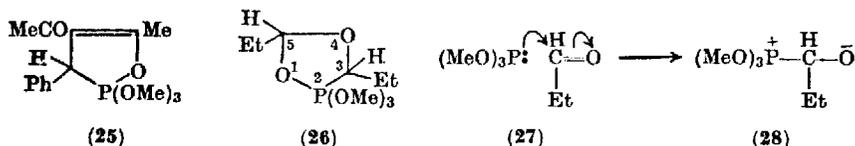


occurs however very slowly at room temperature, *e.g.*, after 14 days only 60% conversion had occurred: higher temperatures cause side-reactions. The mechanism of the formation of (26) is similar to that of

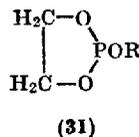
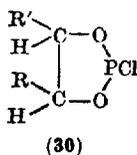
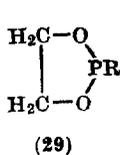


the compound (22), namely, an initial slow reaction of the phosphite and the aldehyde (27) to give the polar intermediate (28), which then reacts rapidly with a second molecule of propionaldehyde to give the cyclic (26).

The wide and various extensions of this field of work by Ramirez and his co-workers, and the very thorough investigation of the structure of their products, have produced a massive volume of very interesting and valuable work. The original papers should certainly be consulted for the full details. A bibliography of papers from various centers up to 1964 has appeared (Ramirez *et al.*³⁸²).

1,3,2-Dioxaphospholanes

Members of this class have often been named after the 1,2-glycol of which they can be regarded as esters: thus the compound (29; R = Cl) has been termed glycol chlorophosphonite or phosphorochloridite; the compound (29; R = OCH₃) has been termed glycol methoxyphosphonite or ethylene methyl phosphite; and the compound (29; R = NEt₂) has been termed glycol *N,N*-diethylamidophosphonite or phosphoroamidite.



In one of the earliest syntheses of this system (Rossiiskaya and Kabachnik³⁸³), ethylene glycol was added to an excess of stirred, ice-cooled phosphorus trichloride; the reaction mixture when heated at 60–70° for 3 hours and then distilled gave (*a*) 2-chloro-1,3,2-dioxaphospholane (29; R = Cl), a colorless liquid, b.p. 66–68°/47 mm, which fumed in air, and (*b*) ethylene 1,2-bis(phosphorodichloridite),



b.p. 93–100°/4.5 mm, but no 2-chloroethyl phosphorodichloridite, $\text{Cl}(\text{CH}_2)_2\text{O}-\text{PCl}_2$. These results conflict with those of Carré (p. 319), whose reactions were performed in ether.

The above preparation is greatly improved by the use of equimolar quantities of the glycol and phosphorus trichloride in CH_2Cl_2 (Lucas *et al.*³⁸⁴), and gives the 2-chloro compound (**30**; $\text{R} = \text{R}' = \text{H}$), b.p. 56°/25 mm, 41.5°/10 mm (66%). 1,2-Propanediol similarly gives the 2-chloro-4-methyl compound (**30**; $\text{R} = \text{CH}_3$, $\text{R}' = \text{H}$), b.p. 58°/25 mm (86%), and *meso*-2,3-butanediol gives the 2-chloro-4,5-dimethyl compound (**30**; $\text{R} = \text{R}' = \text{CH}_3$), b.p. 66.0–66.2° (72%).

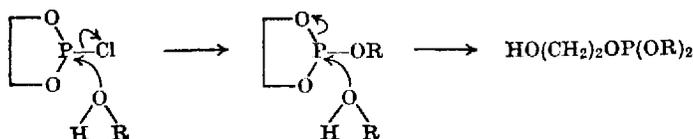
Table 23. 2-Alkoxy-1,3,2-dioxaphospholanes
(**31**)

R	B.p. (°/mm)
Methyl	60.7–60.9
Ethyl	70.4–70.7
<i>n</i> -Propyl	85.6–85.8
Isopropyl	70.3
<i>n</i> -Butyl	100–100.2
Isobutyl	91.1–91.3
<i>sec</i> -Butyl	87.9–88.3
<i>tert</i> -Butyl	77.9–78.6
<i>n</i> -Pentyl	89/12
<i>n</i> -Hexyl	82.5/6

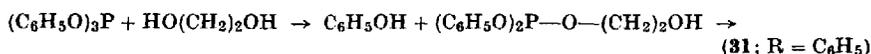
The unsubstituted chloro compound (**29**; $\text{R} = \text{Cl}$) is very readily hydrolyzed; consequently it should always be manipulated under anhydrous conditions.

The addition of an anhydrous alcohol to a solution of one mole of the chloro compound (**29**; $\text{R} = \text{Cl}$) in light petroleum containing pyridine or (better) 4-ethylmorpholine at -5° , followed by filtration (to remove the amine hydrochloride) and distillation, gives the corresponding 2-alkoxy-1,3,2-dioxaphospholane (**31**) (Lucas *et al.*³⁸⁴). The b.p.s in Table 23 are at 25 mm, except the last two (Foxton *et al.*³⁸⁵).

If more than one mole of an alcohol is used, the reaction goes a stage further with the formation of a 2-hydroxyethyl phosphite:



The 2-phenoxy compound (**31**; R = C₆H₅) can be readily prepared by heating triphenyl phosphite at 100° with ethylene glycol (1 mole) in which a small quantity of sodium has been dissolved. Trans-esterification occurs, with liberation of phenol and formation of (**31**; R = C₆H₅) (60%). 1,2-Propanediol similarly gives the 4-methyl-2-phenoxy derivative (52%). The reaction probably proceeds:



The reaction with the lower 1,2-diols will proceed (in lower yield) without the catalytic action of the sodium glycolate, but the latter is essential when more complex diols are used (Ayres and Rydon³⁸⁰).

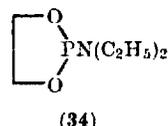
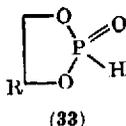
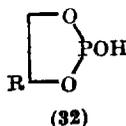
Three other methods for the preparation of 2-alkoxy derivatives (**31**) should be mentioned.

(a) Methyl phosphorodichloridite, CH₃OPCl₂, when added to an ethereal solution of glycol and diethylaniline, gives the 2-methoxy compound (**31**; R = CH₃). The 2-ethoxy compound is similarly prepared but only in low yield.³⁸³

(b) Ethylene oxide is added to the 2-chloro compound (**29**; R = Cl) at 15–20°, and the reaction mixture, after 1 hour at 50°, on distillation gives the 2-(2'-chloroethoxy) compound (**31**; R = ClCH₂CH₂), b.p. 57°/1 mm (Nagy³⁸⁷); many other examples of this reaction have been cited.

(c) It is claimed that, in a novel reaction, *n*-hexyl *N,N,N',N'*-tetraethylphosphorodiamidite, C₆H₁₃O—P[N(C₂H₅)₂]₂, reacts with ethylene glycol in acetic anhydride to form the 2-*n*-hexyloxy compound (**31**; R = C₆H₁₃), b.p. 52–53°/0.5–1.0 mm (74%). The 2-*n*-propoxy compound, similarly prepared, unites with sulfur to give the 2-*n*-propoxy-1,3,2-dioxaphospholane 2-sulfide, b.p. 81–83°/1 mm (Evdakov, Shlenkova, and Bilevich³⁸⁸).

The carefully controlled hydrolysis of the 2-chloro derivatives gives rise to compounds formulated as 2-hydroxy derivatives (**32**), but they are more probably the 1,3,2-dioxaphospholane 2-oxides (**33**). These are



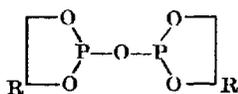
prepared by adding a solution of water (1 mole) in initially anhydrous dioxane in portions with cooling to a solution of the 2-chloro compound (1 mole) also in dioxan; the reaction mixture is kept at room temperature

and 40 mm pressure to remove the HCl as thoroughly as possible; the dioxane is then distilled at this pressure, and the residual (**33**) rapidly distilled at very low pressure. The unsubstituted compound (**33**; R = H) is unstable, but the 4-methyl compound (**33**; R = CH₃) is obtained in 96% yield as a colorless viscous liquid, b.p. 76–82°/0.6 mm; it has the curious property that after 5 days at room temperature the viscosity steadily increases until the liquid will hardly flow, yet redistillation at 76.5°/0.65 mm gives a mobile distillate (with very little residue) which again after 1 week becomes immobile.³⁸⁴

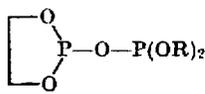
The 2-chloro derivative when treated with primary amines gives intractable products, but when treated with diethylamine (2 moles) in petroleum and worked up as the 2-alkoxy compounds, gives the 2-diethylamino compound (**34**), b.p. 98.7–99.1°/25 mm; piperidine similarly gives the 2-piperidino compound,³⁸⁴ b.p. 132°/25 mm.

It is noteworthy that the optically pure D(-)-2,3-butanediol, [α]_D -13.17°, gave the 2-chloro compound (**30**; R = R' = CH₃), [α]_D +97.12°, b.p. 49.1–49.2°/10 mm (66%), which in turn gave the 2-methoxy compound, [α]_D +53.63°, b.p. 46.0–46.2°/10 mm (47%), and the 2-diethylamino compound, [α]_D -11.18°, b.p. 85.1–85.2°/10 mm (61%); all rotations measured at 25° (Garner and Lucas³⁸⁹).

If the above hydrolysis of the 2-chloro compound is modified by the slow addition of water (1 mole) and a base, such as pyridine, dimethylaniline, or trimethylamine, to the ethereal 2-chloro compound (2 moles) at -5°, followed by stirring at room temperature for 3 hours, filtration, and distillation, the anhydride (**35**; R = H), or oxobis-2,2'-(1,3,2-dioxaphospholane), b.p. 100–101°/4 mm (40%), is obtained. The 4,4'-dimethyl analogue (**35**; R = CH₃), b.p. 118–120°/2 mm (35%), is similarly obtained (Arbuzov, Kikonorov, *et al.*³⁹⁰).



(35)

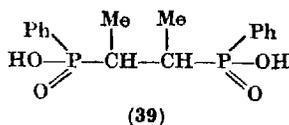
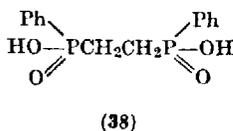
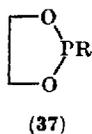


(36)

The interaction of equimolecular quantities of the 2-chloro compound and a sodium dialkyl phosphite, (RO)₂PONa, in chilled ether gives a mixed anhydride; the diethyl and the di-*n*-propyl members (**36**; R = C₂H₅ and C₃H₇) have b.p. 84–85°/2 mm and 93–94°/2 mm, respectively.³⁹⁰

The reaction of the 2-chloro compound with 1,3-dienes gives phospholenes (p. 46), and with 2-keto-3-olefins gives 1,2-oxaphosphol-4-enes (p. 256).

As an example of the preparation of 2-aryl derivatives, an equimolecular mixture of *p*-tolylphosphonous dichloride, $\text{CH}_3\text{C}_6\text{H}_4\text{PCl}_2$, and ethylene glycol in ethereal solution, when treated with pyridine at -10° , gives the 2-*p*-tolyl derivative (**37**; $\text{R} = \text{CH}_3\text{C}_6\text{H}_4$), b.p. $128-131^\circ/12 \text{ mm}$,

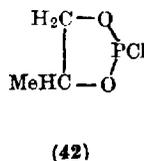
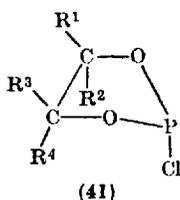
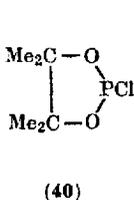


but much polymeric material is formed (Kamai and Ismagilov³⁹¹). Better results are apparently obtained when anhydrous solutions of phenylphosphonous dichloride in benzene and of glycol in pyridine are slowly and simultaneously added to a pyridine-benzene mixture at $10-20^\circ$. Distillation gives the 2-phenyl derivative (**37**; $\text{R} = \text{C}_6\text{H}_5$), b.p. $80.5-82^\circ/1.8 \text{ mm}$, a compound which is very sensitive to water (Harwood³⁹²).

When this phenyl derivative, mixed with a very small proportion of aluminum chloride, is heated under nitrogen in a sealed tube at 160° for 65 hours, it gives a hard colorless polymer, soluble in chloroform and insoluble in benzene. This material when immersed in water swells considerably, giving an acidic oil, which on purification yields 1,2-ethylenebis(phenylphosphinic acid) (**38**), m.p. $266-266.7^\circ$. When ethylphosphonous dichloride, 1,2-butanediol, and aluminum chloride are similarly heated together, hydrolysis of the polymeric product with water yields the corresponding 1,2-dimethylethylenbis(ethylphosphinic acid) (**39**).³⁹²

Conformation

The conformation of 1,3,2-dioxaphospholane derivatives having trivalent phosphorus has been investigated by Goldwhite.³⁹³ The ^1H -nmr spectra of the 2-chloro-4,4,5,5-tetramethyl compound (**40**) give



strong evidence that at room temperature this compound has two kinds of methyl group in magnetically different environments. It is considered

unlikely that these environments arise from a stable non-planar conformation of the ring, for there is evidence that in similar compounds in which the $>P\text{Cl}$ group is replaced by $>CH_2$ or by $>SO$ the five-membered ring undergoes rapid flexing. The results for (40) are therefore attributed to a stable pyramidal configuration of the phosphorus atom, leading to the two kinds of methyl groups (41), namely, the pair of methyl groups R^1 and R^3 which are *trans* to the Cl atom and the pair R^2 and R^4 which are *cis*.

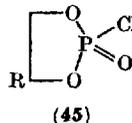
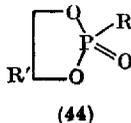
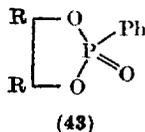
The spectra of the 2-chloro-4-methyl compound (42) also indicate the presence of two different methyl groups, which suggests that (42) is a mixture of two geometric isomers, one being (41; $R^3 = CH_3$, $R^1 = R^2 = R^4 = H$) and the other (41; $R^4 = CH_3$, $R^1 = R^2 = R^3 = H$). Similar results were obtained with 2-methoxy-4-methyl-1,3,2-dioxaphospholane.

A similar investigation of 2-methoxy-, 2-ethoxy-, and 2-diethylamino-1,3,2-dioxaphospholane (Foster and Fyfe³⁹⁴) showed in each case a multiplet splitting of the CH_2 protons, which are further split by the nuclear spin of the phosphorus. The phosphorus atom must have a tetragonal (*i.e.*, pyramidal) configuration, but analysis of these multiplets was not attempted.

The following types of 1,3,2-dioxaphospholane derivatives have formally 5-covalent phosphorus.

When a mixture of phenylphosphonyl chloride, $C_6H_5POCl_2$, and ethylene glycol (1.1 moles) is warmed at 25° under reduced pressure to remove hydrogen chloride, the residue on distillation gives 2-phenyl-1,3,2-dioxaphospholane 2-oxide (43; $R = H$), b.p. $210^\circ/6-7$ mm (75%), and 2,3-butanediol similarly affords the 4,5-dimethyl derivative (43; $R = CH_3$), b.p. $210-215^\circ/15$ mm (79%) (Toy³⁹⁵). Historically this is apparently the first recorded synthesis of the 1,3,2-dioxaphosphole ring system.

In a different synthesis, Petrov *et al.*³⁹⁶ record that (chloromethyl)phosphonyl dichloride, $ClCH_2POCl_2$, when treated cautiously at 20° with water (1 mole) and then heated at 100° for 3 hours and finally under



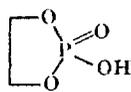
reduced pressure, gives (chloromethyl)phosphonic anhydride, $ClCH_2PO_2$, m.p. $65-72^\circ$. The analogous $C_2H_5PO_2$, m.p. $115-123^\circ$, is similarly prepared. When a mixture of an anhydride of this type and an olefin

oxide (4 moles) in chloroform is heated in a sealed tube at 80–100° for 3–6 hours, distillation of the product gives the 2,4-disubstituted-1,3,2-dioxaphospholane 2-oxides (44) listed in Table 24.

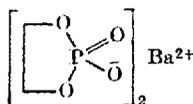
Table 24. Substituted 1,3,2-dioxaphospholane 2-oxides (44)

R	R'	B.p. (°/mm)
CH ₃	H	63–64/0.2
CH ₃	CH ₃	78–80/0.2
C ₂ H ₅	H	83–84/0.2
C ₂ H ₅	CH ₃	87–88/0.2
CH ₃	ClCH ₂	125–130/0.02
C ₆ H ₅	CH ₃	130–135/0.03
ClCH ₂	H	105–115/0.07
ClCH ₂	CH ₃	100–110/0.007

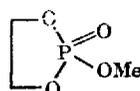
The preparation of 2-chloro-1,3,2-dioxaphospholane 2-oxides (45) by the interaction of a glycol and phosphorus oxychloride in the presence of an amine works well only if the compound (45) is stable at distillation temperatures to traces of amine or amine hydrochloride; ethylene glycol, in particular, reacts with POCl₃ under these conditions to give insoluble oils which rapidly polymerize. The 2-oxides (45) can, however, be readily prepared by passing dry oxygen into a solution of the 2-chloro compound (30) in dry benzene until the exothermic reaction is complete, and then isolating the required product by distillation. Starting with the appropriate (30), Edmundson³⁹⁷ has prepared the 2-chloro oxide (45; R = H), b.p. 79°/0.4 mm, and the 2-chloro-4-methyl oxide (45; R = CH₃), b.p. 74°/0.4 mm, each in 80% yield.



(46)



(47)



(48)

The 2-chloro 2-oxide (45; R = H) reacts with water to form the 2-hydroxy 2-oxide (46) ('ethylene phosphate') which, however, readily hydrolyzes further to 2-hydroxyethyl phosphate,



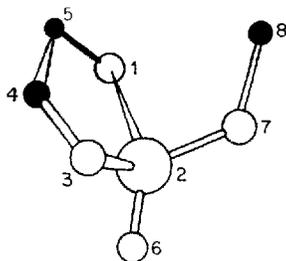
and the internal ester-acid (46) is isolated usually as its metallic salts. The barium salt has been prepared by adding water (1 mole) slowly to phosphorus oxychloride and, after complete reaction, cooling to 0° and adding ethylene bromohydrin. The reaction mixture is warmed under

reduced pressure to remove hydrogen chloride, and then suitably treated with barium hydroxide to give barium 2-bromoethyl phosphate. An aqueous solution of this phosphate is warmed to 75° for 15 minutes, and then treated again with barium hydroxide; rapid evaporation under reduced pressure gives a mixture of barium bromide and the barium salt (47), which can be isolated by suitable aqueous-ethanolic extraction (Kumamoto, Cox, and Westheimer³⁹⁸).

Esters of the acid (46) are obtained by oxidation of the corresponding 2-alkoxy-1,3,2-dioxaphospholane: thus the 2-methoxy compound (31; R = CH₃) when treated in dichloromethane solution at

Figure 7. Structure of 2-methoxy-1,3,2-dioxaphospholane 2-oxide (48).

Interatomic Distances (Å): P—O(3) = P—O(6) = P—O(7) = 1.57; P—O(6) = 1.44; O(3)—C(4) = 1.41; O(1)—C(5) = 1.45; O(7)—C(8) = 1.44; C(4)—C(5) = 1.52. Intervalency Angles: P—O(3)—C(4) = P—O(1)—C(5) = 112.0° ; P—O(7)—C(8) = 118.0° ; O(1)—P—O(3) = 99.1° ; O(1)—P—O(7) = 109.2° ; O(3)—P—O(7) = 105.7° ; O(6)—P—O(1) = 117.3° ; O(6)—P—O(3) = 116.0° ; O(6)—P—O(7) = 108.7° ; O(3)—C(4)—C(5) = 107.8° ; C(4)—C(5)—O(1) = 106.8° . [Adapted, by permission, from T. A. Steitz and W. N. Lipscomb, *J. Amer. Chem. Soc.*, **87**, 2488 (1965)]



-10° to -15° with dinitrogen tetraoxide gives the crystalline 2-methoxy 2-oxide (48), commonly known as methyl ethylene phosphate, m.p. -6° to -5° (75%) (Covitz and Westheimer³⁹⁹).

The structure of the compound (48) has been determined by X-ray crystal analysis, using a single crystal grown from a melt at -5° and maintained at -40° during the investigation (Steitz and Lipscomb⁴⁰⁰). The structure is shown in the annexed Figure 7, in which the atoms in the ring are given their normal numbers, the remaining two oxygen and one carbon atoms being numbered 6, 7, and 8.

Certain points in this structure are of particular interest.

(a) The five-membered ring is puckered, so that the normal of the O(1)—P—O(3) plane is about 11° from the normal of the O(3)—C(4)—O(1) plane.

(b) The angle O(1)—P—O(3) is 99° , *i.e.*, 10° less than the tetrahedral angle. The fact that this angle (99°) is virtually identical with the 'natural' angle (p. 186) of a symmetric phosphine, PR₃, may be fortuitous.

(c) The P—O(7)—C(8) angle (118.8°) in the unstrained part of the

molecule is reduced to 112° within the 'strained' ring; cf. P—O(3)—C(4), P—O(1)—C(5).

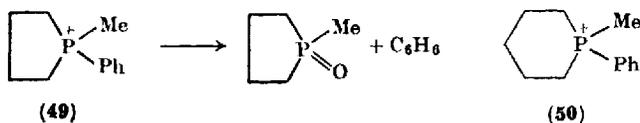
(d) The equality of the three 'esterified' P—O bonds is apparently independent of angle strain; this value (1.57 Å) is significantly shorter than that of the ring P—O bonds (1.60 and 1.76 Å) found in the pentaoxyphosphorane (5; R = iso-C₃H₇) (p. 265).

An X-ray structure analysis of 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide, termed 'methyl pinacol phosphate', shows a very similar ring arrangement to that of (48), although the C atom of the CH₃O group has changed position; the corresponding bond lengths and intervalency angles of the two compounds are tabulated (Newton, Cox, and Bertrand⁴⁰¹).

The conditions and the mechanism of the hydrolysis of esters such as (48) are of considerable theoretical and biochemical importance, as such phosphate esters are intermediates in the hydrolysis of ribonucleic acids. The subject has been studied in great detail by Westheimer and his co-workers.

The particular qualities of a five-membered ring containing a phosphorus atom, namely, that ring closure, ring opening, and displacement of exocyclic substituents all occur far more rapidly than in larger analogous ring systems, have become increasingly recognized. The considerable readiness with which five-membered rings containing an arsenic atom are formed was recognized much earlier (pp. 536–539).

The effect of ring size is not limited to the hydrolysis rate of esters. The rate of conversion of the methylphenylphospholanium cation (49) by hydroxyl ions into 1-methylphospholane 2-oxide and benzene is



ca. 1300 times more rapid than the analogous reaction of the methylphenylphosphorinanium cation (50) (Aksnes and Bergesen⁴⁰²).

More strikingly, five-membered cyclic esters of phosphoric acid such as (48), and of phosphonic acid such as (51), undergo acid and alkaline hydrolysis at rates 10^2 – 10^8 times as fast as their acyclic analogues, and some of these reactions, in both acid and base hydrolysis,



occur at these high rates without ring cleavage (Dennis and Westheimer,^{403, 404} and references given therein). The rate of alkaline hydrolysis of (51; R = C₂H₅) drops rapidly in turn in the six-membered and seven-membered homologous ethyl esters (Aksnes and Bergesen⁴⁰⁵).

Consideration of these and earlier results, and of the fact that the esters (52), (53), and (54) undergo acid and alkaline hydrolysis more slowly than their open-chain analogues, led Dennis and Westheimer^{403, 404} to postulate a trigonal bipyramid as an intermediate in the hydrolysis of esters of phosphorus acids. It is considered that an alkyl group is energetically less favorably situated in an apical position of the bipyramid than in an equatorial position (or alternatively that oxygen atoms are most favorably situated at the apical positions). This general situation is analogous to that of the stable alkylfluorophosphoranes, R_nPF_{5-n}, where alkyl groups occupy equatorial positions (Schmutzler⁴⁰⁶).

The formation of a trigonal bipyramidal intermediate would relieve the normal strain of a five-membered ring system, but this relief is apparently insufficient in the esters (52), (53), and (54) to overcome the barrier to the presence of an alkyl group in an apical position, while angle strain prevents the ring adopting a diequatorial position.

The hydrolysis of the methyl ester (51; R = CH₃) occurs at the very high rate but almost exclusively by ring cleavage, only traces of methanol being detectable, yet the acid-catalyzed hydrolysis of the methyl ester (48) occurs with 30% of the product arising from hydrolysis of the methyl group without ring opening. The rates of both hydrolyses—with and without ring opening—are about 1,000,000 times those of their acyclic analogues. These results can be interpreted on the basis of a 'pseudorotation' of the trigonal bipyramidal intermediates, similar to that suggested to explain the rapid interchange of fluorine atoms in R₂PF₃, where R is various alkyl groups.⁴⁰⁶

For a discussion of inhibited pseudorotation and kindred matters, see Gorenstein and Westheimer.⁴⁰⁷

A brief account cannot possibly do justice to Westheimer's very considerable work in this field—work which will assuredly be regarded as a classical elucidation of reaction mechanisms in a very difficult field. For a fuller account see Kirby and Warren.⁴⁰⁸

For the preparation of 2-[bis(2'-chloroethyl)amino]-1,3,2-dioxaphospholane 2-oxide, see p. 324.

1,4,6,9-Tetraoxa-5-phospha(v)spiro[4.4]nona-2,7-diene

This is a correct name for the spirocyclic system (1), [RIS —]; it can however more conveniently but less accurately be numbered as in