Structural Determination of *cis*- and *trans*-5-Hydroxymethyl-5-methyl-2-thiono-r-2-ethoxy-1,3,2-dioxaphosphorinane by NMR and X-ray Crystallography: Model Compounds for the Reaction Mechanism Study of Organophosphorus Pesticides

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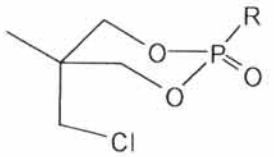
1,3,2-Dioxaphosphorinanes are suitable compounds for studying the stereochemistry of substitution at phosphorus. *Cis*- and *trans*-5-hydroxymethyl-5-methyl-2-thiono-2ethoxy-1,3,2-dioxaphosphorinane were prepared, and their structures and stereochemistry unambiguously assigned by NMR and X-ray crystallography with acetoxy and 3,5-dinitrobenzoyloxy derivatives, respectively. Trans isomer gave ^{31}P NMR signal at higher field than cis isomer, and the ring proton spectrum of cis isomer showed characteristic pattern for identifying its geometry. In X-ray crystallography they adopted a chair conformation with the ethoxy groups in the axial positions, and the sulfide groups in the equatorial positions. A flattening of the ring around the phosphorus center was noted, the POC bond angles were about 120°, and the C-O bonds in the ring were significantly longer than the C-O bond for the ethoxy group or the C-O bond for hydroxyl group.

Key words: *1,3,2-dioxaphosphorinanes, stereochemistry, NMR, X-ray crystallography, chair conformation, bond angle.*

Of the organophosphorus pesticides in current use, phosphorothioates account for more than two thirds.[1] The chemistry of phosphorothioates has been the subject of much attention, particularly with respect to defining the mechanism of "Bioactivation" and "Detoxification". In many instances, these transformations are oxidatively or hydrolytically induced, and, of these transformations, oxidative desulfuration of phosphorothioate to phosphate normally results in a bioactivated compound while hydrolysis gives opposite results.

The stereochemistry of the phosphorothioate-phosphate transformation in oxidation-displacement reactions is complex, and substituted 1,3,2-dioxaphosphorinanes have been employed by a number of workers to study the stereochemistry of substitution at phosphorus[2-5] because these compounds have distinctive chemical shifts (^{1}H and ^{31}P) with ^{1}H- ^{31}P coupling constants which often enable the conformation of these systems to be established, at least to a degree of certainty. Thus, whether inversion or retention of configuration occurs at the phosphorus center can quite easily be determined. For example, 2-substituted-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane (**1**) is conformationally immobile and the cis- and trans- isomers are easily distinguished by the characteristic chemical shifts of the methyl and chloromethyl protons.[3-5] Furthermore, a number of these compounds are crystalline, and their crystal structures may also be determined.[6]



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In the present work, *cis*- and *trans*-5-hydroxymethyl-5-methyl-2-thiono-r-2-ethoxy-1,3,2-dioxaphosphorinanes were synthesized and their structures and stereochemistry unambiguously assigned through NMR and X-ray crystallography for use in the investigation of the mechanism and stereochemistry of phosphorothionate oxidation-displacement .

Materials and Methods

Synthesis. All reagents used in syntheses and reaction were purchased from Aldrich. Solvents were dried before use, and syntheses were carried out in an inert atmosphere.

Chromatography. Analytical and preparative t.l.c. utilized layers of silica gel GF 254 type 60 (Merck) of 0.25

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and 1.0 mm thickness, respectively. The plates were visualised either under U.V. light or with iodine vapour.

Instrumental analysis. Melting points (m.p.) were determined on Kofler Hot Stage Microscope melting point appratus and are uncorrected. Mass spectra were taken on a AEI-MS12 spectrometer (operating at 70 eV, electron impact mode) attached to a VG-display digispec data acquisition system. ^{1}H NMR spectra were recorded either on a Bruker AM 500 (500 MHz), AM 300 (300 MHz) or CXP-300 (300 MHz) spectrometer with $CDCl_3$ as the internal standard unless otherwise specified. ^{13}C NMR spectra were recorded with a Bruker AM 500 (125.77 MHz) with $CDCl_3$ as internal standard unless otherwise specified. ^{31}P NMR spectra were recorded either on a Bruker AM 300 (121.47 MHz) or CXP-300 (121.47 MHz) spectrometer generally with broad band proton decoupling, and with 85% H_3PO_4 in D_2O as external standard unless otherwise specified. X-ray reflection data were measured with an Enraf-Nonius CAD-4 diffractometer, and the structure was determined using direct phasing and Fourier methods.

5-Hydroxymethyl-5-methyl-2-thiono-2-ethoxy-1,3,2-dioxaphosphorinane (2). A solution of 1,1,1-tris (hydroxymethyl)ethane (3.6 g, 0.03 mol) and pyridine (4.84 ml, 0.06 mol) in CH_3CN (200 ml) was added dropwise to a stirred, cooled (ice bath) solution of *O*-ethyl phosphorodichloridothionate (5.37 g, 0.03 mol) in CH_3CN (30 ml). Upon completion of the addition, the reaction mixture was stirred (1 h) at room temperature and refluxed (2 h) and then the solvent was evaporated. The residue was taken up in $CHCl_3$, washed consecutively with dilute HCl solution (10 ml×2, 5% w/v), $NaHCO_3$ (10 ml×2, 5% w/v) and brine (10 ml×1), then was dried (Na_2SO_4). Upon evaporation of the solvent, a pale yellow oil (4.42 g, 65.2%) containing a mixture of isomers was obtained. The mixture of isomers was separated through preparative TLC [1 mm plates, 7 times developed in $CHCl_3$/petroleum ether (5 : 1)]. The less polar isomer (Rf = 0.47) was obtained as a colorless oil, and the more polar isomer (Rf = 0.35) as fine needles from acetone/petroleum ether.

Less polar isomer: *cis*-5-Hydroxymethyl-5-methyl-2-thiono-r-2-ethoxy-1,3,2-dioxaphosphorinane [*cis*-**(2)**]; ^{31}P NMR ($CDCl_3$): δ64.4 , MS [m/z (%)]: 226 (M^+, 100), 195 (54), 167 (45), 165 (28), 149 (43), 143 (58), 115 (66).

More polar isomer: *trans*-5-Hydroxymethyl-5-methyl-2-thiono-r-2-ethoxy-1,3,2-dioxaphosphorinane [*trans*-**(2)**]; m.p.: 79-81°C, ^{31}P NMR (CH_3OH): δ62.6, MS [m/z (%)]: 226 (M^+, 10), 143 (100), 115 (79).

5-Acetoxymethyl-5-methyl-2-thiono-2-ethoxy-1,3,2-dioxaphosphorinane (3). Acetic anhydride (2.0 g) was added to a stirred, cooled (ice bath) solution of a mixture of the desired isomer of 5-hydroxymethyl-5-methyl-2-thiono-2-ethoxy-1,3,2-dioxaphosphorinane (2.0 g) in pyridine (20 ml). After stirring for 24 h at room temperature, the reaction mixture was poured into an ice/water mixture (100 ml) with vigorous stirring. The aqueous solution was extracted with $CHCl_3$ (30 ml×3), washed consecutively with saturated $NaHCO_3$ (10 ml×2) and brine (10 ml×1), then dried (Na_2SO_4), and the solvent wasevaporated to yield product isomers as a brownish oil (1.52 g, 64.1%)

The mixture of the isomers was separated through column chromatography with petroleum ether/ether as eluents. Both isomers were obtained as white crystalline solids.

Less polar isomer: *cis*-5-Acetoxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane [*cis*-**(3)**]; m.p.: 89~92°C, ^{31}P NMR (CH_2Cl_2): δ63.7, MS [m/z (%)]: 268 (M^+, 38), 195 (26), 185 (28), 149 (36), 143 (100), Crystal data.-monoclinic, space group $P2_1/c$, *a* 10.618, *b* 6.675, *c* 21.025Å, β 120.19°, z 4

More polar isomer: *trans*-5-Acetoxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane [*trans*-**(3)**]; m.p.: 102~105°C, ^{31}P NMR ($CDCl_3$): δ61.1, MS [m/z (%)]: 268 (M^+, 17), 185 (23), 143 (100), 115 (43).,

5-Benzoyloxymethyl-5-methyl-2-thiono-2-ethoxy-1,3,2-dioxaphosphorinane (4). Benzoyl chloride (1.1 ml) was added dropwise to a cooled (ice bath), stirred solution of a mixture of isomers of 5-hydroxymethyl-5-methyl-2-thiono-2-ethoxy-1,3,2-dioxaphosphorinane (1.44 g) and pyridine (0.4 ml) in CH_3CN (10 ml), and the reaction mixture was stirred at room temperature (24 h). Normal work up gave the mixture of product isomers as a yellow oil which solidified upon cooling (2.0 g, 95%).

The mixture was separated [1 mm plates, 2 developments in petroleum ether/ether (1 : 1)], and the less polar isomer (Rf = 0.74) was obtained as a colorless oil, which slowly solidified into an amorphous solid; the more polar isomer (Rf = 0.59) was obtained as colorless crystals from acetone/petroleum ether.

Less polar isomer: *cis*-5-Benzoyloxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane [*cis*-**(4)**]; m.p.: 42~43°C, ^{31}P NMR ($CDCl_3$): δ64.7, MS [m/z (%)]: 330 (M^+,8), 105 (100),

More polar isomer: *trans*-5-Benzoyloxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane [*trans*-**(4)**]; m.p.: 134~135°C, ^{31}P NMR ($CDCl_3$): δ59.5, MS [m/z (%)]: 330 (M^+, 4), 105 (100)

5-Tosyloxymethyl-5-methyl-2-thiono-2-ethoxy-1,3,2-dioxaphosphorinane (5). *p*Toluenesulfonyl chloride (440.0 mg) was added portionwise to a cooled (ice bath), stirred solution of a mixture of isomers of 5-hydroxymethyl-5-methyl-2-thiono-2-ethoxy-1,3,2-dioxaphosphorinane (519.0 mg) in pyridine (1.5 ml). The solution was stirred (30 min, ice bath), and stored at +5°C for 16 h, then at room temperature for 2 h. The excess reagent was destroyed by addition of ice, then the mixture was extracted with $CHCl_3$ (100 ml), dried (Na_2SO_4), and the solvent evaporated to give a yellow oil (640 mg, 76.1%). The product isomers were separated by preparative TLC [1mm plates, 2 developments in petroleum ether/ether (1 : 1)]. The less polar isomer (Rf = 0.67) was obtained as an amorphous solid from $CHCl_3$ and the more polar isomer (Rf = 0.55) as colorless crystals from

acetone/petroleum ether.

Less polar isomer: *cis*-5-Tosyloxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane [*cis*-**(5)**]; m.p.: 43~45°C, ^{31}P NMR ($CDCl_3$), δ65.0, MS [m/z (%)]: 380 (M^+,50), 225 (50), 155 (58), 91 (100),

More polar isomer: *trans*-5-Tosyloxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane [*trans*-**(5)**]; m.p. 87~89°C, ^{31}P NMR ($CDCl_3$): δ60.7, MS [m/z (%)]: 225 (M155, 100), 197 (78),

5-(3,5-Dinitro)Benzoyloxymethyl-5-methyl-2-thiono-2-ethoxy-1,3,2-doxaphosphorinane (6). A solution of 3,5-dinitrobenzoyl chloride (1.7 g) in CH_3CN (2 ml) was added dropwise to a cooled (ice bath), stirred solution of a mixture of the isomers of 5-hydroxymethyl-5-methyl-2-thiono-2-ethoxy-1,3,2-dioxaphosphorinane (1.46 g) and pyridine (1.0 ml) in CH_3CN (10 ml). The reation mixture was then stirred overnight at room temperature. Work up, as described for the benzoyl derivative, gave the product as a brown oil (2.26 g, 83.1%) which was further purified by flash column chromatography (petroleum ether/ether). The mixture of isomers was separated (1 mm t.l.c. plates) by developing once in petroleum ether/ether (2 : 3) then twice in petroleum ether/ether (1 : 1). The less polar (Rf = 0.71) and more polar (Rf = 0.53) isomers were obtained as offwhite crystals and colorless needles, respectively, from acetone/petroleum ether in each case.

Less polar isomer: *cis*-5-(3,5-Dinitro)Benzoyloxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane [*cis*-**(6)**]; m.p.: 167~169°C, ^{31}P NMR ($CDCl_3$): δ65.5, MS [m/z (%)]: 420 (M^+,10), 195 (100)

More polar isomer: *trans*-5-(3,5-Dinitro)Benzoyloxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane [*trans*-**(6)**]; m.p.: 153~154°C, ^{31}P NMR ($CDCl_3$): δ61.0, MS [m/z (%)]: 420 (M^+, 20), 195 (100), Crystal data.-monoclinic, space group $P2_1/c$, *a* 15.753, *b* 11.868, *c* 10.304 Å, β 97.21°, z 4.

Results and Discussion

Synthesis and derivatization. 5-Hydroxymethyl-5-methyl-2-thiono-2-ethoxy-1,3,2-dioxaphosphorinane **(2)** was prepared by reaction of 2-methyl-2-hydroxymethyl-propane-1,3-diol with *O*-ethyl dichlorophosphorothionate (Fig. 1).

Table 1. ^{31}P NMR Chemical shifts (d, ppm) of isomers of compounds prepared.

Isomers \ Compounds	(2)	(3)	(4)	(5)	(6)
Less polar	64.4	63.7	64.7	65.0	65.5
More polar	62.6	61.1	59.5	60.7	61.0

These reactions proceeded smoothly to give the products in reasonable yield and, as expected, the crude dioxaphosphorinanes consisted of a pair of geometric stereoisomers, which could readily be evidenced by ^{31}P NMR spectroscopy (Table 1) in which the ^{31}P NMR specrum gave singlet for each of the isomers, and these isomers were present in an approximately 1 : 1.2~1.5 molar ratio, with an excess of the more polar isomer (at higher field) as defined by relative Rf values on silica gel TLC (the upper band was designated as the less polar isomer and the lower band was designated as the more polar isomer).

The geometric isomers of the crude **(2)** were separated by preparative tlc with multiple developments and the more polar isomers was crystallized as colorless needles while the less polar isomer remained as a sticky colorless oil.

Since isolated isomers of **(2)** were unsuitable for X-ray structure determination, its acetate **(3)**, benzoate **(4)**, tosylate **(5)**, and 3,5-dinitrobenzoate **(6)** derivatives were prepared in an attempt to obtain crystals suitable for single crystal X-ray analysis to determine the actual stereochemistry of each isomer. Derivatization was readily achieved by reacting **(2)** with an excess of the appropriate reagents in the presence of pyridine. No difficulties were encountered in any of these esterifications, and the reactions proceeded in reasonable yields (Fig. 1).

The geometric isomers of the acetate **(3)** were readily separated through column chromatography. Separations for **(4)**, **(5)** and **(6)** were achieved using preparative TLC with multiple developments, with the advantage that the separation of isomers during preparative TLC could be monitored between successive developments of the plate by visualising the plate under U.V. light. The separation of the isomers of **(6)** was found to be more difficult due to tailing of the more polar isomer. The separated isomers of the

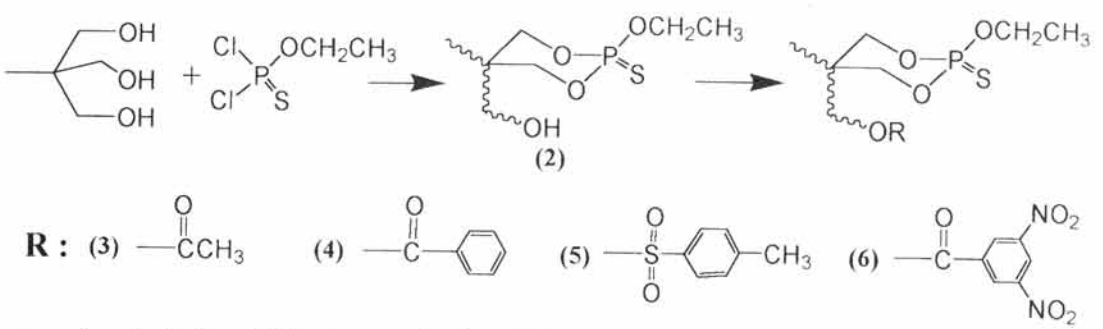

Fig. 1. Synthesis and derivatization of 5-hydroxymethyl-5-methyl-2-thiono-r-2-ethoxy-1,3,2-dioxaphosphorinane (2).

compounds were crystallized from acetone and light petrol as colorless needles or plates, except for the less polar isomers of **(4)** and **(5)** which were obtained as amorphous solids. Of these, less polar isomer of **(3)** and more polar isomer of **(6)** were suitable for single crystal X-ray analysis.

Structural assignment of the isomers. NMR spectra analysis The ^{1}H-NMR spectra of the dioxaphosphorinanes **(2)** had some characteristic features which proved useful in discerning between the isomers of each compound; in addition to ^{31}P NMR chemical shifts, the chemical shift of the protons was attached to the substituents at the 5-position of the dioxaphosphorinane ring.[3-5]

The more polar isomers of compounds prepared gave the methyl protons of the 5-methyl group at 0.2~0.4 ppm to higher field than the corresponding singlet of the less polar isomer. The 5-hydroxymethyl group provided a similar marker; the sharp singlet of the methylene protons of the more polar isomer was observed at 0.2~0.4 ppm to lower field than the corresponding peak for the less polar isomer.

For assigning structure and conformation, the axial and equatorial ring protons which absorbed in the 3~5 ppm region (^{1}H NMR) proved to be most useful. These generally appeared as ABX system by virture of their coupling to phosphorus (Fig. 2). Assignment of the chemical shift to the axial and equatorial protons in the ^{1}H-NMR spectrum was based on the observed coupling values of these protons to phosphorus (J_{POCH}), and on anisotropy arguments.

The Karplus relationship (Fig. 3) between J_{POCH} and dihedral angle (q) between the protons and the phosphorus atom predict that J_{POCH} approaches a minimum as q approaches 90°, and J_{POCH} reaches a maximum as q approaches 0° or 180°.[7] Thus, in a six-membered ring, the coupling between an axial proton and phosphorus will be substantially smaller (J_{POCHa} = 10.98 Hz) than the coupling of phosphorus to an equatorial proton (J_{POCHe} = 15.96 Hz) (Fig. 2, Table 2). Axial and equatorial protons coupled each other

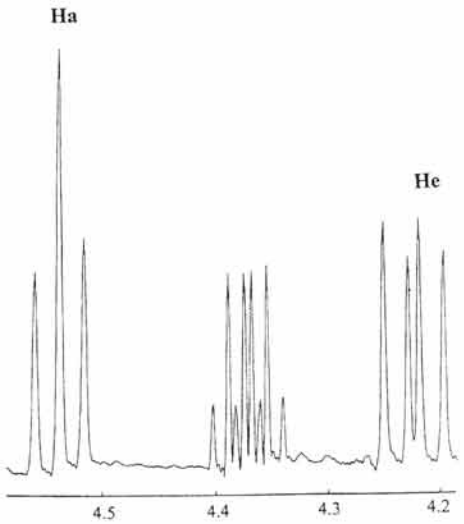

Fig. 2. ^{1}H-NMR Spectrum of ring proton region of less polar isomer of (2). Ha ; Axial protons, He; Equatorial protons

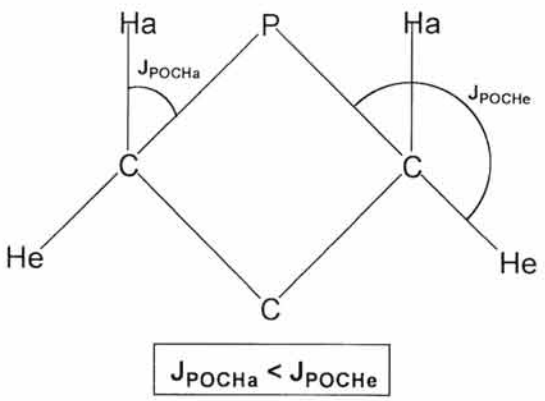

Fig. 3. Relationship between dihedral angle and J_{POCH}.

Table 2. Chemical shifts (d, ppm) and J-values (Hz) for ring protons of the less polar isomer of (2) in CD_3OD.

Axial protons (Ha)			Equatorial protons (He)		
d	J_{POCHa}	J_{HaHe}	d	J_{POCHa}	J_{HaHe}
4.54	10.89	- 11.0	4.22	15.96	-11.0

(J_{HaHe} = -11.00 Hz) and J_{HaHe} and J_{POCHe} was very similar to give apparent triplet by overlapping of two peaks of axial protons. A doublet of quartet around d 4.37 is from the methylene protons of ethyl group (P-OC**H**$_2$CH$_3$) which was splitted by the three methyl protons into a quartet (J = 7.07 Hz) and then by phosphorus into a doublet (J_{POCH} = 10.31 Hz).

The relative position of axial and equatorial protons was found to be very useful to assign cis- or trans-stereochemistry to the isomers of each compound. Generally, the phosphoryl group has a strong tendency for the equatorial position.[8] Hence, the structural difference between the isomers is the position of the hydroxymethyl group relative to the 2-alkoxy group. Therefore, for the purpose of this study, a molecule is defined as having cis-stereochemistry when the 2-alkoxy group and the hydroxymethyl group are on the same side of the dioxaphosphorinane ring, and trans-stereochemistry when they are on opposite sides of the ring (Fig. 4).

Molecular models clearly showed that the distance between the hydroxyl group and the axial protons in the cis-isomer is substantially shorter than the distance between the hydroxyl group and the equatorial protons in the trans-isomer. As a result, the deshielding effect of the hydroxyl group on the axial protons of the cis-isomer should be

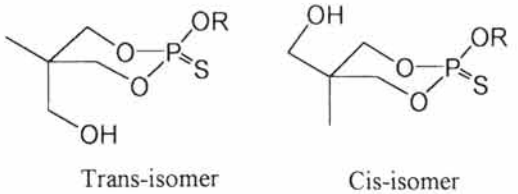

Fig. 4. Definition of stereochemical terminology as used in this study.

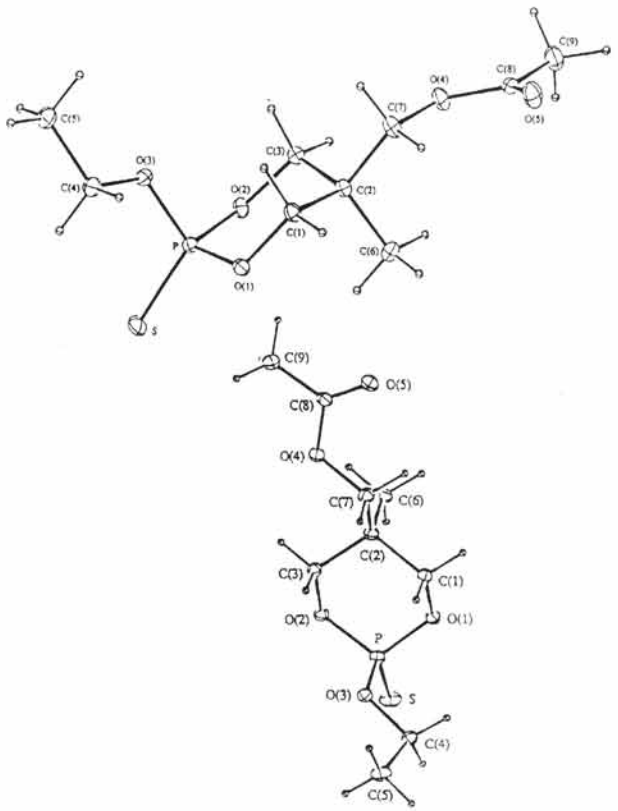

Fig. 5. A single molecule of *cis*-5-acetoxymethyl-5-methyl-2-thiono-r-2ethoxy-1,3,2-dioxa-phosphorinane [*cis*-(3)] showing crystallographic numbering of non-hydrogen atoms. The ellipsoid probability is 10% and the hydrogen atom radius 0.1 Å.

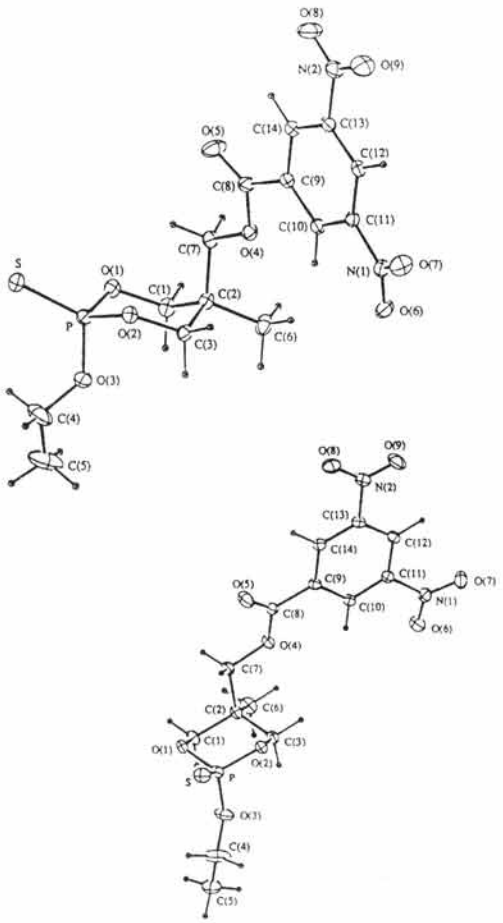

Fig. 6. A single molecule of *trans*-5(3,5-dinitro) benzoyloxy-methyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxa-phosphorinane [*trans*-(6)] showing crysrallographic numbering of non-hydrogen atoms. The ellipsoid probability is 10% and the hydrogen atom radius 0.1 Å.

greater than that on the equatorial protons of the trans-isomer. Thus, the axial protons are expected to resonate further downfield than the equatorial protons, as observed for the less polar isomers of **(2)** (Fig. 2, Table 2).

On the basis of the above considerations and ^{1}H-^{31}P coupling values, the less polar isomers of **(2)** was assigned as the cis-stereochemistry and more polar isomer as trans- stereochemistry. *Trans*-(**2**) had a very small chemical shift difference between the axial and equatorial protons to give a so called deceptively-simple ABX spectrum. This has been reported with other dioxaphosphorianes.[9, 10]

Therefore, the singlets from the 5-substituent can be used, in turn, as a simple and absolute marker for distinguishing between the cis- and trans-isomers of the dioxa-phosphorinanes; the singlet for the 5-methyl protons of the trans-isomer occurs at higher field than the singlet for the 5-methyl group of the cis-isomer. The ^{31}P NMR spectrum also presented a clear picture; the trans-isomer of the pair always resonated at higher field (Table 1).

X-ray crystallography. X-ray crystallographic studies[11-24] showed that, generally, the 1,3,2-dioxaphosphorinane ring adopts a chair conformation, somewhat flatened at the phosphorus center. In terms of conformational tendencies as determined also by NMR or IR studies, the P = O bond has a strong tendency to occupy the equatorial position in phosphate esters[8,10,24,26] such that the exocyclic alkoxy group is axial. However, this conformation disposition of substituents does vary. For example, for 2-alkyl[25-30] or 2-amino phosphates,[25,26,29] the P = O bond occupies the axial position. Similar tendencies to these are found in 2-thiono-2-substituted derivatives.[31]

The conformation of the dioxaphosphorinane ring is also sensitive to other substituents. For instance, a half chair (chaise longue) conformation was found for *trans*-2-triphenylmethyl-2-oxo-4,6-dimethyl-1,3,2-dioxaphos-phorinane[32,33] while, for *cis*-2,5-di-t-butyl-2-oxo-1,3,2-dioxaphosphorinane,[18] a boat conformation was reported. These conformational preferences presumably arose from the effects of the steric bulk of the triphenylmethyl and *t*-butyl group.

The X-ray crystallographic analyses in the present study (Figs. 5 and 6) showed that both less polar isomer-**(3)** and more polar isomer-**(6)** adopted a chair conformation with the ethoxy groups in the axial positions, and the sulfide groups in the equatorial positions. The less polar isomer-**(3)** was found to have the acetoxy group and the ethoxy group on the same side of the ring, i.e. defined as cis-geometry (Fig. 5), and the more polar-**(6)** (Fig. 6) showed the ethoxy group and

3,5-dinitrobenzoxy group to be trans, thereby establishing the relative stereochemistry of *cis*- and *trans*-**(2)** by their derivatives *cis*-**(3)** and *trans*-**(6)**.

This stereochemical arrangement of the substituents and ring conformation are in agreement with that anticipated from general tendency of phosphate esters previously discussed.[10-25]

A flattening of the ring around the phosphorus center was noted, as can be seen from examination of the ring torsion angles. Bond lengths and angles are normal compared with those of other related 5,5-dimethyl-1,3,2-dioxaphosphorinanes.[34-36]

The POC bond angles approximate 120°, indicating that the oxygen atoms are sp^2-like. The C-O bonds in the ring are significantly longer than the C-O bond for the ethoxy group or the C-O bond for hydroxyl group; the latter are those normally found in ethers and alcohols. This bond lengthening is a typical feature of anomeric centers and is attributed to the anomeric delocalization.[37] Similar elongations of these bonds have been found in other anomeric systems, including acetals[37,38] and cyclic sulfites.[39] In the molecules in this study, the ethyl group is directed away from the six-membered ring thereby avoiding the severe steric interaction that would otherwise occur with the axial protons on C(3) and C(1).

Conclusion

Cis- and *trans*5-hydroxymethyl-5-methyl-2-thiono-r-2-ethoxy-1,3,2-dioxaphospho-rinane were prepared and derivatized into 5-acetoxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane, 5-benzoyloxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane, 5-tosyloxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane and 5-(3,5-Dinitro)benzoyloxymethyl-5-methyl-2-thionor-2-ethoxy-1,3,2-dioxaphosphorinane. Trans-isomer gave ^{31}P NMR signal at higher field than cis-isomer and the ring proton spectrum of cis-isomer showed characteristic pattern to identify its geometry. Stereochemistry of *cis*- and *trans*5-hydroxymethyl-5-methyl-2-thiono-r-2-ethoxy-1,3,2-dioxaphosphorinane was also assigned by X-ray crystallography with acetoxy and 3,5dinitrobenzoyloxy derivatives. They adopted a chair conformation with the ethoxy groups in the axial positions, and the sulfide groups in the equatorial positions. A flattening of the ring around the phosphorus center was noted, the POC bond angles were about 120° and the C-O bonds in the phosphate ring were significantly longer than the C-O bond for the ethoxy group or the C-O bond for hydroxyl group. The ethoxy group was directed away from the six-membered ring thereby avoiding the severe steric interaction that would otherwise occur with the axial protons on C(3) and C(1).

References

1. Worthing, C. R. (1987) In *Pesticide Manual: World Compendium* (8th ed.) British Crop Protection Council, Lavenham Press, Lavenham, Great Britain.
2. Bauman, M. and Jr. Wadsworth, W. S. (1978) Nucleophilic Substitution at Phosphorus. The Effect of Ion Association on the Stereochemistry and Rate of Substitution at Phosphorus in a Six-Membered Ring Phosphate. *J. Am. Chem. Soc,* **100**, 6388-6394.
3. Wadsworth Jr., W. S., Larsen, S. and Horton, H. L. (1973) Nucleophilic Displacement at Phosphorus. *J. Org. Chem.* **38**, 256-263.
4. Wadsworth Jr., W. S. (1973) The Effect of Added Salts on the Stereochemistry of Nucleophilic Displacement at Phosphorus in Phosphate Ester and Their Analogs. *J. Org. Chem.* **38**, 2921-2927.
5. Wadsworth, W. G. and Wadsworth Jr. W. S. (1983) A Cyclic Phosphate: Base and Metal Acetate Catalyzed Ring Opening. *J. Am. Chem.* **105**, 1631-1637.
6. Warrent, R. W., Caughlan, C. N., Hargis, J. H., Yee K. C. and Bentrude, W. G. (1978) Effect of Axial *tert*-Butyl Substituents on Conformation and Geometries of Saturated Six-Membered Rings. Crystal and Molecular Structure of *trans*-2-Methoxy-2-oxo-5-*tert*-butyl-and *cis*-2,5-Di-*tert*-buty l-2-thio-1,3,2-dioxaphosphorinane. *J. Org. Chem.* **43**, 4266 -4270.
7. Gorenstein, D. G. (1984) In *Phosphorus ^{31}NMR-Principles and Applications*, Academic Press, New York.
8. Geise, H. J. (1967) The Conformation of Non-Aromatic Ring Compounds. Part 37 The Crystal Structure of 2-Oxo-2-Phenoxy-1,3,2-dioxaphosphorinane. *Rec. Trav. Chim. Pays-Bas*. **86**, 362-370.
9. Bartle, K. D., Edmundson, R. S. and Jones, D. W. (1967) Cyclic Organophosphorus Compound-V High Resolution Magnetic Spectra of Some 5,5,-Dialkyl-1,3,2-Dioxaphosphorinane and Related Compounds. Tetrahedron **23**, 1701-1711.
10. Hall, L. D. and Malcolm, R. B. (1972) Studies of Phosphorus Derivatives. Part I. Nuclear Magnetic Resonance Studies of the 2-Oxo-1,3,2-dioxaphosphorinane System. *Can. J. Chem.* **50**, 2092-2101.
11. Silver, L., and Rufman, R. (1972) The Crystal and Molecular Structure of 5,5,-Diemthyl-2-chloro-2-oxo-1,3,2-dioxaphosphorinane. *Acta Cryst*. **B28**, 574-578
12. Kok, A. M. G., Wynberg H., Garcia-Granda, S., Beurskens, P. T. and Smits, J. M. M. (1988) Structure of the Diastereomeric Salt of (-)-4-*o*-Chlorophenyl-2-hydroxy-2-oxo-1,3,2-dioxaphosphorinane-5-spirocyclohexane and (1S,2R)-(+)-α-[(1-Methylamino)-ethyl]benzyl Alcohol Monohydrate. *Acta Cryst,* **C44**, 2235-2237.
13. Garcia-Granda, S., Beurskens, P. T., Smits, J. M. M., Kok, A. M. G. and Wynberg H. (1988) Structure of the Diastereomeric Salt of (-)-4-*o*-Chlorophenyl-2-hydroxy-2-oxo-1,3,2-dioxaphosphorinane-5-spirocyclohexane and (1R, 2S)-(-)-α-[(1-Methylamino)-ethyl]benzyl Alcohol. *Acta Cryst.* **C44**, 2233-2235.
14. Kok, A. M. G, Wynberg H., Parthasarathi, V., Smits, J. M. M., and Beurskens, P. T. (1987) Structure of the

Diastereomeric Salt of (+)-4-*o*-Chlorophenyl-2-hydroxy-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane and (1S,2R)-(+)-α-[(1-Methylamino)ethyl]-benzyl Alcohol. *Acta Cryst.* **C43**, 1336-1341.

15. Smits, J. M. M., Beurskens, P. T., Parthasarathi, V., Rijk, E. V. A., Kok, A. M. G. and Wynberg, H. (1987) Structure of the Diastereomeric Salt of (+)-4-*o*-Chlorophenyl-2-hydroxy-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane and (1R,2S)-(-)-α-[(1-Methylamino) ethyl]benzyl Alcohol. *Acta Cryst.* **C43**, 1334-1336.
16. Smits, J. M. M., Beurskens, Kok, A. M. G. and Wynberg, H. (1987) Structure of the Diastereomeric Salt of (+)-2-Hydroxy-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxa-phosphorinane and (1S,2R)-(+)-α-[(1-Methylamino)ethyl] benzyl Alcohol. *Acta Cryst.* **C43**, 1331-1333.
17. Kok, A. M. G, Wynberg H., Smits, J. M. M., Beurskens, P. T. and Parthasarathi, V. (1987) Structure of the Diastereomeric Salt of (+)-2-Hydroxy-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane and (1R,2S)-(-)-α-[(1-Methylamino)ethyl]benzyl Alcohol. *Acta Cryst.* **C43**, 1328-1331.
18. Day, R. O., Bentrude, W. G., Yee, K. C., Setzer, W. N., Deiters, J.A. and Holmes, R.R. (1984) The First Monocyclic 1,3,2-Dioxaphosphorinane in a Boat Form. Synthesis, Structure, and Stability. *J. Am. Chem. Soc.* **106**, 103-106.
19. Day, R. O., Gorenstein, D. G. and Holmes, R. R. (1983) Crystal Structure of an Axially and an Equatorially Oriented 2-(Aryloxy)-2-oxy-1,3,2-Dioxaphosphorinane. *Inorg. Chem.* **22**, 2192-2195.
20. Bartczak, T. J., Wolf, W., Swepston, P. N. and Zerong, L. L. (1987) The Stereochemistry of the Phosphorus-Selenium Bond VI. Structure of 5,5-dimethyl-2-methylseleno-1,3,2-dioxaphosphorinane 2-Selenide. *Acta Cryst.* **C43**, 1788-1790.
21. Bartczak, T. J., Galdecki, Z. and Wolf, W. (1986) Structure of 5,5-Dimethyl-2-ethylamino-1,3,2-dioxaphosphorinane 2-Selenide. *Acta Cryst.* **C42**, 244-246.
22. Bartczak, T. J., Galdecki, Trzezwinska, H. B. and Wolf, W. (1983) Structure of 5,5-Dimethyl-2-phethylamino-1,3,2-dioxaphosphorinane 2-Selenide, $C_{11}H_{16}NO_2PSe$. *Acta Cryst.* **C39**, 731-732.
23. Bartczak, T. J., and Wolf, W. (1983) Structure of 2-[(3,5-Dichlorophenyl)amino]-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-Selenide, $C_{11}H_{14}Cl_2NO_2PSe$. *Acta Cryst.* **C39**, 224-227.
24. Edmundson, R. S., Johnson, O. and Jones, D. W. (1989) Conformation of Dioxaphosphorinanes: Crystal and Molecular Structure of 2-Cyclohexyl-5,5-dimethyl-1,3,2-dioxaphosphorinane-2-oxide. *Phosphorus, Sulfur and Silicon* **46**, 61-67.
25. Mosob, J. A. and Verkade, J. G. (1977) Dipole Moment, Nuclear Magnetic resonance, and Infrared Studies of Phosphorus Configurations and Equilibria in 2-R-Oxo-1,3,2 dioxaphosphorinanes. *J. Org. Chem.* **42**, 1549-1555.
26. Mosob, J. A. (1978) Ring Conformation of 2-Substituted 2-oxo-4-methyl-1,3,2 dioxaphosphorinanes. Evidence of a Boat Conformation in Equilibrium with Two Interconverting Chair. *Org. Mag. Res.* **11**, 281-282.
27. Yee, K. C. and Bertrude, W. G. (1971) Six-Membered Ring Phosphorus Heterocycles. Use of Euporium Shift Reagent in the Analysis of the P.M.R. Spectrum of *trans*-2-Methyl-5-*t*-butyl-2-oxo-1,3,2 dioxaphosphorinane. *Tetrahedron Lett.* **29**, 2775-2778.
28. Bertrude, W. G. and Yee, K. C. (1972) Conformation of Saturated Six-membered Ring Phosphorus Heterocycles. Non-chair conformation of *cis*-2,5-Di-*t*-butyl-1,3,2 dioxaphosphorinan-2-one. *Chem. Comm.* 169-170.
29. Bertrude, W. G., Tan, H-W, and Yee, K. C. (1972) Conformation of Saturated Six-membered Ring Phosphorus Heterocycles. Effect of Euporium Dipivaloylmethane and Euporium Heptafluorodimethyloctanedione on Conformational Equilibria of 2-Substituted-5-*tert*-Butyl-2-oxo-1,3,2 dioxaphosphorinanes. *J. Am. Chem. Soc.* **94**, 3264-3266.
30. Dale, A. J. (1972) Lanthanide Induced Chemical Shifts in 5,5-Dimethyl-1,3,2 dioxaphosphorinan-2-ones with Respect to the Conformational Preference of the 2-Substituent. *Acta Chem. Scand.* **26**, 2985-2987.
31. Dutasta, J. P., Grand, A., Robert, J. B. and Taieb, M. (1974) Conformational Analysis of 2-Thiono-1,3,2 dioxaphosphorinanes. *Tetrahedron Lett.* **31**, 2659-2662
32. Drew, M. G. B., and Rodgers, J. (1972) The Crystal and Molecular Structure of *cis*-4,6-Dimethyl-2-oxo-2-triphenylmethyl-1,3,2-dioxaphosphorinan. *Acta Cryst.*, **B28**, 924.
33. Drew, M. G. B., Rodgers, White, D. W. and Verkade, J. G. (1971) The Crystal Structure of *cis*-4,6-Dimethyl-2-oxo-2-triphenylmethyl-1,3,2-dioxaphosphorinan *Chem. Comm.* 227.
34. Nuffel, P. V., Lenstra, A. T. H. and Geise, H. J. (1980) 5,5-Dimethyl-2-methoxy-2-oxo-1,3,2-dioxaphosphorinane, $C_6H_{13}O_4P$. *Cryst. Struct. Comm.* **9**, 733-738.
35. Grand, A., Martin, J., Robert, J. B. and Tordjman, I. (1975) 2-Seleno-2-methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinane. *Acta Cryst.* **B31**, 2523-2524.
36. Nuffel, P. V., Lenstra, A. T. H. and Geise, H. J. (1981) The Structure of 2-Mehtoxy-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-Sulphide. *Acta Cryst.* **B37**, 133-136.
37. Jaffery, G. A., Pople, J. A., Binkeley, J. S. and Vishveshwara, S. (1978) *J. Am. Chem. Soc.* **100**, 378-379.
38. Van de Mieroop, W. and Lenstra, A. T. H. (1978) *Cryst. Struct. Commu.* **7**, 577-582.
39. Petit, G. H., Lenstra, A. T. H. and Geise, H. J. (1978) *Bull. Soc. Chim. Belg.* **87**, 659-666.