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Phosphorus-proton Spin-spin Coupling in the P–O–C–H Group. A Comparison of Cyclic and Acyclic Systems

Masatsune KAINOSHO,* ASAO NAKAMURA* and Masamichi TSUBOI**

* *Central Research Laboratory, Ajinomoto Co., Inc., Kawasaki, Kanagawa*

** *Faculty of Pharmaceutical Sciences, The University of Tokyo, Bunkyo-ku, Tokyo*

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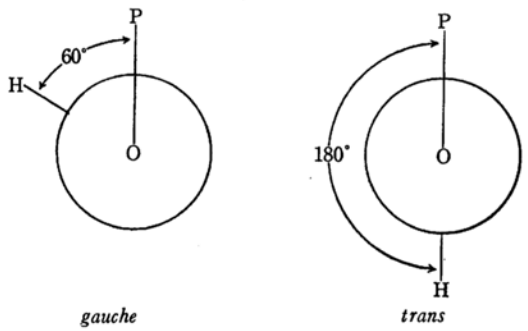
Proton magnetic resonance spectra for eleven compounds with the POCH system have been examined. They are three 4-phenyl-2,2-disubstituted(X,Y)-1,3,2-dioxaphosphorinanes where X=Cl, Y=O (I); X=Cl, Y=S (II); and X=O⁻K⁺, Y=O (III); four 5,5-dimethyl-2,2-disubstituted (X,Y)-1,3,2-dioxaphosphorinanes where X=Cl, Y=O (IV); X=Br, Y=O (V); X=Cl, Y=S (VI); and X=OH, Y=O (VII); and four dimethyl phosphates, Y=P(-X)-(-OCH_3)$_2$, where X=Cl, Y=O (VIII); X=Br, Y=O (IX); X=Cl, Y=S(X); and X=O⁻ ½Ba^{2+}, Y=O (XI). It has been found that the *1,3,2-dioxaphosphorinane* ring in each of I—VIII is virtually fixed in a chair form in the solution, and there is no appreciable ring inversion as confirmed by NMR spectra. The phosphorus-proton coupling constant of the POCH system with the *gauche* relation (J_g) and that with the *trans* relation (J_t) were determined in each of these compounds (I—VII). The $\frac{2}{3}J_g+\frac{1}{3}J_t$ values calculated from the determined J_g and J_t values are always smaller than the $\frac{2}{3}J_g+\frac{1}{3}J_t$ values observed for the corresponding acyclic compounds (VIII—XI). This difference was explained in terms of a slight flattening of *1,3,2-dioxaphosphorinane* ring from the ideal chair conformation.

In our previous papers,[1,2] it has been shown that the phosphorus-proton coupling constants in the POCH group show a marked stereospecificity; *i. e.*, 1.5—2.3 Hz for J_g and 22—28 Hz for J_t.

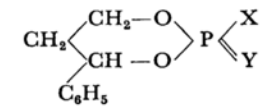


gauche *trans*

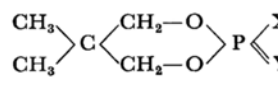
Fig. 1. The POCH system with *gauche* and *trans* conformations. Projected along the C–O axis.

The values of J_g and J_t, so far given, have rather large range of ambiguity. Nevertheless, they were very useful in determining the approximate conformation of a few phosphoric acid esters[1] and nucleotides.[2] A few other reports about the dihedral angular dependence of J_{POCH} have been made.[3,4] In this paper we present more precise knowledge of the J_g and J_t values on the basis of the NMR spectra of seven 1,3,2-dioxaphosphorinanes and four dimethyl phosphate derivatives.

Two series of the cyclic compounds were examined; they are 4-phenyl-2,2-disubstituted-1,3,2-dioxaphosphorinanes (I, II, III) and 5,5-dimethyl-2, 2-disubstituted-1,3,2-dioxaphosphorinanes (IV, V, VI, and VII):



I: X=Cl, Y=O
II: X=Cl, Y=S
III: X=O⁻K⁺, Y=O



IV: X=Cl, Y=O
V: X=Br, Y=O
VI: X=Cl, Y=S
VII: X=OH, Y=O

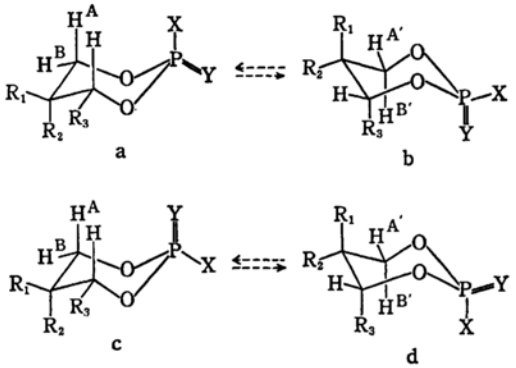
As will be detailed below, each of these cyclic compounds has been found to have a virtually frozen conformation, which is similar to the chair form of the cyclohexane ring as shown in Fig. 2. Therefore, J_g should be approximately equal to J_{AP} (or $J_{B'P}$) and J_t should be equal to J_{BP} (or $J_{A'P}$). The J_t and J_g values thus determined for various compounds will then be compared with

1) M. Tsuboi, F. Kuriyagawa, K. Matsuo and Y. Kyogoku, This Bulletin, **40**, 1813 (1967).

2) M. Tsuboi, M. Kainosho and A. Nakamura, "Recent Developments of Magnetic Resonance in Biological System," ed. by S. Fujiwara and L. H. Piette, Hirokawa Publishing Co., Tokyo (1968), p. 43.

3) J. G. Verkade and R. W. King, *Inorg. Chem.*, **1**, 948 (1962).

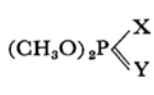
4) L. D. Hall and R. B. Malcolm, *Chem. & Ind.*, **1968**, 92.



I—III $R_1,R_2=$; $R_3=C_6H_5$-
IV—VII $R_1,R_2=CH_3$-; $R_3=H$ (in this case a≡d, b≡c)

Fig. 2. Possible chair conformations of substituted 1,3,2-dioxaphosphorinanes.

one another. A question next arises: Are these values of J_t and J_g applicable to the acyclic system? For an answer to this question, we examined the NMR spectra of the following four acyclic dimethyl phosphate derivatives:



VIII: X=Br, Y=O
IX: X=Br, Y=O
X: X=Cl, Y=S
XI: X=O⁻½Ba, Y=O

In each of these acyclic compounds, the observed POCH coupling constant should be considered as the mean of the values of equally populated three rotamers; *i. e.*, $J_{obs}=\frac{2}{3}J_g+\frac{1}{3}J_t$. A comparison will be made for the values of $\frac{2}{3}J_g+\frac{1}{3}J_t$ of cyclic (I—VII) and acyclic (VIII—XI) systems, and a discussion will be given to the differences found in these values.

Conformations of the 1,3,2-Dioxaphosphorinanes (I—VII). The NMR spectrum of I is shown in Fig. 3, a. As is seen here, the spectrum is too complicated to be analyzed on itself. The analysis was made by adopting two techniques. One of them is a triple resonance. On irradiating C and D protons simultaneously, the complex signals of E, A, and B protons become simpler (see Fig. 3, b), while on irradiating A and B signals simultaneously, the signals of C and D protons become simpler (see Fig. 3, c). The other method for the simplification of the spectra is to substitute C and D protons with deuterium. The NMR spectrum of the deuterated I is shown in Fig. 4. The signals of A, B, and E are now simpler patterns which can be readily analyzed. As an example, the parameters thus determined with II by a first order approximation are given in Table 1.

The observed values of the proton-proton coupling constants (Table 1) are in good agreement with what is expected when the *1,3,2-dioxaphosphorinane* ring is fixed to a chair form carrying the bulky phenyl group on the equatorial bond (Fig. 2, a, c). Thus, the coupling constants J_{AD} and J_{DE} are 11.3—11.9 Hz, and these values are expected when A, D and D, E are nearly in the *trans* relations[5] (see Table 1). On the other hand J_{AC}, J_{BC}, J_{BD} and J_{CE} are all small (2.4—5.0 Hz), and they are just what is expected for *gauche* coupling.[5]

The NMR spectrum of IV is given in Fig. 5, a. There are two methyl signals observed corresponding to the two methyl groups on C_5. When the lower-field methyl signal is irradiated strongly, the lower-field transitions of the ring methylene protons become sharper (see Fig. 5, b). This

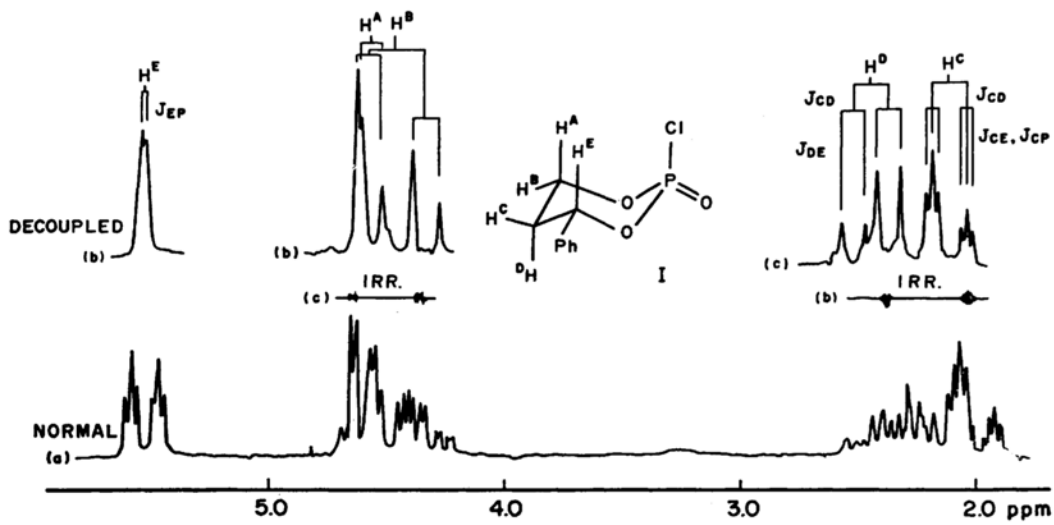


Fig. 3. 100 MHz spectrum of 2-oxo-2-chloro-4-phenyl-1,3,2-dioxaphosphorinane (I). Solvent $CDCl_3$ with ~5% C_6H_6.

5) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963).

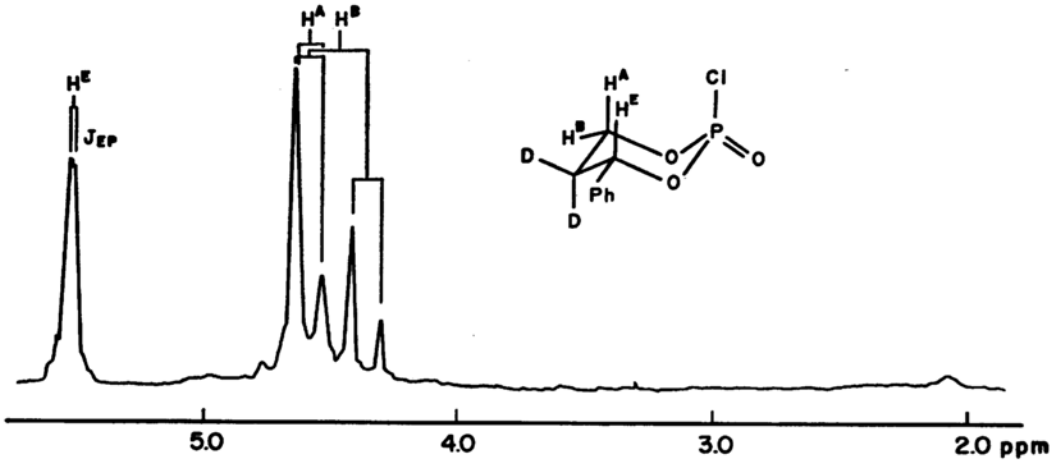
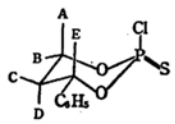


Fig. 4. 100 MHz spectrum of 5,5-dideuterio-2-oxo-2-chloro-1,3,2-dioxaphosphorinane. Solvent $CDCl_3$ with ~5% C_6D_6.

TABLE 1. NMR PARAMETERS OF II (benzene solution; 100 MHz)

Proton[a)]	Chemical shift[b)] (Multiplicity[c)])	Coupling constant[d)]				
		P	A	B	C	D
A	4.98(d,d,d,d)	5.4				
B	4.68(d,d,d,d)	29.2	11.7			
C	2.11(d,d,d,d,d)	2.5	2.4	1.9		
D	2.76(d,d,d,d)	—	11.9	5.0	14.8	
E	6.12(d,d,d)	3.6	—	—	3.6	11.3

a)  II

b) ppm from internal TMS.
c) d,d···indicates doublet of doublets···and so on.
d) each element of this table corresponds to the coupling constant; *i.e.* J_{AP} is 5.4 Hz.

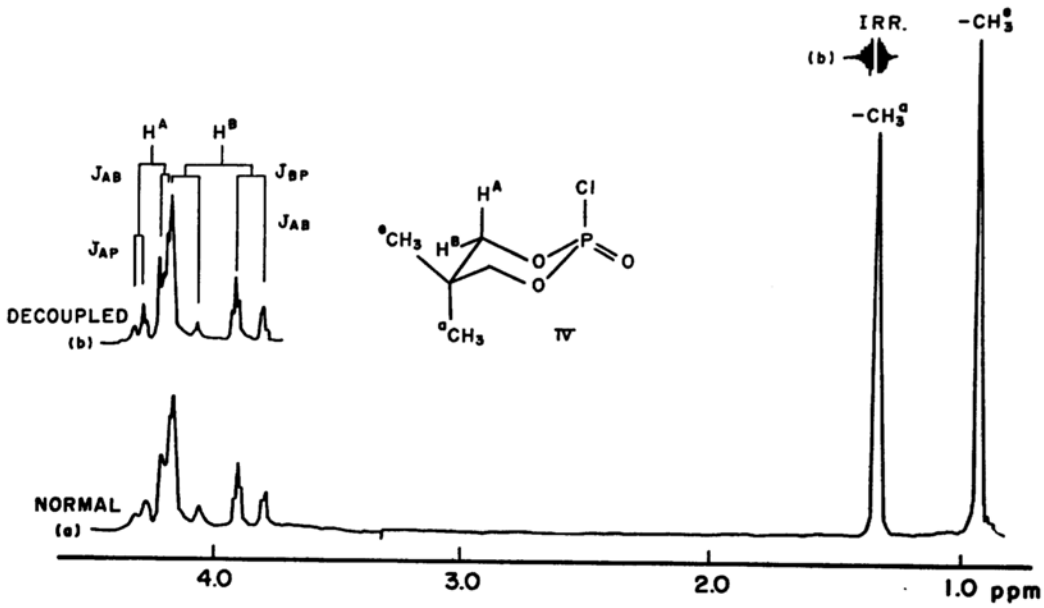


Fig. 5. 100 MHz spectrum of 5,5-dimethyl-2-oxo-2-chloro-1,3,2-dioxaphosphorinane (IV). Solvent $CDCl_3$.

observation indicates that there is a long range coupling existing between these protons.[6] Such an appreciable long range coupling through four bonds is known to take place only when the interacting nuclei are arranged so as to have the coplanar zigzag orientation ("W" letter orientation) with each other.[7,8] Therefore, the lower-field methyl signal must be assigned to the axial one. This implies that IV should have a nearly fixed conformation, either (a) or (b) in Fig. 2. If these two conformers were mixed with each other to a considerable amount, both two methyl groups would have a chance to experience the zigzag orientation with ring protons. Actually, however, no effect was observed in the methylene signals on irradiating at the upper-field methyl signal.

J_t and J_g Values in the Cyclic Systems (I —VII). Now that the conformation of *1,3,2-dioxaphosphorinane* systems is found to be fixed at one of the possible chair structures (Fig. 2), the J_g and J_t values are readily obtained. Those values, obtained by the ABX treatments of the simplified methylene spectra, are given in Table 2.

It has been shown that the J_t value (ranging, 22.3—32.2 Hz) is much greater than the J_g value (1.5—4.3 Hz). Thus the spin-spin coupling in the POCH system has a similar stereospecificity to that of the HCCH system.[5] It is interesting to point out that the substituent effect on the J_t value seems to be greater than that on the J_g value (see Table 2).

TABLE 2. PHOSPHORUS-PROTON COUPLING CONSTANTS (J_{POCH}) OF 1,3,2-DIOXAPHOSPHORINANES[a]

Compound	Solvent	J_g	J_t	J_g+J_t	X	Y
I[b]	$CDCl_3$	—(2.2)[c]	—	33.2	Cl	O
IV	$CDCl_3$	2.9	27.5	30.4		
V	$CDCl_3$	3.6	30.0	33.6	Br	O
II	$CDCl_3$	3.6(3.6)	32.2	35.8	Cl	S
VI	$CDCl_3$	4.3	28.6	32.9		
III	D_2O	1.9(1.5)	22.3	24.2	O^-K^+	O
VII	D_2O	12.2[d]			OH	O

a) Coupling constants are obtained by ABX treatment for the ring methylene protons.
b) Spectrum of I seems to be unsuitable for ABX treatment because of the line overlapping (see Fig. 3, 4).
c) Values in the parentheses show the coupling constant between phosphorus and E proton as defined in Table 1.
d) Estimated by the spacing of the doublet; equal to $\frac{1}{2}(J_g+J_t)$.

J_{POCH} Values in the Acyclic Systems (VIII —XI). In an acyclic system the J_t and J_g are not obtained separately. The observed J_{POCH} in a CH_3OP system, however, is considered to be exactly equal to $\frac{2}{3}J_g+\frac{1}{3}J_t$. The $\frac{2}{3}J_g+\frac{1}{3}J_t$ values, listed in Table 3, have been observed for VIII, IX, X and XI.

TABLE 3. PHOSPHORUS-PROTON COUPLING CONSTANTS IN VARIOUS DIMETHYL PHOSPHATES; $(CH_3O)_2P(=Y)X$[a]

Compound	Solvent	J_{obs}[b]	J_{calcd}[c]	ΔJ[d]	X	Y
VIII	$CDCl_3$	13.6	11.1	2.5	Cl	O
IX	$CDCl_3$	14.3	12.4	1.9	Br	O
X	$CDCl_3$	18.9	13.1 12.4	5.8 6.5	Cl	S
XI	D_2O	10.8	8.7	2.1	$O^-\frac{1}{2}Ba^{2+}$	O

a) Preparation of these compounds were carried out by conventional methods.
b) Obtained directly from the spacing of doublets.
c) Estimated using the corresponding J_g and J_t valuses in Table 2, by $J_{calcd}=\frac{1}{3}J_t+\frac{2}{3}J_g$.
d) $\Delta J=J_{obs}-J_{calcd}$

Discussion

As may be seen in Table 3, the $\frac{2}{3}J_g+\frac{1}{3}J_t$ value is always greater in an acyclic system than that in the corresponding cyclic system (the difference is 1.9—6.5 Hz). One might attribute this difference to an inversion of the *1,3,2-dioxaphosphorinane ring*. As was already shown, the six-membered ring is almost frozen to (a) or (c) given in Fig. 2. But the possibility that the ring experiences other conformations, such as (b) or (d), in a small fraction (α) of time has never been completely excluded. This would give slightly different coupling constants (J'_t and J'_g) from the strict J_t and J_g. The situation might make the $\frac{2}{3}J'_g+\frac{1}{3}J'_t$ value always greater than the $\frac{2}{3}J_g+\frac{1}{3}J_t$ value.
Thus,

$$\begin{aligned}\tfrac{1}{3}J'_t + \tfrac{2}{3}J'_g &= \tfrac{1}{3}[(1-\alpha)J_t + \alpha J_g] \\ &\quad + \tfrac{2}{3}[(1-\alpha)J_g + \alpha J_t] \\ &= (\tfrac{1}{3}J_t + \tfrac{2}{3}J_g) + \alpha/3(J_t - J_g) \\ &> \tfrac{1}{3}J_t + \tfrac{2}{3}J_g,\end{aligned}$$

as far as $J_t > J_g$. Therefore, the possible inversion of the ring, if any, does not explain the fact that the apparent $\frac{1}{3}J_t+\frac{2}{3}J_g$ value of the cyclic system is smaller than that of the acyclic system.

Instead, this fact can be explained by considering a slight deviation of the dihedral angle from 60° or 180°. X-ray studies of three 1,3,2-dioxaphosphorinanes, as are listed in Table 4, show that there is actually a ring flattening in each of the compounds examined. As may be seen in the table, the dihedral angle for the "*gauche*" and "*trans*" POCH group is 65° and 185°, respectively. It is

6) K. D. Bartle, R. S. Edmundson and D. W. Jones, *Tetrahedron*, **23**, 1701 (1967).
7) M. Barfield, *J. Chem. Phys.*, **41**, 3825 (1964).
8) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

Table 4. Dihedral angles of P-O-C-H system in 1,3,2-dioxaphosphorinanes[a]

Compound	∠P-O-C-H_A[b]	∠P-O-C-H_B[b]
2-Oxo-2-phenoxy[9]	67°	187°
5-Methyl-5-bromomethyl-2-oxo-2-bromo-[10]	64	184
VII[11]	65	185

a) All angles are estimated by the assumption of tetrahedral carbon atom, using X-ray crystallographc data.
b) See Fig. 2.

probable that these dihedral angles are kept not only in the crystals but also in solutions. If the curve for J_{POCH} *versus* dihedral angle is similar to the curve for J_{HCCH} *versus* dihedral angle given by Karplus[5], these greater dihedral angles should cause smaller values of apparent J_g and J_t than what would be observed when the dihedral angles were exactly 60° and 180°, respectively. Therefore, a correction should be made of each of the observed values of J_g and J_t, so as to bring it to the value corresponding to 60° or 180°.

As was already shown in a previous paper,[2] ^{31}P spectra in D_2O solution of inosine-5'-monophosphate (IMP) and guanosine-5'-monophosphate (GMP) give a triplet whose spacings are considered to correspond to two approximately equal J_{POCH}'s where J_{POCH}=4.5 Hz. The fact that two equal J_{POCH}'s are observed means that the two dihedral angles $POC_5'H$ are both 60° in IMP or in GMP. Therefore, let us assume that J_g equals 4.5 Hz when the dihedral angle POCH equals exactly 60° (instead of 65°). The correction of the J_{POCH} value from that of the dihedral angle 185° to that of 180°C is considered to be about +5%, on the basis of the curve presented by Karplus[5] for J_{HCCH}. This leads the J_t value to about 23.5 Hz for H-C-O-P(=O)O$^-$ system. With these values of J_g and J_t, the $\frac{2}{3}J_g+\frac{1}{3}J_t$ value (10.8 Hz) of the cyclic system is in an exact agreement with that of the acyclic system.

In summarizing, what has so far been observed can be explained by postulating the following items:

1) The *1,3,2-dioxaphosphorinane* ring of each of I—VII is fixed in a chair form in solution, and there is no appreciable inversion taking place.

2) In the fixed chair form, the dihedral angle of $POCH_A$ (see Fig. 2, a) is about 65° (instead of 60°) and that of $POCH_B$ (see Fig. 2, a) about 185° (instead of 180°).

3) The $^{31}POCH$ coupling constant depends upon the dihedral angle in a similar way to that of HCCH.

4) We do not need to assign different values of the coupling constant to cyclic and acyclic systems, as far as the same set of atoms (X and Y) are placed on P.

5) The nuclear spin coupling constant in the  group is 4.5 Hz if the dihedral angle is 60°, and 23.5 Hz if the dihedral angle is 180°.

Experimental

NMR Measurements. All spectra were recorded with a Varian A-60 and a HA-100 spectrometer. The 100 MHz frequency sweep decoupling experiments were achieved with two Hewlett-Puckard 200 ABR oscilators at the field-frequency controlled mode.

Lithium Aluminum Hydride Reduction of Ethyl Benzoylacetate. A solution of ethyl benzoylacetate (7.69 g, a mixture of 58% *keto* and 42% *enol* forms, determined by NMR analysis) in dry ether (50 m*l*) was added to an ice-cold solution of $LiAlH_4$ (24 g) in ether (100 m*l*), over a period of an hour. Stirring was continued for an additional 1 hr, then the mixture was treated with a small amount of water, dried ($MgSO_4$) and was fractionally distilled. The diol was distilled at 125°C/1.5 mmHg and the yield was 85% from *keto* form of ethyl benzoylacetate.

Found: C, 70.88; H, 7.66%. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95%.

Ethyl(α,α-dideuterio) benzoylacetate. The deuteration was achieved by the deuterium-hydrogen exchange reactions between ethyl benzoylacetate and *O*-deuterioethanol. The process of the reaction was followed by the NMR measurement.

2,2-Dideuterio-1-phenyl-1,3-propanediol. Lithium aluminum hydride reduction of ethyl (α,α-dideuterio)-benzoylacetate afforded the dideuterio diol. Its NMR spectrum showed that deuterium-hydrogen exchange was negligible during the course of preparation.

2-Oxo-2-chloro-4-phenyl - 1, 3,2 - dioxaphosphorinane (I). The cyclic phosphorochloridate was prepared by a similar method to that of Lanham.[12] The yield was 29%.

Found: C, 46.55; H, 4.53; Cl, 15.32%. Calcd for $C_9H_{10}ClO_3P$: C, 46.47; H, 4.33; Cl, 15.24%.

2- Thiono -2- chloro - 4 - phenyl - 1,3,2 - dioxaphosphorinane (II). This compound was synthesized by following the procedure given in Lanham's patent,[12] and was obtained as light yellow oil, which partly changed to colorless needles while it was kept in a refrigerator in a vacuum dessicator. Purification through vacuum distillation was not successful because a decomposition of the oil took place. Its purity was judged only by the NMR measurement.

Potassium 2-Oxo-2-hydroxy-4-phenyl-1,3,2-dioxaphosphorinane (III). To a solution of II (1.02 g) in a mixture of dioxane-water (17 : 3) was added 2 N KOH solution (5 m*l*). After stirring for a few minutes, the solvent was distilled off, and the residue was extracted.

9) H. J. Geise, *Res. Trav. Chim. Pays-Bas*, **86**, 362 (1967).
10) T. A. Beineke, *Chem. Commun.*, **1966**, 860; *Acta Crystal.*, in press. The preprint of this paper was kindly sent from Dr. Beineke before the publication.
11) W. Murayama and M. Kainosho, to be published.
12) W. Lanham, U. S. Pat. 2894016 (1959).

with ethanol. After removal of ethanol the product was deposited as colorless solid, which was washed with acetone, and dried in air. The yield was 1.04 g (94%). The structure was characterized by NMR.

5,5-Dideuterated Compounds of I, II, and III. These compounds were prepared from 1-phenyl-1,3-(2,2-dideuterio)-propanediol by similar methods to those described for I, II, and III, above. The products were identified by their NMR spectra.

5,5-Dimethyl-2-thiono-2-chloro-1,3,2-dioxaphosphorinane (IV). To a solution of neopentylglycol (0.3 mol) in 150 m*l* of dichloroethane, was added gradually thiophosphoryl chloride (0.3 mol) in 50 m*l* of dichloroethane, with continuous stirring, while the reaction mixture was kept below 26°C by ice-water cooling. After the addition of thiophosphoryl chloride was completed, hydrogen chloride was removed by the vigorous bubbling of dry nitrogen. Removing the solvent under the reduced pressure, colorless crystals were obtained. Recrystallization from *n*-hexane gave colorless needles. Yield, 69%. Mp 92—93.5°C.

Found: C, 29.72; H, 5.11%. Calcd for $C_5H_{10}O_2SClP$: C, 29.93; H, 5.02%.

5, 5-Dimethyl-2-oxo-2-bromo-1,3,2-dioxaphosphorinane (V). To a solution of neopentylglycol (5.2 g) in 30 m*l* dichloroethane was added slowly phosphoryl bromide in 20 m*l* dichloroethane. The orange colored product was obtained by a similar procedure to that for IV. The product was crystallized as colorless needles from *n*-hexane solution and they turned gradually to yellow with moisture. Mp 98—99°C.

Found: C, 27.06; H, 4.71%. Calcd for $C_5H_{10}O_3BrP$: C, 26.22; H, 4.40%.

V was also prepared by the Michaelis-Arbuzov reaction between 5,5-dimethyl-2-methoxy-1,3,2-dioxaphosphorinane and bromine.

5,5-Dimethyl-2-oxo-2-chloro-1,3,2-dioxaphosphorinane (VI). VI was prepared by a known procedure[13] with 68% Yield. Mp 107—108°C.

Found: C, 32.83; H, 5.54%. Calcd for $C_5H_{10}O_3ClP$: C, 32.54; H, 16.46%.

5, 5-Dimethyl-2-oxo-2-hydroxy-1,3,2-dioxaphosphorinane (VII). VII was prepared by the hydrolysis of VI in aqueous acetone. Recrystallization from hot aqueous solution gave colorless needles. A *thermogravimetric* analysis showed the product contained one water molecule.

Found: C, 33.16; H, 7.06%. Calcd for $C_5H_{11}O_4P \cdot H_2O$: C, 32.51; H, 7.12%.

The authors wish to express their gratitude to Miss Masako Kaneko for her help throughout this study, and to Dr. M. C. Woods and Mr. Iwao Miura of the Tohoku University for their help in the NMR measurements at an early stage of this work.

Note Added in Proof. After the completion of this work, the authors have extensively studied the conformation of 2,2-disubstituted-1,3,2-dioxaphosphorinanes by dipole moment measurements[14], infra-red[15] and NMR spectra.[16] The results thus far obtained strongly indicates a-conformation of Fig. 2 is the preferred one.

13) R. L. McConnel and H. W. Coover, Jr., *J. Org. Chem.*, **24**, 630 (1967).

14) M. Kainosho and T. Shimozawa, *Tetrahedron Letters*, **1969**, 865.

15) M. Kainosho, T. Morofushi and A. Nakamura, This Bulletin, **42**, 845 (1969).

16) M. Kainosho, to be published.