

CHAPTER 6

THE SYNTHESIS OF PHOSPHONIC AND PHOSPHINIC ACIDS

GENNADY M. KOSOLAPOFF

Alabama Polytechnic Institute

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INTRODUCTION

The phosphonic acids, RP(O)(OH)_2 , and the phosphinic acids, $\text{RR}'\text{P(O)OH}$, may be regarded as derivatives of phosphoric acid in which one or two hydroxyls are replaced by organic radicals.* Derivatives of the type RP(O)HOH , which are termed phosphonous acids by the current *Chemical Abstracts* system, contain phosphorus in a lower state of oxidation than is present in the phosphonic and the phosphinic acids and have chemical properties decidedly different from those of the latter classes. Phosphonous acids are not considered in this chapter, except as they are involved in the synthesis of phosphonic and phosphinic acids.

Although individual phosphonic and phosphinic acids have been known for several decades, the syntheses of these two classes of compounds have not been so well developed as have the methods for the corresponding arsenic compounds. Much of the work has been devoted to the parent substances of the various possible series, and there is but little information concerning the syntheses of compounds with a high degree of substitution.

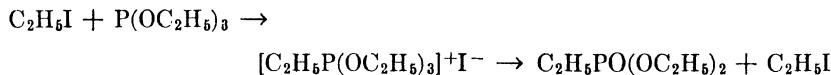
This chapter is concerned only with the introduction of the phosphorus-containing functions, that is to say, with the synthesis of acids or their functional derivatives which can be isolated and hydrolyzed to

* *Note on nomenclature.* Phosphonic acids are named with reference to the *hydrocarbons* from which they are derived, whereas phosphinic acids are named with reference to the *alkyl and/or aryl groups* which they contain. Thus $\text{C}_6\text{H}_5\text{PO(OH)}_2$ is benzene-phosphonic acid, but $(\text{C}_6\text{H}_5)_2\text{P(O)OH}$ is diphenylphosphinic acid. Esters of both series have names ending in *-ate*, e.g., diethyl (or ethyl) benzenephosphonate, ethyl diphenylphosphinate. If it is desirable to indicate the phosphonic group by means of a prefix, *phosphono-* is used. Thus, $(\text{HO})_2\text{P(O)CH}_2\text{CO}_2\text{H}$ may be called phosphonoacetic acid and $(\text{C}_2\text{H}_5\text{O})_2\text{P(O)CH}_2\text{CO}_2\text{C}_2\text{H}_5$ triethyl phosphonoacetate. Esters of phosphonous acids are given names ending in *-ite*. Thus, $\text{C}_6\text{H}_5\text{P(OC}_2\text{H}_5)_2$ is diethyl benzenephosphonite.

the acids. It does not cover the further possible modifications of the organic portions of the molecule, because most such modifications are quite similar to those of comparable carbon compounds with strongly electronegative substituents.

ALKYLATION OF THE PHOSPHORUS ATOM IN PHOSPHOROUS ESTERS

One of the most versatile methods for the synthesis of esters of phosphonic acids is based on the reaction of a trialkyl phosphite with an alkyl halide.¹ If the alkyl groups of the two reagents are identical, the process amounts to an isomerization of the phosphite, as illustrated in the accompanying equation. The general procedure often is referred



to as the "isomerization method," whether or not the several alkyl groups are identical; it is also called the Arbuzov transformation.

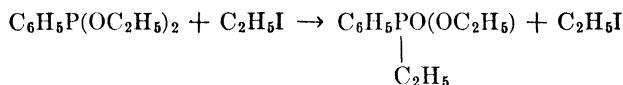
When the alkyl groups of the phosphite and of the halide are identical, as in the above example, only one phosphonate can be formed. When the alkyl halide employed is not identical with that eliminated in the second stage of the reaction, a mixture obviously may be formed. Even so, the reaction may be controlled to give a high yield of the desired phosphonate. For example, 1-chloromethylnaphthalene reacts with triethyl phosphite (in small excess) at 150–160° to give diethyl 1-naphthylmethanephosphonate in 87% yield (p. 286).



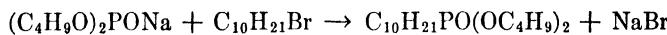
Presumably, the success of the reaction is related both to the greater reactivity of the arylmethyl chloride, as compared to ethyl chloride, and to the volatility of the ethyl chloride, most of which escapes from the hot mixture through the condenser. When the alkyl halide employed and that formed are of approximately the same reactivity, the control of the reaction may be aided by the use of a large excess of the reagent. Thus, when a mixture of 5 moles of trimethylene bromide and 1 mole of triethyl phosphite is refluxed under a fractionating column (for removal of ethyl bromide), the ester of 3-bromopropanephosphonic acid is obtained in 90% yield (p. 287).

¹ Michaelis and Kaehne, *Ber.*, **31**, 1048 (1898).

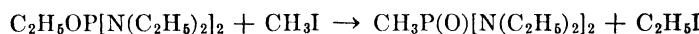
Derivatives of phosphinic acids are obtained when a phosphonite is substituted for the phosphite. The preparation of ethyl ethylphenylphosphinate is an example.² Only a few phosphinates have been prepared in this way (see Table I) owing to the relatively difficult preparation of the necessary phosphonites.



Since only one alkoxy group of a phosphite participates in the reaction leading to the phosphonates, it might be anticipated that partial esters of phosphorous acid and esters of amidophosphorous acids would react in the same way. Such variations of the process were developed by Michaelis,^{3,4} and the use of the salts of dialkyl acid phosphites has proved particularly satisfactory. This method is illustrated by the preparation of dibutyl 1-decanephosphonate from sodium dibutyl phosphite and decyl bromide.⁵



An example of the use of amidophosphites is provided by the synthesis of the bisdiethylamide of methanephosphonic acid.⁴



Several other syntheses of phosphonic acids and their derivatives probably can be included in the general category of alkylation of phosphite derivatives. They represent rather isolated examples and warrant further study and confirmation. These syntheses include the isomerization of triaryl phosphites by alcohols at high temperatures,⁶ the formation of phosphonic acid derivatives from methylol derivatives of acyl amides and phosphorus trichloride,⁷ and the formation of triaryl-methanephosphonic acid derivatives from triarylcarkinols and phosphorus trichloride.^{8,9} If these reactions can be formulated, as shown

² Arbuzov, *J. Russ. Phys. Chem. Soc.*, **42**, 395 (1910) [*C. A.*, **5**, 1397 (1911)].

³ Michaelis and Becker, *Ber.*, **30**, 1003 (1897).

⁴ Michaelis, *Ann.*, **326**, 129 (1903).

⁵ Kosolapoff, *J. Am. Chem. Soc.*, **67**, 1180 (1945).

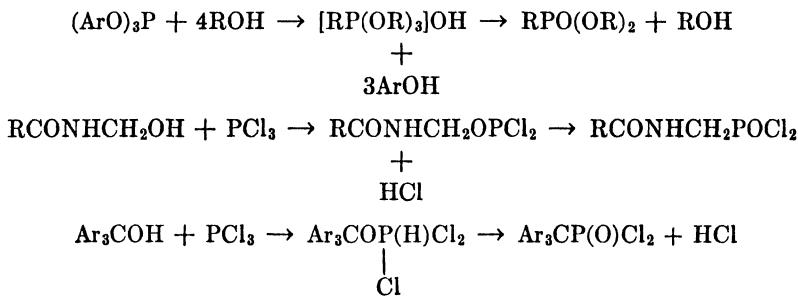
⁶ Milobendzki and Szulgin, *Chem. Polsk.*, **15**, 66 (1917) [*C. A.*, **13**, 2867 (1919)].

⁷ Plik, U. S. pat. 2,304,156 [*C. A.*, **37**, 3262 (1943)].

⁸ Arbuzov and Arbuzov, *J. Russ. Phys. Chem. Soc.*, **61**, 217 (1929) [*C. A.*, **23**, 3921 (1929)].

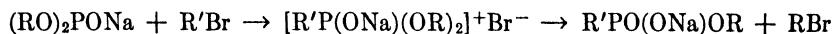
⁹ Boyd and Smith, *J. Chem. Soc.*, **1926**, 2323; **125**, 1477 (1924); Boyd and Chignell, *ibid.*, **123**, 813 (1923).

below, as proceeding through a phosphonium-type addition complex, the analogy to the previously discussed "normal" isomerization of phosphite esters is obvious.

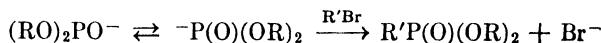


Mechanism

The mechanisms that have been proposed for the reactions are illustrated in the first equation given on p. 276 above. The principal feature is the formation of an intermediate salt, shown in brackets above, which undergoes the loss of a molecule of a simple halide. Michaelis and Kaehne¹ isolated the methiodides of triphenyl phosphite and tri-*m*-cresyl phosphite, and they reported the formation of a solid product, which could not be crystallized, from triphenyl phosphite and benzyl chloride. There is no direct evidence for the formation of an intermediate salt from an aliphatic phosphite and an alkyl halide; however, the induction period observed in such a reaction has been considered a measure of the stability of the intermediate salt. Likewise, there is no direct evidence for an intermediate in the reaction of the sodium salt of a dialkyl acid phosphite and an alkyl halide. The existence of such an intermediate has been inferred from induction periods during which no sodium halide forms. The fact that prolonged heating of such a reaction mixture may result in the formation of the sodium salt of an acid phosphonate and a molecule of alkyl halide¹⁰ has been cited as an argument for the re-formation of the intermediate salt.

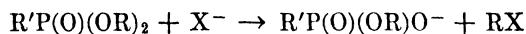


Neither of the arguments concerning the reactions of the salts seems very persuasive. It is possible that the alkylation of the acid phosphite is merely a displacement, most readily portrayed as involving the anion of the tautomeric form of the acid phosphite, as follows.



¹⁰ P. Nylen, dissertation, Uppsala, 1930.

Analogously, the reaction of the phosphonate with sodium halide may be a simple alkylation of the halide ion, operating through a displacement rather than through an addition.

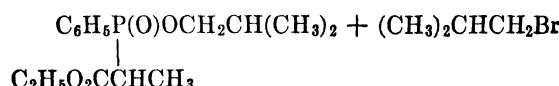
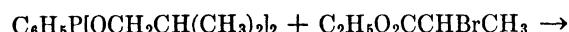
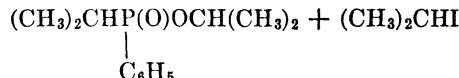
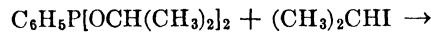


Scope and Limitations

SYNTHESIS OF PHOSPHONIC ACIDS AND ESTERS

Only one aryl halide has been used successfully in the preparation of a phosphonic acid derivative by these methods; 9-phosphonoacridine was obtained in 60% yield by hydrolysis of the ester from 9-chloroacridine and triethyl phosphite. Simple aryl halides evidently are too unreactive, but from the example just cited it would appear that activated aryl halides, and especially those containing heterocyclic nuclei, might be employed.

The aliphatic halides used have been almost invariably primary halides. Only two secondary halides reacted satisfactorily; isopropyl isopropylphenylphosphinate has been obtained from isopropyl iodide and diisopropyl benzenephosphonite,¹¹ and α -phenylphosphonopropionic acid has been obtained from ethyl α -bromopropionate and diisobutyl benzenephosphonite.¹² Other secondary halides and simple



tertiary halides either fail to react or give olefins. However, triaryl-methyl halides react normally with triethyl phosphite to give esters of triarylmethanephosphonic acids.⁸ These compounds cannot be prepared by the use of the sodium salt of the dialkyl acid phosphite; with this reagent an abnormal reaction occurs and the hexaarylethane (or triarylmethyl) is produced.

¹¹ Arbuzov, Kamai, and Belorossova, *J. Gen. Chem. U.S.S.R.*, **15**, 766 (1945) [*C. A.*, **41**, 105 (1947)].

¹² Arbuzov and Arbuzov, *J. Russ. Phys. Chem. Soc.*, **61**, 1599 (1929) [*C. A.*, **24**, 5289 (1930)].

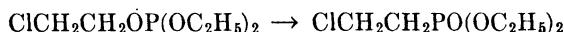
The order of reactivity of the simple primary alkyl halides is the usual one, iodides being most and chlorides least reactive. Bromides have been used most often.

A considerable number of alkyl halides has been used in both the ester and the sodium salt procedures.^{1,3,5,10,13,14} Various functional substituents can be present in the alkyl halide. Neutral phosphite esters have been alkylated with the chloromethyl derivatives of various aromatic hydrocarbons and with 2-chloromethylthiophene, with triarylmethyl chlorides, with chloromethyl ethers and with one β -bromo ether, with ethyl chloroacetate and with esters of various ω -halo acids, with N,N-diphenylchloroacetamide, with 3-cyanopropyl chloride, with a bromomethyl ketone, with N-(bromoalkyl)phthalimides, and, as mentioned above, with 9-chloroacridine. α -Bromo nitro compounds, however, do not give the expected nitroalkane phosphonates; oxidation-reduction reactions intervene, the triethyl phosphite being oxidized to the phosphate, apparently with reduction of the nitro group. The exact nature of the reactions that occur is not understood.¹⁵

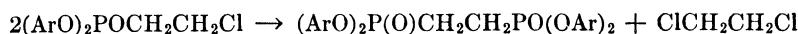
Esters of 2-chloroethanol may be converted to phosphonates by heat alone; thus, tri- β -chloroethyl phosphite yields an ester of 2-chloroethane-phosphonic acid.



Tri- β -bromoethyl phosphite isomerizes similarly. Evidently only one haloalkyl group is necessary, for the mixed ester, diethyl 2-chloroethyl phosphite, was converted to diethyl 2-chloroethanephosphonate.



However, when the phosphite contains two aryloxy residues the reaction takes a different course and produces esters of ethane-1,2-diphosphonic acids.¹⁶ Though the nature of the process is not clear, the overall result may be shown in the formulation given by Kabachnik.



From experiments with ethylene bromide and trimethylene bromide it appears that the reaction of primary dihalides can be controlled to give either haloalkanephosphonates or alkanediphosphonates. The course of the reaction is determined by the ratio of phosphite to dihalide,

¹³ Arbuzov, *J. Russ. Phys. Chem. Soc.*, **38**, 687 (1906).

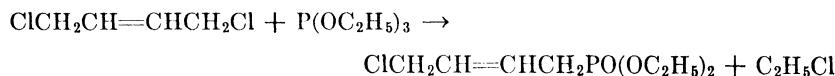
¹⁴ Ford-Moore and Williams, *J. Chem. Soc.*, **1947**, 1465.

¹⁵ Arbuzov, Arbuzov, and Lugovkin, *Bull. acad. sci. U.R.S.S., classe sci. chim.*, **1947**, 535 [*C. A.*, **42**, 1886 (1948)].

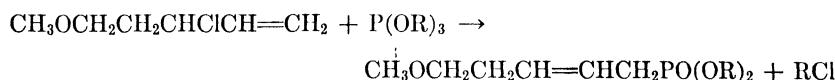
¹⁶ Kabachnik and Rossiiskaya, *Bull. acad. sci. U.R.S.S., classe sci. chim.*, **1947**, 631 [*C. A.*, **42**, 5845 (1948)].

the dihalide being used in considerable excess when the haloalkane-phosphonate is desired. Methylene iodide reacts with triethyl phosphite, and both the iodomethanephosphonate^{14,17} and the methanediphosphonate¹⁴ have been isolated. Carbon tetrachloride reacts readily with trialkyl phosphites, yielding the esters of trichloromethanephosphonic acid; chloroform does not react at the reflux temperature.^{18,19}

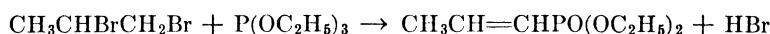
1,4-Dichloro-2-butene is the simplest allylic halide that has been treated with a phosphite. The product obtained with an excess of the halide was dehydrohalogenated and hydrolyzed by treatment with potassium hydroxide. As 1,3-butadiene-1-phosphonic acid was obtained, evidently the alkylation did not occur with allylic rearrangement.



Examples of allylic rearrangement have been reported, however; 1-methoxy-3-chloro-4-pentene reacts with phosphites to give esters of the straight-chain phosphonic acid in good yield;²⁰ details of this work have not been published.



An unsaturated phosphonic acid derivative is formed when propylene bromide is heated with triethyl phosphite, evidently as a result of dehydrohalogenation of the primary reaction product.¹⁴ The yield is poor.



Acid chlorides react readily with triethyl phosphite to yield α -keto-phosphonic esters.²¹ These compounds cannot be hydrolyzed to the free acids, the phosphono group being eliminated from the molecule under all hydrolytic conditions that have been tested.

If the reaction of triarylcarkinols with phosphorus trichloride is to be considered a variant of the phosphite isomerization reaction, as mentioned earlier, the following successful examples of its application may be mentioned here: triphenylcarbinol, *p*-chlorophenoxydiphenylcarbinol,

¹⁷ Arbuzov and Kushkova, *J. Gen. Chem. (U.S.S.R.)*, **6**, 283 (1936) [*C. A.*, **30**, 4813 (1936)].

¹⁸ Kosolapoff, *J. Am. Chem. Soc.*, **69**, 1002 (1947).

¹⁹ Kamai and Egorova, *J. Gen. Chem. U.S.S.R.*, **16**, 1521 (1946) [*C. A.*, **41**, 5439 (1947)].

²⁰ A. N. Pudovik, Report at the October, 1947, meeting of the Chemical Section of the Academy of Sciences, U.S.S.R., in Kazan.

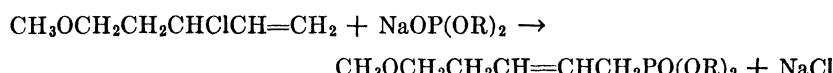
²¹ Kabachnik and Rossiiskaya, *Bull. acad. sci. U.R.S.S., classe sci. chim.*, **1945**, 364 [*C. A.*, **40**, 4688 (1946)].

p-bromophenyldiphenylcarbinol, *p*-anisyldiphenylcarbinol, *m*-anisyldiphenylcarbinol, 1-naphthyldiphenylcarbinol, 2-naphthyldiphenylcarbinol, *p*-nitrophenyldiphenylcarbinol, and *p*-tolyldiphenylcarbinol,^{8,9} all of which give the corresponding triarylmethanephosphonic acids after hydrolysis.

The reaction of methylol acylamides with phosphorus trichloride has been described only in the patent literature;⁷ several compounds so reported were not well enough characterized for inclusion in this chapter. Sufficient information is given about the preparation and the properties of stearamidomethanephosphonic acid (see p. 290).

The reaction of alkyl halides with salts of dialkyl acid phosphites has been employed somewhat less frequently than the reaction with neutral phosphites. A number of simple primary alkyl halides have been converted to phosphonates. Primary halides having other functional groups which have been employed successfully include arylmethyl chlorides, α -halo ethers, α -halo ketones, ethyl chloroacetate and ethyl β -bromopropionate, N-(bromoalkyl)phthalimides,²² and the hydrobromide of 2-aminoethyl bromide.²² Methylene iodide reacted with sodium diethyl phosphite, but only methanediphosphonic acid was isolated.¹⁰ Evidently the intermediate ester reacted with the sodium iodide, as discussed above (p. 278). Ethylene bromide is dehydrohalogenated by sodium dialkyl phosphites. The tetraethyl ester of propane-1,3-diphosphonic acid has been obtained from trimethylene dibromide and sodium diethyl phosphite, but in unrecorded yield. Only dehydrohalogenation occurs when the same sodium salt is treated with 1,2-dibromopropane, 2,3-dibromobutane, or 1,2-dibromo-2-methylpropane.¹⁰

When 1-methoxy-3-chloro-4-pentene is treated with a sodium dialkyl phosphite in slight excess, reaction occurs with allylic rearrangement.



If the phosphite derivative is not in excess, a complex mixture is produced.²⁰

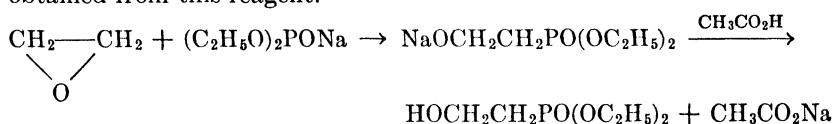
When the ethyl ester of a haloacetic acid is treated with sodium diethyl phosphite the expected phosphonate is produced in yields of 45–50% along with ethyl succinate in about 5% yield.^{10,23} Esters of higher α -bromo acids yield the coupling products in unspecified yields, but none of the phosphonates. The coupling has been explained on the basis of an exchange of bromine and sodium atoms between the reactants.²³

²² Chavane, *Compt. rend.*, **224**, 406 (1947).

²³ Chavane and Rumpf, *Compt. rend.*, **225**, 1322 (1947).

As mentioned above, triarylmethyl halides do not give phosphonates when they react with sodium dialkyl phosphites. Acid chlorides, which react normally with trialkyl phosphites (p. 281), give complex mixtures with sodium dialkyl phosphites.

Ethylene oxide²⁴ evidently is the only halogen-free alkylating agent that has been used successfully on a salt of a dialkyl phosphite. Moderately good yields (40%) of diethyl β -hydroxyethanephosphonate can be obtained from this reagent.



SYNTHESIS OF PHOSPHINIC ACIDS AND ESTERS

A number of mixed aliphatic-aromatic phosphinic acids and their esters have been prepared in excellent yields from dialkyl arylphosphonites and alkyl halides. The products that have been reported are methyl phenylmethylphosphinate from methyl iodide and dimethyl benzenephosphonite,^{25,26} ethyl phenylethylphosphinate from ethyl iodide and diethyl benzenephosphonite,² isobutyl isobutylphenylphosphinate from diisobutyl benzenephosphonite and isobutyl iodide,²⁷ and isobutyl phenyltritylphosphinate from triphenylbromomethane and diisobutyl benzenephosphonite.²⁷ Similarly successful were the preparations of the corresponding phosphinates from dialkyl benzenephosphonites with propyl iodide,²⁶ chloromethyl ethyl ether,²⁶ chloromethyl methyl ether,²⁶ isopropyl iodide,¹¹ ethyl chloroacetate,¹² and ethyl α -bromopropionate.¹²

Although di-*n*-alkyl aryl phosphonites react readily with alkyl halides, the *iso* esters exhibit a tendency to yield the free acids, rather than the expected alkyl phosphinates.^{2,11,25} This reaction occurs especially when the reactants are heated and the resulting phosphinate esters break down to the free acid and the corresponding olefin. This difficulty is avoided if the reactants are mixed at room temperature. The addition of a trace of dimethylaniline serves to catalyze the normal reaction to a remarkable degree.¹¹

No instance of the preparation of a phosphinate by the alkylation of the sodium salt of a phosphonite has been reported.

²⁴ Chelintsev and Kuskov, *J. Gen. Chem. U.S.S.R.*, **16**, 1481 (1946) [C. A., **41**, 5441 (1947)].

²⁵ Arbuzov, *J. Gen. Chem. U.S.S.R.*, **4**, 898 (1934) [C. A., **29**, 2146 (1935)].

²⁶ Arbuzov and Razumov, *Bull. acad. sci. U.R.S.S., classe sci. chim.*, **1945**, 167 [C. A., **40**, 3411 (1946)].

²⁷ Arbuzov and Arbuzova, *J. Russ. Phys. Chem. Soc.*, **61**, 1905 (1929) [C. A., **24**, 5289 (1930)].

Selection of Experimental Conditions and Procedures

Although it is impossible to give the specific conditions in which the use of either the neutral ester or the salt of a dialkyl acid phosphite is to be preferred, it may be said that the ester variant yields the normally expected products when the reaction can be made to take place at all. The salt variant tends to give abnormal results in the instances discussed above; in addition, if the sodium halide formed in the reaction is not removed before the distillation of the product, the phosphonate may react with the sodium halide (p. 278) to give a mixed ester-salt, with elimination of a molecule of alkyl halide.²⁸

The removal of sodium halide can be effected in a number of ways. Filtration is practicable at times, although one frequently encounters a non-filterable dispersion of the salt which either runs through the filter or clogs its pores. In such cases the use of a centrifuge is indicated. If the precipitate does not separate cleanly in the process, the addition of a small amount of water to the mixture generally aids the coagulation. If the phosphonate ester is not appreciably soluble in water and is not rapidly hydrolyzed by it, it is possible to wash the sodium halide out of the mixture with cold water. It may be pointed out that the use of alkyl phosphites with three or four carbon atoms in each alkyl group suffices to bring about this condition of water insolubility. The esters made from the higher phosphites are essentially insoluble in water and have but little tendency to hydrolyze at room temperature.

The choice of the size of alkyl groups in the phosphite derivative is conditioned chiefly by the choice of either the neutral ester or the sodium dialkyl phosphite as the reagent. In the trialkyl phosphite variant, increasing size of the alkyl groups decreases the reactivity of the phosphite and requires progressively higher operating temperatures.¹³ In the salt variant, the reagents do not show any particularly noticeable difference in reactivity when higher alkyl phosphites are substituted for diethyl phosphite. The use of dibutyl phosphite may be recommended because its sodium salt is readily soluble in hydrocarbon solvents such as petroleum ether and benzene, whereas sodium diethyl phosphite has only a limited solubility in such solvents, particularly at lower temperatures.⁵ The resulting tendency to crystallize on cooling may be troublesome in reactions in which cooling is necessary, because of the vigor of the interaction of the phosphite reagent with the halide, as in the reaction with ethyl chloroacetate.

The ester variant of the reaction is generally carried out by heating

²⁸ Abramov, Sergeeva, and Chelpanova, *J. Gen. Chem. U.S.S.R.*, **14**, 1030 (1944) [*C. A.*, **41**, 700 (1947)].

the reactants to the necessary temperature until the reaction is complete. When low-boiling materials are used, sealed tubes or autoclaves are advisable, although there is insufficient evidence at hand that sealed vessels are necessary for many of the preparations so described in the older literature. The mixtures resulting from the reactions are usually subjected to fractional distillation to isolate the products, which, in turn, are readily converted to the free acids by hydrolysis with acids or bases. It is generally advantageous to distil the generated alkyl halide as it is formed in hydrolysis with hydrochloric or hydrobromic acids. It is decidedly advantageous to distil the alkyl halide generated during the isomerization reaction itself; this serves to suppress the side reaction that may result from its interaction with the as yet unreacted phosphite ester (see p. 276). For this reason, the use of apparatus suitable for slow distillation is recommended for many of the preparations.^{14,29}

The sodium salt reaction is carried out generally by heating a solution of the halogen derivative with an equimolar amount of the sodium dialkyl phosphite in an inert solvent until the precipitation of sodium halide is complete. The latter is then removed by filtering, centrifuging, or washing with water, and the product is isolated by fractional distillation. The ester can be converted to the free acid by acidic or alkaline hydrolysis.

Non-distillable esters, principally those of high molecular weight, may be hydrolyzed directly without purification since the resulting phosphonic or phosphinic acids are readily separable from the crude hydrolyzates by virtue of their alkali solubility. This procedure is frequently satisfactory because the isomerization reaction gives very good yields, often approaching the theoretical.

Most of the work on this reaction has been done with alkyl phosphites, which lead to esters of phosphonic acids. The examples of the use of alkyl phosphonites have been relatively few, principally because of the lack of simple syntheses for these esters.

The hydrolysis of the phosphonic esters to the free acids is readily performed by boiling hydrochloric or hydrobromic acids. Although the older publications favor the use of sealed tubes for such hydrolyses, in which dilute hydrochloric acid was generally used at 130–150°, the present author has found that the hydrolyses can be readily done in excellent yields by refluxing with the concentrated acids at atmospheric pressure. If the ester is resistant to hydrochloric acid, the use of 48% hydrobromic acid serves to accomplish the desired result in a few hours. The notable exceptions to the normal hydrolyses are phosphonates in which the phosphono group is adjacent to a carbonyl or a carboxyl

²⁹ Kosołapoff, *J. Am. Chem. Soc.*, **66**, 109 (1944).

group; hydrolyses of esters with such structures lead to complete dephosphonation under any conditions. Similarly, acidic hydrolysis of diethyl benzyloxymethanephosphonate leads not only to de-esterification but also to the cleavage of the ether bridge to yield hydroxymethane-phosphonic acid.²⁸ Although the use of an alkaline hydrolytic agent is not reported in this instance, the use of 10% sodium hydroxide solution at 150–160° in a sealed tube led to a smooth de-esterification of an analogous diethyl 2-phenoxyethanephosphonate.³⁰

Experimental Procedures

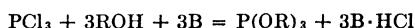
THE TRIALKYL PHOSPHITE PROCEDURE *

Diethyl Ethanephosphonate.¹⁴ A mixture of 50 g. of triethyl phosphite and 46.8 g. of ethyl iodide is refluxed for four hours. Distillation of the mixture gives 48 g. (95%) of diethyl ethanephosphonate, b.p. 62°/2 mm.

1-Naphthylmethanephosphonic Acid.³¹ A mixture of 43 g. of 1-chloromethylnaphthalene and 41 g. of triethyl phosphite is heated for four hours at 150–160°. Distillation of the mixture gives 58 g. (87%) of diethyl 1-naphthylmethanephosphonate, b.p. 205–206°/5 mm. The ester is refluxed for eight hours with 200 ml. of concentrated hydrochloric acid, and the precipitated 1-naphthylmethanephosphonic acid is filtered from the cooled mixture. After recrystallization from hot water, the pure acid, m.p. 212–212.5°, is obtained in the form of small lustrous plates (90% yield).

Diethyl α -Oxo- α -toluenephosphonate.²¹ To 13.7 g. of benzoyl chloride contained in a flask equipped with a dropping funnel and a reflux con-

* There is but one practical method of preparation of trialkyl phosphites: the addition of 1 mole of phosphorus trichloride to a solution of 3 moles of the appropriate alcohol in an inert solvent in the presence of 3 moles of a tertiary amine.



The principle of the reaction, laid down by Milobendzki and Sachnowski, *Chem. Polsk.*, **15**, 34 (1917) [*C. A.*, **13**, 2865 (1919)], has not been changed by later investigators.

The reaction is best conducted with cooling, at 10° to 15°, in the presence of dry pyridine or diethylaniline. Diethylaniline is somewhat better than dimethylaniline, since its hydrochloride is less hygroscopic. The hygroscopicity of the hydrochloride and the difficulty of obtaining the completely anhydrous base make pyridine less desirable than the dialkylanilines. The solvent may be ether, benzene, or the lower kerosene fractions. The last are best from the standpoint of clean-cut removal of the base hydrochloride; ether and benzene retain appreciable amounts of the latter.

After filtration of the hydrochloride, the solution is distilled under reduced pressure to yield the phosphite in conversions which usually range from 80% to 95%.

²⁸ Mikhailova, *Uchenye Zapiski Kazan. Gosudarst. Univ.*, **2**, 58 (1941) [*C. A.*, **40**, 555 (1946)].

³⁰ Kosolapoff, *J. Am. Chem. Soc.*, **67**, 2259 (1945).

denser protected by a calcium chloride tube, there is added in the course of thirty minutes 16.2 g. of triethyl phosphite at room temperature. The solution turns yellow-green and begins to evolve ethyl chloride. The mixture is heated on a steam bath for forty-five minutes and is distilled in vacuum to yield 15.7 g. (66.5%) of diethyl α -oxo- α -toluenephosphonate, as a yellowish liquid, b.p. 141°/2.5 mm.

3-Bromopropane-1-phosphonic Acid.³² A mixture of 16.6 g. of triethyl phosphite and 101 g. of trimethylene bromide is placed in a flask equipped with a 12-in. Vigreux column. The mixture is heated by means of an oil bath kept at 150°, and ethyl bromide is collected in a graduated receiver. When 8.0 ml. of ethyl bromide is collected (approximately eighty minutes is required), the oil bath is removed and 100 ml. of 48% hydrobromic acid is added to the cooled reaction mixture. Heating is resumed, after the addition of boiling chips to reduce bumping, and the excess trimethylene bromide is distilled, along with ethyl bromide and hydrobromic acid, in the course of four hours. The distillation is continued until the solution in the reaction flask is concentrated to approximately 30 ml. The residual solution is poured into a beaker and evaporation is continued by means of an infra-red lamp until constant weight is attained. The dark gum is chilled in an ice-water mixture and rubbed vigorously until crystallization occurs. The product is sucked dry on a fritted-glass filter, dissolved in a small amount of warm water, decolorized with 0.5 g. of activated charcoal, filtered, and concentrated on a steam bath until crystallization begins. After cooling, filtering, and drying in a vacuum desiccator, 3-bromopropane-1-phosphonic acid, m.p. 107–108°, is obtained in 80–90% yield.

Di- β -chloroethyl β -Chloroethanephosphonate (Intramolecular Isomerization).³³ In a three-necked flask, equipped with a gas inlet tube, a stirrer, and a calcium chloride tube, there is placed 137.5 g. of phosphorus trichloride. Ethylene oxide is passed into the flask with vigorous stirring and effective cooling by means of an ice bath. The temperature of the solution is kept below 10–15°. The reaction is highly exothermic, but it may be kept under precise control by regulation of the rate of addition of ethylene oxide. When the temperature of the mixture no longer tends to rise (after somewhat more than 132 g. of ethylene oxide has been absorbed) the ethylene oxide supply is disconnected, the gas inlet tube is replaced with a stopper, and the mixture is allowed to stand overnight at room temperature without stirring.

The solution is then warmed with stirring to expel any residual eth-

³² Kosolapoff, *J. Am. Chem. Soc.*, **66**, 1511 (1944).

³³ Kabachnik and Rossiiskaya, *Bull. acad. sci. U.R.S.S., classe sci. chim.*, **1946**, 403 [*C. A.*, **42**, 7242 (1948)].

ylene oxide. The steam bath is replaced by an oil bath, and the mixture is slowly heated with stirring to 150–160°. The ensuing isomerization reaction is rather exothermic and careful control of temperature is necessary. The temperature of the solution should not be allowed to rise above 165–170°, for secondary reactions begin to take place at higher temperatures. Heating is continued for five hours, after which the drying tube is replaced by a distillation head and the mixture is distilled in vacuum. The distillate is redistilled, and the fraction boiling at 170–172°/5 mm. is collected as bis- β -chloroethyl β -chloroethanephosphonate. The yield is generally over 40% (110 g. or more). If the temperature prescribed is closely followed, yields in excess of 70% are common. The product may be induced to crystallize by cooling and scratching. It forms colorless crystals, m.p. 37°.

It is possible to isolate the intermediate tris- β -chloroethyl phosphite, after the reaction mixture has been allowed to stand overnight, by distilling it at a pressure of not more than 2–3 mm. Under conditions of rapid distillation it is possible to recover the phosphite as a mobile liquid, b.p. 112–112.5°/2.5 mm. However, the ester tends to isomerize during the distillation, and accurate fractionation is impossible. The yields of the phosphite are variable, because of the isomerization, but it is possible to obtain 30–40% yields of rather pure product. In this connection it is interesting to note the patent disclosure of the addition of 3 moles of ethylene oxide to phosphorus trichloride under conditions similar to those given above. The product, described as tris- β -chloroethyl phosphite, is stated to boil at 50°/12 mm. and no mention is made of the occurrence of isomerization.³⁴

Tetraphenyl Ethane-1,2-diphosphonate.¹⁶ A flask equipped with a calcium chloride tube is charged with 3.6 g. of diphenyl 2-chloroethyl phosphite. After being heated to 250° for three and a half hours the mass is allowed to cool. Recrystallization from toluene gives 2.1 g. (60%) of tetraphenyl ethane-1,2-diphosphonate as colorless needles, m.p. 155–155.5°.

Hydrolysis may be effected by heating 0.5 g. of the ester and 10 ml. of 1:1 hydrochloric acid in a sealed tube for eight hours at 130°, then for thirty minutes at 140°. On cooling, the mixture is freed of phenol by extraction with ether and the aqueous layer is evaporated to dryness. Recrystallization of the residual solid from acetic acid yields 0.15 g. (90%) of ethane-1,2-diphosphonic acid, m.p. 220–221°.

Isopropyl Isopropylphenylphosphinate.¹¹ A mixture of 12 g. of diisopropyl benzenephosphonite and 9 g. of isopropyl iodide is allowed to stand for ten days in a closed vessel. Distillation of the mixture yields

³⁴ I.G. Farbenindustrie A.G., U. S. pat. 1,936,985 [C. A., 28, 1151 (1934)].

5.3 g. (44%) of isopropyl isopropylphenylphosphinate, b.p. 145–146°/10 mm. However, the addition of a drop of dimethylaniline to the original mixture catalyzes the isomerization to such an extent that after only two days' standing the yield is 95%.

THE SODIUM SALT PROCEDURE

Triethyl β -Phosphonopropionate.³⁵ To 68 g. of dry sodium ethoxide in 500 ml. of dry xylene is added with stirring 138 g. of diethyl phosphite, the mixture being protected from moisture by a calcium chloride tube. To the resulting salt 181 g. of ethyl β -bromopropionate is added dropwise with stirring and cooling by an ice-salt bath. After standing overnight the mixture is heated for two hours on a steam bath, after which the precipitated sodium chloride is filtered. Distillation of the filtrate gives 193 g. (78%) of triethyl β -phosphonopropionate, b.p. 141–143°/9 mm.

Dibutyl Alkanephosphonates.⁵ One-tenth mole of dibutyl phosphite is added dropwise to a suspension of 0.1 atom of sodium in 300–500 ml. of a dry hydrocarbon solvent (petroleum ether, benzene, toluene, or xylene), with stirring and heating at gentle reflux until the sodium dissolves. The alkyl halide (bromides are most satisfactory) is then added dropwise during thirty to sixty minutes. The amount of the halide need not exceed the theoretical 0.1 mole. After fifteen or twenty minutes the precipitation of sodium halide begins. It is completed by refluxing the mixture with stirring for two to six hours. The end of the reaction is indicated by a clean separation of the salt from the organic solution. On cooling, the mixture is shaken with two or three portions of cold water and the organic layer is run through a dry filter paper to remove the bulk of moisture. The filtrate is then freed of solvent at water-pump vacuum at approximately room temperature. This also serves to remove the residual moisture without an additional drying step. Distillation of the residue under reduced pressure (oil-pump vacuum for the higher members of the series) results in the isolation of 80–95% yields of dibutyl alkanephosphonates as colorless liquids. These may be hydrolyzed by refluxing with 2–3 volumes of concentrated hydrochloric acid. This is most satisfactorily done in a flask provided with a Vigreux distillation column which permits the continuous removal of butyl chloride. When the latter is completely removed, as indicated by the temperature of the condensing vapor in the still head, the bulk of the hydrochloric acid is distilled and the phosphonic acid is allowed to crystallize on cooling the residual mixture. Purification by crystal-

³⁵ Finkelstein, *J. Am. Chem. Soc.*, **68**, 2397 (1946).

lization from petroleum ether gives substantially quantitative yields of the alkanephosphonic acids.

TRIARYLMETHANE DERIVATIVES

Triphenylmethanephosphonic Acid.⁸ A solution of 42.5 g. of triphenylcarbinol in boiling benzene is added in two or three portions to 50 g. of phosphorus trichloride contained in a flask provided with a reflux condenser and a calcium chloride tube for protection from moisture. The reaction is conducted at reflux temperature, and the additions are timed so that uncontrollable reflux is avoided. After the addition, the mixture is refluxed for one hour, the solvent is removed in vacuum, and the solid residue of triphenylmethylphosphonyl chloride is washed with dry ether and dried in a vacuum desiccator. The product is obtained in 95% yield in the form of colorless crystals, m.p. 189.5–190°.

Five grams of the above chloride is heated on a steam bath with 3.8 g. of potassium hydroxide in 38 ml. of ethanol until the precipitation of potassium chloride is complete. An equal volume of water is added to the mixture, and the ethanol is almost completely removed by evaporation. The cooled solution is filtered, and the clear filtrate is acidified with hydrochloric acid to precipitate the monoethyl ester of the phosphonic acid. This is separated, dried, and refluxed for one hour with 25 ml. of acetic acid and 12 ml. of hydriodic acid. On cooling, the product is filtered, washed with dilute hydrochloric acid, ethanol, and ether, in succession, and recrystallized from benzene to give 4–4.1 g. (91%) of triphenylmethanephosphonic acid, m.p. 275°.

SPECIAL METHODS

Diethyl 2-Hydroxyethanephosphonate.²⁴ To 2.3 g. of powdered sodium suspended in 120 ml. of dry ether is added with stirring 13.9 g. of diethyl phosphite. The mixture is stirred with gentle warming until the sodium has reacted, and the mixture is treated with 4.5 g. of ethylene oxide with stirring. The clear solution is stirred for one hour, and then 6.1 g. of glacial acetic acid is added dropwise. The precipitated sodium acetate is collected by filtration, and the filtrate is evaporated under reduced pressure. Traces of sodium acetate are removed by filtration, and the residual oil is dried in a desiccator over sulfuric acid. There is obtained 7.6 g. (42%) of diethyl 2-hydroxyethanephosphonate, which can be distilled with some decomposition at 120–130°/9 mm.

Stearamidomethanephosphonic Acid.⁷ One hundred grams of N-methylolstearamide is added to a solution of 91.0 g. of phosphorus tri-

chloride in 45 g. of carbon tetrachloride contained in a flask protected with a calcium chloride tube. After standing for one hour, the mixture is treated with 40 g. of glacial acetic acid, and the flask is allowed to stand at room temperature for four days. The resulting viscous mass is warmed to 50° with 8% hydrochloric acid until it changes to a crystalline solid, which is separated by filtration. Crystallization from ethanol yields 67 g. (40%) of stearamidomethanephosphonic acid, a colorless crystalline solid, which has an indefinite melting point, softening at 108°.

ADDITION OF PHOSPHORUS PENTACHLORIDE TO UNSATURATED COMPOUNDS

Olefins having reactive double bonds undergo the addition of phosphorus pentachloride to give substances that can be regarded as the chlorides of phosphonic acids.³⁶ Hydrolysis converts the addition products to phosphonic acids, usually with simultaneous dehydrochlorination as illustrated in the reaction with styrene.



Branched-chain olefins sometimes lead to chloroalkanephosphonic acids. Acetylenes yield phosphonic acids containing the chlorovinyl group. Such compounds, which do not undergo spontaneous loss of hydrogen chloride during hydrolysis, can be dehydrohalogenated by treatment with an alkaline reagent like potassium hydroxide.³⁷ The initial addition reaction takes place under mild conditions in an inert solvent, and the yields of α,β -unsaturated phosphonic acids usually range between 40 and 50%.

Scope and Limitations

The most obvious limitation to the reaction is the fact that groups capable of reacting with phosphorus pentachloride must either be absent or be protected. Such reactive groups are the hydroxyl, amino, sulfhydryl, and carboxyl.

The reaction has been successfully applied to the following unsaturated compounds: styrene,^{36,38,39} α -methylstyrene,³⁸ α -chlorostyrene,³⁷ in-

³⁶ Thiele, *Chem. Ztg.*, **36**, 657 (1912); K. Harnist, dissertation, Strassburg, 1910; F. Bulle, dissertation, Strassburg, 1912.

³⁷ Bergmann and Bondi, *Ber.*, **66**, 278 (1933).

³⁸ Bergmann and Bondi, *Ber.*, **63**, 1158 (1930).

³⁹ Kosolapoff and Huber, *J. Am. Chem. Soc.*, **68**, 2540 (1946).

dene,^{36,38} 1,1-diphenylethylene,³⁸ 1-phenyl-1-*o*-tolylethylene,⁴⁰ 1-phenyl-1-*p*-methoxyphenylethylene,⁴¹ 1-phenyl-1-*p*-chlorophenylethylene,⁴¹ 1,1-di-*p*-chlorophenylethylene,⁴¹ 1-*p*-chlorophenyl-1-*p*-methoxyphenylethylene,⁴¹ 1-phenyl-1-*o*-fluorophenylethylene,⁴¹ 1-phenyl-1-*p*-biphenylylethylene,⁴¹ 1-*p*-tolyl-1-*p*-biphenylylethylene,⁴¹ 1-phenyl-1-*m*-chlorophenylethylene,⁴¹ 1-phenyl-1-(α - and β)-naphthylethylenes,⁴⁰ 1,4-phenylenebis(α -phenylethylene),⁴¹ 4-phenyl-1,3-butadiene,^{39,41} isobutylene,³⁹ butadiene,⁴² 10,10-diphenyl-9-methyleneanthracene,⁴⁰ 2,4-dimethylstyrene,³⁹ 2,4,6-trimethylstyrene,³⁹ *p*-ethylstyrene,³⁹ *o*-*tert*-butylstyrene,³⁹ *p*-*tert*-butylstyrene,³⁹ *o*-, *m*-, and *p*-phenylstyrene,³⁹ 2-vinylnaphthalene,³⁹ 2-vinylfluorene,³⁹ phenylacetylene,³⁷ *o*-chlorophenylacetylene,³⁷ *o*-methoxyphenylacetylene,³⁷ *p*-methoxyphenylacetylene,³⁷ phenylmethylacetylene,³⁷ and 1-heptyne.³⁷

Although the earlier work^{36,38} indicated that lack of symmetry of the starting compound is a necessary condition for this reaction, it has been shown that symmetrical compounds may be capable of normal addition.^{41,42} It appears, however, that the reaction is limited to unsaturated compounds that contain a terminal unsaturated carbon-carbon bond. Indene, which has a cyclic double bond, is an exception and appears to be reactive mainly because of the exposed, unhindered position of this double bond.

The steric factors that may further limit the reaction have not been satisfactorily clarified to permit any generalizations. The following compounds failed to yield phosphonic acids, although many of them have a double bond which is not apparently blocked by steric factors: benzylstilbene,³⁸ 1,1-diphenyl-1-propene,⁴¹ 1,1-diphenyl-1-butene,⁴¹ 1,1,3-triphenyl-1-propene,⁴¹ 1,1-diphenyl-2,2-dimethylethylene,⁴¹ α -benzylstyrene,⁴¹ 1-phenyl-1-ethyl-2-methylethylene,⁴¹ allylbenzene,⁴¹ 1-phenyl-1,3-pentadiene,⁴¹ 1,4-diphenylbutadiene,⁴¹ isoeugenol methyl ether,⁴¹ isosafrole,⁴¹ triphenylethylene,⁴¹ stilbene,⁴¹ isostilbene,⁴¹ 1,1-bis-*o*-methoxyphenylethylene,⁴¹ 1-phenyl-1-(*o*-chloro- and *o*-bromo-phenyl)ethylenes,⁴¹ 1-phenyl-1-*o*-biphenylylethylene,⁴¹ 1,1-phenyl-(*o*- and *m*-methoxyphenyl)ethylenes,⁴¹ tolan,³⁷ diphenylacetylene,³⁷ *p*-nitrophenylacetylene,³⁷ and phenylethylacetylene.³⁷

Experimental Procedures

β -Styrenephosphonic Acid. (a)³⁸ To an ice-cooled stirred suspension of 104 g. of phosphorus pentachloride in dry benzene, 26.2 g. of styrene

⁴⁰ Bergmann and Bondi, *Ber.*, **66**, 286 (1933).

⁴¹ Bergmann and Bondi, *Ber.*, **64**, 1455 (1931).

⁴² Kosolapoff, U. S. pat. 2,389,576 [*C. A.*, **40**, 1536 (1946)].

is added dropwise in one hour. The mixture is protected from moisture by means of a calcium chloride tube. After stirring for two or three hours, the creamy suspension of the adduct is allowed to stand for twenty-four hours, after which it is poured into ice water. The mixture is allowed to stand for two or three days, with spontaneous evaporation of benzene. Shiny colorless crystals of the product gradually appear at the interface of the two layers. The yield of the crude product is 27 g. It is a mixture of *cis-trans* isomers and is composed of 3 g. of needles, m.p. 146°, and 24 g. of a granular solid, m.p. 150°. These can be readily separated mechanically. Recrystallization from ethylene bromide gives the same product from either isomer. The final product is obtained in the form of needles, m.p. 146°, and represents the stable isomer.

(b)³⁹ Dry chlorine gas is introduced slowly into an ice-cold stirred solution of 52.1 g. of styrene in 68.7 g. of phosphorus trichloride and 500 ml. of dry benzene until the solution becomes yellow from an excess of chlorine. Hydrolysis of the mixture as described in (a) results in 32.9 g. of crude 2'-styrenephosphonic acid. This is purified by dissolving it in dilute sodium hydroxide and pouring the solution slowly into warm, stirred, dilute hydrochloric acid. Crystallization of the precipitate from water gives 29–31 g. of the pure acid, m.p. 154.5–155.5°.

Phenylethyneephosphonic Acid.³⁷ To an ice-cold, stirred suspension of 83 g. of phosphorus pentachloride in 150 ml. of dry benzene is added slowly 20.4 g. of phenylacetylene. After standing for two days, the mixture is poured into an ice-water mixture, the organic layer is diluted with ether, and the aqueous layer is discarded. Evaporation of the organic layer gives 1.5 g. (3%) of α -chloro- β -styrenephosphonic acid, m.p. 162° (from 1:1 hydrochloric acid). Five grams of this acid is refluxed for six hours with 80 ml. of 5% potassium hydroxide. On cooling, the mixture is treated with an excess of hydrochloric acid and the product is taken up in ether. Evaporation of the solvent gives a substantially quantitative conversion to the phenylethyneephosphonic acid, m.p. 142°.

THE GRIGNARD REACTION

The application of the usually versatile Grignard reaction to the synthesis of phosphonic and phosphinic acids has not received the attention it probably deserves. References to its use in this connection are few, and the precise conditions for optimum yields have not been explored adequately.

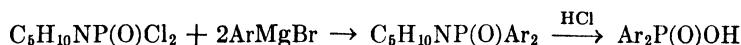
The obvious advantage of the Grignard reaction resides in the mild conditions necessary for its use. The method favors the preservation of

sensitive substituents, which might be destroyed in a more drastic reaction such as a Friedel-Crafts synthesis.

The earliest reference to the formation of phosphonic or phosphinic acids by the Grignard method is that of Auger and Billy,⁴³ who added methylmagnesium bromide to an excess of phosphorus trichloride at -30° and hydrolyzed the resulting mixture of trimethylphosphine and methylchlorophosphines; oxidation of the crude mixture with nitric acid resulted in isolation of traces of methanephosphonic acid and dimethylphosphinic acid. Sauvage⁴⁴ treated phosphorus oxychloride with one-third of the molar quantity of Grignard reagents from bromobenzene, benzyl chloride, and 1-bromonaphthalene. The reaction products consisted of mixtures of, predominantly, triarylphosphine oxides and small amounts of the corresponding phosphinic acids, i.e., dibenzylphosphinic acid, diphenylphosphinic acid, and di-1-naphthylphosphinic acid.

Michaelis and Wegner⁴⁵ made the first step toward control of the reaction by using substituted phosphorus oxychlorides, thus leaving only two available chlorine atoms for the reaction. They found, however, that blocking by a phenoxy group was ineffective; the use of phenoxyphosphoryl dichloride gave mostly the trisubstituted phosphine oxides in reactions with Grignard reagents. In other words, the Grignard reagents displace the phenoxy group as readily as they displace the chlorine atoms in the phosphoryl chloride derivative. Unfortunately, the ease of such displacement has not been investigated for radicals other than phenyl. In the light of modern knowledge of the behavior of phosphate esters, such displacement of the phenoxy group may be connected with the ready cleavage of phenyl phosphates by hydrogenation. The reductive action of the Grignard reagents used may well have been responsible for this failure of the Michaelis-Wegner attempt. If this explanation is correct, attempts to effect blocking by means of the benzyloxy groups should be fruitless for the same reason.

However, Michaelis and Wegner found a more suitable reagent in N-piperidylphosphonyl dichloride. The piperidine residue resisted attack by the Grignard reagents, which therefore could react with only the two available chlorine atoms. The resulting N-piperidides of diarylphosphinic acids were readily hydrolyzed by hydrochloric acid to the corresponding free acids. The reaction sequence is shown in the accompanying equation.



⁴³ Auger and Billy, *Compt. rend.*, **139**, 597 (1904).

⁴⁴ Sauvage, *Compt. rend.*, **139**, 674 (1904).

⁴⁵ Michaelis and Wegner, *Ber.*, **48**, 316 (1915).

These authors applied this method to the Grignard reagents from bromobenzene, *o*- and *p*-bromotoluene, 1-bromonaphthalene, and benzyl chloride. Although the yields are stated to be "good," no numerical data are given. However, yields in excess of 50% may be expected.

There is no recorded instance of an attempt to extend such a blocking modification of phosphoryl chloride in order to synthesize phosphonic acids. This would require a doubly blocked reagent of a type B_2POCl , where B is a blocking group.

The main difficulty with the use of the Grignard reaction results from the tendency for complete substitution of phosphorus oxychloride. Therefore, an attempt was made by the present author to counteract this tendency by reversing the mode of mixing the reactants, that is, by adding the Grignard reagent to a moderate excess of phosphorus oxychloride solution. This method of addition, combined with the additional favorable factor of very dilute solutions, gave 50–55% yields of phosphinic acids from phenyl- and *p*-chlorophenyl-magnesium bromides.⁴⁶

Mingoia⁴⁷ used the magnesium derivatives of α -methylindole, indole, and pyrrole in a reaction analogous to that of Sauvage to obtain low yields of di-3-(2-methylindolyl)phosphinic acid, di-3-indolylphosphinic acid, and di-2-pyrrylphosphinic acid.

A modification of the blocking procedure of Michaelis and Wegner has been reported in the work of Bode and Bach,⁴⁸ who treated phosphonitrilic chloride, $(PNCl_2)_3$, with a large excess of phenylmagnesium bromide and hydrolyzed the resulting product, $(C_6H_5)_7P_3N_3H \cdot HBr$, with hydrochloric acid to the diphenylphosphinic acid. The yield of the intermediate product was less than 10% and, although the hydrolysis step is essentially quantitative, the overall yields do not compare with those from the Michaelis-Wegner method. The tedious preparation of the phosphonitrilic chloride is an additional drawback to this procedure.

An entirely different approach was made by Malatesta and Pizzotti,⁴⁹ who treated phosphorus pentasulfide * with Grignard reagents from ethyl bromide, isopropyl bromide, and bromobenzene, and obtained mixtures of the corresponding tertiary phosphine sulfides, thiophosphinic acids, and thiophosphonic acids. The thio acids were readily oxidized to the oxygen analogs by treatment with nitric acid or bromine. This procedure appears to be the first reasonably practical method of preparation of phosphonic acids by the Grignard reaction. As mentioned above, the reaction gave the products of all three possible types. The course

* See the footnote on p. 412 concerning the formulas of the phosphorus sulfides.

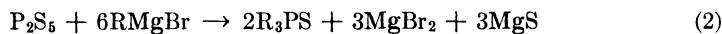
⁴⁶ Kosolapoff, *J. Am. Chem. Soc.*, **64**, 2982 (1942).

⁴⁷ Mingoia, *Gazz. chim. ital.*, **62**, 333 (1932).

⁴⁸ Bode and Bach, *Ber.*, **75**, 215 (1942).

⁴⁹ Malatesta and Pizzotti, *Gazz. chim. ital.*, **76**, 167, 182 (1946).

of the reaction may be represented by the three equations given by Malatesta and Pizzotti.



Although reaction 1 takes place best at moderately low temperatures, all three reactions always take place and the yields of the acidic derivatives do not exceed 20% for any class under the best conditions. The mixtures of the thiophosphonic and thiophosphinic acids were separated by virtue of the different solubility of the nickel salts of the sulfur and oxygen acids. The reaction is best carried out with a suspension of phosphorus pentasulfide in an inert solvent, usually ether. The heterogeneous character of the reaction under such conditions may be responsible to a large extent for the difficulty of the control of the reaction.

The information given above includes all the pertinent data on the use of the Grignard reaction. It is readily seen that the scope of the reaction cannot be limited to the few examples that have been tried to date. Probably the reaction can be used with any substance capable of forming a Grignard reagent.

Experimental Procedures

Diphenylphosphinic Acid (Michaelis-Wegner Procedure).⁴⁵ The Grignard reagent from 31.4 g. of bromobenzene and 5 g. of magnesium, in ether solution, is treated slowly with 20.2 g. of N-piperidylphosphoryl dichloride. The mixture is refluxed until reaction is complete. After addition to water, the organic layer is separated. Evaporation of the solvent on a steam bath leaves a viscous residue of the amide, which is boiled with concentrated hydrochloric acid until solution is complete. Dilution with cold water causes the separation of the crude diphenylphosphinic acid. Purification by solution in sodium carbonate solution, followed by precipitation with hydrochloric acid and crystallization from ethanol, gives the pure compound, m.p. 190–191°. The yield is reported as “good.”

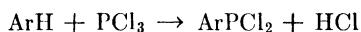
Diphenylphosphinic Acid (Kosolapoff Procedure).⁴⁶ The Grignard reagent from 31.4 g. of bromobenzene and 4.86 g. of magnesium in 500 ml. of dry ether is filtered with exclusion of atmospheric moisture and is then added during three and a half hours to a gently refluxing, stirred solution of 30.6 g. of phosphorus oxychloride in 500 ml. of dry ether.

After standing overnight, the clear solution is decanted from the yellow precipitate. The precipitate is digested with ice water, and the insoluble residue is washed thoroughly with water. Extraction of the solid with 1 l. of warm dilute sodium hydroxide solution and acidification of the extract with hydrochloric acid, followed by crystallization from dilute ethanol, gives 12 g. (55%) of diphenylphosphinic acid, m.p. 190–192°.

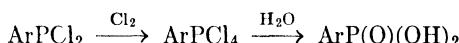
Ethanephosphonic Acid (Malatesta-Pizzotti Procedure).⁴⁹ Two hundred milliliters of 1 M ethylmagnesium bromide in dry ether solution is added dropwise to a stirred suspension of 22 g. of phosphorus pentasulfide in dry ether. The mixture is refluxed for a brief time after the addition is complete. Cold water is added to the mixture, and the aqueous layer is separated. After treatment with charcoal, followed by filtration, an excess of nickel sulfate solution is added and the mixture is acidified to Congo red with dilute hydrochloric acid. Extraction with benzene removes any nickel diethyldithiophosphinate. The aqueous solution is extracted with ether, the extract is evaporated to dryness, and the residue is taken up in water. Bromine water is added to oxidize the sulfur compound to the corresponding oxygen analog. The addition is continued until a permanent color is attained. After filtration and evaporation, the residue is dissolved in dilute aqueous ammonia. Evaporation to dryness to remove the excess ammonia, followed by treatment of the residue with hydrogen sulfide in aqueous solution, serves to remove any residual nickel. Acidification of the filtrate with nitric acid, after the removal of nickel sulfide, and evaporation to dryness give crude ethanephosphonic acid. This is distilled under reduced pressure to give the pure product, b.p. 330–340°/8 mm.; m.p. 30–35°. The yield is approximately 15%.

THE FRIEDEL-CRAFTS REACTION

The preparation of aromatic dichlorophosphines by the interaction of aromatic hydrocarbons with phosphorus trichloride in the presence of aluminum chloride was accomplished for the first time by Michaelis.⁵⁰ This reaction, which takes place according to the accompanying equation, was subsequently used for the conversion of aromatic hydrocarbons into a variety of phosphonic acids. The conversion of the dichloro-

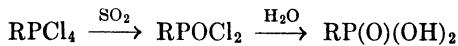


phosphines into the phosphonic acids was effected by chlorination, which yields the corresponding tetrachlorides, followed by hydrolysis.

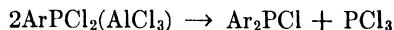


⁵⁰ Michaelis, *Ber.*, **12**, 1009 (1879).

Instead of the direct hydrolysis of the tetrachlorides, the latter can be converted to the corresponding oxychlorides, which on hydrolysis also give phosphonic acids. Usually there is little choice between the two alternatives.



A number of the aromatic dichlorophosphines have been prepared by later workers without significant changes of the original procedure of Michaelis. The formation of small amounts of diaryl monochlorophosphines, R_2PCl , in the original reaction mixtures has been also observed for a few compounds.⁵¹⁻⁵⁴ These could be isolated in small amounts only, and the Friedel-Crafts reaction was not regarded as a suitable source of the disubstituted products by the Michaelis school. The diaryl monochlorophosphines can be converted to the corresponding diarylphosphinic acids by a reaction sequence analogous to that above. Later work by the present writer⁵⁵ indicated that the diaryl chlorophosphines are formed as a result of a general reaction, which is apparently catalyzed by aluminum chloride, and which proceeds through disproportionation of the monoaryl derivatives.



The difficulties encountered in the isolation procedure used by the Michaelis school for the chlorophosphines prevented the discovery of the generality of this reaction. The isolation procedure of Michaelis is extremely inefficient. It is performed by extraction of the reaction mixture with an inert hydrocarbon solvent (petroleum ether has been generally favored). The extract is concentrated, and the residual chlorophosphines are distilled under reduced pressure. The bulk of the reaction products, however, remains in the rather intractable evil-smelling aluminum chloride complex layer which is insoluble in petroleum ether. The actual yields of the isolated dichlorophosphines rarely exceed 15–20% of the theoretical. The dichlorophosphines, after isolation, are treated with an equimolar quantity of dry chlorine gas, which may be added in solution in a suitable solvent (carbon tetrachloride has been usually employed) or may be introduced in the gaseous state into the dichlorophosphine, which is preferably dissolved in an inert solvent. The use of a solvent with external cooling moderates the very vigorous reaction. The resulting tetrachlorophosphine may be added directly to water to yield the corresponding phosphonic acid or may be treated

⁵¹ Michaelis, *Ann.*, **315**, 43 (1901).

⁵² Michaelis, *Ann.*, **293**, 193 (1896); **294**, 1 (1897).

⁵³ Sachs, *Ber.*, **25**, 1514 (1893).

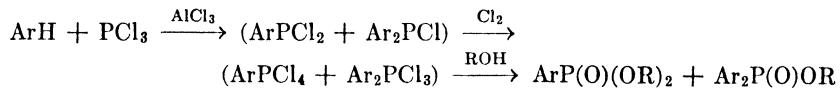
⁵⁴ Lindner and Strecker, *Monatsh.*, **53/54**, 263 (1929).

⁵⁵ Kosolapoff and Huber, *J. Am. Chem. Soc.*, **69**, 2020 (1947).

with gaseous sulfur dioxide which converts it to the oxychloride, RPOCl_2 , which may be purified by distillation. Treatment with warm water converts the oxychloride to the desired phosphonic acid.

A very useful modification of the Michaelis procedure has been developed by Dye.⁵⁶ In this procedure the dichlorophosphines are isolated by the removal of the aluminum chloride in the form of very stable complexes, either with water or with phosphorus oxychloride. In the first instance, the cooled mixture, after the Friedel-Crafts reaction proper has been completed, is treated with cold water added dropwise. The amount of water used is three times the molar amount of aluminum chloride, and it is advisable to remove the excess phosphorus trichloride before the hydrolysis. The resulting solid complex, which contains all the aluminum chloride, is removed, and the filtrate is used for the recovery of the aromatic dichlorophosphine by distillation. In the second variant, the reaction mixture is treated with phosphorus oxychloride, the molar quantity of which is slightly greater than that of the aluminum chloride used in the reaction. The mixture is warmed to approximately 50° with stirring to aid the formation of the $\text{AlCl}_3 \cdot \text{POCl}_3$ complex, which separates as a solid. The separation is assisted by the addition of petroleum ether to the mixture. After filtration of the mixture, the filtrate is used for isolation of the dichlorophosphines in the usual way. The yields by either procedure have been studied with benzene; consistent values of 60–70% of the theoretical can be attained. There are indications that the procedure can be used for other aromatic hydrocarbons.

A different variation of the Michaelis procedure has been developed by the present writer.⁵⁶ In this procedure the chlorophosphines are not isolated, but the entire reaction mixture is treated with chlorine in an inert solvent and the resulting mixture is esterified. Aluminum chloride is then removed by washing with water, and the resulting esters of phosphonic and phosphinic acids are readily recovered and isolated by vacuum distillation. Hydrolysis of the esters yields the corresponding free acids. This procedure not only eliminates the handling and the isolation of malodorous and sensitive chlorophosphines but also serves to produce the phosphonic and the phosphinic acid derivatives in much higher yields than those obtained by the Michaelis method. The yields are frequently nearly theoretical, based on the amount of the aromatic hydrocarbon used. The overall scheme of this method may be illustrated by the accompanying representation.



⁵⁶ Dye, *J. Am. Chem. Soc.*, **70**, 2595 (1948).

The use of this procedure, with its excellent recoveries, established that the formation of the disubstituted products is a general reaction, but that it can be essentially suppressed if the reaction period is relatively short (three to eight hours).

A variation of the above-described procedures has been reported by Bode and Bach.⁴⁸ They reacted trimeric phosphonitrilic chloride, $(\text{PNC}_2)_3$, with benzene in the presence of aluminum chloride. The resulting diphenyl derivative, $(\text{C}_6\text{H}_5)_2\text{P}_3\text{N}_3\text{Cl}_4$, was hydrolyzed to diphenylphosphinic acid by heating with water to 150–160° in sealed tubes for twenty-four hours. Since the yield of the intermediate is poor, the significance of this procedure as a synthetic tool appears to be slight.

Scope and Limitations

The Friedel-Crafts reaction has been successfully applied to the preparation of phosphonic and phosphinic acid derivatives of the following aromatic compounds: benzene,^{50, 55, 57} chlorobenzene,^{52, 55} *o*-chlorotoluene,⁵⁸ bromobenzene,⁵² toluene,^{50, 51, 52, 54, 55, 59} ethylbenzene,⁵² isopropylbenzene,⁵² cymene,^{52, 59} anisole,^{52, 60} phenetole,⁵² *m*- and *p*-xylenes,^{52, 59, 61} the trimethylbenzenes,^{52, 62} naphthalene,⁶⁴ diphenylmethane,^{51, 52} *sym*-diphenylethane,^{51, 52} *o*- and *p*-dichlorobenzene,⁵⁵ biphenyl,^{51, 52, 63} diphenyl ether,⁶⁴ thiophene,⁵³ and dimethylaniline.⁶⁵ In addition, monoaryl dichlorophosphines were prepared from N,N-diethylaniline, N,N-methylethylaniline, N,N-methylbenzylaniline, and N,N-ethylbenzylaniline,⁶⁶ but the products were not converted to the phosphonic acids.

The reaction failed to take place to a detectable extent with trichlorobenzene,⁵⁵ benzonitrile,⁵² iodobenzene,⁵² benzophenone,⁵² ethyl benzoate,⁵² and *x*-bromotoluene.⁵²

The rather limited number of the compounds listed above cannot be considered as the true scope of the reaction. The reaction can probably be applied to all aromatic compounds that can undergo the acylation-type Friedel-Crafts reaction. However, the reaction has some inherent limitations which restrict its usefulness, particularly in the attempts to obtain compounds with a specific structure. Thus, the work done to

⁵⁷ Kurnai, *J. Russ. Phys. Chem. Soc.*, **64**, 524 (1932) [*C. A.*, **27**, 966 (1933)].

⁵⁸ Melchiker, *Ber.*, **31**, 2915 (1898).

⁵⁹ Michaelis and Panek, *Ann.*, **212**, 203 (1882).

⁶⁰ Kurnai, *J. Gen. Chem. U.S.S.R.*, **4**, 192 (1934) [*C. A.*, **29**, 464 (1935)].

⁶¹ Weller, *Ber.*, **20**, 1718 (1887); **21**, 1492 (1888).

⁶² Davies, *J. Chem. Soc.*, **1935**, 462.

⁶³ Lindner, Wirth, and Zannbauer, *Monatsh.*, **70**, 1 (1937).

⁶⁴ Davies and Morris, *J. Chem. Soc.*, **1932**, 2880.

⁶⁵ Michaelis and Schenk, *Ber.*, **21**, 1497 (1888); *Ann.*, **260**, 1 (1890).

date does not include the study of the possible isomerizations or migrations of the alkyl substituents on the aromatic nucleus. Such changes may be expected to take place in reactions involving the use of aluminum chloride at elevated temperatures. It will be noted that the compounds studied had comparatively short side chains, whose isomerization is rather improbable. The reaction with bromobenzene gives a poor yield of the desired product because of extensive debromination by the aluminum chloride. The identity of the dichlorophosphine obtained by Michaelis⁵² from anisole has been seriously questioned by Kamai,⁶⁰ who showed that anisole suffers an extensive cleavage of the ether linkage and that the yield of the pure *p*-methoxy derivative is but 26%. It was also shown that the successful application of the Friedel-Crafts reaction to anisole and to phenetole requires the use of partially hydrated aluminum chloride,⁵² because pure aluminum chloride, which is necessary for all the other reactions, yields phenyl dichlorophosphite, $C_6H_5OPCl_2$, instead of the dichlorophosphine.

The phosphorus residue enters the aromatic nucleus in orientations that are normally expected for the compounds that have been tried. Thus, the *para* isomer of the toluene derivative has been isolated and the presence of the *ortho* isomer has been deduced from the low melting point of the dichlorophosphine which remains after the removal of the *para* isomer by freezing.⁵² The formation of two isomeric products has been established in the reaction of *meta*-xylene,⁵² but the products from chlorobenzene and from the phenyl ethers have been assigned the *para* structure exclusively.⁵² It is possible that a closer study of the products, which will be available in good yields as a result of the modifications of the isolation procedure, will reveal the presence of other isomers. Apparently an isomer of unknown structure has been isolated from bromobenzene,⁵² besides the authentic *para* isomer. No definite assignment of structure has been given to the derivatives of naphthalene, biphenyl, diphenylmethane, or diphenylethane, although the last three products may be expected to be largely the *para* isomers.

Experimental Procedures

***p*-Toluenephosphonic Acid (Michaelis Procedure).**^{50,52} A mixture of 150 g. of toluene, 200 g. of phosphorus trichloride, and 30 g. of aluminum chloride is refluxed for thirty-six hours with protection from atmospheric moisture. The cooled reaction mixture is mixed with 2 volumes of a hydrocarbon solvent (preferably petroleum ether), and the mixture is allowed to stand in a loosely stoppered separatory funnel until the layers separate cleanly. This may require a day. The extract is sepa-

rated and transferred carefully to a distillation apparatus, and the mixture of isomeric tolyldichlorophosphines is recovered by distillation under reduced pressure, preferably in an inert atmosphere to prevent oxidation. Approximately 50 g. of the mixture is recovered in the form of a fraction which boils at 236–260° at atmospheric pressure. The *para* isomer may be largely recovered by freezing the mixture, and up to 25 g. of the pure product may be obtained. The liquid fraction is not the pure *ortho* isomer, and attempts to purify it have not been successful. The *para* isomer melts at 25°. The dichlorophosphine is treated with chlorine, either in carbon tetrachloride solution or without dilution,⁵⁹ until the absorption of an equimolar amount of chlorine takes place. The resulting tetrachlorophosphine is treated with dry sulfur dioxide until the conversion to the oxychloride is complete as shown by the liquefaction of the solid tetrachloride. The resulting product is treated with ice water and boiled briefly to complete the hydrolysis, and *p*-toluenephosphonic acid is isolated by cooling the solution. After recrystallization from aqueous ethanol the acid melts at 189°. The conversion from the dichlorophosphine to the acid is substantially quantitative.

Small amounts of the crude ditolyl derivatives are left behind after the isolation of the dichlorophosphines. They may be isolated by treating the viscous aluminum chloride complex residue, after the hydrocarbon extraction, with water, separating the semisolid insoluble mass, washing it with water, and extracting it with dilute aqueous ammonia. Acidification of the alkaline extract gives variable amounts of the ditolyl derivatives as a non-crystalline viscous mass.

Benzeneephosphonic Acid (Kosolapoff Procedure).⁵⁵ A mixture of 78 g. (1 mole) of benzene, 411 g. (3 moles) of phosphorus trichloride, and 133 g. (1 mole) of aluminum chloride is refluxed for three hours with protection from atmospheric moisture. The excess phosphorus trichloride is removed under reduced pressure (water pump) with stirring, with the bath temperature below 60°. The residue is dissolved in 250 ml. of dry tetrachloroethane, and, with efficient stirring and ice-water cooling, dry chlorine is led into the solution until its absorption ceases, as indicated by escaping chlorine. This requires one to two hours. The gas inlet tube is replaced with a dropping funnel, and the flask is evacuated (water pump) by means of a connection to the top of the reflux condenser. With stirring and ice-water cooling, 230 g. (5 moles) of dry ethanol is added to the mixture in one to two hours, the mixture being kept at 10–15°. The connection to the water pump is maintained for one or two hours after the addition to facilitate the removal of the bulk of hydrogen chloride. The nearly colorless solution is then poured into

ice water, and the organic layer is separated. After washing with two or three portions of water until the wash water is essentially free of aluminum ions, the solvent is stripped off at the water pump, the residual moisture being removed as an azeotrope at the lowest possible temperature. It is advisable to add 50–100 ml. of dry carbon tetrachloride to the solution before the distillation in order to facilitate the removal of moisture at room temperature. Distillation of the residue gives 174 g. (80.4%) of diethyl benzenephosphonate, as a colorless oil, b.p. 117–118°/1.5 mm. Refluxing the ester for eight hours with 2 volumes of concentrated hydrochloric acid, followed by evaporation of the clear solution, gives a quantitative conversion to benzenephosphonic acid, m.p. 158–159°.

If the refluxing period is extended to forty hours, the formation of the diphenylphosphinic acid derivative takes place to a substantial extent and the procedure as given above yields only 59% of the diethyl benzenephosphonate together with 30% of ethyl diphenylphosphinate, which boils at 173–175°/1.5 mm. The phosphinate is readily hydrolyzed by concentrated hydrochloric acid, as described above, to yield diphenylphosphinic acid, m.p. 190.5–192°, after crystallization from dilute ethanol. The distillation residue after the removal of the two esters consists of 11 g. of crude bis-substituted acid. The total amount of recovered products accounts for 99% of the benzene used.

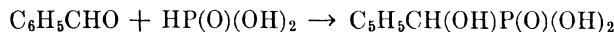
The high molecular ratio of phosphorus trichloride used above favors the monosubstitution reaction in the short refluxing period and increases the rate of the reaction. In addition, it facilitates the stirring of the mixture. The amounts of aluminum chloride are not very critical, and the most suitable range is 0.25–1.0 mole per mole of hydrocarbon. Smaller amounts of aluminum chloride give lower yields; larger amounts are not economical. Although other alcohols may be used for esterification, ethanol is preferred because of the moderate temperatures which suffice for the distillation of the resulting esters.

THE ADDITION OF PHOSPHORUS COMPOUNDS TO THE CARBONYL GROUP

The addition of certain phosphorus-containing reagents to carbonyl compounds affords valuable methods for the synthesis of a variety of phosphonic and phosphinic acids. The reagents customarily are divided into two groups: those containing the phosphorus-hydrogen linkage, and the phosphorus halides. The details of the mechanisms of the reactions are unknown, and it is possible that the two processes are more closely related than this division suggests.

Addition of Compounds Containing the Phosphorus-Hydrogen Linkage

The synthesis of phosphonic acids by the addition of substances containing the phosphorus-hydrogen linkage to a carbonyl compound may be represented by an aldol-like condensation, with the formation of a phosphorus-containing acid having a hydroxyl group in the α position to the phosphorus atom. An example is the formation of α -hydroxy- α -toluenephosphonic acid from benzaldehyde and phosphorous acid.



The reaction in its most primitive form was used by Litthauer,⁶⁶ who heated a mixture of phosphonium iodide, PH_4I , and benzaldehyde to 100° in a sealed tube and obtained a mixture of α -toluenephosphonic acid, $\text{C}_6\text{H}_5\text{CH}_2\text{PO(OH)}_2$, dibenzylphosphinic acid, $(\text{C}_6\text{H}_5\text{CH}_2)_2\text{PO(OH)}$, and tribenzylphosphine oxide, $(\text{C}_6\text{H}_5\text{CH}_2)_3\text{PO}$. It is evident that the hydrogen atoms of phosphonium iodide participated in the reaction and that the resulting α -hydroxy derivatives were reduced by hydriodic acid. Such reduction of α -hydroxyphosphonic acids has been observed by Fossek.⁶⁷

A rather extensive series of experiments by Ville⁶⁸⁻⁷¹ and by Marie⁷²⁻⁸³ between 1889 and 1904 established the general nature of this reaction of ketones and aldehydes. In reactions with hypophosphorous acid, phosphorous acid, and various phosphonous acids a large number of phosphonic and phosphinic acids were prepared. These compounds are listed in Table IV.

The reaction is conducted by heating a mixture of the carbonyl compound with the desired phosphorous acid for a prolonged period of

⁶⁶ Litthauer, *Ber.*, **22**, 2144 (1889).

⁶⁷ Fossek, *Monatsh.*, **5**, 121 (1884); **7**, 20 (1886).

⁶⁸ Ville, *Compt. rend.*, **109**, 71 (1889).

⁶⁹ Ville, *Compt. rend.*, **107**, 659 (1888).

⁷⁰ Ville, *Compt. rend.*, **110**, 348 (1890).

⁷¹ Ville, *Ann. chim. phys.*, (6), **23**, 289 (1891).

⁷² Marie, *Compt. rend.*, **133**, 219 (1901).

⁷³ Marie, *Compt. rend.*, **135**, 106 (1902).

⁷⁴ Marie, *Compt. rend.*, **135**, 1118 (1902).

⁷⁵ Marie, *Compt. rend.*, **133**, 818 (1901).

⁷⁶ Marie, *Compt. rend.*, **134**, 286 (1902).

⁷⁷ Marie, *Compt. rend.*, **134**, 847 (1902).

⁷⁸ Marie, *Compt. rend.*, **136**, 508 (1903).

⁷⁹ Marie, *Compt. rend.*, **136**, 48 (1903).

⁸⁰ Marie, *Compt. rend.*, **136**, 234 (1903).

⁸¹ Marie, *Compt. rend.*, **138**, 1707 (1904).

⁸² Marie, *Ann. phys. chim.*, (8), **3**, 335 (1904).

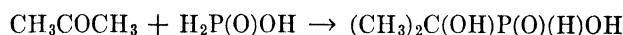
⁸³ Marie, *Compt. rend.*, **137**, 124 (1903).

time. Evaporation of the mixture yields the crude reaction product, which may be isolated by crystallization from suitable solvents.

When hypophosphorous acid is used, both its hydrogen atoms bound to phosphorus, i.e., hydrogens which are not titratable, can participate in the reaction. Such disubstitution is favored, as might be expected, by an excess of the carbonyl compound and by prolonged reaction time. The final product is a phosphinic acid, as illustrated by the following representation of the reaction of acetone.



If the reaction is interrupted before the completion of disubstitution, it is possible to isolate both the disubstituted (phosphinic) acid, shown above, and the monosubstituted (phosphonous) acid, which is formed in the primary reaction in which only one hydrogen atom of hypophosphorous acid is involved. Usually the reaction mixture contains appre-



ciable amounts of a phosphonic acid, which is produced by oxidation of the phosphonous acid, probably by the action of atmospheric oxygen. In the reaction described above, this acid is 2-hydroxy-2-propanephosphonic acid, $(\text{CH}_3)_2\text{C(OH)PO(OH)}_2$.

The α -hydroxy phosphonous acids, obtained at the intermediate stage of the reaction, are obviously capable of further condensation with carbonyl compounds, because they still have one phosphorus-hydrogen linkage. It is possible to isolate these phosphonous acids and to use them in condensations with carbonyl compounds which are different from those used in the first stage. Such a procedure results in the formation of unsymmetrical phosphinic acids.

When phosphorous acid or a phosphonous acid is used in the carbonyl condensation, only one hydrogen atom is available for the reaction and, hence, the formation of a single product is assured. The products made with the aid of phosphorous acid are phosphonic acids; those made with the aid of a phosphonous acid are phosphinic acids.

Although the formation of the phosphinic acids by the condensations with hypophosphorous acid can be made to proceed almost quantitatively, there is no information about the yields of the intermediate phosphonous acids under such conditions. Similarly, there has not appeared any information about the variations of experimental conditions, such as temperature.

The reaction has been applied to a variety of aldehydes and ketones, including acetaldehyde (in the form of paraldehyde), isovaleraldehyde,

heptanal, benzaldehyde, acetone, methyl ethyl ketone, diethyl ketone, methyl propyl ketone, acetophenone, and benzophenone.

The main difficulty in this reaction is the necessity of working with phosphorus acids which generate some phosphine on heating. This tendency is particularly pronounced with hypophosphorous acid. *Proper ventilation is required for this work in order to reduce the health hazard.*

The reaction is conducted with crystalline, essentially anhydrous, acids merely by heating them with the carbonyl compounds on a steam bath with suitable protection from atmospheric moisture. The duration of each reaction must be determined empirically, because no precise information can be found in the literature. When the phosphinic acids are being prepared, it suffices to purify the final product by removing any excess carbonyl compound and crystallizing the residual matter from a suitable solvent; water and ethanol have been favored. The α -hydroxyphosphonic acids, prepared from phosphorous acid, are purified similarly, although the purification through a salt of a heavy metal (usually lead) may be necessary to remove inorganic impurities. The α -hydroxy phosphonous acids are usually isolated from the filtrates after the removal of phosphinic acids, which are less soluble; such recovery may involve either a simple evaporation or, more commonly, a purification through a lead salt. The lead phosphonites are water soluble, in contrast to the lead salts of the corresponding phosphonic acids. The lead salts are readily converted to the free acids by treatment with hydrogen sulfide. The α -hydroxy phosphonous acids can be oxidized to the corresponding α -hydroxy phosphonic acids by mercuric chloride or, preferably, by a small excess of bromine water.

EXPERIMENTAL PROCEDURES

α -Toluenephosphonic and Dibenzylphosphinic Acids.⁶⁶ A mixture of 10 g. of phosphonium iodide and 5 g. of benzaldehyde is heated in a sealed tube to 100° for four to five hours. On cooling, the tube is opened and appreciable amounts of phosphine and hydrogen iodide are allowed to escape. The reaction mixture is warmed with a small amount of water, and the warm solution is filtered. Evaporation of the solution gives α -toluenephosphonic acid, m.p. 166°. The yield is variable, averaging 10–15%. The water-insoluble mass is triturated with dilute potassium hydroxide, and the filtrate is acidified with hydrochloric acid to give 15–20% of dibenzylphosphinic acid, which, after crystallization from ethanol, melts at 191°.

Di(α -hydroxyisopropyl)phosphinic Acid.⁷² A mixture of 400 g. of dry acetone and 250 g. of crystalline hypophosphorous acid is refluxed

with protection from atmospheric moisture. After seventy hours, the mixture attains a boiling point of 69°, at which time the reaction is stopped by cooling the mixture. After standing in an ice bath for several hours, the mixture is filtered and the crude di(α -hydroxyisopropyl)phosphinic acid is washed with a little cold acetone. The filtrate is again heated as described above and the process is repeated until complete conversion of hypophosphorous acid is accomplished. The product is recrystallized from hot ethanol and melts at 185–186° with decomposition.

If the filtrate from the initial isolation of the phosphinic acid is worked up, the phosphonous and phosphonic acids can be recovered as follows. The filtrate is freed of excess acetone by vacuum distillation, and the residual syrup is dissolved in water. The solution is neutralized with lead carbonate, and after filtration of the insoluble lead salts the filtrate is evaporated carefully to dryness. The dry residue is extracted with hot 95% ethanol. On cooling, the lead salt of α -hydroxyisopropyl-phosphonous acid separates. It is taken up in water, and hydrogen sulfide is passed into the solution until the precipitation of lead sulfide is complete. The filtrate is evaporated cautiously on a water bath, and the residue is made to crystallize by chilling. 2-Hydroxy-2-propane-phosphonous acid is obtained in the form of extremely hygroscopic colorless crystals, which melt at 40–41°. The water-soluble fraction of the lead salts being removed, the insoluble residue of the lead salts of the phosphonic acid is suspended in water and the mixture is treated with hydrogen sulfide as described above. Evaporation of the filtrate and cooling yield 2-hydroxy-2-propanephosphonic acid, which after crystallization from acetic acid melts at 169–170°.

The phosphonous acid, obtained above, may be readily oxidized to the corresponding phosphonic acid by treating its water solution with 2 molecular equivalents of mercuric chloride,⁷⁶ ferric chloride,⁷⁶ or, preferably, bromine water.⁷⁴ If the metal salts are used for oxidation, the mixture is treated with hydrogen sulfide, and the filtrate is evaporated to recover the product. The use of bromine water simplifies the recovery, because it is merely added to the aqueous solution of the phosphonous acid until a permanent color is obtained and the resulting solution is evaporated to dryness. Usually an additional evaporation with water is advisable in order to remove the residual hydrobromic acid.

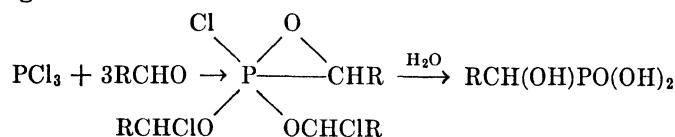
α -Hydroxyethanephosphonic Acid.⁷⁹ Crystalline phosphorous acid is heated on a steam bath with a large excess of paraldehyde under a reflux condenser which is protected by a calcium chloride tube. After one hundred hours, the dark mixture is poured into cold water and the tarry matter is removed by filtration. The residual phosphorous acid

is destroyed by the addition of bromine water until permanent color is established. The excess bromine is removed by bubbling air through the solution, and, after the solution is made alkaline with aqueous ammonia and the phosphate ion is precipitated by magnesia mixture, the precipitate is discarded and the filtrate is evaporated to dryness. The residue is taken up in water and is neutralized with acetic acid. Lead acetate solution is added to precipitate the lead salt of the desired product. The lead salt is collected, washed with cold water, and suspended in water into which hydrogen sulfide is passed until the precipitation of lead sulfide is complete. The sulfide is removed by filtration, and the filtrate is evaporated to dryness to give, after standing in a vacuum desiccator, colorless crystals of α -hydroxyethanephosphonic acid, m.p. 74–78°. The yield varies, averaging 25–35%.

Addition of Phosphorus Chlorides

The synthesis of phosphonic and phosphinic acids by the addition of certain phosphorus chlorides to carbonyl compounds provides an alternative method for the preparation of α -hydroxy derivatives. In addition, this reaction serves as a source of certain β -keto phosphonic and phosphinic acids.

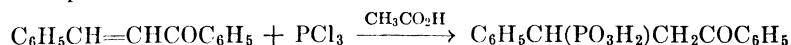
The reaction was discovered by Fossek,⁶⁷ who found that a number of aldehydes, including acetaldehyde, propionaldehyde, isobutyraldehyde, heptanal, and benzaldehyde, react with phosphorus trichloride, forming substances containing 3 units of the aldehyde to 1 unit of phosphorus trichloride. When one of these products was treated with water, 2 molecular equivalents of the aldehyde and 3 equivalents of hydrogen chloride were liberated. Evaporation of the aqueous solution gave a crystalline acid which was identified as the corresponding α -hydroxy phosphonic acid. Fossek visualized the reaction in the following manner.



Several years later, Michaelis⁶² showed that the same reaction can be used with phenyldichlorophosphine. He reported the reactions of this substance with acetaldehyde and with benzaldehyde. The hydroxy phosphinic acids produced had the structures shown below.



Except for minor variations,⁸⁴ the subject was dormant for twenty years, when Conant resumed a study of this reaction under somewhat different experimental conditions. He showed that mixtures of phosphorus trichloride with an essentially equimolar amount of saturated aldehyde or ketone, on treatment with an excess of acetic acid or acetic anhydride and then with water, give α -hydroxyphosphonic acids in yields comparable to those obtained by Fossek. The main difference between the procedures used by these investigators was that in the later work of Conant the excess of the carbonyl compound, which was advocated by Fossek, was replaced by the acetic acid or anhydride. In the course of this work it was also found that α,β -unsaturated ketones undergo an analogous reaction, yielding on hydrolysis the corresponding β -keto phosphonic acids. The overall reaction is shown for benzalacetophenone.



Similar reactions were successfully conducted when phosphorus trichloride was replaced by substituted trivalent phosphorus chlorides. These included phenyldichlorophosphine ($\text{C}_6\text{H}_5\text{PCl}_2$),^{85,86} diphenylchlorophosphine ($\text{C}_6\text{H}_5)_2\text{PCl}$,⁸⁷ phenyl dichlorophosphite ($\text{C}_6\text{H}_5\text{OPCl}_2$),⁸⁸ methyl dichlorophosphite (CH_3OPCl_2),⁸⁸ and ethyl dichlorophosphite ($\text{C}_2\text{H}_5\text{OPCl}_2$).⁸⁸ In a subsequent paper by Drake and Marvel⁸⁹ it was shown that butyl dichlorophosphine, $\text{C}_4\text{H}_9\text{PCl}_2$, also reacts in the expected manner. It may be said, qualitatively at least, that this reaction is general for trivalent phosphorus chlorides. The quantitative aspect of the problem has not been explored adequately, but there are indications of some inexplicably low yields with several substituted phosphorus chlorides.⁸⁸ It was also found that benzophenone and camphor fail to react under the conditions cited above. Attempts to raise the reaction temperature above approximately 30–35° led to a vigorous reaction between phosphorus trichloride and acetic acid (or anhydride) which took precedence over the other reaction. It was found, however, that when benzoic acid was used instead of acetic acid the normal reaction could be carried out at higher temperatures.

When acetic anhydride is used in the reaction of an α,β -unsaturated ketone, evaporation of the reaction mixture leaves a residue of a very reactive substance, which on heating with phenol or an alcohol forms

⁸⁴ Page, *J. Chem. Soc.*, **101**, 423 (1912).

⁸⁵ Conant and Pollack, *J. Am. Chem. Soc.*, **43**, 1665 (1921).

⁸⁶ Conant, Bump, and Holt, *J. Am. Chem. Soc.*, **43**, 1677 (1921).

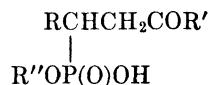
⁸⁷ Conant, Braverman, and Hussey, *J. Am. Chem. Soc.*, **45**, 165 (1923).

⁸⁸ Conant, Wallingford, and Gandheker, *J. Am. Chem. Soc.*, **45**, 762 (1923).

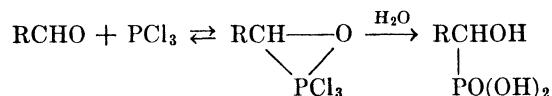
⁸⁹ Drake and Marvel, *J. Org. Chem.*, **2**, 387 (1937).

an ester of the β -keto phosphonic acid which would be normally obtained by hydrolysis of the reaction mixture. This behavior of the intermediate suggested to Conant that its structure is that of a cyclic mixed chloride anhydride, containing phosphorus, oxygen, and carbon atoms in the ring, which is formed by a 1,4 addition across the carbonyl group and the double bond. (See below.)

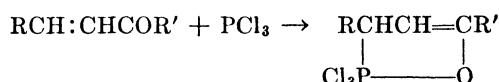
The subsequent work of Drake and Marvel⁸⁹ showed that the above-mentioned intermediate reacts with long-chain alcohols to yield mono-alkyl esters of the type mentioned above. The alcohols used in this work included 1-decanol, 1-dodecanol, 1-tetradecanol, 1-hexadecanol, 1-octadecanol, and octadec-9-en-1-ol. Although the products were insoluble in alkali, they were assigned the structures of mono esters shown in the accompanying formula (R'' is the alcohol residue), because the analyses and the determination of active hydrogen by the Grignard reagents indicated the existence of a reactive hydrogen atom.



The behavior of mixtures of phosphorus trichloride and saturated carbonyl compounds was explained by Conant⁹⁰ by the formation of a 1,2 addition product across the carbonyl group with the consequent formation of a three-membered ring structure. Reaction of such a compound with water would be expected to give the α -hydroxy phosphonic acids. Such a reaction scheme for benzaldehyde is shown in the accompanying formulation originated by Conant.



A similar mechanism, involving the 1,4 addition, was proposed for the reaction of α,β -unsaturated ketones.



It was believed that acetic acid, or acetic anhydride, could react with the primary adduct more readily than with more phosphorus trichloride. This was taken to be the reason for the fact that the reaction goes to completion instead of coming to a definite equilibrium, such as is attained by mixtures of phosphorus trichloride and the carbonyl compounds without added reagents.

⁸⁹ Conant and Cook, *J. Am. Chem. Soc.*, **42**, 830 (1920).

A precise study of the reaction rates, however, forced Conant to abandon the mechanisms shown above as untenable.⁹¹ Not only did the kinetic studies show the improbability of the above reaction mechanism, but also the existence of the cyclic intermediates was shown to be the result of a secondary reaction. It was further shown that the very slow addition of 1 mole of water to a mixture of benzaldehyde and phosphorus trichloride, followed by hydrolysis of the mixture with cold water, leads to good yields of α -hydroxy- α -toluenephosphonic acid. If the reaction mixture after the addition of a mole of water was heated, a mole of hydrogen chloride was evolved and the resulting syrup behaved like a lactone, i.e., like the products obtained by the older technique when acetic anhydride was used in the reaction mixture. As a result of this work, Conant was unable to supply a satisfactory alternative mechanism. He suggested that the overall reaction may be best represented by a trimolecular interaction.



or



The phosphoryl chlorides shown above may be expected to give the free acids on treatment with water, or esters upon treatment with alcohols.

SCOPE AND LIMITATIONS

The reaction performed according to Conant's procedures has been used with success with the following carbonyl compounds: acetone,⁹² methyl ethyl ketone,⁹² ethyl propyl ketone,⁹² methyl *tert*-butyl ketone,⁹² acetophenone,⁹² dibenzyl ketone,⁹² benzylacetophenone,⁹² dibenzyl-acetone,⁹² and benzophenone,⁹² as well as acetaldehyde,⁵² heptanal,⁹² and benzaldehyde.^{52, 93} The Fossek procedure was successfully used with formaldehyde,⁸⁴ acetaldehyde,^{52, 67} propionaldehyde,⁶⁷ isobutyraldehyde,⁶⁷ isovaleraldehyde,^{67, 84} hexanal,⁶⁷ and benzaldehyde.^{52, 67} A procedure similar to that of Conant was successfully used with pyruvic acid⁹⁴ to produce α -hydroxy- α -phosphonopropionic acid.

Successful additions to the following α,β -unsaturated ketones were reported: benzalacetophenone,^{89, 90, 95} *p*-methoxybenzalacetophenone,⁹⁵ dibenzalacetone,^{86, 95} cinnamylideneacetophenone,⁸⁶ *p*-chlorobenzalacetone.

⁹¹ Conant and Wallingford, *J. Am. Chem. Soc.*, **46**, 192 (1924).

⁹² Conant, MacDonald, and Kinney, *J. Am. Chem. Soc.*, **43**, 1928 (1921).

⁹³ Conant and MacDonald, *J. Am. Chem. Soc.*, **42**, 2337 (1920).

⁹⁴ Bernton, *Ber.*, **58**, 661 (1925).

⁹⁵ Conant, *J. Am. Chem. Soc.*, **39**, 2679 (1917).

phenone,⁹⁶ mesityl oxide,⁸⁹ *sym*-dibenzoylethylene,⁸⁹ and 5-ethyl-3-nonen-2-one.⁸⁹

Whereas aldehydes react satisfactorily in this reaction, ketones tend to yield mixtures from which appreciable amounts of the corresponding unsaturated phosphonic acids can be isolated. These result from dehydration or dehydrohalogenation of the primary reaction products. Thus, acetophenone readily yields the corresponding styrenephosphonic acid derivative, $C_6H_5C(PO_3H_2)=CH_2$,^{92, 97} and aliphatic ketones yield α -hydroxy phosphonic acids contaminated with varying amounts of similar by-products. This leads to considerable difficulty in crystallization of the reaction mixtures, and the products often have to be purified through metallic salts. Conant⁹² recommends the use of lead salts. The reaction of acetophenone was studied in some detail, and it was shown that, besides the normally expected α -hydroxy acid and the styrene derivative, it is possible to secure good yields of the corresponding α -chloro phosphonic acid if the primary reaction mixture is saturated with hydrogen chloride.

As was mentioned earlier, benzophenone is too sluggish for the usual reaction in the presence of acetic acid, and the reaction must be run at approximately 150° in benzoic acid. A similar procedure was necessary for camphor, although the final product was not obtained in a pure state. Benzil and anthraquinone failed to react even under these conditions.⁹²

Although Drake and Marvel⁸⁹ showed that phosphorus trichloride can be made to add to 9-ethyltridec-7-en-6-one, 5-ethylhept-3-en-2-one, 3,9-diethylhendec-4,7-dien-6-one, 3-ethyldodec-4-en-6-one, and 3-ethylhendec-4-en-6-one, pure products could not be isolated.

The tendency of the ketones to yield unsaturated products of the type discussed above was successfully utilized by Hamilton,⁹⁸ who found that the crude products can readily be converted to the pure unsaturated derivatives by passage through a tube heated to 190–220°, or by heating the mixtures with acetic anhydride to 150°. Heating with phosphorus pentachloride serves not only to yield the unsaturated acids but also to convert them to the corresponding unsaturated phosphoryl dichlorides, which can be readily purified by distillation under reduced pressure. The procedure is most clearly described for the product of the acetone-phosphorus trichloride reaction; the dehydration treatment described above gives 70–80% yields of 1-propene-2-phosphonyl dichloride, $CH_2=C(CH_3)POCl_2$, which can be readily purified by vacuum distillation.

⁹⁶ Conant and Jackson, *J. Am. Chem. Soc.*, **46**, 1003 (1924).

⁹⁷ Conant and Coyne, *J. Am. Chem. Soc.*, **44**, 2530 (1922).

⁹⁸ Hamilton, U. S. pat. 2,365,466 [*C. A.*, **39**, 4619 (1945)].

The final modification of the reaction, introduced by Conant, i.e., the slow addition of water to the reaction mixture, was used by him only for benzaldehyde. The scope and the limitations of this very simple procedure cannot be estimated because it succeeds probably by the virtue of differential reactivities of the reaction intermediates with water.

The nature of the phosphorus chloride derivative seems to be unimportant in this reaction provided that it is a chloride of trivalent phosphorus.

EXPERIMENTAL PROCEDURES

α -Hydroxy- α -toluenephosphonic Acid (Fossek Procedure).⁸⁴ Thirty-seven grams of phosphorus trichloride is slowly added to 114 g. of benzaldehyde. The mixture is allowed to stand overnight with protection from moisture. The resulting oil is poured into 3 l. of cold water, and the aqueous layer is separated, filtered, and evaporated on a steam bath. After the addition of 500 ml. of water to the residue, the solution is re-evaporated to dryness to expel the residual hydrochloric acid. The resulting syrup is rubbed with dry ether to induce crystallization, and the product is recrystallized from a 2:1 mixture of benzene and acetic acid to give 42 g. (84%) of α -hydroxy- α -toluenephosphonic acid, m.p. 170°.

A similar reaction with formaldehyde is too vigorous to control. The use of paraformaldehyde, however, in a procedure similar to the above readily gives a 93% yield of hydroxymethanephosphonic acid, m.p. 85°.

Conant Procedures (Saturated Carbonyl Compounds).⁹² The carbonyl compound is mixed with a 10% molar excess of phosphorus trichloride at 30–35°, and, after standing for two or three hours, the solution is treated with 3 moles of acetic acid, which is added with cooling at 20–30°. The mixture is allowed to stand for six to twelve hours at room temperature with protection from atmospheric moisture. It is then poured into cold water, and the solution is evaporated to dryness. If the product fails to crystallize, it is converted to the lead salt with lead acetate, after the removal of inorganic phosphorus with magnesium nitrate and aqueous ammonia. This procedure gives, when 10 g. of acetone and 30 g. of phosphorus trichloride are used, a 91% yield of 2-hydroxy-2-propanephosphonic acid, m.p. 167–169° after crystallization from acetic acid.

α -Chloro- α -phenylethanephosphonic Acid.⁹⁷ Ten grams of acetophenone and 14.2 g. of phosphorus trichloride are mixed at room temperature, and after standing for two hours with protection from atmospheric moisture the solution is treated with 25 g. of glacial acetic acid

at 25°. The solution is allowed to stand overnight, after which a stream of dry hydrogen chloride is passed through it for two hours. The resulting solid is sucked dry on a sintered-glass filter. Recrystallization from ether gives 16 g. (87%) of α -chloro- α -phenylethane- α -phosphonic acid, m.p. 174–175°.

α -Hydroxy- α -phenylethanephosphonic Acid. The normally expected hydroxy acid is readily obtained only by careful hydrolysis of the above chloro acid. It cannot be obtained by the normal procedure, because it is too readily attacked by hydrochloric acid on heating. The hydrolysis procedure is as follows: Ten grams of the chloro acid, obtained above, is dissolved in 200 ml. of cold water, and the solution is allowed to stand at room temperature for two days. The solution is evaporated without warming by means of an air jet, and the residual syrup is placed in a vacuum desiccator, where it crystallizes after several days. There is obtained 7.5 g. (81%) of α -hydroxy- α -phenylethane- α -phosphonic acid, which melts at 154–155° after crystallization from a chloroform-ether mixture.

The chloro acid is also the best source of the styrene derivative, $C_6H_5C(PO_3H_2)=CH_2$. The chloro acid evolves hydrogen chloride on being heated to 180°; the cooled product on crystallization from a chloroform-ether mixture gives 80–90% yields of the unsaturated acid, m.p. 112–113°.

α,α -Diphenyl- α -hydroxymethanephosphonic Acid. Sluggish compounds like benzophenone can be phosphonated at elevated temperatures. A mixture of 10 g. of benzophenone and 20 g. of benzoic acid is melted on a steam bath, and 10 g. of phosphorus trichloride (55% excess) is added to the hot mixture during five to ten minutes. The mixture is heated to 155° in the course of ten minutes and is then allowed to cool to 130°, at which temperature it is kept for two or three hours. After cooling to 90°, the mixture is poured into 500 ml. of water. Sodium hydroxide solution is added to faint alkalinity, and the mixture is heated on a steam bath for four to five hours. The mixture is diluted to 750 ml., cooled, and extracted with ether to remove the unreacted ketone. The aqueous solution is acidified with hydrochloric acid and cooled in ice water, and the precipitated benzoic acid is filtered. The filtrate is evaporated to 250 ml., and the residual solution is extracted with ether. Evaporation of the extract gives a rapidly solidifying oil, which is fractionally crystallized from water slightly acidified with hydrochloric acid. There is obtained 7 g. (50%) of α,α -diphenyl- α -hydroxymethanephosphonic acid,⁹² m.p. 171–172°.

α -Hydroxy- α -toluenephosphonic Acid.⁹¹ A mixture of 10 g. of benzaldehyde and 13 g. of phosphorus trichloride is cooled by means of an ice

bath, and, with vigorous stirring, 1.7 g. (1 mol. eq.) of water is added in small droplets in the course of fifteen minutes. The solution is kept at 10–15° until the evolution of hydrogen chloride subsides. The resulting yellow oil is poured into cold water, and the solution is evaporated to dryness at room temperature by means of an air jet. The residual oily product is converted to the aniline salt by treatment with aniline in ether solution. There is obtained 13.5 g. (57%) of the aniline salt of α -hydroxy- α -toluenephosphonic acid, which melts at 201–202° after crystallization from ethanol.

1-(4'-Methoxyphenyl)-2-benzoylethane-1-phosphonic Acid.⁹⁵ A suspension of 19 g. of *p*-anisalacetophenone in 40 ml. of glacial acetic acid is treated with 14 g. of phosphorus trichloride. The solution becomes cool and turns red. On standing overnight the color fades to yellow. The solution is poured into 500 ml. of water, and the rapidly solidifying oil is collected. It is redissolved in dilute sodium carbonate solution, the solution is extracted with ether to remove the unreacted ketone, and the aqueous solution is acidified with hydrochloric acid to give 23 g. (89%) of the keto phosphonic acid, m.p. 189°, after crystallization from dilute ethanol.

α -Phosphono- α -hydroxypropionic Acid.⁹⁴ Ten grams of pyruvic acid is treated with 15.5 g. of phosphorus trichloride with efficient stirring and cooling. Considerable amounts of hydrogen chloride are evolved. The mixture is stirred until a homogeneous solution is formed. This is allowed to stand overnight with protection from moisture. Then, 20.4 g. of acetic acid is added with stirring and cooling, and the mixture is allowed to stand for twelve hours. The resulting oil is poured into water, and the solution is evaporated under reduced pressure at 30–40°. The oily residue crystallizes on standing in a vacuum desiccator. Recrystallization from acetic acid gives 5–6 g. (about 40%) of somewhat hygroscopic colorless crystals, m.p. 165–170°.

THERMAL DECOMPOSITION REACTIONS

The preparation of certain intermediates for the synthesis of phosphonic and phosphinic acids by reactions which involve thermally induced dissociation or displacement may be divided for convenience into four categories. It must be understood that this division is arbitrary and that it does not necessarily imply that a different reaction mechanism operates in each category. As a matter of fact, the exact mechanisms involved in these reactions are essentially unknown, and only fragmentary uncorrelated observations have been made on most of them. The preparations have been conducted in a purely empirical

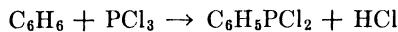
in manner; undoubtedly, considerable improvements in the yields and on the procedures may be expected in the future. The arbitrary classification adopted here is as follows.

- a.* Pyrolytic reactions.
- b.* Displacements with organomercury compounds.
- c.* Thermal decomposition of phosphonium compounds.
- d.* Disproportionation of phosphonous acids.

Pyrolytic Reactions

Pyrolysis is used to prepare a very limited number of monosubstituted dichlorophosphines of the aromatic series. The dichlorophosphines can be converted to the corresponding phosphonic acids by reactions which were discussed under the Friedel-Crafts reaction.

Michaelis⁹⁹ observed that when vapors of a mixture of phosphorus trichloride and benzene are allowed to contact a hot surface (at red heat) phenyldichlorophosphine is formed in accordance with the following equation.



This observation led to the construction of various pieces of equipment in which the reaction could be carried out in a convenient manner.¹⁰⁰⁻¹⁰³ The essential feature of all of them is a provision for leading the vapor mixture over the heated surface. The phenyldichlorophosphine, prepared as indicated above, is purified by distillation of the reaction mixture in a carbon dioxide atmosphere. The distillate, b.p. 225°, usually contains some free phosphorus and phosphine. It is best purified by heating for several hours at nearly reflux temperature in a stream of carbon dioxide.¹⁰¹

The use of the pyrolysis for preparative purposes appears to be limited to benzene. Only two other substances, thiophene⁵³ and toluene,^{52,104} have been converted to the corresponding dichlorophosphines by this method. With both compounds the yields were discouragingly poor. In a run of eight days' duration only 14 g. of the dichlorophosphine was obtained from 100 g. of thiophene. The use of toluene gave principally pyrolytic products of toluene, free phosphorus, and a trace of a tolyldichlorophosphine, which was obtained in such a

⁹⁹ Michaelis, *Ber.*, **6**, 601, 816 (1873).

¹⁰⁰ Michaelis, *Ann.*, **181**, 265 (1876).

¹⁰¹ A. E. Arbuzov, dissertation, Kazan, 1914.

¹⁰² Lecoq, *Bull. soc. chim. Belg.*, **42**, 199 (1933).

¹⁰³ Bowles and James, *J. Am. Chem. Soc.*, **51**, 1406 (1929).

¹⁰⁴ Michaelis and Lange, *Ber.*, **8**, 1313 (1875).

small amount that it could not be characterized as such, but was converted to the acid, which appeared to be the *meta* isomer.

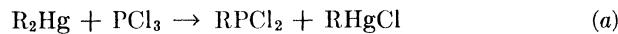
The above summary indicates the present scope of this reaction when phosphorus trichloride is used. However, a related reaction has been extended to phenyldichlorophosphine.^{101,105} This substance on being heated to 300° undergoes disproportionation to phosphorus trichloride and diphenylchlorophosphine, $(C_6H_5)_2PCl$; this reaction is best carried out by heating the dichlorophosphine in a sealed tube for seventy-two hours to 300°.¹⁰¹ The cooled solution is filtered, and the filtrate is fractionated to give 40–50% yields of diphenylchlorophosphine, b.p. 178°/14 mm. The reaction does not seem to be applicable to other dichlorophosphines.

Displacements with Organomercury Compounds

Michaelis¹⁰⁰ found that phenyldichlorophosphine can be obtained from phosphorus trichloride and diphenylmercury.



The reaction has been used by many later workers for the preparation of mono- and di-substituted chlorophosphines. It appears to be a two-step reaction, with both reactions usually occurring, as shown below.



The second step is favored by higher temperature and by an excess of phosphorus trichloride.¹⁰⁶ The reaction can be used for the synthesis of disubstituted chlorophosphines by employing monosubstituted dichlorophosphines instead of phosphorus trichloride. It is obvious that a mixture from such a reaction contains mono- and di-substitution products and may even contain traces of tertiary phosphines. The presence of the higher substitution products has been recognized for a long time,^{100,107} but no detailed study of the extent of the side reactions has been reported. The desired product can be readily separated from the products of higher degree of substitution by distillation. However, the chlorophosphines obtained in this manner are usually contaminated with considerable amounts of organomercury compounds, which are extremely difficult to remove by distillation.^{89,100,107} It is doubtful that a product completely free of mercury can be isolated from reaction

¹⁰⁵ Dörken, *Ber.*, **21**, 1505 (1888).

¹⁰⁶ Michaelis, *Ber.*, **13**, 2174 (1880).

¹⁰⁷ Guichard, *Ber.*, **32**, 1572 (1899).

mixtures of this category. This difficulty is of little importance, however, if the product is to be converted to a phosphonic or a phosphinic acid by methods given in the earlier sections. The mercury contaminants are best removed after such conversion.

The most favorable factor in this reaction lies in its capacity to produce definite products having the same carbon structures as those of the organomercury intermediates. Phosphorus enters the molecule at the site of the mercury attachment. For this reason, the reaction has been used for identification, by providing compounds of definite structures as reference substances suitable for comparison with compounds obtainable from the Friedel-Crafts reaction.

The present scope of the reaction includes both aliphatic and aromatic compounds, the list of which is given in Table V. The yield has been reported for only one alkyldichlorophosphine, butyldichlorophosphine, 61%.⁸⁹ The yield of aromatic dichlorophosphines usually exceeds 50%, except for the 2,4-dimethylphenyl derivative (20%)⁶¹ and the 2,4,5-trimethylphenyl derivative (20%).⁵² The yields of diarylmonochlorophosphines vary between 30% and 64%.

The reactions are conducted at approximately 200°, using either sealed tubes or ordinary reflux apparatus with a provision for an inert atmosphere. Although many compounds appear to react at fairly low temperatures, it is generally advisable to heat the mixture near the end of the reaction to temperatures in excess of 150°, principally to convert the mercury compounds to mercuric chloride, the bulk of which may be removed by filtration. The necessity for high temperatures limits the usefulness of this reaction to compounds that can withstand such heat.

EXPERIMENTAL PROCEDURES

p-Tolylphenylchlorophosphine.¹⁰⁸ A mixture of 78 g. of phenyldichlorophosphine and 60 g. of di-p-tolylmercury is heated in a reflux apparatus in a carbon dioxide atmosphere for two or three hours to 270°. On cooling, the mixture is extracted with benzene and filtered, and the filtrate is distilled to give 30 g. (63.5%) of *p*-tolylphenylchlorophosphine, b.p. 230–240°/100 mm.

Phenyldichlorophosphine.¹⁰⁰ Ten grams of diphenylmercury and 34 g. of phosphorus trichloride are heated in a sealed tube for five hours at 180°. On cooling, the mixture is filtered and the filtrate, on distillation, gives crude phenyldichlorophosphine, which is allowed to stand until the metallic mercury droplets settle. Filtration and distillation

¹⁰⁸ Pope and Gibson, *J. Chem. Soc.*, **101**, 735 (1912).

give 5 g. of essentially mercury-free product, b.p. 216–220°; the yield is nearly quantitative, if calculated by equation (a), p. 317.

n-Butyldichlorophosphine.⁸⁹ Fifty grams of di-n-butylmercury was placed in a Pyrex tube, which was flushed with dry nitrogen, and 100 g. of phosphorus trichloride was slowly run in. A white precipitate began to form almost immediately. The sealed tube was heated at 200° for nine hours. The cooled mixture was washed out with phosphorus trichloride and, upon distillation, gave 17 g. of n-butyldichlorophosphine, b.p. 157–160°, which still contained mercury, probably as butylmercury chloride.

Phenyl-p-bromophenylchlorophosphine.¹⁰⁹ A mixture of 98 g. of p-bromophenyldichlorophosphine and 85 g. of diphenylmercury was heated to 210° for seventy-five minutes in a nitrogen atmosphere. The cooled mixture was shaken with 200 ml. of dry petroleum ether and filtered. Distillation of the filtrate gave 35–40 g. (47–53%) of the product, b.p. 203–204°/11 mm.

Thermal Decomposition of Phosphonium Compounds

Thermal decomposition of true quaternary phosphonium halides gives derivatives of tertiary phosphines. However, when the related tertiary phosphine dichlorides are heated, the products contain disubstituted chlorophosphines which can be converted to phosphinic acids by methods indicated in previous sections. The general reaction scheme may be illustrated by the following representation.



The reaction was observed by Michaelis and Soden¹¹⁰ for the triphenyl derivative and by Collie and Reynolds¹¹¹ for the triethyl compound, although neither group was able to use the reaction for practical syntheses. Plets¹¹² developed a workable procedure based on this reaction. The results of his work are outlined below in some detail, because of the inaccessibility of the original publication.

The tertiary phosphine dichlorides are prepared either by addition of chlorine to the corresponding tertiary phosphines in an inert solvent (preferred for non-alkylated aromatic compounds), or by the reaction of phosphorus pentachloride with tertiary phosphine oxides (preferred

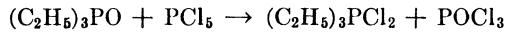
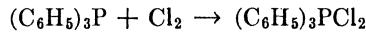
¹⁰⁹ Davies and Mann, *J. Chem. Soc.*, **1944**, 276.

¹¹⁰ Michaelis and Soden, *Ann.*, **229**, 295 (1885).

¹¹¹ Collie and Reynolds, *J. Chem. Soc.*, **107**, 367 (1915).

¹¹² V. M. Plets, dissertation, Kazan, 1938.

for alkyl or alkaryl compounds). It is possible to use thionyl chloride, sulfuryl chloride, sulfur monochloride, chlorosulfonic acid, or titanium



chloride in the second reaction instead of phosphorus pentachloride, but the yields are poor.

The resulting dichlorides are decomposed by heating at 150–220° in a distilling apparatus in an inert atmosphere. The products are distilled, and the yields of disubstituted chlorophosphines obtained in this manner range from 40% to 70%. The compounds prepared by Plets are listed in Table VI.

The present scope of this reaction is indicated by the extent of the table. It is probable, however, that the reaction can be run with many other tertiary phosphine derivatives. The variety of the compounds listed in the table indicates good versatility.

Although Plets indicates that the reaction possibly can be extended to the preparation of monosubstituted dichlorophosphines by a repetition of the reaction sequence on the monochloro compounds obtained as indicated above, no experimental proof has been presented. From the material on hand, it is impossible to set down the specific order of the ease of cleavage of the substituent groups from tertiary phosphine dichlorides in this reaction, as has been done for the true quaternary phosphonium compounds by Ingold and co-workers.¹¹³

A related reaction was used by Michaelis and others^{52, 108, 114} for the preparation of methylphenyl- and methyl-*p*-tolyl-phosphinic acids by thermal decomposition of the corresponding dipiperidylphosphonium hydroxides, according to the following scheme.



The exact mechanism of this reaction is obscure; it has been used only for the two compounds listed above. The procedure may be illustrated by the following example. Phenyl dipiperidylphosphine (prepared from phenyldichlorophosphine and piperidine) is treated with an equimolar amount of methyl iodide; the resulting phosphonium iodide is treated with an excess of moist silver oxide and filtered; and the filtrate is evaporated to dryness. The residue is dissolved in water and is re-evaporated to dryness, and the residue is heated to 150° for three or four hours. It is dissolved in water, treated with aqueous ammonia, and evaporated to dryness, and the residue is taken up in a little water. The solution is

¹¹³ Hey and Ingold, *J. Chem. Soc.*, **1933**, 531; Fenton, Hey, and Ingold, *ibid.*, **1933**, 989.

¹¹⁴ Michaelis, *Ber.*, **31**, 1037 (1898).

treated with silver nitrate; the silver salt is separated, suspended in water, and decomposed with the calculated amount of hydrochloric acid. After filtration from silver chloride, the solution is evaporated to give a 75% yield of methylphenylphosphinic acid, m.p. 133–134°.

With only the two examples in existence, it is impossible to define the scope or the limitations of this reaction.

EXPERIMENTAL PROCEDURES

Di-n-propylchlorophosphine.¹¹² A distillation apparatus, with a provision for the introduction of dry carbon dioxide, is charged with 17.6 g. of tri-n-propylphosphine oxide; 25 g. of phosphorus pentachloride is added, and the mixture is heated to 190–220°, at which point a considerable degree of foaming occurs. Heating must be carefully regulated, because any overheating produces appreciable amounts of yellow phosphorus and phosphines. When the reaction subsides, distillation under reduced pressure gives 9.1 g. (60%) of di-n-propylchlorophosphine, b.p. 99–101°/15 mm.

Diphenylchlorophosphine.¹¹² A solution of 26.2 g. of triphenylphosphine in 100 ml. of freshly distilled chloroform or carbon tetrachloride is treated with dry chlorine until the absorption is complete. A distillation condenser is attached, and while the apparatus is being swept by carbon dioxide the solvent is distilled; the residue is carefully heated to 190–210°, when a vigorous reaction commences. When the reaction subsides, the product is distilled and the distillate is redistilled in vacuum, yielding 9.9 g. (40%) of diphenylchlorophosphine, b.p. 178°/14 mm. (300–320°/760 mm.).

Disproportionation of Phosphonous Acids

Thermal disproportionation of phosphonous acids is a reaction common to oxygen acids of phosphorus which have a P-H linkage. The reaction has been observed with the aliphatic¹⁰⁷ and the aromatic¹¹⁵ compounds. It may be presented as a mutual oxidation-reduction reaction which proceeds according to the accompanying equation.



The reaction occurs on heating and generally requires temperatures above 100°. It is of no significance for preparative purposes, since the phosphonous acids employed in it usually are made from dichlorophosphines which can be converted directly and in almost quantitative yields

¹¹⁵ Michaelis and Ananoff, *Ber.*, **7**, 1688 (1874).

to phosphonic acids by reactions indicated in earlier sections. The simultaneous formation of the phosphines is another serious disadvantage to this reaction; *phosphines are generally very toxic*, and they possess disagreeable odors. The procedure is essentially that of dry distillation until the elimination of the phosphine is complete. Recrystallization of the residue from water yields the phosphonic acid. The yields are variable because the phosphonic acid may undergo dephosphonation at the temperatures employed. In most cases the reaction has been observed only qualitatively. Apparently it cannot be applied to α -hydroxy derivatives, for they suffer decomposition, with the loss of a carbonyl compound, before the oxidation-reduction can set in.

MISCELLANEOUS SYNTHESES

This section deals with synthetic methods that cannot be classified with the previously described procedures. Most of the reactions cited here have been explored but little, and their usefulness cannot be estimated accurately.

Oxidation of Phosphines and Phosphonous Acids

Primary and secondary phosphines, RPH_2 and $RR'PH$, can be oxidized by a variety of means to the corresponding phosphonic and phosphinic acids. However, the possible usefulness of this method is limited by a number of important factors. At the present time there is no satisfactory and safe way to prepare the phosphines in high purity. The venerable synthesis by heating mixtures of alkyl iodides, zinc oxide, and phosphonium iodide in sealed tubes gives poor yields of complex mixtures. It has been used only for very small-scale preparations. A possible solution is the synthesis of phosphines from sodium hydrogen phosphides (i.e., sodium derivatives of phosphine) and organic halides.¹¹⁶ The information about this synthesis is too meager to be evaluated here. Under any circumstances, the oxidation of phosphines presents serious difficulties because of the *toxicity of phosphines* and the inflammable nature of the lower members of the series. A number of acids have been prepared on a minute scale by evaporation of solutions of the phosphines in nitric acid.¹⁰⁷ There is information neither about the best conditions nor about the yields.

Oxidation of phosphonous acids is not a particularly good source of phosphonic acids, as mentioned in the preceding section on the disproportionation reactions. The only important exception to this gen-

¹¹⁶ Walling, U. S. pats. 2,437,795-8, [C. A., 42, 4198-4199 (1948)].

eralization is the oxidation of the α -hydroxy derivatives, which can be readily obtained from condensation reactions of carbonyl compounds. The methods of oxidation of these compounds have been discussed (p. 306). Another possible exception is the oxidation of N-dialkylaminobenzenephosphorous acids; these substances cannot be oxidized without decomposition by acidic reagents such as nitric acid, which is a common oxidant for other phosphonous acids.¹⁰⁷ Although the dimethylamino compound could be oxidized to the corresponding phosphonic acid⁶⁵ by 2 moles of mercuric chloride in aqueous solution, the higher members of the series suffered decomposition under these circumstances. Warming the acid with oxygenated water was found to be a good method for oxidizing both the dimethylamino and the diethylamino compounds, but there is no detailed information about the experimental conditions.¹¹⁷

Syntheses from Dialkylanilines

It will be recalled that in the section dealing with the Friedel-Crafts reaction mention was made of an early synthesis of *p*-dimethylamino-benzenephosphonic acid by that method.⁶⁵ It was found later by Bourneuf¹¹⁷ and Raudnitz¹¹⁸ that aluminum chloride is not necessary in the primary reaction, and that both the mono- and the di-substituted phosphine chlorides can be made by a direct reaction with phosphorus trichloride. Raudnitz worked only with dimethylaniline; Bourneuf used both dimethylaniline and diethylaniline, and he devised means for the direct synthesis of phosphonic and phosphinic acids in this series by using phosphorus oxychloride instead of phosphorus trichloride. The reactions used are shown in the accompanying equations. It will



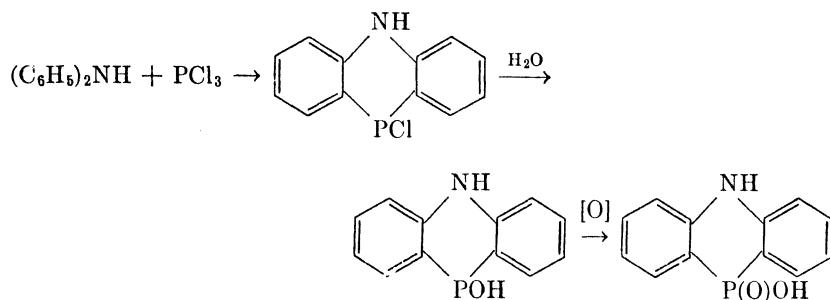
be noted that an excess of the amine is used to take up the hydrogen chloride generated in the reaction. The chlorides obtained in the reaction are then hydrolyzed to the corresponding acids.

A related reaction which depends on the reactivity of the *ortho* hydrogen atoms in diphenylamine has been used to prepare a derivative of the heterocyclic compound, dibenzophosphazine, in the form of the corresponding phosphinic acid.¹¹⁹

¹¹⁷ Bourneuf, *Bull. soc. chim. France*, **33**, 1808 (1923).

¹¹⁸ Raudnitz, *Ber.*, **60**, 743 (1927).

¹¹⁹ Sergeev and Kudryashov, *J. Gen. Chem. U.S.S.R.*, **8**, 266 (1938) [*C. A.*, **32**, 5403 (1938)].



The above interactions of phosphorus trichloride and phosphorus oxychloride with the dialkylanilines have been described only for dimethylaniline and diethylaniline. It is probable that other dialkylanilines can be used. The formation of the heterocyclic phosphinic acid described above is the only instance reported. It may be expected that substituted diphenylamines will produce the corresponding cyclic compounds.

EXPERIMENTAL PROCEDURES

Bis(4-dimethylaminophenyl)-phosphonic and -phosphinic Acids (Bourneuf Procedures).¹¹⁷ A mixture of 242 g. of dimethylaniline and 137 g. of phosphorus trichloride is heated on a steam bath for three hours under a reflux condenser with protection from moisture. The cooled mixture is added to a solution of 320 g. of sodium carbonate in 1 l. of water, and the excess dimethylaniline is removed by steam distillation. The residue is cooled for twenty-four hours, and 40 g. of insoluble solid is removed. The solution is treated with barium chloride until the precipitation of barium phosphate is complete, and the filtered solution is treated with excess saturated copper sulfate solution. The copper salt of the phosphonic acid is collected, suspended in water, and treated with hydrogen sulfide. Evaporation of the filtrate gives 110 g. (60%) of 4-dimethylaminobenzene phosphonic acid, m.p. 163°. The alkali-insoluble solid is extracted with boiling benzene, in which almost all of it dissolves. Cooling of the extract gives bis(4-dimethylaminophenyl)-phosphine oxide (or phosphinous acid), m.p. 169°, in 10% yield. This oxide is readily converted to the corresponding phosphinic acid by allowing a mixture of 4 g. of the oxide and 50 ml. of oxygenated water, to which just enough dilute sulfuric acid is added to effect solution, to stand for two days. Sodium carbonate is added until complete solution is attained, and the solution is acidified with acetic acid to give 4.2 g. (100%) of pure bis(4-dimethylaminophenyl)phosphinic acid, m.p. 249°.

The oxidation reactions may be avoided if phosphorus oxychloride is used. Thus, 75 g. of phosphorus oxychloride and 142 g. of dimethylaniline are heated to 130° for eight to nine hours in a reflux apparatus protected from moisture. Heating is stopped when the open-arm manometer attached to the reflux condenser begins to indicate a partial vacuum in the flask. The cooled mixture is carefully added to 1.5 l. of 10% sodium hydroxide solution, and the excess amine is removed by steam distillation. The residual solution is filtered after standing for twenty-four hours. The alkaline filtrate is acidified with acetic acid to give 85 g. (40%) of bis(4-dimethylaminophenyl)phosphinic acid, which is recrystallized from a mixture of benzene and methanol; m.p. 249° (on a copper block).

Dibenzophosphazinic Acid.¹¹⁹ A mixture of 21 g. of diphenylamine and 17 g. of phosphorus trichloride is heated in a reflux apparatus which is protected from atmospheric moisture. The heating is effected by an oil bath, the temperature of which is raised to 200–220° in the course of six hours. The hot solution is poured into 1 l. of cold water. (It is advisable to conduct this operation in an open-top box in which several lumps of Dry Ice are placed, so as to provide an inert atmosphere. The reaction mixture contains some free phosphorus which will burst into flame on exposure to air.) The solidified reddish mass is broken up under water and is repeatedly extracted with a total of 4 l. of hot water. On cooling, the hydroxyphosphine is collected, dried in a vacuum desiccator, and suspended in 200 ml. of tetralin which is contained in a reflux apparatus. The tetralin is brought to the boiling point, and air is bubbled slowly through the solution for one to two hours. The cooled mixture is filtered, and the dibenzophosphazinic acid is purified by precipitation from dilute sodium hydroxide solution by hydrochloric acid. The substance does not melt at 250°. The yield is approximately 17%.

Oxidative Phosphonation

This reaction is less well understood than any of the other procedures discussed in this chapter. The structures of the compounds formed have not been proved, but the potentialities of the reaction are sufficiently interesting to justify its mention. The process involves the reaction of unsaturated compounds with elemental phosphorus and oxygen simultaneously. The primary reaction product appears to be an adduct of phosphorus tetroxide to the double bond. Hydrolysis of this adduct yields a substance with two acidic phosphorus-containing groups at the previous site of the double bond. Drastic hydrolysis removes one acidic group, indicating that it is connected to the hydrocarbon by an ester

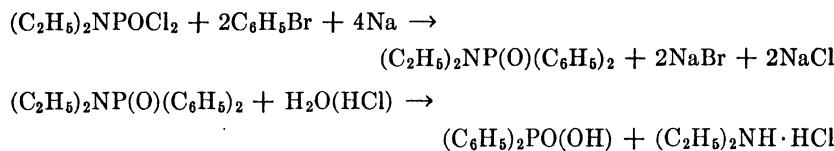
linkage. The remaining group is stable to hydrolysis and is a phosphorous acid group which can be oxidized to a phosphonic acid group.

The reaction was discovered by Willstätter and Sonnenfeld,¹²⁰ who applied it to cyclohexene, menthene, pinene, trimethylethylene, allyl alcohol, ethyl cinnamate, oleic acid, and olive oil. The products of hydrolysis were not characterized in detail, nor were the positions taken by the phosphono group and the ester phosphate group established. The phosphorous acid from cyclohexene was oxidized to the phosphonic acid by nitric acid. The reaction was also used by Montignie,¹²¹ who obtained an alkali-soluble product from a similar reaction of cholesterol. This product, which retains the hydroxyl group of cholesterol, was characterized as the acetate, which melted at 250°.

It is impossible to define the scope and the limitations of this reaction from the limited information available. However, it is one of the mildest methods for introduction of a phosphono group into an organic molecule.

Wurtz Reaction

Although the Wurtz reaction has been used freely to prepare tertiary phosphines, it appears to have been used but once for the synthesis of a definite acidic compound. Michaelis⁴ treated diethylamidophosphonyl chloride with 2 moles of bromobenzene and 4 atoms of sodium in ether solution, obtaining the N-diethylamide of diphenylphosphinic acid. Hydrolysis with hydrochloric acid gave the free acid. No yields were given. The reaction sequence may be shown by the equations below.



It is possible to visualize the extension of this reaction to many other compounds that have been prepared by means of the Grignard reaction in the past.

Direct Phosphonation of a Nitrogen Heterocycle

One instance of direct phosphonation by the reaction of phosphorus oxychloride with a pyrazole has been recorded. Michaelis and Pasternack¹²² heated phosphorus oxychloride with antipyrine (1-phenyl-

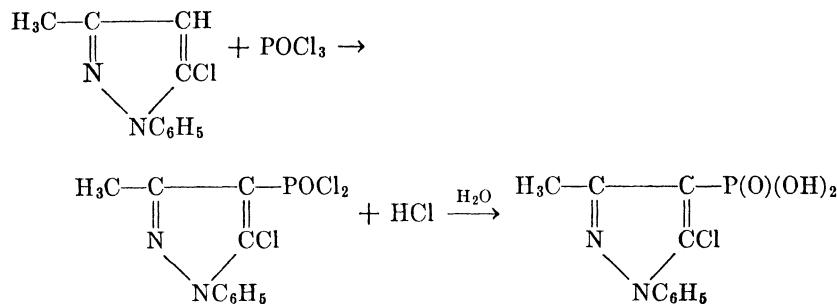
¹²⁰ Willstätter and Sonnenfeld, *Ber.*, **47**, 2801 (1914).

¹²¹ Montignie, *Bull. soc. chim. France*, (4), **49**, 73 (1931).

¹²² Michaelis and Pasternack, *Ber.*, **32**, 2411 (1899).

3-methyl-5-chloropyrazole) or its methochloride for twelve hours in a sealed tube to 200°. On treatment with water a white solid was obtained which, after washing with ether and recrystallization from water, melted at 191°. It was given the structure of 1-phenyl-3-methyl-5-chloropyrazole-4-phosphonic acid. No yields were given. It is impossible to judge whether the particular pyrazole used possessed a unique configuration which made this reaction possible.

The overall reaction scheme is shown below.



TABLES OF COMPOUNDS REPORTED BEFORE MAY, 1948

The following tables summarize the syntheses of the compounds covered by this chapter which had been reported in the literature before May, 1948. The compounds prepared by the primary reactions which introduce the phosphorus atom into the molecule are listed; the tables of compounds prepared by the organomercury derivatives and by thermal decomposition of phosphonium-type compounds list the chlorophosphines which can be converted to the acids by hydrolysis.

TABLE I
DERIVATIVES OF PHOSPHONIC AND PHOSPHINIC ACIDS PREPARED BY ALKYLATION
OF PHOSPHITES OR OTHER TRIVALENT ESTERS

Compound	Method*	Yield %	Reference
CH ₃ PO(OCH ₃) ₂	A	100	13
	D	—	6
CH ₃ PO(OC ₂ H ₅) ₂	A	100, 95	1, 13, 14
	B	45	10
CH ₃ PO(OC ₃ H ₇ - <i>i</i> so) ₂	A	95	14
CH ₃ PO(OC ₆ H ₅) ₂	A	—	1, 13
CH ₃ PO(OC ₆ H ₄ CH ₃ - <i>p</i>) ₂	A	—	1
CH ₃ PO(OC ₆ H ₄ CH ₃ - <i>m</i>) ₂	A	—	1
CH ₃ PO(OC ₆ H ₄ Cl- <i>p</i>) ₂	A	—	1
CH ₃ PO[OC ₆ H ₂ (CH ₃) ₃] ₂	A	—	1
CH ₃ PO(O ₂ C ₆ H ₄ - <i>o</i>)	A	100	123
CH ₃ PO[N(C ₂ H ₅) ₂] ₂	A	—	4
C ₂ H ₅ PO(OC ₂ H ₅) ₂	A	95	14
	B	35	3, 10
C ₂ H ₅ PO(O ₂ C ₆ H ₄ - <i>o</i>)	A	100	123
CH ₃ (CH ₂) ₂ PO(OC ₂ H ₅) ₂	A	100	13
	B	67	10
CH ₃ (CH ₂) ₂ PO(OC ₃ H ₇ - <i>n</i>) ₂	A	—	101
	D	—	6
CH ₃ CH=CHPO(OC ₂ H ₅) ₂	A	—	14
CH ₃ (CH ₂) ₃ PO(OC ₂ H ₅) ₂	A	—	14
CH ₃ (CH ₂) ₃ PO(OC ₄ H ₉ - <i>n</i>) ₂	A	—	124
	B	90	5
<i>i</i> so-C ₄ H ₉ PO(OC ₄ H ₉ - <i>i</i> so) ₂	A	—	125
CH ₃ (CH ₂) ₄ PO(OC ₂ H ₅) ₂	A	—	14
CH ₃ (CH ₂) ₄ PO(OC ₄ H ₉ - <i>n</i>) ₂	B	85	5
<i>i</i> so-C ₅ H ₁₁ PO(OC ₂ H ₅) ₂	A	—	14
CH ₃ (CH ₂) ₅ PO(OC ₂ H ₅) ₂	A	65	5, 14
CH ₃ (CH ₂) ₅ PO(OC ₄ H ₉ - <i>n</i>) ₂	B	93	5
CH ₃ (CH ₂) ₆ PO(OC ₂ H ₅) ₂	A	—	14
CH ₃ (CH ₂) ₆ PO(OC ₄ H ₉ - <i>n</i>) ₂	B	96	5
CH ₃ (CH ₂) ₇ PO(OC ₂ H ₅) ₂	A	—	14
CH ₃ (CH ₂) ₇ PO(OC ₄ H ₉ - <i>n</i>) ₂	B	88	5
CH ₃ (CH ₂) ₈ PO(OC ₂ H ₅) ₂	A	—	5
CH ₃ (CH ₂) ₈ PO(OC ₄ H ₉ - <i>n</i>) ₂	B	86	5
CH ₃ (CH ₂) ₉ PO(OC ₂ H ₅) ₂	A	—	5
CH ₃ (CH ₂) ₉ PO(OC ₄ H ₉ - <i>n</i>) ₂	B	90	5

* A = ester procedure; B = sodium salt procedure; C = triarylecarbinol-phosphorus trichloride procedure; and D = special methods.

TABLE I—Continued
DERIVATIVES OF PHOSPHONIC AND PHOSPHINIC ACIDS PREPARED BY ALKYLATION
OF PHOSPHITES OR OTHER TRIVALENT ESTERS

Compound	Method*	Yield %	Reference
$\text{CH}_3(\text{CH}_2)_{11}\text{PO}(\text{OC}_2\text{H}_5)_2$	A	63, 24	14, 126, 5
$\text{CH}_3(\text{CH}_2)_{11}\text{PO}(\text{OC}_4\text{H}_9-n)_2$	B	91	5
$\text{CH}_3(\text{CH}_2)_{13}\text{PO}(\text{OC}_2\text{H}_5)_2$	A	—	5
$\text{CH}_3(\text{CH}_2)_{13}\text{PO}(\text{OC}_4\text{H}_9-n)_2$	B	84	5
$\text{CH}_3(\text{CH}_2)_{15}\text{PO}(\text{OC}_4\text{H}_9-n)_2$	B	88	5
$\text{CH}_3(\text{CH}_2)_{17}\text{PO}(\text{OC}_4\text{H}_9-n)_2$	B	84	5
$\text{HOCH}_2\text{PO}(\text{OC}_2\text{H}_5)_2$	B	100	17
$\text{HOCH}_2\text{CH}_2\text{PO}(\text{OC}_2\text{H}_5)_2$	D	40	24
$\text{ICH}_2\text{PO}(\text{OC}_2\text{H}_5)_2$	A	60	14, 17
$\text{Cl}_3\text{CPO}(\text{OCH}_3)_2$	A	—	19, 127
$\text{Cl}_3\text{CPO}(\text{OC}_2\text{H}_5)_2$	A	93	18, 19, 127
$\text{Cl}_3\text{CPO}(\text{OCH}_2\text{CH}=\text{CH}_2)_2$	A	—	19, 127
$\text{Cl}_3\text{CPO}(\text{OC}_3\text{H}_7-n)_2$	A	—	19, 127
$\text{Cl}_3\text{CPO}(\text{OC}_3\text{H}_7-iso)_2$	A	60	19, 127
$\text{Cl}_3\text{CPO}(\text{OC}_4\text{H}_9-n)_2$	A	25	18, 19, 127
$\text{Cl}_3\text{CPO}(\text{OC}_4\text{H}_9-iso)_2$	A	60	19, 127
$\text{ClCH}_2\text{CH}_2\text{PO}(\text{OC}_2\text{H}_5)_2$	A	25	128
$\text{ClCH}_2\text{CH}_2\text{PO}(\text{OCH}_2\text{CH}_2\text{Cl})_2$	A	40	33, 129
$\text{BrCH}_2\text{CH}_2\text{PO}(\text{OC}_2\text{H}_5)_2$	A	39	14
		61	130
$\text{BrCH}_2\text{CH}_2\text{PO}(\text{OCH}_2\text{CH}_2\text{Br})_2$	A	32	131
$\text{Br}(\text{CH}_2)_3\text{PO}(\text{OC}_2\text{H}_5)_2$	A	90	32, 132
$\text{NC}(\text{CH}_2)_3\text{PO}(\text{OC}_2\text{H}_5)_2$	B	35-40	133
$\text{C}_2\text{H}_5\text{O}_2\text{CPO}(\text{OC}_2\text{H}_5)_2$	A	—	134
	B	50	10, 135
$\text{CH}_3\text{O}_2\text{CCH}_2\text{PO}(\text{OC}_2\text{H}_5)_2$	B	—	135
$\text{C}_2\text{H}_5\text{O}_2\text{CCH}_2\text{PO}(\text{OC}_2\text{H}_5)_2$	A	50	13, 134
	B	50, 58, 95	10, 134-137
$\text{C}_2\text{H}_5\text{O}_2\text{CCH}_2\text{PO}(\text{OC}_4\text{H}_9-iso)_2$	A	50	138
	B	32	139
$\text{C}_4\text{H}_9\text{O}_2\text{CCH}_2\text{PO}(\text{OC}_4\text{H}_9-n)_2$	B	69	137
$\text{C}_6\text{H}_5\text{O}_2\text{CCH}_2\text{PO}(\text{OC}_2\text{H}_5)_2$	A	Poor	138
	B	10	138
$\text{C}_2\text{H}_5\text{O}_2\text{CCH}(\text{CH}_3)\text{PO}(\text{OC}_2\text{H}_5)_2$	A	Poor	10, 134

* A = ester procedure; B = sodium salt procedure; C = triarylcarkinol-phosphorus trichloride procedure; and D = special methods.

TABLE I—Continued
DERIVATIVES OF PHOSPHONIC AND PHOSPHINIC ACIDS PREPARED BY ALKYLATION
OF PHOSPHITES OR OTHER TRIVALENT ESTERS

Compound	Method*	Yield %	Reference
C ₂ H ₅ O ₂ CCH ₂ CH ₂ PO(OC ₂ H ₅) ₂	A	35	10, 134
	B	35, 78	35, 133
C ₂ H ₅ O ₂ CCH(C ₂ H ₅)PO(OC ₂ H ₅) ₂	A	—	134
C ₂ H ₅ O ₂ C(CH ₂) ₁₀ PO(OC ₄ H _{9-n}) ₂	B	—	22
(C ₂ H ₅ O ₂ C) ₂ CHPO(OC ₂ H ₅) ₂	A	30	137
(C ₂ H ₅ O ₂ C) ₂ CHPO(OC ₄ H _{9-n}) ₂	A	50	137
(C ₂ H ₅ O)(NaO)P(O)CH ₂ PO(ONa)(OC ₂ H ₅)	B	—	10
(C ₂ H ₅ O) ₂ P(O)CH ₂ PO(OC ₂ H ₅) ₂	A	—	14
(C ₂ H ₅ O) ₂ P(O)CH ₂ CH ₂ PO(OC ₂ H ₅) ₂	A	26	14
(C ₆ H ₅ O) ₂ P(O)CH ₂ CH ₂ PO(OC ₆ H ₅) ₂	A	60	16
(o-C ₆ H ₄ O ₂)P(O)CH ₂ CH ₂ PO(O ₂ C ₆ H _{4-o})	A	60	16
(C ₂ H ₅ O) ₂ P(O)CH ₂ CH ₂ CH ₂ PO(OC ₂ H ₅) ₂	A	75	14, 32
	B	—	10
(C ₂ H ₅ O) ₂ P(O)CH ₂ OCH ₂ PO(OC ₂ H ₅) ₂	A	63	140
	B	85	28, 140
C ₆ H ₅ CH ₂ OCH ₂ PO(OC ₂ H ₅) ₂	A	48	28
	B	26	28
C ₆ H ₅ CH ₂ OCH ₂ PO(OC ₄ H _{9-n}) ₂	B	33	28
C ₆ H ₅ OCH ₂ CH ₂ PO(OC ₂ H ₅) ₂	A	45	30
CH ₃ OCH ₂ CH ₂ CH=CHCH ₂ PO(OCH ₃) ₂	A, B	70	20
CH ₃ OCH ₂ CH ₂ CH=CHCH ₂ PO(OC ₂ H ₅) ₂	A, B	70	20
CH ₃ OCH ₂ CH ₂ CH=CHCH ₂ PO(OC ₄ H _{9-isot}) ₂	A, B	70	20
CH ₂ =CHCH=CHPO(OC ₂ H ₅) ₂	A, B	—	42
(C ₆ H ₅) ₂ NCOCH ₂ PO(OC ₂ H ₅) ₂	A	43	141
CH ₃ COP(O)OCH ₃) ₂	A	58, 80	21, 142
CH ₃ COP(O)O(OC ₂ H ₅) ₂	A	12, 50	21, 142
CH ₃ COP(O)O(OC ₄ H _{9-n}) ₂	A	50	142
C ₆ H ₅ COP(O)OCH ₃) ₂	A	72	21
C ₆ H ₅ COP(O)O(OC ₂ H ₅) ₂	A	62	21
CH ₃ COCH ₂ PO(OC ₂ H ₅) ₂ (?)	B	—	10
C ₆ H ₅ COCH ₂ PO(OC ₂ H ₅) ₂	A	30	138
	B	37	138
C ₆ H ₅ CH ₂ PO(OC ₄ H _{9-n}) ₂	B	85	31
C ₆ H ₅ CH ₂ PO(OC ₆ H ₅) ₂	A	—	1
C ₆ H ₅ CH ₂ PO(O ₂ C ₆ H _{4-o})	A	70	123
4-CH ₃ C ₆ H ₄ CH ₂ PO(OC ₂ H ₅) ₂	A	78	31
4-CH ₃ C ₆ H ₄ CH ₂ PO(OC ₄ H _{9-n}) ₂	B	85	31

* A = ester procedure; B = sodium salt procedure; C = triarylcarbinol-phosphorus trichloride procedure; and D = special methods.

TABLE I—Continued
DERIVATIVES OF PHOSPHONIC AND PHOSPHINIC ACIDS PREPARED BY ALKYLATION
OF PHOSPHITES OR OTHER TRIVALENT ESTERS

Compound	Method*	Yield %	Reference
4-C ₂ H ₅ C ₆ H ₄ CH ₂ PO(OC ₂ H ₅) ₂	A	78	31
4-C ₂ H ₅ C ₆ H ₄ CH ₂ PO(OC ₄ H _{9-n}) ₂	B	88	31
4-C ₄ H ₉ C ₆ H ₄ CH ₂ PO(OC ₄ H _{9-n}) ₂	B	70	31
1-C ₁₀ H ₇ CH ₂ PO(OC ₂ H ₅) ₂	A	87	31
4-C ₆ H ₅ C ₆ H ₄ CH ₂ PO(OC ₄ H _{9-n}) ₂	B	60	31
9-Phenanthrylmethanephosphonic acid	B	50	31
1,3,5-(CH ₃) ₃ C ₆ H[CH ₂ PO(OC ₄ H _{9-n}) ₂] ₂ -2,4	B	70	31
Bis-9,10-anthracenylmethanephosphonic acid	B	75	31
(C ₆ H ₅) ₃ CPO(OCH ₃) ₂	A	60	8
(C ₆ H ₅) ₃ CPO(OC ₂ H ₅) ₂	A	100	8
(C ₆ H ₅) ₃ CPO(OC ₃ H _{7-n}) ₂	A	80	8
(C ₆ H ₅) ₃ CPO(OC ₃ H _{7-iso}) ₂	A	80	8
(C ₆ H ₅) ₃ CPO(OC ₄ H _{9-n}) ₂	A	—	8
4-ClC ₆ H ₄ (C ₆ H ₅) ₂ CPO(OH) ₂	C	93	9
4-BrC ₆ H ₄ (C ₆ H ₅) ₂ CPO(OH) ₂	C	90	9
3-HOC ₆ H ₄ (C ₆ H ₅) ₂ CPO(OH) ₂	C	—	9
1-C ₁₀ H ₇ (C ₆ H ₅) ₂ CPO(OH) ₂	C	—	9
2-C ₁₀ H ₇ (C ₆ H ₅) ₂ CPO(OH) ₂	C	—	9
4-CH ₃ C ₆ H ₄ (C ₆ H ₅) ₂ CPO(OH) ₂	C	75	9
H ₂ NCH ₂ CH ₂ PO(OH) ₂	A	50	143
	B	—	22
H ₂ NCH ₂ CH ₂ CH ₂ PO(OH) ₂	B	—	22
9-Acridinephosphonic acid	A	60	18
2-Thienylmethanephosphonic acid	B	71	144
C ₆ H ₅ (CH ₃)PO(OCH ₃)	A	34, 92	25, 26
C ₆ H ₅ (C ₂ H ₅)PO(OC ₂ H ₅)	A	90	2
C ₆ H ₅ (iso-C ₄ H ₉)PO(OC ₄ H _{9-iso})	A	72	27
	(Isolated as the free acid)		
C ₆ H ₅ (n-C ₃ H ₇)PO(OC ₃ H _{7-n})	A	90	26
C ₆ H ₅ (iso-C ₃ H ₇)PO(OC ₃ H _{7-iso})	A	95	2, 11
(C ₆ H ₅) ₃ C(C ₆ H ₅)PO(OC ₄ H _{9-iso})	A	58	27
C ₆ H ₅ (C ₂ H ₅ OCH ₂)PO(OC ₂ H ₅)	A	84	26
C ₆ H ₅ (CH ₃ OCH ₂)PO(OC ₂ H ₅)	A	80	26
C ₆ H ₅ (C ₂ H ₅ O ₂ CCH ₂)PO(OC ₄ H _{9-iso})	A	64	12
C ₆ H ₅ [C ₂ H ₅ O ₂ CCH(CH ₃)]PO(OC ₄ H _{9-iso})	A	76	12
C ₆ H ₅ (Cl ₃ C)PO(OCH ₃)	A	—	127
C ₆ H ₅ (Cl ₃ C)PO(OC ₂ H ₅)	A	—	127

* A = ester procedure; B = sodium salt procedure; C = triarylecarbinol-phosphorus trichloride procedure; and D = special methods.

TABLE I—Continued

DERIVATIVES OF PHOSPHONIC AND PHOSPHINIC ACIDS PREPARED BY ALKYLATION
OF PHOSPHITES OR OTHER TRIVALENT ESTERS

Compound	Method *	Yield %	Reference
C ₆ H ₅ (Cl ₃ C)PO(OC ₃ H _{7-n})	A	—	127
C ₆ H ₅ (Cl ₃ C)PO(OC ₄ H _{9-isoo})	A	—	127
n-C ₁₇ H ₃₅ CONHCH ₂ PO(OH) ₂	D	60	7
C ₆ H ₅ CONHCH ₂ PO(OH) ₂	D	—	7
n-C ₁₇ H ₃₅ CO(CH ₃)NCH ₂ PO(OH) ₂	D	—	145

* A = ester procedure; B = sodium salt procedure; C = triarylcarkinol-phosphorus trichloride procedure; and D = special methods.

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TABLE II
PHOSPHONIC ACIDS PREPARED BY ADDITION OF PHOSPHORUS PENTACHLORIDE TO
UNSATURATED COMPOUNDS

Compound	Yield %	Reference
$C_6H_5CH=CHPO_3H_2$	55, 36	38, 39, 36
$C_6H_5(CH_3)C=CHPO_3H_2$	10	38
$(C_6H_5)_2C=CHPO_3H_2$	45	38
$C_6H_5(4-ClC_6H_4)C=CHPO_3H_2$	15	41
$C_6H_5(2-CH_3C_6H_4)C=CHPO_3H_2$	35	40
$(4-ClC_6H_4)_2C=CHPO_3H_2$	60	41
$(4-CH_3OC_6H_4)(C_6H_5)C=CHPO_3H_2$	40	41
$(4-ClC_6H_4)(4-CH_3OC_6H_4)C=CHPO_3H_2$	30	41
$C_6H_5(2-FC_6H_4)C=CHPO_3H_2$	30	41
$C_6H_5(4-C_6H_5C_6H_4)C=CHPO_3H_2$	33	41
$(4-C_6H_5C_6H_4)(4-CH_3C_6H_4)C=CHPO_3H_2$	30	41
$C_6H_5(3-ClC_6H_4)C=CHPO_3H_2$	25	41
$C_6H_5(1-C_{10}H_7)C=CHPO_3H_2$	—	40
$C_6H_5(2-C_{10}H_7)C=CHPO_3H_2$	—	40
$2,4-(CH_3)_2C_6H_3CH=CHPO_3H_2$	45	39
$2,4,6-(CH_3)_3C_6H_2CH=CHPO_3H_2$	55	39
$4-C_2H_5C_6H_4CH=CHPO_3H_2$	40	39
$2-tert-C_4H_9C_6H_4CH=CHPO_3H_2$	35	39
$2-C_6H_5C_6H_4CH=CHPO_3H_2$	45	39
$3-C_6H_5C_6H_4CH=CHPO_3H_2$	30	39
$4-C_6H_5C_6H_4CH=CHPO_3H_2$	45	39
$2-C_{10}H_7CH=CHPO_3H_2$	40	39
2-Indenephosphonic acid	50	36, 38
2-Vinylfluorene-2'-phosphonic acid	30	39
$CH_2=CHCH=CHPO_3H_2$	—	42
$C_6H_5CH=CHCH=CHPO_3H_2$	55, 88	41, 39
$1,4-H_2O_3PCH=C(C_6H_5)C_6H_4C(C_6H_5)=CHPO_3H_2$	—	41
$(CH_3)_3CCH_2(CH_3)C=CHPO_3H_2$	50	39
$C_6H_5CCl=CHPO_3H_2$	3	37
$(CH_3)_2CClCH_2PO_3H_2$	Low	40
$(2-ClC_6H_4)CCl=CHPO_3H_2$	50	37
$(2-CH_3OC_6H_4)CCl=CHPO_3H_2$	100	37
$(4-CH_3OC_6H_4)CCl=CHPO_3H_2$	65	37
$(C_6H_5)_2C(C_6H_4-o)_2C=CHPO_3H_2$	—	40
$C_6H_5CH_2CCl=CHPO_3H_2$	15	37
$CH_3(CH_2)_4CCl=CHPO_3H_2$	—	37

TABLE III
PHOSPHONIC AND PHOSPHINIC ACIDS PREPARED BY THE FRIEDEL-CRAFTS REACTION

Aromatic Compound	Phosphonic Acids		Phosphinic Acids	
	Yield %	Reference	Yield %	Reference
Benzene	5, 80	50, 55, 57	40	55
Chlorobenzene	25, 82	52, 55	33	55
Bromobenzene	10	52		
Toluene	25, 57	50, 54, 55, 59	22	55, 51
Ethylbenzene	15	52	—	52
Cymene	5	52, 59		
Cumene	—	52	—	52
2-Chlorotoluene	10	58		
1,2-Dichlorobenzene	36	55	2	55
1,4-Dichlorobenzene	3	55		
1,2,4-Trimethylbenzene	25	52	10	52
1,3,5-Trimethylbenzene	5	52, 64		
Biphenyl	5	51, 52, 63		
<i>sym</i> -Diphenylethane	—	52, 51		
Diphenylmethane	—	52, 51		
Naphthalene	15	54		
Anisole	20, 26	52, 60		
Phenetole	—	52		
Diphenyl ether	10	64		
Thiophene	5	53		
N,N-Dimethylaniline	30	65		

TABLE IV
PHOSPHONIC AND PHOSPHINIC ACIDS PREPARED BY THE ADDITION TO CARBONYL COMPOUNDS

A. By Addition of P-H Linked Compounds

Products	Reference
CH ₃ CH(OH)PO ₃ H ₂	79
(CH ₃) ₂ C(OH)PO ₃ H ₂	72, 73, 76, 77
<i>iso</i> -C ₄ H ₉ CH(OH)PO ₃ H ₂	79, 84
(CH ₃)(C ₂ H ₅)C(OH)PO ₃ H ₂	80
(C ₂ H ₅) ₂ C(OH)PO ₃ H ₂	83
(CH ₃)(<i>n</i> -C ₃ H ₇)C(OH)PO ₃ H ₂	78
C ₆ H ₅ CH(OH)PO ₃ H ₂	74
(C ₆ H ₅) ₂ C(OH)PO ₃ H ₂	78
C ₆ H ₅ CH ₂ PO ₃ H ₂	66
[(CH ₃) ₂ C(OH)] ₂ PO ₂ H	72, 76
[(CH ₃) ₂ C(OH)](CH ₃ CHOH)PO ₂ H	81
(<i>iso</i> -C ₄ H ₉ CHOH) ₂ PO ₂ H	68, 71, 82
(<i>n</i> -C ₆ H ₁₃ CHOH) ₂ PO ₂ H	68, 71
(<i>n</i> -C ₆ H ₁₃ CHOH)(CH ₃ CHOH)PO ₂ H	81
(<i>n</i> -C ₆ H ₁₃ CHOH)(<i>iso</i> -C ₃ H ₇ CHOH)PO ₂ H	81
[(CH ₃)(C ₂ H ₅)C(OH)](<i>n</i> -C ₆ H ₁₃ CHOH)PO ₂ H	82
(CH ₃ CHOH)(C ₆ H ₅ CHOH)PO ₂ H	80
[(CH ₃) ₂ C(OH)](<i>n</i> -C ₆ H ₁₃ CHOH)PO ₂ H	82
[(CH ₃) ₂ C(OH)](C ₆ H ₅ CHOH)PO ₂ H	82
[(C ₂ H ₅) ₂ C(OH)](C ₆ H ₅ CHOH)PO ₂ H	82
[(CH ₃)(<i>n</i> -C ₃ H ₇)C(OH)](C ₆ H ₅ CHOH)PO ₂ H	82
[(C ₆ H ₅)(CH ₃)C(OH)](CH ₃ CHOH)PO ₂ H	82
(C ₆ H ₅ CHOH) ₂ PO ₂ H	69
(C ₆ H ₅ CH ₂) ₂ PO ₂ H	66

B. By Addition of Phosphorus Chlorides

Products	Yield %	Reference
HOCH ₂ PO ₃ H ₂	93	84
CH ₃ CH(OH)PO ₃ H ₂	—	67
C ₂ H ₅ CH(OH)PO ₃ H ₂	—	67
<i>iso</i> -C ₃ H ₇ CH(OH)PO ₃ H ₂	—	67
<i>iso</i> -C ₄ H ₉ CH(OH)PO ₃ H ₂	65	67, 84
<i>n</i> -C ₆ H ₁₃ CH(OH)PO ₃ H ₂	—	67
(CH ₃) ₂ C(OH)PO ₃ H ₂	91	92
(CH ₃)(C ₂ H ₅)C(OH)PO ₃ H ₂	76	92

TABLE IV—*Continued*
PHOSPHONIC AND PHOSPHINIC ACIDS PREPARED BY THE ADDITION TO CARBONYL COMPOUNDS

B. By Addition of Phosphorus Chlorides—Continued

Products	Yield %	Reference
(CH ₃) ₃ CC(OH)(CH ₃)PO ₃ H ₂	56	92
(C ₂ H ₅)(n-C ₃ H ₇)C(OH)PO ₃ H ₂	50	92
CH ₃ (CH ₂) ₅ C(OH)(H)PO ₃ H ₂	81	97
(CH ₃) ₂ C(OH)PO(OC ₆ H ₅) ₂	50	88
(CH ₃)(C ₂ H ₅)C(OH)PO(OC ₆ H ₅) ₂	50	88
(CH ₃)(ClCH ₂)C(OH)PO(OC ₆ H ₅) ₂	10	88
(CH ₃) ₂ C(CH ₂ COCH ₃)PO(OH)C ₄ H _{9-n}	—	89
(CH ₃) ₂ C(CH ₂ COCH ₃)PO(OC ₆ H ₅) ₂	41	89
CH ₃ COCH ₂ CH ₂ PO(OC ₆ H ₅) ₂	14	89
CH ₃ (CH ₂) ₃ CH(C ₂ H ₅)CH(PO ₃ H ₂)CH ₂ COCH ₃	20	89
(CH ₃) ₂ C(PO ₃ H ₂)CH ₂ COCH ₃	33	89
CH ₃ C(PO ₃ H ₂)(OH)CO ₂ H	40	94
C ₆ H ₅ CH(OH)PO ₃ H ₂	84, 72	67, 84, 93
(C ₆ H ₅) ₂ C(OH)PO ₃ H ₂	50	92
(C ₆ H ₅ CH ₂ CH ₂) ₂ C(OH)PO ₃ H ₂	56	92
C ₆ H ₅ C(PO ₃ H ₂)(Cl)CH ₃	82	97
C ₆ H ₅ C(PO ₃ H ₂)(OH)CH ₃	81	97
CH ₂ =C(PO ₃ H ₂)C ₆ H ₅	63, 90	92, 97
C ₆ H ₅ COCH ₂ CH(PO ₃ H ₂)COC ₆ H ₅	81	89
C ₆ H ₅ CH(PO ₃ H ₂)CH ₂ COC ₆ H ₅	78	90, 95
4-CH ₃ OC ₆ H ₄ CH(PO ₃ H ₂)CH ₂ COC ₆ H ₅	89	95
C ₆ H ₅ CH(PO ₃ H ₂)CH ₂ COC ₆ H ₄ Cl-4	91	96
C ₆ H ₅ CH(PO ₃ H ₂)CH ₂ COCH=CHC ₆ H ₅	90	95
C ₆ H ₅ P(O)(OH)[CH(C ₆ H ₅)CH ₂ COC ₆ H ₅]	90	85
C ₆ H ₅ CH=CHCH(PO ₃ H ₂)CH ₂ COC ₆ H ₅	—	86
C ₆ H ₅ CH ₂ C(PO ₃ H ₂)(OH)CH ₂ C ₆ H ₅	50	92
C ₆ H ₅ C(PO ₃ H ₂)(OH)CH ₂ CH ₂ C ₆ H ₅	48	92
C ₆ H ₅ CH[P(C ₆ H ₅)O ₂ H]CH ₂ COCH=CHC ₆ H ₅	70	86
C ₆ H ₅ CH=CHCH[P(C ₆ H ₅)O ₂ H]CH ₂ COC ₆ H ₅	64	86
C ₆ H ₅ CH(CH ₂ COC ₆ H ₅)P(O)(OH)C ₄ H ₉	50	89
C ₆ H ₅ CH(OH)P(O)(OH)OC ₆ H ₅	90	88
C ₆ H ₅ CH(OH)P(O)(OH)OCH ₃	50	88
C ₆ H ₅ CH(OH)P(O)(OH)OC ₂ H ₅	50	88
C ₆ H ₅ CH(CH ₂ COC ₆ H ₅)P(O)(OC ₆ H ₅) ₂	30	88
(CH ₃)(C ₆ H ₅)C(OH)P(O)(OC ₆ H ₅) ₂	60	88
C ₆ H ₅ CH(OH)P(O)(OC ₆ H ₅) ₂	40	88
C ₆ H ₅ P(O)(OH)(CHOHC ₆ H ₅)	—	52
C ₆ H ₅ P(O)(OH)(CHOHC ₆ H ₅)	—	52
9-Keto-10-hydroxyphenanthrene-10-phosphonic acid	—	67

TABLE V
CHLOROPHOSPHINES PREPARED FROM ORGANOMERCURY INTERMEDIATES

Products	Yield %	Reference
$C_2H_5PCl_2$	—	106, 107
$n-C_3H_7PCl_2$	—	107
$iso-C_3H_7PCl_2$	—	107
$n-C_4H_9PCl_2$	61	89
$iso-C_4H_9PCl_2$	—	107
$iso-C_5H_{11}PCl_2$	—	107
$C_6H_5PCl_2$	100	100
$(C_6H_5)_2PCl$	64	146, 147
$2-CH_3C_6H_4PCl_2$	78	52, 59, 148
$3-CH_3C_6H_4PCl_2$	50	52
$4-CH_3C_6H_4PCl_2$	100	59
$4-CH_3OC_6H_4PCl_2$	Poor	52
$4-C_2H_5OC_6H_4PCl_2$	Poor	52
$2,4-(CH_3)_2C_6H_3PCl_2$	20	61
$2,4,5-(CH_3)_3C_6H_2PCl_2$	20	52
$1-C_{10}H_7PCl_2$	—	149
$2-C_{10}H_7PCl_2$	—	54
$4-(CH_3)_2NC_6H_4PCl_2$	45	65
$C_6H_5(4-CH_3C_6H_4)PCl$	64	51, 108, 150
$C_6H_5(4-BrC_6H_4)PCl$	47-53	109
$C_6H_5(4-CH_3OC_6H_4)PCl$	35	109
$C_6H_5[2,4,5-(CH_3)_3C_6H_2]PCl$	30	51
$(4-CH_3C_6H_4)_2PCl$	35	51

¹⁴⁶ Michaelis, *Ber.*, **10**, 627 (1877).

¹⁴⁷ Michaelis and Link, *Ann.*, **207**, 193 (1881).

¹⁴⁸ Michaelis and Panek, *Ber.*, **13**, 653 (1880).

¹⁴⁹ Kelbe, *Ber.*, **9**, 1051 (1876); **11**, 1499 (1878).

¹⁵⁰ Wedekind, *Ber.*, **45**, 2933 (1912).

TABLE VI
CHLOROPHOSPHINES PREPARED BY THERMAL DECOMPOSITION OF PHOSPHONIUM COMPOUNDS

Starting Material	Product	Yield %	Reference
$(C_6H_5)_3PCl_2$	$(C_6H_5)_2PCl$	40	110, 112
$(2-CH_3C_6H_4)_3PCl_2$	$(2-CH_3C_6H_4)_2PCl$	50	112
$(4-CH_3C_6H_4)_3PCl_2$	$(4-CH_3C_6H_4)_2PCl$	50	112
$(1-C_{10}H_7)_3PCl_2$	$(1-C_{10}H_7)_2PCl$	30	112
$(4-CH_3C_6H_4)_2(C_6H_5)PCl_2$	$(4-CH_3C_6H_4)(C_6H_5)PCl$	50	112
$(2-ClC_6H_4)_3PCl_2$	$(2-ClC_6H_4)_2PCl$	60	112
$(4-ClC_6H_4)_3PCl_2$	$(4-ClC_6H_4)_2PCl$	55	112
$(4-O_2NC_6H_4)_3PCl_2$	$(4-O_2NC_6H_4)_2PCl$	60	112
$[4-(CH_3)_2NC_6H_4]_3PCl_2$	$[4-(CH_3)_2NC_6H_4]_2PCl$	50	112
$(CH_3)_2(C_6H_5)PCl_2$	$(CH_3)(C_6H_5)PCl$	60	112
$(C_2H_5)_2(C_6H_5)PCl_2$	$(C_2H_5)(C_6H_5)PCl$	50	112
$(C_2H_5)_3PCl_2$	$(C_2H_5)_2PCl$	70	111, 112
$(n-C_3H_7)_3PCl_2$	$(n-C_3H_7)_2PCl$	60	112
$(n-C_4H_9)_3PCl_2$	$(n-C_4H_9)_2PCl$	55	112
$(CH_3)(C_2H_5)_2PCl_2$	$(CH_3)(C_2H_5)PCl$	45	112
$(CH_3)(4-CH_3C_6H_4)(C_5H_{10}N)_2POH$	$(CH_3)(4-CH_3C_6H_4)PO_2H$	75	108, 114
$(CH_3)(C_6H_5)(C_5H_{10}N)_2POH$	$(CH_3)(C_6H_5)PO_2H$	75	52, 108, 114