaction had subsided, 3.0 g (0.023 mol) of 1-methyl-4-phosphorinanol (55% cis, 45% trans) was added dropwise over a 10-min period. The solution was then refluxed for 2 hr, cooled to room temperature, and treated with acetone (0.87 g, 0.015 mol). After 1 hr reflux, the solution was cooled with an ice bath and cautiously hydrolyzed first with 5 ml of water and then with 10 ml of 10 *N* NaOH. The product was extracted with two 30-ml ether portions. After removing the ether on the rotary evaporator, the residue was distilled to give 1.0 g of **4**, having the expected ir spectrum. The nmr spectrum in benzene showed the isomer composition to be 53% cis, 47% trans.

In another approach, the $AlCl_3$–phosphine complex was formed first by adding 4.06 g (0.0304 mol) of $AlCl_3$ to 4.00 g (0.0304 mol) of **4**. The complex from 4.06 g (0.0304 mol) of $AlCl_3$ and 0.309 g (0.00815 mol) of $LiAlH_4$ was formed separately in 20 ml of THF. The lumpy phosphine complex was added to the lithium aluminum hydride–aluminum chloride compound (exothermic). The solution was refluxed for 4 hr and cooled to room temperature. Acetone (0.87 g, 0.015 mol) and a drop of 1-methyl-4-phosphorinanone were added; the solution was refluxed for 18 hr and worked up as before. Distillation gave 1.55 g of **4** (56% cis, 44% trans). Repetitions with variations in the molar ratios of the reagents caused no significant difference in isomer ratio.

Thermal Equilibration of 1-Methyl-4-phosphorinanol (4).—A sample of **4** (55% cis, 45% trans) was held at 170 ± 10° under nitrogen. Samples were withdrawn at various intervals and nmr spectra were taken. Infrared spectra were also taken to determine if any dehydration to 1-methyl-1,2,5,6-tetrahydrophosphorin occurred. Although the spectra after 9 and 12 days of heating showed no dehydration, the sample after 18 days did show slight double-bond absorption at 1660 cm^{-1}. The nmr spectra of the various samples showed no change in the starting isomer ratio. After 22 days, the sample had become very viscous, although it was still colorless, and was no longer soluble in benzene.

1-Methyl-4,4-dimethoxyphosphorinane (5).—Trimethyl orthoformate (8.2 g, 0.039 mol) was added to a solution of 1-methyl-4-phosphorinanone (5.00 g, 0.039 mol) in 100 ml of anhydrous methanol. Hydrogen chloride was generated by adding NaCl (16 g, 0.27 mol) to concentrated H_2SO_4, and passed into the phosphine mixture. An exotherm occurred and the hydrochloride of the phosphine usually precipitated; this dissolved with vigorous stirring and heating. The solution was then refluxed for 2 hr and stirred at room temperature for 2 days. The methyl formate formed (bp 31°) was removed by distilling to the boiling point of methanol (64°). More trimethyl orthoformate was added, and after 2 days the methyl formate was again removed. This process was repeated three additional times to drive the reaction to completion. The solution was then made basic with sodium methoxide in methanol, and the methanol was removed on a rotary evaporator. After addition of water (20 ml) to dissolve the salt, the phosphine was extracted with five 50-ml portions of ether. The ether was removed on a rotary evaporator, and the residue was distilled to give crude **5** (1.88 g, 27%), bp 43–45° (0.33 mm). The infrared spectrum showed a small carbonyl signal, and gas chromatography on an SE-30 column at 150° indicated the composition as 91% **5**, 9% **3**. The sample was purified by preparative gas chromatography (25% SE-30 on Chromosorb W, 60–80 mesh, at 150°), using 100-μl injections of a 50% solution in benzene. The eluate was collected in benzene, which was later removed by vacuum sublimation. Attempts were made to convert the phosphine to a less sensitive salt for analysis, but it proved necessary to analyze the phosphine directly, with moderate success.

Anal. Calcd for $C_8H_{17}O_2P$: C, 54.93; H, 9.73; P, 17.58. Found: C, 54.55; H, 9.85; P, 17.02.

Nmr Study of 1-Methyl-4,4-dimethoxyphosphorinane (5).—The nmr spectrum (neat) of **5** (containing about 4% of ketone **3**) had the expected features: 3 H doublet (PCH_3) (J = 3.0 Hz) at δ 0.98, 6 H singlet (OCH_3, sharp) at δ 3.13, and a multiplet for the ring methylenes centered at about δ 2. The spectra over the range −40 to 100° were essentially the same. Spectra in various solvents are described in Table I, and a temperature study in toluene in Table II.

Table II

Nmr Temperature Study of 1-Methyl-4,4-dimethoxyphosphorinane (5) in Toluene[a]

Temp, °C	Wt % 5	PCH_3 signal—— δ	J, Hz	OCH_3 signals, ν Hz
−47	14.8	0.72	3.0	170.4, 173.1
40	7	0.78	3.1	171.7, 173.4
75	7	0.81	3.1	175.4, 176.7
95	7	0.84	3.0	177.1, 178.4

[a] Taken on a Varian A-60 spectrometer with external TMS.

Ketals of Cyclohexanones.—The ketals were prepared by treating the ketones with trimethyl orthoformate.[24] 1,1-Dimethoxycyclohexane had bp 60° (20 mm) [lit.[25] bp 63° (20 mm)], and gave a single OCH_3 nmr signal (δ 3.10 neat, 3.03 in toluene). 1,1-Dimethoxy-4-methylcyclohexane[12] had bp 57° (20 mm); a neat sample at room temperature had two OCH_3 signals (1:1) centered at δ 3.10, separated by 2.0 Hz. No significant change occurred in the spectrum when taken at 120°. A 0.095-g sample in 0.327 g of benzene had these signals centered at δ 3.08, separated by 3.4 Hz. 1,1-Dimethoxy-4-*tert*-butylcyclohexane, mp 36–37° (lit.[24] mp 38°), in $CDCl_3$ had two OCH_3 peaks (1:1) centered at δ 3.20, separated by 2.8 Hz. A 0.142-g sample in 0.59 g of benzene had the signals at δ 3.11, with separation of 4.1 Hz.

1-Methyl-4-*tert*-butyl-4-phosphorinanol (6).—1-Methyl-4-phosphorinanone (**3**, 10.0 g, 0.077 mol) in 100 ml of pentane was added dropwise over 1 hr to 135 ml of 1.54 *M* *tert*-butyllithium (0.20 mol) in pentane. An exotherm was noted, and a white solid precipitated. The solution was refluxed for 24 hr, cooled with an ice bath, and then cautiously hydrolyzed by adding 40 ml of water dropwise. After separation of the organic layer, the aqueous layer was extracted with three 100-ml ether portions. The combined organic layers were stripped of solvent on a rotary evaporator, leaving a solid yellow residue. Vacuum distillation gave 2.0 g of unreacted **3** at 55–60° (0.20–0.25 mm) and a product fraction (8.1 g, 56%) at 70–80° (0.20 mm) with mp 62–65°.

Anal. Calcd for $C_{10}H_{21}OP$: C, 63.80; H, 11.24; P, 16.46. Found: C, 63.97; H, 11.55; P, 16.38.

Gas chromatography on OV-17 or SE-30 columns at 175° showed the presence of two isomers, that with the lower retention time comprising 42% of the mixture. The nmr spectrum in benzene showed two PCH_3 doublets at δ 0.96 (J = 2 Hz) and 0.91 (J about 3–4 Hz). The latter doublet was partly obscured by the *tert*-butyl protons (two sharp singlets centered at δ 0.87 with a separation of about 1 Hz) and was broader than the downfield doublet. The ^{31}P nmr spectrum of a 35.2% solution in benzene had two peaks at 57.7 and 67.3 ppm, in the ratio 40:60.

The isomers were separated (retention times, cis 9.5, trans 11.8 min) by gas chromatography on a 1 × 150 cm column of OV-17 on Chromosorb G (4%), 175°, 75 ml of helium per minute, collecting the eluate in distilled benzene. The benzene was removed by vacuum sublimation of a frozen sample, leaving the crystalline isomer. Gas chromatography of the products showed complete separation of the two isomers. Each isomer was further purified by vacuum sublimation. The nmr spectrum of a 35.1% solution of the major isomer (trans) in benzene had the PCH_3 doublet at δ 0.89 (J = 4 Hz) and the *tert*-butyl singlet at δ 0.85. The ^{31}P nmr signal (in benzene) appeared at 64.6 ppm. The melting point was 84–85°. The sample was resublimed and analyzed. *Anal.* Found: C, 64.05; H, 11.20; P, 16.75.

The nmr spectrum of a 13.1% solution of *cis*-**6** in benzene had the PCH_3 doublet (sharp) at δ 0.95 (J = 2.1 Hz) and the *tert*-butyl singlet at δ 0.84. The methylene region (δ 1–2) of this isomer was simpler than that of the trans isomer, but for neither were the signals well defined.

Quaternization of *cis,trans*-1-Methyl-4-*tert*-butyl-4-phosphorinanol (6).—A 0.114 *M* solution of the isomers of **6** (42% cis, 58% trans) in methanol was mixed with a tenfold excess of 0.157 *M* isobutyl iodide in methanol at 25.0°. The isomer ratio for unreacted **6** was determined periodically for 78% of the reaction

(24) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Amer. Chem. Soc.*, **84**, 2371 (1962).

(25) N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521 (1961).

(200 min) by gas chromatography. The ratio did not vary more than could be attributed to experimental error, and the final composition was 40% cis, 60% trans. There was also no change in the isomer ratio during reaction of excess isobutyl bromide (2.43 *M*) with **6** (0.112 *M*; 45% cis, 55% trans), which was followed to 47% completion (230 min).

Registry No.—**3**, 16327-48-3; **4a**, 16327-50-7; **4b**, 16327-49-4; **5**, 33834-95-6; *cis*-**6**, 33835-61-9; *trans*-**6**, 33835-62-0.

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Synthesis of Some Benzeneazo Derivatives of Phosphonic Acid Monoesters

V. JAGODIĆ* AND LJ. TUŠEK

Rudjer Bošković Institute, 41000 Zagreb, Croatia, Yugoslavia

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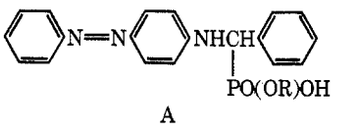
Neutral esters of α-anilinobenzylphosphonic acid were prepared by addition of dialkyl phosphites to Schiff's base. Their hydrolysis with alcoholic sodium hydroxide solution, followed by the acidification of the sodium salts obtained, afforded the corresponding monoesters.

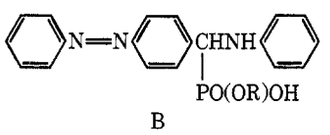
Since the first benzeneazophosphonic acid was reported,[1] a number of various benzeneazo or naphthylazo derivatives of phosphonic acid and its neutral esters have been prepared.[2-4] However, no attempt has been made to synthesize arylazo derivatives of phosphonic acid monoesters. As the syntheses of some monoesters of α-anilinobenzylphosphonic acid were described earlier[5,6] we have undertaken the present investigation to prepare several arylazo derivatives of α-anilinobenzylphosphonic acid.

Results and Discussion

Monoesters of [α-(4-benzeneazoanilino)-*N*-benzyl]-phosphonic acid (type A) and of [4-benzeneazo-α-(anilino)benzyl]phosphonic acid (type B) have been synthesized. In addition to the monoesters the corresponding diesters, *i.e.*, diethyl and dibutyl [α-(4-benzeneazoanilino)-*N*-benzyl]phosphonate (I and IV) and diethyl and dibutyl [4-benzeneazo-α-(anilino)benzyl]-phosphonate (VII and IX), were prepared. Only sodium salts of monoethyl and monobutyl esters [α-(benzeneazoanilino)-*N*-benzyl]phosphonic acid (II and V, respectively), obtained by hydrolysis of I and IV, were isolated in pure form. Neutral esters were obtained by reaction of dialkyl phosphites to Schiff's bases. They were subjected to alkaline hydrolysis to give sodium salts of the monoesters. The latter were converted to the free monoesters by acidification with a diluted mineral acid. Essentially the same reaction was applied to prepare both types of compounds. An illustration (Scheme I) is given for the preparation of the type A only. All phosphonic acid diesters are stable compounds. However, when subjected to alkaline hydrolysis they exhibit various degrees of stability. The compounds of the A type appear to be more stable than that of the B type. Thus the monoesters III and VI were obtained from the corresponding diesters I and IV in over 60% yield. Hydrolysis of diesters VII and IX yielded only about 25% of the monoesters VIII and X, together with an unidentified product (25–30%), which was insoluble in water and did not contain phosphorus, and a product (about 17%) which was identified as benzeneazocarboxylic acid-(4) (XIII) (Table I). The acid was obtained from its sodium salt by acidification with diluted hydrochloric acid and separated from a monoester due to better solubility in ethanol.



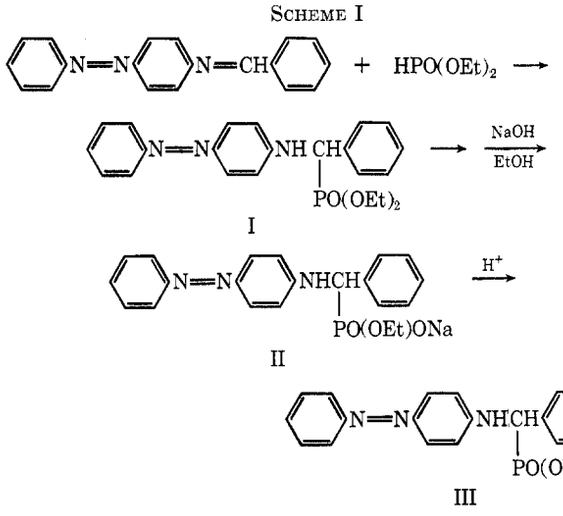
A



B

R = C_2H_5, compound III
R = C_4H_9, compound VI
R = C_2H_5, compound VIII
R = C_4H_9, compound X

SCHEME I



Attempts have been made to prepare the monoester of the following formula.

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