SOME ASPECTS OF THE ORGANIC CHEMISTRY OF DERIVATIVES OF PHOSPHORUS OXYACIDS

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The only naturally occurring organic derivatives of phosphorus are the esters and amides of phosphoric acid and the esters of polyphosphoric acids, these compounds being present in the living organism as structural units, co-enzymes, and enzyme substrates. During the present century, numerous compounds of these types have been isolated and identified, thus enabling the establishment of the rôle played by phosphorus-containing materials and, in particular, the elucidation of the pattern of carbohydrate metabolism. It is now known that the phosphate residues introduced into metabolites serve not only to facilitate breakdown, but also as prospective carriers of energy, metabolic processes being so designed as to accumulate the energy of individual stages in " energy-rich " phosphate bonds. These " energy-rich " phosphate bonds are distinguished by the large amount of energy liberated by bond-fission (*ca.* 11,000 cals.) in comparison with fission for a normal phosphoric ester (*ca.* 3000 cals.). The types of compounds possessing such bonds are those containing the linkages carboxyl–P, enol–P, N–P, and P–O–P. The first two types are formed in metabolic processes by reactions which occur with little energy change, but involve a redistribution of the energy of the molecules so that a considerable part becomes associated with the phosphate bonds. The other types, which are concerned with the storage and utilisation of phosphate bond-energy, do not arise directly but are the result of trans-phosphorylations. Enzymes, acting as catalysts in these and other biological processes, have in many cases been found to possess co-enzyme components which are phosphorus-containing materials.

Since compounds of phosphorus occur ubiquitously and play such varied rôles in the living organism, it is only to be expected that related types of compounds would possess physiological activity. Indeed, research during the war-years led to the discovery of phosphorus compounds of extreme toxicity which act by inhibiting choline-esterase, the enzyme which hydrolyses acetylcholine. The difference between a toxic compound and one with therapeutic action being of degree and not of type, it is likely that many new drugs will be found among phosphorus compounds. There is already some evidence that this is the case.

Much of the present interest in the organic compounds of phosphorus lies in the development of methods for the synthesis of the more complex naturally-occurring derivatives of phosphoric acid and the search for compounds with physiological activity. It is, however, by no means restricted to these aspects, for, in addition to the many interesting theoretical points connected with their chemistry, the patent literature indicates the most diverse uses for phosphorus compounds.

The present article deals only with certain aspects of the chemistry of the substituted acids, esters, and chlorides of phosphorus. As the available space does not permit a full discussion of all classes of compounds containing these groupings, the subject-matter presents some of the reactions characteristic of the individual types of groupings. The nomenclature used is that recently put forward by the Chemical Society, in which compounds are derived by the replacement of hydrogen in the following parent acids :

$HO\cdot PH_2$	$(HO)_2PH$	$HO\cdot PO\cdot H_2$	$(HO)_2PO\cdot H$
Phosphinous acid.	Phosphinic acid.	Phosphonous acid.	Phosphonic acid.

In American usage the terms phosphinic and phosphonous are inverted.

1. Hydroxy-compounds of Quinquevalent Phosphorus

Compounds containing the characteristic grouping $>PO\cdot OH$ exhibit well-marked acidic properties, forming stable salts with both inorganic and organic bases. The most important reactions of the group are the replacement of the hydroxyl by halogen and its conversion into esters.

(*a*) **Formation of Halides.**—This reaction does not seem yet to have been widely employed, chiefly because many halides are more easily obtained by other methods. It is most likely to be of use for those compounds which do not contain ester groups.

The reaction can be effected by treating the acid with phosphorus pentachloride under mild conditions :

$$>PO\cdot OH + PCl_5 \longrightarrow >POCl + HCl + POCl_3$$

In this manner alkylphosphonic and dialkylphosphonous acids have been converted into the corresponding chlorides.[1]

The above reaction proved less successful when applied to dibenzyl hydrogen phosphate,[2] but in this case conversion has been achieved by the action of thionyl chloride on the potassium salt [3] :

$$(C_6H_5\cdot CH_2\cdot O)_2PO\cdot OK + SOCl_2 \longrightarrow (C_6H_5\cdot CH_2\cdot O)_2PO\cdot Cl + KCl + SO_2$$

(*b*) **Formation of Esters.**—The direct esterification of acids derived from phosphorus with alcohols, though one of the earliest known reactions, [4, 5] can be accomplished only under drastic conditions and has little application. On the other hand, the formation of esters by the reaction of halides with silver salts has been so widely employed as to merit no further mention. Among the other methods of producing esters from the acids are the reactions occurring with diazo-compounds and olefin oxides.

(i) Reaction with substituted diazomethanes. Diazomethane and substituted diazomethanes react smoothly to give the corresponding esters.

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[1] A. W. Hofmann, *Ber.*, 1873, **6**, 306. [2] L. Zervas, *Naturwiss.*, 1939, **27**, 317.
[3] A. Deutsch and O. Fernö, *Nature*, 1945, **156**, 604.
[4] T. J. Pelouze, *Annalen*, 1833, **6**, 129. [5] J. von Liebig, *ibid.*, p. 149.

Phosphorous acid, which contains only two true acid groups, gives the corresponding diesters : [6, 7]

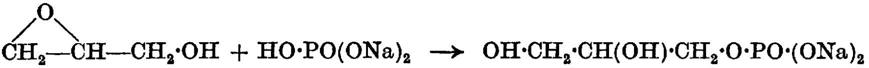
$$2RR'CN_2 + (HO)_2PHO \longrightarrow (RR'CH{\cdot}O)_2PHO + 2N_2$$

whilst phosphoric acid has been preferentially monosubstituted : [8]

$$R{\cdot}CHN_2 + HO{\cdot}PO(OH)_2 \longrightarrow R{\cdot}CH_2{\cdot}O{\cdot}PO(OH)_2 + N_2$$

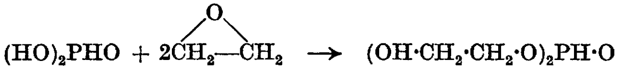
Fully substituted phosphoric esters have been obtained by the action of diazoalkanes on monoesters [9] and diesters.[7]

(ii) Reaction with olefin oxides. The oxide ring in olefin oxides can be opened by the acids of phosphorus to produce hydroxyalkyl esters. In order to effect mono-substitution of phosphoric acid, O. Bailly [10] treated disodium hydrogen phosphate with glycidol to give the disodium salt of α-glycerol phosphate :



$$\overbrace{CH_2—CH}^{O}—CH_2{\cdot}OH + HO{\cdot}PO(ONa)_2 \longrightarrow OH{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}O{\cdot}PO{\cdot}(ONa)_2$$

Other workers have treated olefin oxides with free phosphoric acid to get partial [11, 12] or complete substitution.[13] The hydroxyl groups of the products may react further with excess of olefin oxide.[13] As would be expected, phosphorous acid gives only diesters,[13] *e.g.*,



$$(HO)_2PHO + 2\overbrace{CH_2—CH_2}^{O} \longrightarrow (OH{\cdot}CH_2{\cdot}CH_2{\cdot}O)_2PH{\cdot}O$$

Olefin imines undergo analogous reactions [13, 14] as do olefin sulphides.[13]

(*c*) **Formation of Amides.**—Amide formation from oxyacids of phosphorus and amines has not been reported. Dianilinodithiophosphonous acid, however, reacts at high temperatures with aniline : [15]

$$(C_6H_5NH)_2{\cdot}PS{\cdot}SH + C_6H_5{\cdot}NH_2 \longrightarrow (C_6H_5NH)_3PS + H_2S$$

(*d*) **Formation of Anhydrides.**—(i) With carboxylic acids. Monoacyl phosphates may be prepared by the action of acyl chlorides on monosilver phosphate : [16, 17]

$$R{\cdot}CO{\cdot}Cl + AgO{\cdot}PO(OH)_2 \longrightarrow R{\cdot}CO{\cdot}O{\cdot}PO(OH)_2 + AgCl$$

or of a keten on excess of phosphoric acid : [18] *e.g.*,

$$CH_2{:}CO + HO{\cdot}PO(OH)_2 \longrightarrow CH_3{\cdot}CO{\cdot}O{\cdot}PO(OH)_2.$$

The dibenzyl esters of acyl phosphates are similarly prepared from dibenzyl hydrogen phosphate.[18, 19]

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[6] F. C. Pallazo and F. Maggiacomo, *Gazzetta*, 1908, **38**, II, 115.

[7] F. R. Atherton, H. T. Howard, and A. R. Todd, *J.*, 1948, 1106.

[8] T. Reichstein and W. Schindler, *Helv. Chim. Acta*, 1940, **23**, 669.

[9] E. Muller, A. Langerbeck, and W. Riedel, *Z. physiol. Chem.*, 1944, **281**, 29.

[10] *Ann. Chim.*, 1916, **6**, 133.

[11] F. Zetzche and F. Aeschlimann, *Helv. Chim. Acta*, 1926, **9**, 708.

[12] E. Eiderbenz and M. Depner, *Arch. Pharm.*, 1942, **280**, 227.

[13] C. E. Adams and B. M. Shoemaker, U.S.P. 2,372,244.

[14] H. N. Christensen, *J. Biol. Chem.*, 1940, **135**, 399.

[15] A. C. Buck, J. D. Bartleson, and H. P. Lankelma, *J. Amer. Chem. Soc.*, 1948, **70**, 744.

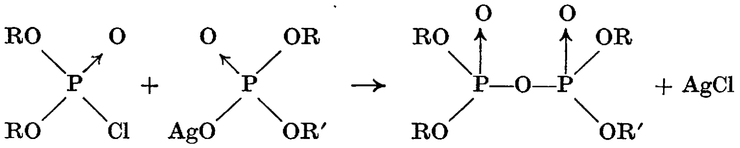
[16] F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, 1944, **153**, 571.

[17] A. L. Lehninger, *ibid.*, 1946, **162**, 333.

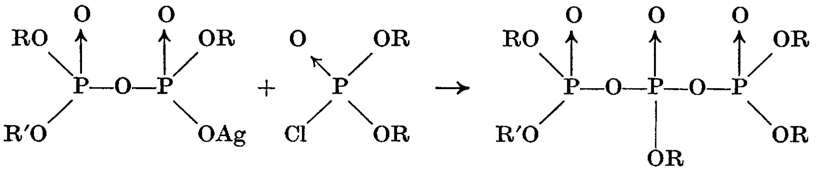
[18] R. Bentley, *J. Amer. Chem. Soc.*, 1948, **70**, 2183.

[19] F. Lynen, *Ber.*, 1940, **73**, 367.

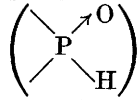
(ii) With acids of phosphorus. Polyphosphoric esters may be synthesised by condensation of the silver salt of an acid with a phosphorus halide. Thus chlorophosphonic esters react with the silver salt of a diester of phosphoric acid[20] to give the substituted pyrophosphate:



and with the silver salts of triesters of pyrophosphoric acid to give the substituted triphosphate[21]:

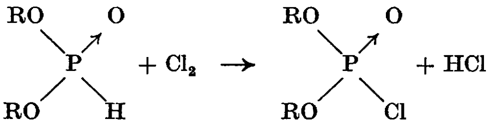


2. Hydroxy-compounds of Tervalent Phosphorus

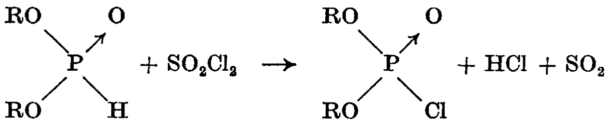
The compounds which might, from their mode of synthesis, be expected to be hydroxy-derivatives of tervalent phosphorus are not acidic and do not form stable salts, although the hydrogen may be replaced by alkali metals. Their reactions, which have been mainly studied with diesters of phosphorous acid, are best interpreted as those of the tautomeric form .

The most important of these reactions are those occurring with halogens and halogen-containing materials.

(*a*) **Formation of Halogenophosphonates.**—Chlorophosphonates are formed from dialkyl[22, 23] and diaralkyl[24] phosphites by the action of chlorine at low temperatures,



or of sulphuryl chloride at room temperature:[7]



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[20] J. Baddiley and A. R. Todd, *J.*, 1947, 648.

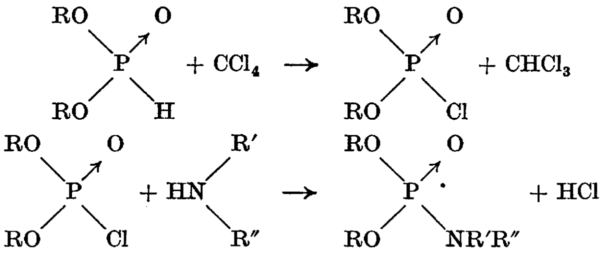
[21] J. Baddiley, A. M. Michelson, and A. R. Todd, *Nature*, 1948, **161**, 761.

[22] H. McCombie, B. C. Saunders, and G. J. Stacey, *J.*, 1945, 380.

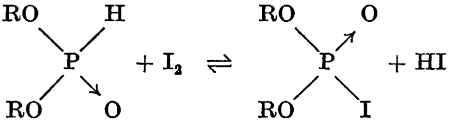
[23] H. G. Cook, H. McCombie, and B. C. Saunders, *ibid.*, p. 873.

[24] F. R. Atherton, H. T. Openshaw, and A. R. Todd, *ibid.*, p. 382.

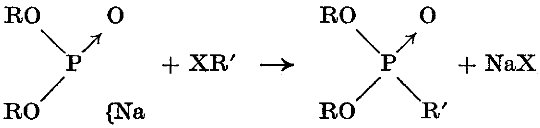
Although the intermediate product cannot be isolated, chlorination almost certainly takes place in the reaction which occurs when diesters of phosphorous acid are treated with a polychlorinated hydrocarbon and an amine,[25, 26] *e.g.*,



The formation of bromophosphonates can be effected by the action of bromine on diaralkyl phosphites,[27] but iodine does not give iodophosphonates,[28] probably because the hydrogen iodide produced is capable of reducing the iodophosphonate.



(*b*) **Formation of Phosphonates.**—The sodium derivatives of dialkyl phosphites, which may be produced by the action of metallic sodium or sodium ethoxide, react with halogen compounds when heated with them under reflux for several hours in an inert solvent, to form phosphonates :



This reaction, originally observed with ethyl iodide,[29] has been extended to many other alkyl halides,[30] aralkyl halides,[31] halogeno-carboxylic esters,[32, 33] cyanoalkyl halides,[33] and diaryl-, arylalkyl-, and dialkyl-arsine halides.[34] It is of no use when applied to trialkyl- and triaryl-tin halides[35] and proceeds only very poorly with dialkyltin dihalides.[36] Abnormal reactions occur

[25] F. R. Atherton, H. T. Openshaw, and A. R. Todd, *J.*, 1945, 660.

[26] F. R. Atherton and A. R. Todd, *J.*, 1947, 674.

[27] F. R. Atherton, F. Bergel, A. Cohen, J. W. Haworth, H. T. Openshaw, and A. R. Todd, B.P. 593,480.

[28] H. McCombie, B. C. Saunders, and G. J. Stacey, *J.*, 1945, 921.

[29] A. Michaelis and T. Becker, *Ber.*, 1897, **30**, 1003.

[30] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, 1945, **67**, 1180.

[31] *Idem, ibid.*, p. 2259.

[32] P. Nylen, *Ber.*, 1924, **57**, 1023.

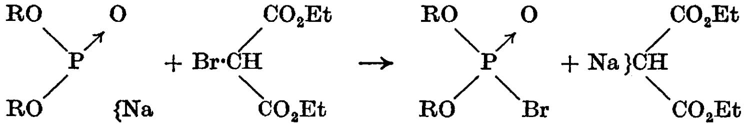
[33] *Idem, ibid.*, 1926, **59**, 1119.

[34] G. Kamaĭ and O. N. Belorossova, *Bull. Acad. Sci. U.R.S.S., Classe sci. chim.*, 1947, 191.

[35] B. A. Arbusov and A. N. Pudovick, *J. Gen. Chem. Russia*, 1947, **17**, 2158.

[36] B. A. Arbusov and N. P. Grechkin, *ibid.*, p. 2166.

when the halogen is " positive " ; thus the reaction of ethyl bromomalonate and sodium dibutyl phosphite[37] gives tetraethyl ethanetetracarboxylate. Although no explanation has been published, it would appear that the ethyl bromomalonate halogenates the sodium derivative, *i.e.*,



and further reaction then occurs among the components of the reaction mixture, leading to the desired product, tetraethyl ethanetetracarboxylate and probably tetrabutyl hypophosphate. This would account for the high phosphorus content of the phosphorus-containing fraction which was observed. An abnormal reaction also takes place with 9-chloroacridine to give acridone.[38]

3. Esters of Quinquevalent Phosphorus

These esters can be converted into the acids by acid or alkaline hydrolysis or, in the case of phenyl and benzyl esters, by hydrogenolysis. The aryl esters are comparatively inert and will not be considered here. The most interesting reactions of the alkyl and aralkyl esters, which are in many respects similar to esters derived from the sulphur acids, are alkylation and the reactions they undergo in the presence of phosphorus halides.

(*a*) **Alkylating Properties.**—Although in published work at the present time, these properties have been demonstrated only with esters of phosphoric acid, they are not restricted to these compounds.

(i) Alkylation of phenols. The alkylation of phenols by alkyl phosphates was first demonstrated 50 years ago when A. Morel[39] observed the production of phenetole in the reactions of triphenyl and diphenyl ethyl phosphate with sodium ethoxide, *e.g.*,

$$(PhO)_3PO + 3EtONa \longrightarrow (EtO)_2PO\cdot ONa + 2PhONa + PhOEt$$

This reaction undoubtedly proceeds by a trans-esterification, followed by alkylation of the phenoxide by an ethyl phosphate. It has been shown more recently[40] that trialkyl phosphates will alkylate phenols and that not all of the alkyl groups are utilised.

(ii) Alkylation of alcohols. At temperatures over 160°, high-boiling alcohols are converted into their methyl ethers by trimethyl phosphate,[41] whilst, in addition to trans-esterification, ether formation has been observed when trialkyl phosphates react with sodium butoxide.[42]

$$(EtO)_3PO + BuONa \longrightarrow (EtO)_2PO\cdot ONa + BuOEt$$

(iii) Alkylation of amines. At high temperatures many trialkyl phos-

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[37] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, 1946, **68**, 1103.

[38] *Idem, ibid.*, 1947, **69**, 1002.

[39] *Compt. rend.*, 1899, **128**, 507.

[40] C. R. Noller and G. R. Dutton, *J. Amer. Chem. Soc.*, 1933, **55**, 424.

[41] A. D. F. Toy, *ibid.*, 1944, **66**, 499.

[42] W. H. C. Rueggeberg and J. Chernack, *ibid.*, 1948, **70**, 1802.

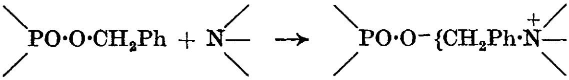
phates convert arylamines into the tertiary amines,[43] all three alkyl groups being utilised in the reaction :

$$3NH_2Ar + 2(RO)_3PO \longrightarrow 3NArR_2 + 2H_3PO_4$$

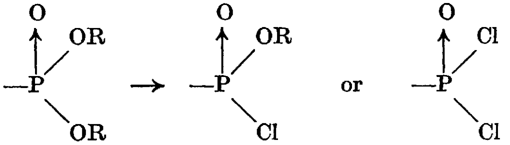
Tri*iso*propyl phosphate, however, gives only the secondary amine. 4-Ethylmorpholine is produced by the action of triethyl phosphate on morpholine at 150°.[42]

It should be emphasised that, as with dialkyl sulphates, there is considerable difference in the alkylating powers of successive groups, the neutral esters being far more powerful alkylators than the salts produced by the primary alkylation. The aralkyl esters of phosphates and pyrophosphates are, as would be expected, considerably more powerful alkylating agents than alkyl esters—with tertiary amines they form quaternary salts under comparatively mild conditions.

These properties have been used to achieve the selective debenzylation necessary for the synthesis of the biologically important adenosine triphosphate.[21]



(*b*) **Interchange Reactions with Phosphorus Halides.**—(i) Direct replacement. On heating with phosphorus pentachloride, ester groups may be replaced directly by chlorine. When this reaction is applied to a dialkyl alkylphosphonate,[44] either one or both of the ester groups may be replaced.



(ii) Redistribution. It has been observed that trialkyl phosphates react when warmed with phosphorus oxychloride. Thus W. Gerrard [45] demonstrated the successive replacement of the butyloxy-groups in tributyl phosphate, the extent of the replacement being dependent on the excess of phosphorus oxychloride present.

$$(BuO)_3PO + POCl_3 \longrightarrow (BuO)_2POCl \quad \text{or} \quad BuO{\cdot}POCl_2$$

Since the reaction will not be discussed elsewhere, it is relevant to point out that similar redistributions occur with trialkyl phosphites and phosphorus trichloride.[45]

(*c*) **Elimination Reactions with Phosphorus Halides.**—Those compounds which contain both a halogen and an ester group are capable of eliminating the alkyl halide and forming a polymeric compound:

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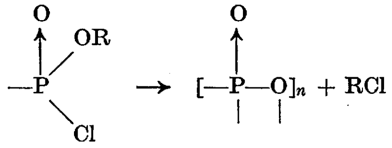
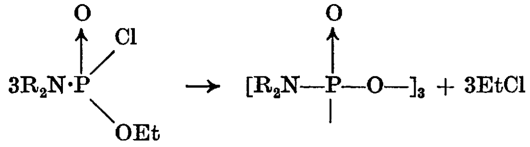
[43] J. H. Billmann, A. Radike, and B. W. Mundy, *J. Amer. Chem. Soc.*, 1942, **64**, 2977.

[44] M. I. Kabachnik and P. A. Rossiĭskaya, *Bull. Acad. Sci. U.R.S.S., Classe sci. chim.*, 1946, 515.

[45] *J.*, 1940, 1464.



The reaction probably occurs in many of the thermal decompositions observed with compounds of this type. In thermal decompositions of the ethyl dialkylaminochlorophosphonites, which occur at about 150°, the phosphorus compounds produced have been shown to be cyclic trimers.[46]



This type of reaction may also be brought about by the action of tertiary bases at room temperature. Thus 4-methylmorpholine reacts with dibenzyl chlorophosphonate to give a high yield of the quaternary salt with benzyl chloride, the other product presumably being benzyl metaphosphate.[7]

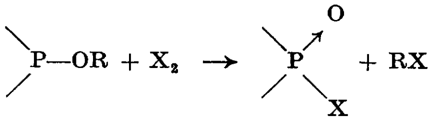
$$(CH_2Ph{\cdot}O)_2POCl \longrightarrow [CH_2Ph{\cdot}O{\cdot}PO_2]_x + CH_2PhCl$$

There is also evidence that the reaction can occur between dissimilar molecules, as the new insecticide, the so-called " hexaethyl tetraphosphate ", which is prepared by the action of phosphorus oxychloride on triethyl phosphate, is now known to be a mixture of ethyl metaphosphate and tetraethyl pyrophosphate. G. M. Kosolapoff [47] has suggested rather a complex mechanism for this reaction, although the formation of the products is simply explained by an initial redistribution reaction to form diethyl chlorophosphonate which could then undergo an elimination reaction, either with itself to give ethyl metaphosphate or with triethyl phosphate to give tetraethyl pyrophosphate.

4. Esters of Tervalent Phosphorus

The most characteristic reactions of this class of compounds occur in the presence of halogens or halogen-containing materials and result in a change of valency.

(*a*) **Action of Halogens.**—Halogens react at low temperatures to split out alkyl halides and effect the reaction :



In this manner trialkyl phosphites are converted into dialkyl chlorophosphonates by chlorine, [22, 45, 48] dialkyl bromophosphonates by bromine,[48] dialkyl iodophosphonates by iodine,[28] and dialkyl cyanophosphonates by

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[46] A. Michaelis, *Annalen*, 1902, **326**, 129.

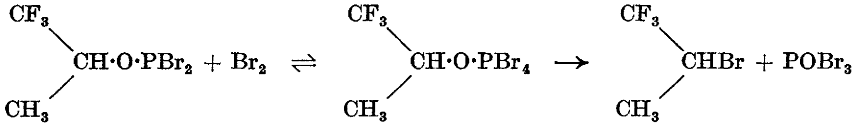
[47] *Science*, 1948, **108**, 485.

[48] H. Wichelhaus, *Annalen*, Suppl., 1867, **6**, 256.

the pseudo-halogen cyanogen iodide.[49] Diethyl chlorophosphinate reacts with chlorine to give ethyl dichlorophosphonite.[48]

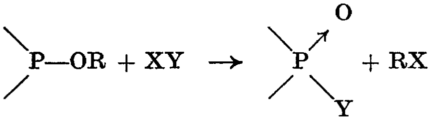
$$(EtO)_2PCl + Cl_2 \longrightarrow EtO{\cdot}POCl_2 + EtCl$$

Although of little practical importance, the conversion of alkyl dichlorophosphinites into phosphorus oxyhalides and alkyl halides by the action of halogens [48, 50] shows the generality of the reaction still further. The action of bromine on 1 : 1 : 1-trifluoro-2-propyl dibromophosphinite [51] is interesting in that these materials give an additive compound in the cold, which decomposes on warming, partly into its components and partly in the usual manner.



$$(CF_3)(CH_3)CH{\cdot}O{\cdot}PBr_2 + Br_2 \rightleftharpoons (CF_3)(CH_3)CH{\cdot}O{\cdot}PBr_4 \longrightarrow (CF_3)(CH_3)CHBr + POBr_3$$

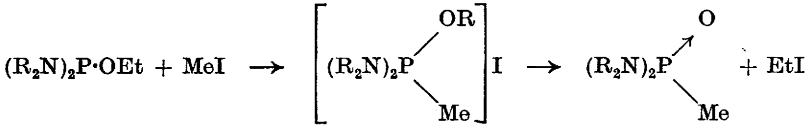
(*b*) **Action of Halides.**—Many halogeno-compounds react with tervalent compounds of phosphorus containing an alkoxy-group in accordance with the equation :



$$\rangle P{-}OR + XY \longrightarrow \rangle P(\rightarrow O)Y + RX$$

This reaction, which usually occurs on heating but may sometimes take place on mixing the components, is known as the Arbusov reaction. It has been demonstrated with a variety of types of tervalent esters but does not appear to occur if the phosphorus atom is halogen-substituted.

Alkyl halides react with trialkyl phosphites to give dialkyl alkylphosphonates,[52] dialkyl arylphosphinates to give alkyl arylalkylphosphonites,[53] and alkyl diarylphosphinites to give diarylalkylphosphine oxides.[53] The ethyl esters of bisdialkylaminophosphinous acids also undergo the reaction,[46] but in this instance an unstable adduct may be isolated which eliminates alkyl halide on standing, *e.g.*,



$$(R_2N)_2P{\cdot}OEt + MeI \longrightarrow \left[(R_2N)_2P(OR)Me\right]I \longrightarrow (R_2N)_2P(\rightarrow O)Me + EtI$$

Moreover, the reaction is not restricted to the oxygen esters, since alkyl diarylthiophosphinites form diarylalkylphosphine sulphides when treated with alkyl halides : [54]

$$Ar_2P{\cdot}SR + RI \longrightarrow Ar_2R{\cdot}PS + RI$$

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[49] B. C. Saunders, G. J. Stacey, F. Wild, and I. G. E. Wilding, *J.*, 1948, 699.

[50] N. Menschutkin, *Annalen*, 1866, **139**, 343.

[51] F. Swarts, *Bull. Soc. chim. Belg.*, 1929, **38**, 99.

[52] A. Arbusov, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 687.

[53] *Idem, ibid.*, 1910, **42**, 395.

[54] *Idem, ibid.*, p. 549.

It has been shown that the reaction occurs with a wide variety of halogen-containing compounds. Thus trialkyl phosphites have been treated successfully with polyhalogenoalkanes,[38, 49, 55] halogenocarboxylic esters,[56] aralkyl halides,[31, 49, 57] halogen derivatives of heterocyclic compounds,[38] halides of disubstituted arsines,[34] trialkyltin halides,[35] dialkyltin dihalides, and alkyltin trihalides.[36] Acid chlorides such as acetyl chloride and benzoyl chloride react readily, even at room temperature, to give esters of acylphosphonic acids.[58]

The above reactions are undoubtedly typical of the corresponding aralkyl esters.

5. Chlorides of Quinquevalent Phosphorus

Compounds of this type exhibit most of the characteristic properties of normal acid chlorides. They are decomposed by water to give the corresponding acids with varying ease and exhibit the usual formation of esters and amides and replacement reactions of the halogens.

(*a*) **Ester Formation.**—(i) With sodium alkoxides. The reaction takes place smoothly, alkyl dichlorophosphine oxides,[29] dialkylaminodichlorophosphine oxides,[46] and aryl dichlorophosphonites [59] undergoing replacement of both halogens, and bisdialkylaminochlorophosphine oxides [46] and diaryl chlorophosphonates [59] replacement of the one halogen atom.

(ii) In the presence of organic tertiary bases. Aryl-,[60] alkyl-,[61] and anilino-dichlorophosphine oxides [62] and aryl dichlorophosphonites [63] usually react with both halogens, but it has been shown that when quinoline is used as the tertiary base it is possible to achieve selective replacement of one chlorine in phenyl dichlorophosphonite.[64] Diaryl [63] and diaralkyl [7, 24] chlorophosphonates and dianilinochlorophosphine oxide [62] react satisfactorily, and removal of the protecting groups from the products may be achieved to yield pure monosubstituted phosphoric esters.

(*b*) **Replacement Reactions.**—(i) By amino-groups. All types of compounds containing halogen atoms may be caused to react successfully with amines to give the corresponding amino-derivatives. A. Michaelis [46] gives a wide range of examples, of both complete and partial substitution.

(ii) By fluorine. Alkyl dichlorophosphonites,[65, 66] dialkyl chlorophosphonates,[65, 66] dialkylaminodichloro- and bisdialkylamino-chloro-phosphine

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[55] A. J. Arbusov and N. P. Kuschkowa, *J. Gen. Chem. Russia*, 1936, **6**, 283.

[56] A. Arbusov and A. Dunin, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 295.

[57] B. P. Lugovkin and B. A. Arbusov, *Doklady Akad. Nauk. S.S.S.R.*, 1948, **59**, 1301.

[58] M. I. Kabachnik and P. A. Rossiĭskaya, *Bull. Acad. Sci. U.R.S.S., Classe sci. chim.*, 1945, 364.

[59] A. Morel, *Bull. Soc. chim.*, 1899, [iii], **21**, 491.

[60] A. D. F. Toy, *J. Amer. Chem. Soc.*, 1948, **70**, 186.

[61] M. I. Kabachnik, P. A. Rossiĭskaya, and N. N. Novikova, *Bull. Acad. Sci. U.R.S.S., Classe sci. chim.*, 1947, 97.

[62] F. Zetzche and W. Büttiker, *Ber.*, 1940, **73**, 47.

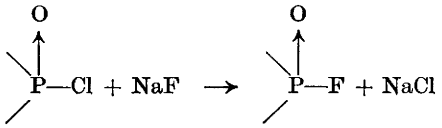
[63] P. Brigl and H. Müller, *ibid.*, 1939, **72**, 2121.

[64] E. Baer and M. Kates, *J. Amer. Chem. Soc.*, 1948, **70**, 1394.

[65] B. C. Saunders and G. J. Stacey, *J.*, 1948, 695.

[66] B.I.O.S., Final Report No. 714, Item 8.

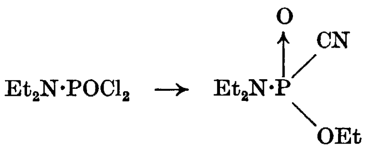
oxides and sulphides [66] are converted into the corresponding fluoro-compounds by the action of sodium fluoride in an inert solvent:



The complete and partial fluorination of ethyl dichlorothiophosphonite may be accomplished by the action of antimony trifluoride.[67]

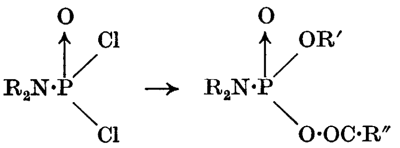
(iii) By the thiocyanato-group. Dialkyl chlorophosphonates [49] react with potassium thiocyanate to give dialkyl thiocyanatophosphonates. The reaction of diethylamino-dichlorophosphine oxide [46] with silver thiocyanate is said to give a thiocyanato-derivative, though from general experience it would not be surprising if this were actually an *iso*thiocyanato-compound.

(iv) By the cyano-group. The action of an alcoholic solution of potassium cyanide on diethylaminodichlorophosphine oxide [46] gives simultaneous replacement by the cyano-group and esterification:

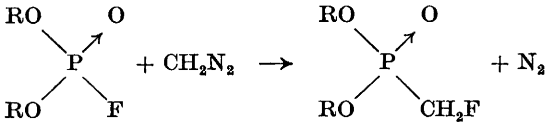


Diethyl chlorophosphonate, however, reacts poorly with potassium cyanide.[49]

(v) By acyloxy-groups. Dialkylaminodichlorophosphine oxides react with the sodium salts of carboxylic acids to replace both halogens,[66] but when the reaction is carried out in alcoholic solutions an ester group is also introduced.



(*c*) **Reaction with diazoalkanes.**—Although only one observation of this type of reaction has been made to date, namely that a dialkyl fluorophosphonate reacts with diazomethane to give the fluoromethylphosphonate,[49]



it is very probable that this will prove to be a general reaction applicable to all types of halides.

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[67] H. S. Booth, D. R. Martin, and F. E. Kendall, *J. Amer. Chem. Soc.*, 1948, **70**, 2523.

6. Chlorides of Tervalent Phosphorus

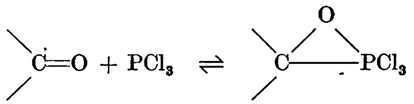
Compounds of this type are, as would be expected, very similar in many respects to the corresponding quinquevalent compounds, giving esters with sodium alkoxides or alcohols in the presence of tertiary bases and undergoing replacement of the halogen by amino- and other groupings. These reactions of the compounds will not, therefore, be discussed further, although it is relevant to point out that irregularities are more likely to occur in this series. Thus whilst diphenylchlorophosphine reacts normally with most sodium alkoxides to give the corresponding esters, sodium methoxide and benzyloxide give the phosphine oxide,[53] *e.g.*,

$$PPh_2Cl + NaOMe \longrightarrow PPh_2MeO + NaCl$$

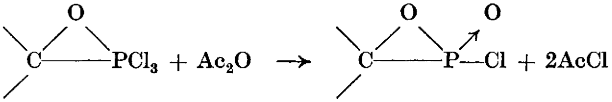
Reactions peculiar to this class of compound are those which they undergo with carbonyl compounds and olefin oxides.

(*a*) **Reaction with Carbonyl Compounds.**—Although earlier workers had found that mixtures of phosphorus trichloride and carbonyl compounds gave α-hydroxy-phosphonic acids when treated with water, our knowledge of this type of reaction is largely due to the studies of J. B. Conant and his co-workers.

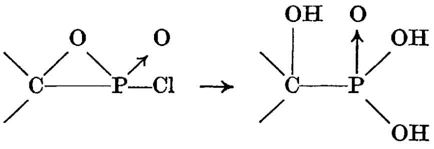
The initial reaction of phosphorus trichloride with carbonyl compounds was found to be reversible,[68, 69] giving an additive product which reacted more readily with acetic acid or anhydride than did phosphorus trichloride. In this way it was possible to disturb the equilibrium and make the reaction proceed virtually to completion. The mechanism of the reaction is postulated by these workers as an extension of valency of the phosphorus trichloride,



as had already been suggested,[70] followed by a disturbance of the equilibrium by interaction of the intermediate with acetic anhydride (or acid), *e.g.*,



Hydrolysis of the reaction mixture would then give the hydroxy-phosphonic acid :



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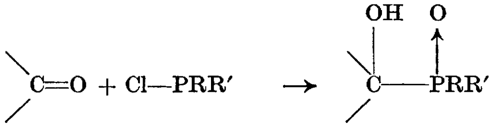
[68] J. B. Conant and A. D. Macdonald, *ibid.*, 1920, **42**, 2337.

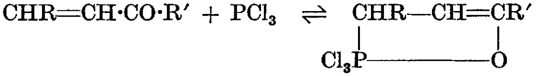
[69] J. B. Conant, A. D. Macdonald, and A. McB. Kinney, *ibid.*, 1921, **43**, 1928.

[70] A. Michaelis and A. Flemming, *Ber.*, 1901, **34**, 1291.

Similar reactions occur with phenyldichlorophosphine,[71] diphenylchlorophosphine,[72] phenyl and alkyl dichlorophosphinites, and diphenyl chlorophosphinate.[73] The general overall reaction may therefore be expressed:

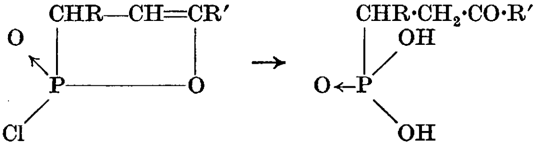


When $\alpha\beta$-unsaturated ketones are treated with phosphorus trichloride,[74, 75] the product is a β-keto-phosphonic acid. The production of this class of compounds is postulated to occur in a similar manner, the initial addition being of the 1 : 4-type,

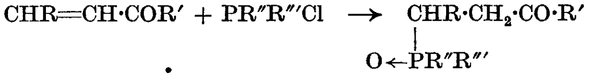


$$CHR{=}CH{\cdot}CO{\cdot}R' + PCl_3 \rightleftharpoons \begin{array}{l}CHR{-}CH{=}CR'\\ \;| \qquad\qquad\quad |\\ Cl_3P\text{————}O\end{array}$$

to give an adduct which then reacts with acetic anhydride (or acid). On hydrolysis, the enol-phosphorus link is severed to give the β-keto-phosphonic acid:



Here, again, similar reactions occur with phenyldichlorophosphine,[76, 77] diphenylchlorophosphine,[72] phenyl dichlorophosphinite, and diphenyl chlorophosphinate,[73] the general reaction therefore being:



$$CHR{=}CH{\cdot}COR' + PR''R'''Cl \longrightarrow \begin{array}{l}CHR{\cdot}CH_2{\cdot}CO{\cdot}R'\\ \;|\\ O{\leftarrow}PR''R'''\end{array}$$

Although the overall reactions as described above are correct, the mechanisms are very probably incorrect, since other experiments [78] suggest that the initial reaction between phosphorus trichloride and benzaldehyde is a more conventional type of addition.

$$Ph{\cdot}CHO + PCl_3 \rightleftharpoons CHPhCl{\cdot}O{\cdot}PCl_2$$

A further point against the above mechanisms is that the reaction can be carried out successfully with alkyl dichlorophosphinites which would necessitate the production of an intermediate compound with an alkoxy-group and a halogen on a phosphorus atom with five substituents.

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[71] A. Michaelis, *Annalen*, 1896, **293**, 222.

[72] J. B. Conant, J. B. S. Braverman, and R. E. Hussey, *J. Amer. Chem. Soc.*, 1923. **45**, 165.

[73] J. B. Conant, V. H. Wallingford and S. S. Gandheker, *ibid.*, p. 762.

[74] J. B. Conant, *ibid.*, 1917, **39**, 2679.

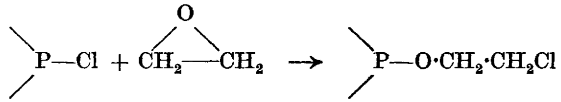
[75] J. B. Conant and A. A. Cook, *ibid.*, 1920, **42**, 830.

[76] J. B. Conant and S. M. Pollack, *ibid.*, 1921, **43**, 1665.

[77] J. B. Conant, A. H. Bump, and H. S. Holt, *ibid.*, p. 1677.

[78] F. R. Atherton and A. R. Todd, unpublished.

(*b*) **Reaction with Olefin Oxides.**—Although halides of quinqevalent phosphorus compounds do not react with olefin oxides in the absence of hydrogen halide, tervalent compounds react very readily to form esters, *e.g.*,



In this way ethylene oxide reacts with diphenyl chlorophosphinate and phenyl dichlorophosphinite to give triesters of phosphorous acid.[79] With phosphorus trichloride, ethylene oxide reacts progressively to give 2-chloroethyl dichlorophosphinite, di-(2-chloroethyl) chlorophosphinate, and tri-(2-chloroethyl) phosphite [80]; propylene oxide behaves similarly.[78]

It is hoped that the above review will serve to give an insight into the chemical behaviour of the more common types of phosphorus compounds. The material represents, however, only one facet of the organic chemistry of phosphorus of which the pioneer, A. Michaelis, is quoted by G. Schrader [66] as having written :

" Even if at this present moment no special possibilities are apparent, yet there will, of that I am sure, be a future for this subject surpassing even its great past."

[79] M. I. Kabachnik, *Bull. Acad. Sci. U.R.S.S., Classe sci. chim.*, 1947, 631.

[80] M. I. Kabachnik and P. A. Rossiĭskaya, *Bull. Acad. Sci. U.R.S.S., Classe sci. chim.*, 1946, 295.