The Chemistry of the 1,3,2 Dioxaphospholanes and Related Compounds

Thesis by

Charles Norman Scully

In Partial Fulfillment of the Requirements
For the Degree of Master of Science

California Institute of Technology
Pasadena, June 1947

I wish to acknowledge with many thanks the help and guidance of Professor Howard J. Lucas during the course of research on this problem.

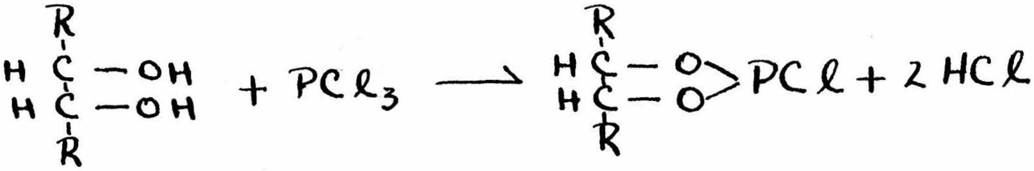
A Summary of Research On The Chemistry of 1,3,2-Dioxaphospholanes and Related Compounds.

Two new classes of compounds designated as the 1,3,2- dioxaphospholanes and 1,3,2-dioxaphosphanes have been synthesized by a general reaction of phosphorous trichloride with 1,2 and 1,3 glycols respectively under specified conditions and their reactions and reactions of numerous derivatives studied. The general reaction gave initially a highly reactive 2-chloro derivative which could be coupled with compounds containing a reactive hydrogen atom such as alcohols, thiols, primary and secondary amines, phenols, etc. The following new compounds have been synthesized: 2-chloro-1,3,2-dioxaphospholane, 2-methoxy-1,3,2-dioxaphospholane, 2-ethoxy-1,3,2-dioxaphospholane, 2-(n-propoxy)-1,3,2-dioxaphospholane, 2-(iso-propoxy)-1,3,2-dioxaphospholane, 2-piperidyl-1,3,2-dioxaphospholane, 4,5-dimethyl-2-chloro-1,3,2-dioxaphospholane, 2-hydroxy-1,3,2-dioxaphosplolane, 2-chloro-1,3,2-dioxaphosphane, 3,9-dichloro-2,4,8,10,3,9-tetraoxadiphosphospiro(5,5) hendecane, have been characterized by physical constants and by chemical reaction. A number of other compounds have been prepared but not definitively characterized. The method of nomenclature of these compounds is explained and is further justified by the demonstrated stability of the five and six membered heterocyclic rings. Molecular refractions are calculated and the anomolous derived values for the atomic refraction of phosphorous is discussed.

Charles Norman Scully

Introduction

The problem of the resolution of optically active glycols has been under consideration in this laboratory for some time. A suggested approach has been the reaction with a trifunctional compound in which two of the functional groups are reactive with hydroxyl and the third remaining group then to be treated with an optically active compound thus combining two asymetric centers within the same compound. The enantiamorphs could then be separated by physical means and the optically active glycol then regenerated by some simple procedure. A program involving the reaction between optically inactive glycols and phosphorous trichloride to produce a cyclic ester of phosphorous acid containing a single reactive chlorine still attached to the phosphorous atom had just been started by F. W. Mitchell. The general reaction is formulated as follows:

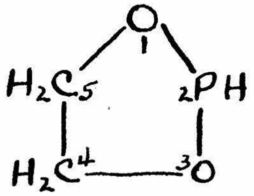


$$\begin{matrix} & R & \\ H & C & -OH \\ H & C & -OH \\ & R & \end{matrix} + PCl_3 \longrightarrow \begin{matrix} & R & \\ H & C & -O \\ H & C & -O \\ & R & \end{matrix} > PCl + 2\,HCl$$

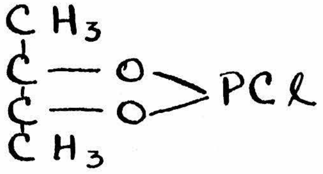
It was decided to learn the chemical properties of this cyclic ester by studying the preparation and reactions of the simplest member of this class. The glycol naturally was ethylene glycol. The phosphorous chloro-ester was prepared and its reactions with various classes of compounds studied. After learning the behavior of these derivatives, this knowledge could be extended to the optically active glycols and the resolution attempted. A literature search revealed only two previous attempts to prepare this type of compound. P. Carre (1) in 1903 reacted ethylene glycol and phosphorous trichloride in anhydrous ethyl ether but the product was not definitively characterized and Carre believed that his compound was linear and contained two phosphorous atoms. Patterson (2) in 1942 prepared the cyclic product of phosphorous trichloride and meso butylene glycol. In the present study the cyclic products were prepared from phosphorous trichloride and ethylene glycol, trimethylene glycol, meso butylene glycol and pentaerythritol. An unsuccessful attempt was made to prepare the cyclic product resulting from phosphorous trichloride and the di sodium salt of stilbene glycol.

Nomenclature

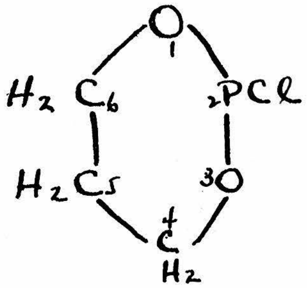
It became apparent early in this study that the system of naming the derivatives as mixed esters, amides, acid chlorides, etc. was unwieldy and not definitive. Since the five membered heterocyclic ring was the outstanding feature of this class, and since the high stability of the ring to hydrolysis and other reactions was in agreement with this consideration, the derivatives are named as compounds based on the parent 1,3,2-dioxaphospholane ring.



This naming and numbering is in accordance with the rules given in the Ring Index (3). Thus VII

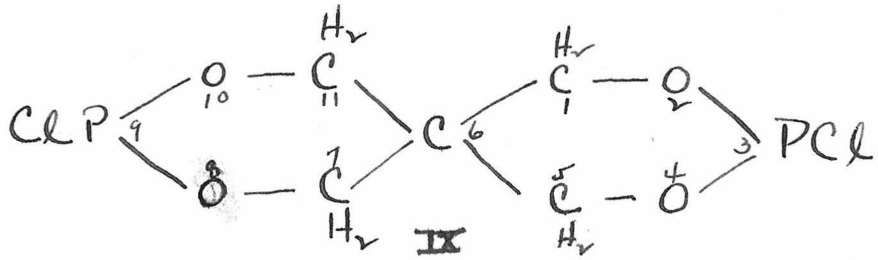


is named 4,5-dimethyl-2-chloro-1,3,2 dioxaphospholane. The proper name for the six membered ring arising from phosphorous trichloride and 1,3-propanediol is 2-chloro-1,3,2 dioxaphosphane, VIII,



The convenience of this system can be seen when an attempt to name IX or derivatives thereof based on the pentaerythritol-phosphorous ester system.

are made.

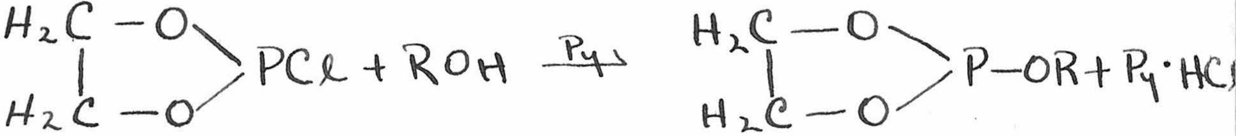


IX

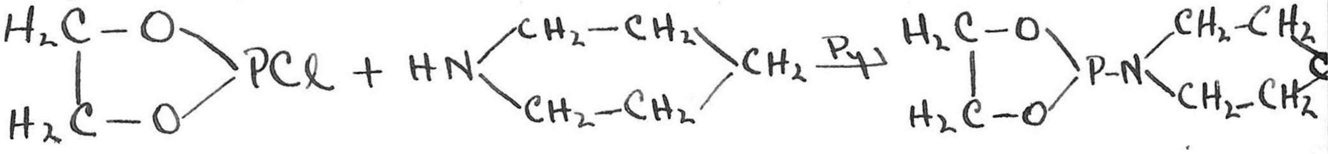
IX 3,9-dichloro-2,4,8,10,3,9-tetraoxadiphosphospiro(5,5) hendecane. For example, the naming of a 9-ethoxy-3-dimethylamino derivative of this spiro compound by any other system would be insurmountable. The chemical behavior of these ring systems completely justifies this nomenclature.

Outline

The basic compound 2-chloro-1,3,2 dioxaphospholane was allowed to react with various classes of compounds to study conditions for the preparation of solid derivatives. The reaction products with alcohols as given by the following scheme

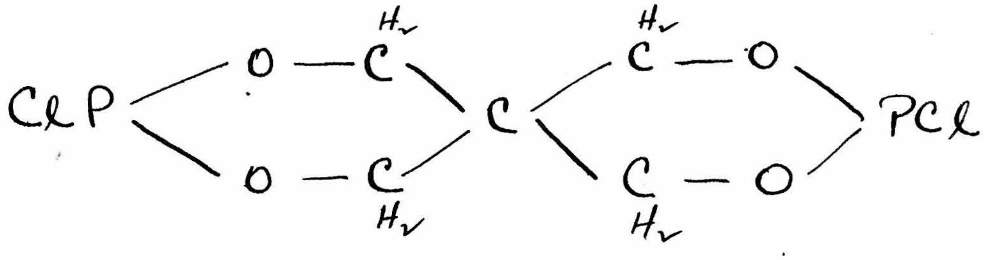


proved to be liquids in which the third alkoxy group was hydrolyzed with some rapidity in water and atmospheric moisture. Attention was next turned to the aliphatic amines. Tertiary amines such as pyridine formed rapidly hydrolyzable solid addition products. The difficulty of reaction with primary amines to produce only the monoamino compound and of separation of the amine hydrochlorides proved a too great difficulty. Secondary amines were quite amenable. The 2-piperidyl derivative formed in the reaction



also proved to be liquid. The ease of hydrolysis was much less than in the case of the 2-alkoxy series. Attention was turned to the secondary aromatic amines. A 2-diphenylamino derivative proved to be solid but was extremely hygroscopic, low melting (m.p. 50-55°C) and crystallizable from solution only by long standing at dry ice temperatures. The aromatic amines did not seem to justify further work. An identifiable product could not be isolated from the reaction of I with urea, thiourea, or phenol. An attempt to replace the 2-chloro by 2-thiocyano failed. A 2-thioethyl derivative was of such a repulsive odor and showed definite toxic properties that the preparation and purification was not completed. A 2-(p-thiocresyl) derivative was a solid but, like other compounds of the aryloxy series, proved too hydroscopic to be handled in the laboratory air. Toward the end of this project, when the 2-hydroxy compound was prepared for the first time, it was discovered by F. W. Mitchell working on analagous compounds that the hydroxy compound could form stable salts with alkaloids. From the standpoint of the glycol resolution, this class seems to have the most promise.

In extending this investigation of a hetrocyclic phosphorous compounds, two members containing six membered rings, were synthesized. They were very readily prepared and showed a slightly higher degree of stability than the five membered compound. They showed no trace of decomposition on six to eight months standing. The spiro compound (IX) was a well characterized solid not readily hydrolyzed by atmospheric moisture.



Experimental

A. Materials

Phosphorous Trichloride. E. K. Co. practical grade phosphorous trichloride was distilled through a 50 cm. glass helices packed column and a 2/3 fraction of the total boiling between 75.0-75.2°C collected.

Ethylene Glycol. Practical grade was allowed to stand over anhydrous calcium oxide for one week and fractionally distilled at 25 mm. Hg pressure. A fraction boiling over 1.0°C was collected.

Pyridine. Bakers Analyzed anhydrous grade. Boiling range 114-116°C.

Dioxane. Practical grade was allowed to stand for one week over potassium hydroxide pellets, fractionally distilled, and stored over potassium hydroxide. Boiling range 100-101°C.

Methanol. Anhydrous methanol was completely dried by reaction with calcium metal turnings and fractionally distilled. Boiling range 64.0-64.5°C.

Ethanol. Laboratory grade anhydrous ethanol was treated with sodium metal and di-ethyl phthalate according to the method of Smith (4) and distilled.

n-Propanol. Was dried for 2 days over anhydrous copper sulfate and fractionally distilled. Boiling range 96-97°C.

iso-Propanol. As above. Boiling range 81-82°C.

Piperidine. Rohm and Haas 98% piperidine was dried over sodium hydroxide and distilled. A fraction was collected between 105-106°C.

ParaThioCresol. E. K. Co. white label.

meso Butylene Glycol. Recrystallized from iso-propyl ether at 5°C. Melting point 34.6°C.

1,3-Propanediol. A fraction boiling between 105-107°C at 20 mm. Hg.

Pentaerythritol. Melting point 257-259°C.

B. Analysis

Carbon, hydrogen and nitrogen determinations were made by Dr. Gertrude Oppenheimer and her staff of this institute.

Phosphorous determination was carried out according to the method of Niederl and Niederl (5). In the case of the chloro-dioxaphospholanes 1 ml. samples were pipetted into 3 ml. of dioxane in a 100 ml. volumetric flask and decomposed slowly by the addition of water up to the mark. Aliquot portions of the solution were withdrawn for analysis.

Chlorine was determined gravimetrically as silver chloride.

Densities were determined by a suspended plummet of approximately 1.5 ml. suspended by a 0.1 mm. diameter platinum wire on an analytical balance. Rough determinations were first made and then with the weights set to the proper value, a fresh sample was used rapidly with protection against moisture for the final values.

C. Preparations

2-chloro-1,3,2 dioxaphospholane.(I). A 3-necked, 1 liter flask was equipped with stirrer, dropping funnel, and reflux condenser with a calcium chloride drying tube. In this flask was placed 500 ml. of methylene chloride and 220 ml. (2.5 moles) of phosphorous trichloride. To this was added with stirring 139 ml. (2.5 moles) of ethylene glycol at a rate to allow gentle refluxing in the condenser. Hydrogen chloride was copiously evolved. A water bath was then placed around the flask and heated to 40°C to drive off remainder of the hydrogen chloride. The flask was quickly adapted for distillation and most of the methylene chloride removed. The remaining solution was transferred to a smaller flask and fractionally distilled at 15 mm. Hg pressure. There was obtained 210 g. of a colorless mobile liquid boiling between 45.5-47.0°C (15 mm.) Yield 66.5% of theory. The chloro compound is soluble in all the usual unreactive organic solvents, fumes in air and is violently hydrolyzed by water, reacts readily with amines and alcohols, decomposes at temperatures above 130° to give a red-orange decomposition product which, upon qualitative tests, were shown to contain carbon, hydrogen, phosphorous, and to be free of chlorine. m.p. -28°C, b.p. 46.5°C (15 mm.). n_d^{25} 1.4878, d^{25} 1.4039.

Anal. Calcd. for $C_2H_4O_2PCl$: C, 19.0; H, 3.19; P, 24.5; Cl, 28.1.

Found: C, 20.1; H, 3.24; P, 24.6, 24.2, 24.8; Cl, 27.9.

An alternate method was previously developed employing dioxane as a solvent for this preparation. Extensive modifications were tried but the yields never rose above 27%. The product was accompanied by the formation of a large amount of a high boiling viscous substance which showed a mean molecular weight of about 520 by isothermal distillation against alpha-naphthylamine as a standard. The I appeared as a dioxane azeotrope boiling about 44.0°C (15 mm.) and of lower density, refractive index, and phosphorous content. The impurity could not be removed by distillation nor by successive freezings out. Samples of I in glass stoppered vessels or sealed in ampules show a characteristic slight decomposition upon long standing. After an induction period of about two months these samples show a faint yellow opalescence, sometimes deepening into a greenish fluorescence in the visible but not in ultra-violet light. Upon much longer standing an orange-yellow suspension accumulates and settles out. The actual mass of this suspension is always extremely small. Simple distillation at reduced pressure allows one to recover 95% of the original material in its former high state of purity. There remains a small quantity of non-volatile material.

2-methoxy-1,3,2-dioxaphospholane.(II). A 200 ml. cylindrical flask was equipped with stirrer, calcium chloride drying tube and separatory funnel in which was placed 65 ml. anhydrous pyridine, 50 ml. of 28-35°C boiling petroleum ether and 9.7 ml. (0.25 moles) of anhydrous methanol. The flask was placed in a cooling bath at -45°C. When cooled 22.6 ml. (0.25 moles) of I was added dropwise. A voluminous white precipitate of pyridine hydrochloride formed. The solution was allowed to warm up to room temperature. The pyridine hydrochloride was rapidly filtered off under vacuum on a sintered glass filter taking care to keep contact between the solution and the laboratory air at a minimum. The hydrochloride was washed with 50 ml. of precooled petroleum ether. The solution was transferred to a distilling flask. Petroleum ether was removed by distillation at atmospheric pressure. Pressure was then reduced to 100 mm. and excess pyridine distilled off. Pressure was reduced again to 35 mm. and II distilled over at 59°C. II was further fractionated at 35 mm. II is a colorless liquid with an unpleasant phosphinic odor. It is hydrolyzed by water into methanol and X. b.p. 60.0-62.0°C (35 mm.), n_d^{25} 1.4406, d^{25} 1.2250. Anal. Calcd. for $C_3H_7O_3P$: C, 29.6; H, 5.80; P, 25.4.

Found: C, 29.2; H, 5.86; P, 25.2, 25.3;

2-ethoxy-1,3,2-dioxaphospholane.(III). In the same apparatus employed for the preparation of II was placed 14.6 ml. of anhydrous ethanol (0.25 moles), 65 ml. of pyridine and 50 ml. low boiling petroleum ether. The addition of I and the removal of pyridine hydrochloride was repeated as before. After the petroleum ether and the pyridine had been removed by vacuum distillation, III was distilled off at 78°C and 28 mm. III was fractionally distilled again at 21 mm. b.p. 60.0-61.0°(21 mm.), 78°C (28 mm.). n_d^{25} 1.4390, d^{25} 1.2259. Anal. Calcd. for $C_4H_9O_2P$: C, 35.2; H, 6.66; P, 22.8.

Found: C, 35.06; H, 7.03; P, 22.6.

2-(n-propoxy)-1,3,2-dioxaphospholane.(IV). 18.7 ml. (0.25 moles) of n-propanol was treated as above. Pyridine was removed at 57°C (100 mm.) and 38°C (40 mm.). IV was distilled over at 84.0°C to 88.0°C (30 mm.).

b.p. 84-86°C (30 mm.), n_d^{25} 1.4432, d^{25} 1.1684.

Anal. Calcd. for $C_{[illegible]}H_{11}O_3P$: C, 40.0; H, 7.40; P, 20.7.

Found: C, 40.8; H, 7.38.

2-(iso-propoxy)-1,3,2-dioxaphospholane.(V). As above. b.p. 64.0-66.0°C (20 mm.), n_d^{25} 1.4347, d^{25} 1.1317.

Anal. Calcd. for $C_5H_{11}O_3P$: C, 40.0; H, 7.40; P, 20.7.

Found: C, 40.5; H, 7.70.

2-piperidyl-1,3,2-dioxaphospholane.(VI). In a closed system 35 ml. (0.333 moles) of anhydrous piperidine and 65 ml. of anhydrous ether were cooled to 5°C by an external ice bath. With continual shaking 15 ml. (0.166 moles) of I in 50 ml. of ether was added dropwise. The hydrogen chloride formed in the reaction reacted with the excess piperidine. Piperidine hydrochloride was filtered off under vacuum. The ether solution was placed in a distilling flask and the ether distilled off at atmospheric pressure. Distillation was continued under vacuum and obtained 15.5 gr. of VI between 108-110°C (10 mm.) yield 55%. VI is a colorless liquid having a distinctive odor, soluble in organic solvents, slowly soluble in water with decomposition. The hydrolysis product is neutral in aqueous solution, and regenerates piperidine instantly upon the addition of alkalis. b.p. 108-110°C (10 mm.), n_d^{25} 1.4971, d^{25} 1.1976.

Anal. Calcd. for $C_7H_{14}NO_2P$: C, 48.0; H, 8.09; N, 8.00.

Found: C, 48.23; H, 8.55; N, 8.00.

4,5-dimethyl-2-chloro-1,3,2-dioxaphospholane.(VII). In a 1 liter, 3-necked flask equipped with dropping funnel, stirrer, and reflux condenser with calcium chloride trap, was placed 600 ml. of methylene chloride and 113.4 gr. (.825 moles) phosphorous trichloride. 74.3 gr. of meso butylene glycol was added to 100 ml. of anhydrous ether and heated gently to the consolution point. This was placed in the dropping funnel and added to the flask at a rate to promote gentle refluxing. The solution was transferred to a distilling flask and the low boiling solvents removed at atmospheric pressure. The product was distilled over at 15 mm. The fraction boiling around 66°C amounted to 92 gr. Yield 72%. The product was redistilled through a fractionating column. VII appears to be more stable at higher temperatures than I, less readily hydrolyzed and shows less decomposition upon long standing.

b.p. 66.0-66.2°C (15 mm.), n_{d}^{25} 1.4696, d^{25} 1.2220.

Anal. Calcd. for $C_4H_8O_2PCl$: C, 31.2; H, 5.22; P, 20.1.

Found: C, 31.4; H, 5.34; P, 20.1, 20.3.

2-chloro-1,3,2-dioxaphosphane.(VIII). In the apparatus described in above was reacted 72.5 ml. (1.0 moles) of 1,3-propanediol and 87.5 ml. (1.0 moles) phosphorous trichloride in 500 ml. methylene chloride. Obtained at 67°C (15 mm.) 96 gr. of product. VIII is less violently reactive with water than either I or VII. b.p. 66.5-67.5°C (15 mm.), n_{d}^{25} 1.4884, d^{25} 1.3489.

Anal. Calcd. for $C_3H_6O_2PCl$: C, 25.7; H, 4.3.

Found: C, 25.5; H, 4.19.

3,9-dichloro-2,4,8,10,3,9-tetraoxadiphospho-spiro(5,5)hendecane.(IX). 68.1 gr. of pentaerythritol (0.5 moles) was added with stirring to 87.5 ml. (1.0 moles) phosphorous trichloride in 750 ml. methylene chloride. The reaction was initiated with difficulty after one hour of refluxing after which it proceeded smoothly. Refluxing was continued for one hour after the last trace of pentaerythritol had disappeared. Solvent was completely removed on a water bath and the residue taken up in the minimum quantity of chloroform and twice recrystallized. Obtained 53 gr. of white c~~h~~rystaline material, relatively stable in moist air. Yield 53.5 gr., 40% of theory. m.p. 121-123°C (corr.).

Anal. Calcd. for $C_5H_8O_4P_2Cl_2$: C, 22.65; H, 3.04;.

Found: C, 22.62; H, 3.37.

2-hydroxy-1,3,2-dioxaphospholane.(X). 87.5 ml. (1.0 moles) of I was dissolved in 250 ml. of anhydrous C. P. dioxane. 18 ml. distilled water dissolved in 50 ml. dioxane was added cautiously to the original solution. Heat was evolved and the solution separated into two phases. A 15% excess (3 ml.) of water was added and the solution shaken for 15 minutes. The upper phase was found upon a test distillation to consist principally of dioxane. The combined phases were distilled at 40 mm. to remove dioxane and excess water. The remaining slightly viscous liquid was distilled between 200-225°C at approximately 1 mm. When approximately one half had distilled over and the temperature risen to 225°C, the material in the distilling flask began to decompose and give off a vapor which passed through the vacuum system into the laboratory with a strong odor of phosphine. Distillation was stopped immediately, oil bath removed, and air readmitted to the system. When the pressure had risen to about 20 mm., the mixed vapors and air in the ballast flask detonated violently, shattering the 3 liter ballast flask so that no piece remained larger than one square centimeter. The odor of phosphine was strong in the liquid of the receiver and in the pump oil. Using a short path distillation setup and at the ultimate vacuum of the pump, the compound already distilled was redistilled at 125°C bath temperature. Successive distillations increased the viscosity of the product. X is a very viscous water soluble liquid, insoluble or only slightly soluble in organic solvents. n_d^{25} 1.4862, d^{25} 1.52, molecular weight 420 (cryoscopic in succinonitrile), 576 (cryoscopic in water). X behaves as a monobasic acid which may be neutralized with alkalis, forms soluble alkali metal salts, slowly reduces silver and mercuric ion. The observed apparent molecular weights and the high viscosity suggest strong association. The behavior of X resembles that of the dialkyl phosphites (6) and further hydrolisis proceeds only with some difficulty, i.e., at elevated temperatures or with warming with strong bases.

The ring possesses a high degree of stability and justifies classification as a heterocyclic compound.

Incompleted Preparations

Many attempts were made to isolate and purify a 2-diphenylamino derivative by reaction of diphenylamine in various solvents with either pyridine or N-ethyl morpholine as the base. The product was extremely hygroscopic and hydrolyzable. A few crystals isolated dissolved in their own absorbed moisture upon standing for one to five minutes in the air. This product was also easily oxidized by atmospheric oxygen. Melting point lies between 50-55°C. The purest samples crystallized slowly from ethyl ether at -80°C after standing at least five days. The susceptibility to oxidation was unexpected. This derivative and solutions, thereof produced blue stains on cellulose materials within 24 hours.

I and p-thiocresol in pyridine reacted at room temperature in 24 hours to produce a compound which has not yet been completely characterized. It was destroyed in heating the mixture with pyridine and pyridine hydrochloride to 60°C. It was obtained by crystallizing from the filtered solution after standing eight months at 5°C. m.p. 120-125°C. Not further characterized.

Molar Refractions

In order to determine the molar refractions of the PO_3, PO_2Cl, and possible ring exaltation, the molar refractions of the individual liquid compounds were computed. The following values for molar refractions were used in these calculations: CH_2 4.618, C 2.418, H 1.100, O 1.643, Cl 5.967, N (secondary amine) 2.502 for the sodium D line (7).

TABLE I.

Compound.			M.R.	PO_3	PO_2Cl	P
1,3,2-dioxaphospholane,	2-chloro	I	25.95		16.7	5.5
"	2-chloro-4,5-dimethyl	VII	35.2		15.8	4.6
"	2-methoxy	II	25.8	7.6		2.7
"	2-ethoxy	III	29.3	6.5		1.6
"	2-(n-propoxy)	IV	34.2	6.8		1.9
"	2-(iso-propoxy)	V	34.4	7.0		2.1
"	2-piperidyl	VI	42.9			5.0
1,3,2-dioxaphosphane,	2-chloro	VIII	28.0		14.2	7.9

The spread of these values is such that a difference in ring exaltation between the five membered rings and the sole six membered ring value is without significance. There is, however, a very striking effect to be noticed about the molar refractions of the PO_3 group in the dioxaphospholanes. The mean value for this group is 7.0. This differs most markedly from the M. R. values calculated for PO_3 by Jones, Davis and Dyke in 1933, who calculated a value of 12.0 from the M. R. values of some tri-alkyl phosphites (8). M. R. values for a series of 2-alkoxy-4-methyl-dioxaphospholanes by F. W. Mitchell give a value of 7.2 for the PO_3 group. No reasonable explanation of this effect is apparent. The calculations of Jones, Davis and Dyke show a marked dependence of the atomic refraction of phosphorous upon the type of compound in which it occurs. The mean value found for the atomic refraction of phosphorous in trialkyl phosphites was 7.09. The lowest value for all classes of phosphorous compounds was a mean of 4.19 in the trialkyl phosphates. The values found here for the atomic refraction in the 2-alkoxy-1,3,2-dioxaphospholanes average 2.2.

Summary

Two new classes of compounds, the 1,3,2-dioxaphospholanes and the 1,3,2-dioxaphosphanes have been synthesized. Chemical reactions and properties of a number of derivatives are described. A definitive nomenclature is proposed. The relation between the molar refractions and the structure is discussed. A new spiro compound is described.

References

(1) P. Carre, Compte Rendu, 136, 756, (1903)

(2) Patterson, Masters Thesis, (1942)

(3) Patterson and Capell, The Ring Index, A.C.S. Monograph No. 84, (1940)

(4) E. L. Smith, J. Chem. Soc., 1228, (1927)

(5) Niederl and Niederl, Micromethods of Qualitative Organic Microanalysis, (1942), Wiley & Sons

(6) Arbuzov, J. Russ. Phys. Chem. Soc., 46, 291-4, CA 8, 2551, (1914)
Milobendzkii, Ber., 45, 298

(7) Landolt-Bornstein, Physikalisch-Chemische Tabellen, Vol. II

(8) Jones, Davis and Dyke, J. Phys. Chem., 37, 583, (1933)