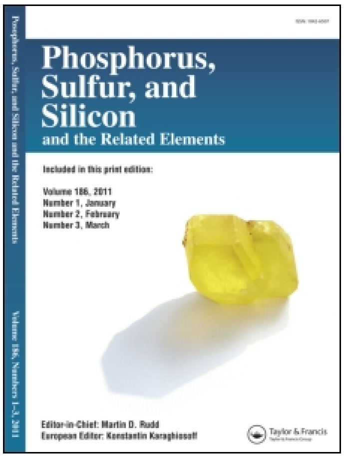

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NEW APPROACHES TO THE SYNTHESIS OF ORGANOPHOSPHORUS COMPOUNDS

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NEW APPROACHES TO THE SYNTHESIS OF ORGANOPHOSPHORUS COMPOUNDS [†]

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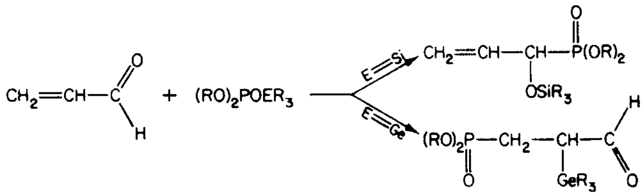
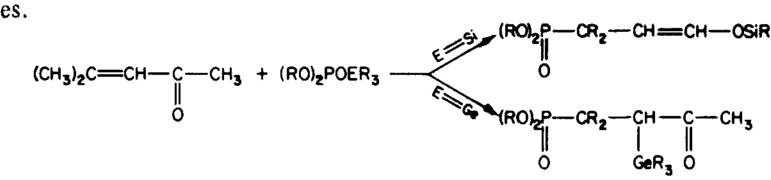
The past two decades have brought us a snowballing development of organophosphorus chemistry. Indeed organophosphorus compounds have found wide practical application (in agriculture, petroleum industry, as drugs, etc.) and continue to afford promising objects for the study of theoretical matters such as tautomerism, ambiphilicity, ambidenticity, and other problems of organic chemistry. On the other hand, however impressive this progress may be, the search for new methods of synthesis, improving the known methods and forecasting new types of organophosphorus compounds remain as challenging problems as before.

These problems will be dealt with in this report. I would like to start with addition of phosphorus acid derivatives of various types to compounds with multiple bonds. The most extensive studies were made for dialkyl phosphites of alkali metals leading to an important method of the synthesis of derivatives of phosphonic acids from dialkyl phosphites in the presence of alkoxides of alkali metals. A feature which the reactions have in common is that trivalent phosphorus attacks an electrophilic spearhead of the unsaturated species to form the energetically favorable phosphoryl group. Apparently a great number of organophosphorus compounds possessing a P–OE group may undergo a similar addition reaction. We will focus our attention on the compounds in which E is an element of the fourth or fifth groups. These reactions are attractive in that they allow one to synthesize element-substituted phosphonates, study the mode of the addition as a function of the organoelement group and the nature of the unsaturated compound, and investigate rearrangements of thermodynamlically less stable organoelement compounds to the more stable ones. Of the group IVB organoelement phosphites we have studied compounds containing silicon, germanium, and tin synthesized *via* methods either known from the literature or designed in this laboratory.

The resulting phosphites were subjected to nucelophilic reactions with alpha-, beta-unsaturated aldehydes, ketones, and carboxylic acid derivatives. The addition of element-substituted phosphites may go *via* three routes, namely: at the carbon-carbon double bond (1,2 addition); at the carbonyl (3,4 addition); or at the terminal atoms of the conjugated system (1,4 addition). For example, with acrolein trialkyl silyl-phosphites react in the 3,4 fasion (at the carbonyl) whereas germyl phosphites react in the 1,2 fashion to give beta-trialkylgermylated phosphonates.



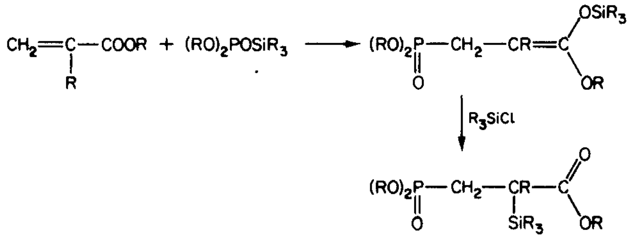
Similar differences are inherent in the reaction of organoelement phosphites with alpha-, beta-unsaturated ketones: silyl phosphites undergo the 1,4 addition and give O-silylated gamma-ketophosphonate enols whereas germyl phosphites (as with acrolein) add in the 1,2 fashion and form beta-trialkylgermylated gamma-ketophosphonates.



[†] Plenary Lecture. Vth International Conference of Organic Phosphorus Chemistry, Gdansk, Poland, September 1974.

Consequently when trialkylsilyl phosphites react with alpha-, beta-unsaturated aldehydes or ketones the silyl group adds at the oxygen and gives the O-silylated phosphonate whereas trialkylgermyl phosphites yield phosphonates containing a germanium-carbon bond.

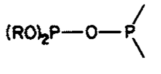
A similar addition mode is observed with organoelement phosphites reacting with unsaturated esters. The product of the 1,4 addition of a trialkyl phosphite, when heated with R_3SiCl, readily rearranges to the isomeric beta-trialkylsilylated phosphonate.



$$CH_2{=}C(R){-}COOR + (RO)_2POSiR_3 \longrightarrow (RO)_2P(O){-}CH_2{-}CR{=}C(OSiR_3)(OR) \xrightarrow{R_3SiCl} (RO)_2P(O){-}CH_2{-}CR(SiR_3){-}C({=}O)OR$$

This reaction resembles irreversible rearrangements of O-alkyl-O-trialkylsilyl ketene acetals studied by us earlier. Trialkyl phosphites may also be thought of as organoelement phosphites of the fourth group. The element in this case is carbon. Trialkyl phosphites are well known to add to unsaturated compounds although the reaction proceeds under more drastic conditions than in the case of germyl- or silyl-phosphites.

A further important step in the study of addition reactions of compounds of the P–OE type was made when anhydrides (1 and 2) of acids of a three- or four-coordinate phosphorus, formally belonging to organoelement phosphites, were employed.



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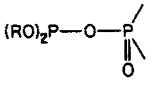

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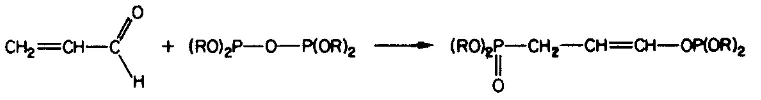
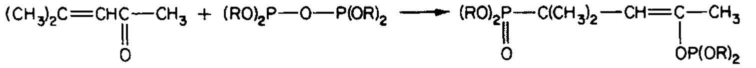
To begin with we studied the addition of tetraalkyl pyrophosphites and isohypophosphites. Tetraethyl pyrophosphite has been found to react with alpha-, beta-unsaturated aldehydes, ketones, and carboxylic esters. Unlike trialkylgermyl phosphites that add to acrolein in the 1,2 fashion or trialkylsilyl phosphites that add in the 3,4 fashion, pyrophosphites add at the ends of the conjugated system in the 1,4 fashion,



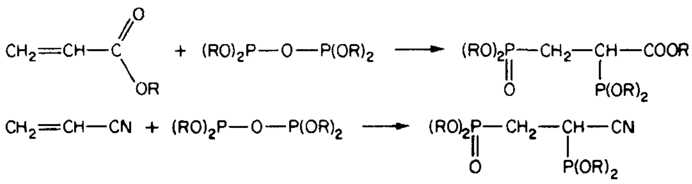
$$CH_2{=}CH{-}CHO + (RO)_2P{-}O{-}P(OR)_2 \longrightarrow (RO)_2P(O){-}CH_2{-}CH{=}CH{-}OP(OR)_2$$

and give a high yield of dialkoxyphosphinylpropionic aldehyde enol phosphite. The 1,4 addition is observed with alpha-, beta-unsaturated ketones as well.



$$(CH_3)_2C{=}CHC(O){-}CH_3 + (RO)_2P{-}O{-}P(OR)_2 \longrightarrow (RO)_2P(O){-}C(CH_3)_2{-}CH{=}C(CH_3){-}OP(OR)_2$$

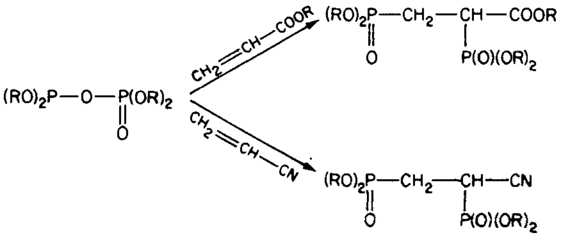
Pyrophosphites react with alpha-, beta-unsaturated carboxylic derivatives such as ethyl acrylate, methyl methacrylate and acrylonitrile to yield compounds containing two P–C bonds in a molecule



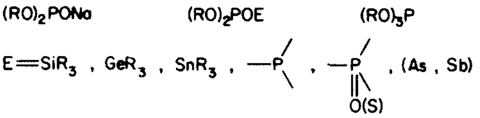
$$CH_2{=}CH{-}C(O)OR + (RO)_2P{-}O{-}P(OR)_2 \longrightarrow (RO)_2P(O){-}CH_2{-}CH(P(OR)_2){-}COOR$$

$$CH_2{=}CH{-}CN + (RO)_2P{-}O{-}P(OR)_2 \longrightarrow (RO)_2P(O){-}CH_2{-}CH(P(OR)_2){-}CN$$

It should be noted that the resulting two-phosphorus compounds contain both a three- and a four-coordinate phosphorus atom; they may enter into further reactions, e.g. the Arbuzov rearrangement. Isohypophosphites also add to alpha-, beta-unsaturated carboxylic esters but their lower nucleophilicity (as compared with pyrophosphites) requires that more drastic conditions be applied.



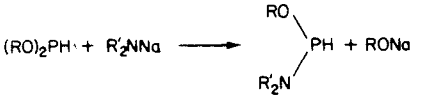
As follows from the examples given above for pyrophosphites and isohypophosphite esters it is likely that various anhydrides of phosphorus-containing acids with at least one three-coordinate phosphorus can add to unsaturated compounds resulting in new types of organophosphorus compounds. Consequently our reactions of unsaturated compounds with organoelement phosphites show that the latter have much in common with the extensively studied trialkyl phosphites and dialkyl phosphites of alkali metals.



Quite unexpected organophosphorus synthetic routes emerged after we found a method for the synthesis of di-esters of hydrogen phosphonous acid (dialkoxyphosphines) containing a three-coordinate phosphorus. They may be synthesized easily from dialkyl chlorophosphites and trialkyl stannanes in yields of 90%.

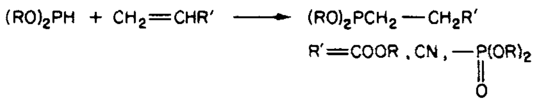
$$R'_3SnH + ClP(OR)_2 \longrightarrow (RO)_2PH + R'_3SnCl$$

Later we found a more convenient technique, reduction of dialkyl chlorophosphites with $NaBH_4$, resulting in a shorter (20-30 minutes instead of several days) synthesis of dialkoxyphosphines. Treating them with sodium dialkylamide allows one to replace an alkoxy group by a dialkylamino group and obtain O-alkyl hydrogenphosphonodialkylamidites.

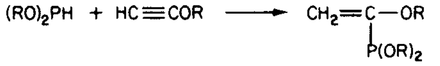


$$(RO)_2PH + R'_2NNa \longrightarrow (RO)(R'_2N)PH + RONa$$

In a predictable way dialkoxyphosphines (hybrids of a phosphite and a phosphine) readily enter into nucleophilic addition at multiple bonds.



$$(RO)_2PH + CH_2{=}CHR' \longrightarrow (RO)_2PCH_2{-}CH_2R' \qquad R'{=}COOR,\ CN,\ {-}P(O)(OR)_2$$

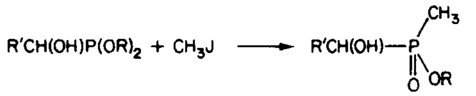


$$(RO)_2PH + HC{\equiv}COR \longrightarrow CH_2{=}C(OR){-}P(OR)_2$$

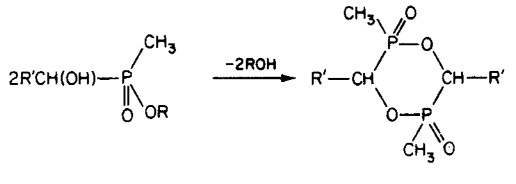
These reactions made it possible to synthesize phosphonous esters with functional groups in the organic portion. The substituted esters were inaccessible earlier since organometallic syntheses as well as the Walsh-Woodstock method (reduction with yellow phosphorus of adducts resulting from phosphorus pentachloride and unsaturated compounds) would have affected the functional groups. The reaction with aldehydes or ketones is even more facile: it results in alpha-hydroxyphosphonites.

$$(RO)_2PH + R'CHO \longrightarrow R'CH(OH)P(OR)_2$$

These could not be isolated because the distillation resulted in polymers. The Arbuzov rearrangement however gives alpha-hydroxyphosphinates in yields of 50-60%.

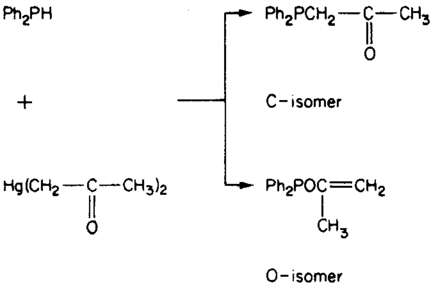


$$R'CH(OH)P(OR)_2 + CH_3J \longrightarrow R'CH(OH){-}P(O)(CH_3)OR$$



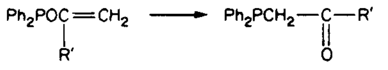
In many cases side products were isolated; crystalline compounds assigned as phosphorus-containing analogs of lactides.

We made extensive use of alpha-metalated carbonyl compounds. The reactions led to methods of obtaining both O- and C-organophosphorus aldehydes, ketones, or carboxylic esters in good yields. We have focused our attention on new types of O- and C-functionally substituted compounds and on rearrangements of the resulting isomers. For example, reactions of primary or secondary phosphines with alpha-mercuriated carbonyl compounds showed that whether O- or C-organophosphorus ketoenols are formed depends on various factors such as structure of the metalated carbonyl compound, substituent attached to the phosphorus and solvent. The reaction of diphenylphosphine with mercury-*bis*-acetone demonstrates that solvents of higher basicity and coordinating ability favor electron transfer reactions resulting in O-isomers (see the table).



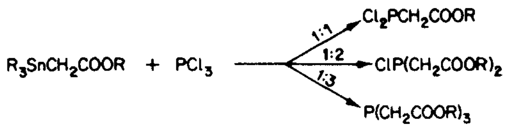
Solvent	Isomer	%
	O-	C-
Benzene	none	100
Chlorobenzene	none	100
Dioxan	30	70
Monoglyme	70	30

When heated, the alkenyl phosphinites do not rearrange to the isomerical beta-ketophosphines. The O-to-C isomerization, however, does occur in the presence of metal halides (HgI_2, CdI_2, R_3SnI).



$$Ph_2POC(R'){=}CH_2 \longrightarrow Ph_2PCH_2{-}C(O){-}R'$$

It should be emphasized that the rearrangement does not affect the phosphorus valence. Isomeric O- and C-derivatives were obtained from alpha-metalated carboxylic esters as well. Earlier we found a good method (yields of 80 to 90%) of attaching a carboalkoxymethyl group to a trivalent phosphorus.

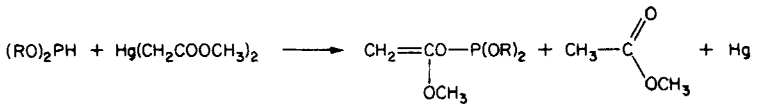


$$R_3SnCH_2COOR + PCl_3 \xrightarrow{1:1} Cl_2PCH_2COOR$$
$$R_3SnCH_2COOR + PCl_3 \xrightarrow{1:2} ClP(CH_2COOR)_2$$
$$R_3SnCH_2COOR + PCl_3 \xrightarrow{1:3} P(CH_2COOR)_3$$

$$R_3SnCH_2COOR' + (RO)_2PCl \longrightarrow (RO)_2PCH_2COOR'$$

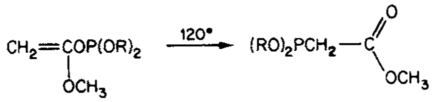
$$R_3SnCH_2COOR' + R''PCl_2 \longrightarrow R''P(CH_2COOR')_2$$

By varying the ratio of reagents, one to three carboalkoxymethyls may be introduced. The isomeric species, phosphorylated ketene semi-acetals, were obtained in high yields by reducing mercuriated acetic esters with dialkoxyphosphines.



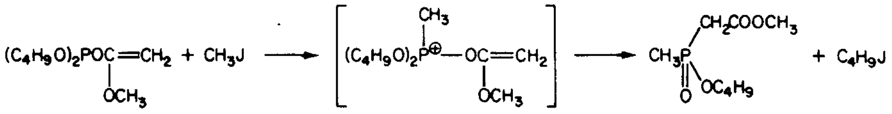
$$(RO)_2PH + Hg(CH_2COOCH_3)_2 \longrightarrow CH_2{=}C(OCH_3){-}O{-}P(OR)_2 + CH_3{-}C({=}O)OCH_3 + Hg$$

Unlike alkenyl phosphites, alpha-alkoxyvinyl phosphites irreversibly rearrange to carboalkoxymethylphosphonites on heating.



$$CH_2{=}C(OCH_3)OP(OR)_2 \xrightarrow{120^\circ} (RO)_2PCH_2{-}C({=}O)OCH_3$$

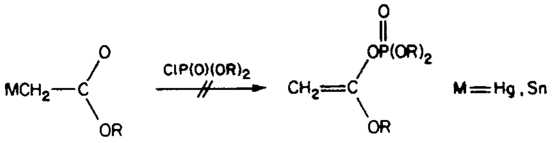
The same O-to-C rearrangement to a thermodynamically more stable isomer may be implemented by a small dialkyl chlorophosphite additive. An interesting example is the reaction of dibutyl alpha-methoxyvinyl phosphite with methyl iodide. The reaction proceeds under mild conditions (50°C) and leads to a phospinate.



$$(C_4H_9O)_2POC(OCH_3){=}CH_2 + CH_3J \longrightarrow \left[(C_4H_9O)_2\overset{CH_3}{P^{\oplus}}{-}OC(OCH_3){=}CH_2\right] \longrightarrow CH_3P(O)(CH_2COOCH_3)(OC_4H_9) + C_4H_9J$$

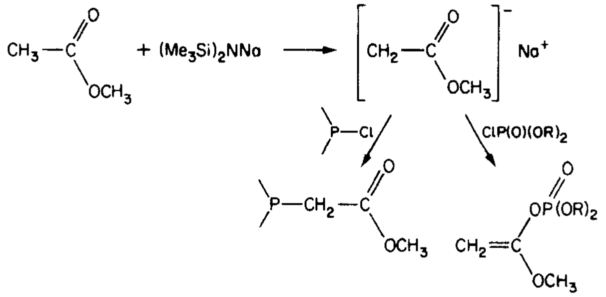
A double isomerization occurs: namely, both the Arbuzov rearrangement as well as the transformation of the O-organophosphorus acetic ester to the isomeric C-ester. The temperature at which these transformations occur is 70-80° lower than the thermal isomerization temperature: therefore the C-ester may be assumed to form at the stage of quasi-phosphonium compound formation.

We also attempted to isomerize alpha-alkoxyvinyl phosphates to carboalkoxymethylphosphonates. We could not obtain alpha-alkoxyvinyl phosphates from mercuriated or stannylated carboxylic esters *via* a reaction-site transfer process.



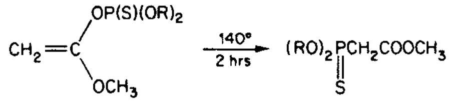
$$MCH_2{-}C({=}O)OR \xrightarrow[\quad\not\quad]{ClP(O)(OR)_2} CH_2{=}C(OR)OP(O)(OR)_2 \qquad M{=}Hg, Sn$$

The sodium derivatives proved more useful. It is known that sodium hexamethyldisilazanyl can metalate carboxylic esters. When treated with trivalent phosphorus halides the metalated derivatives allow one to introduce a phosphorus atom in the alpha-position with respect to the ester group.

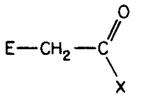


With four-coordinate phosphorus halides alpha-alkoxyvinyl phosphates are formed. Other acid chlorides of four-coordinate phosphorus compounds react in a similar way. The reaction is applicable to homologs of acetic esters as well as to acetic esters bearing various substituents, e.g. dimethylaminoacetic ester.

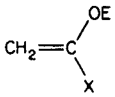
The thermal stability of alpha-alkoxyvinyl phosphates and thiophosphates was studied. Thiophosphates totally rearrange (at 140°, 2 hours) to the respective C-derivatives, alpha-carboalkoxymethyl phosphonothionates whereas 2-alkoxyvinyl phosphates do not isomerize under these conditions.



In all the rearrangements discussed above, a phosphorus-containing group migrated from the internal oxygen in the O-isomer to the internal carbon of the C-isomer; that is, the O-isomer was less stable thermodynamically. On the other hand, not only O-to-C but also C-to-O isomerization was observed by us in organoelement ketoenols of the group IVB elements. Some regularities of the O/C interconversions may depend on the electronic effect of the group X attached to the central atom of the ketoenol triad, where E is a group IVB element. The system is highly sensitive to very slight alterations of the nature of X which affect not only thermal stabilities of the isomers but also the course of the rearrangement.



C-isomer



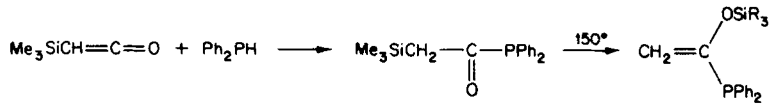
O-isomer

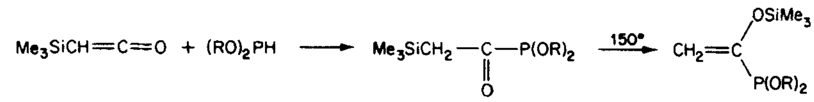
The data obtained may be summarized as follows:

i) The higher the +M effect of X, the more facile the rearrangement and the more stable the C-isomer.
ii) Decreasing the +M effect raises the relative O-isomer stability and favors the C-to-O rearrangement.
iii) This effect is further enhanced when −M groups are introduced.

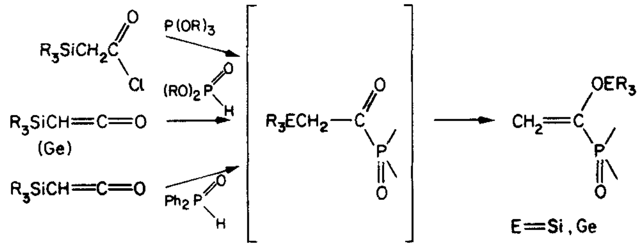
Consequently, differences in electron-withdrawing properties of X in similar structures may be expected to markedly influence thermal stability of the C-isomers. An increase in the electron-withdrawing properties will facilitate the C-to-O transformation significantly. An especially interesting question is how the stability will vary with the valence of X. We studied three- and four-coordinate phosphorus compounds of similar structures.

Diphenylphosphine or a dialkoxyphosphine reacts with trimethylsilylketene to give a C-product which irreversibly rearranges to the O-derivative only when heated to 140-150°.



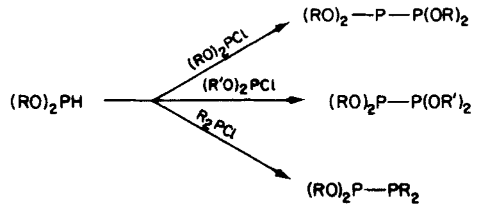


The diphenylphosphine group is known to be an acceptor which, however, is weaker than a strong acceptor such as phosphoryl. That is why some of our most interesting results were obtained when attempting to synthesize similar structures containing a four-coordinate phosphorus. Compounds in which the presence of the E–C bond was proven were tested in reactions aiming at C-isomers of four-coordinate phosphorus compounds.

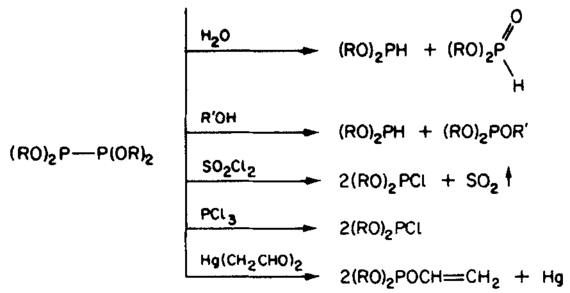


No C-isomer could be detected spectrally in any of the reactions although precisely this isomer should have been formed. O-isomers were isolated in all cases. Consequently when X is a strong electron acceptor, such as phosphoryl, the C-derivative rearranges to the O-isomer at room temperature. Thus the differences between electron-withdrawing properties of three- and four-coordinate phosphorus atoms sharply affects the thermal stability of the C-isomers that are formed. With the more electron-accepting phosphoryl group the process is so facile that the C-isomer expected from the compounds with an established E–C bond cannot be detected at all.

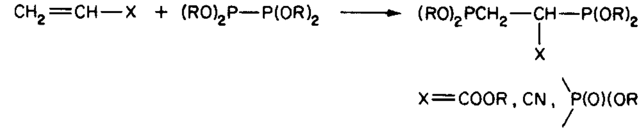
Finally I would like to consider the use of dialkoxyphosphines in synthesizing new P–P compounds. Above all tetraalkoxydiphosphines and their reactions will be concerned. Dialkoxyphosphines are convenient starting compounds for the synthesis of various alkoxydiphosphines.



Tetraalkoxydiphosphines are highly reactive; the P–P bond is readily broken in all their transformations.



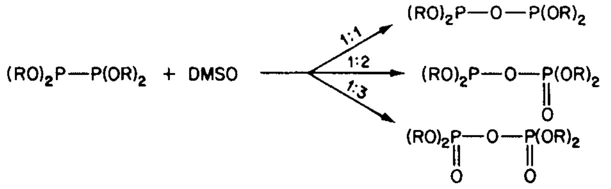
Tetraalkoxydiphosphines add to unsaturated compounds exothermally to give very reactive *bis*-phosphonites. Two new P–C bonds are formed; both phosphorus atoms are trivalent.



$$CH_2{=}CH{-}X + (RO)_2P{-}P(OR)_2 \longrightarrow (RO)_2PCH_2{-}\underset{X}{\underset{|}{CH}}{-}P(OR)_2$$

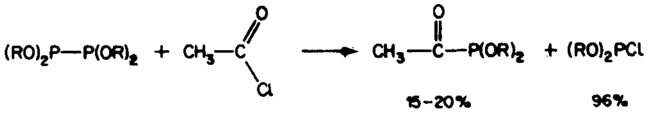
$$X{=}COOR,\ CN,\ P(O)(OR)_2$$

Tetraalkoxydiphosphines are readily oxidized with dimethyl sulfoxide (DMSO).



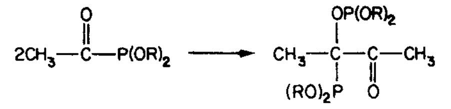
The reaction results in high yields of pyrophosphites, isohypophosphites or pyrophosphates, depending on the reactant ratio.

The P–P bond is also decomposed when acyl halides act on tetralkoxydiphosphines. For example, acetyl chloride enters into an exothermic reaction with tetrabutoxydiphosphine resulting in O, O-dibutyl chlorophosphite isolated in a yield of 96%.



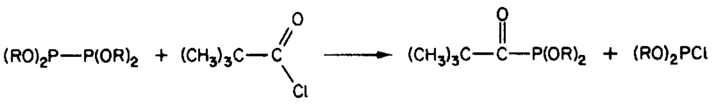
$$(RO)_2P{-}P(OR)_2 + CH_3{-}C(=O)Cl \longrightarrow \underset{15\text{-}20\%}{CH_3{-}\overset{O}{\overset{\|}{C}}{-}P(OR)_2} + \underset{96\%}{(RO)_2PCl}$$

The alpha-ketophosphonite however was isolated in as low yields as 15-20%. A noticeable amount of a high-boiling fraction was also obtained. In addition redistilling the acetylphosphonite always produces a higher-boiling residue whose physical constants and spectra coincide with those of the high-boiling product obtained in the synthesis of the alpha-ketophosphonite. The high-boiling fraction has been found to be alpha-acetylphosphonite dimer; the yield is above 60%.



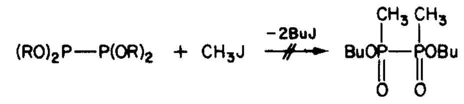
$$2CH_3{-}\overset{O}{\overset{\|}{C}}{-}P(OR)_2 \longrightarrow CH_3{-}\underset{(RO)_2P}{\underset{|}{\overset{OP(OR)_2}{\overset{|}{C}}}}{-}\underset{O}{\underset{\|}{C}}{-}CH_3$$

The ir and nmr spectra agree with the monomer and dimer structures proposed. Acetyl chloride was replaced by pivalic acid chloride in order to hinder the dimerization spatially, resulting in high yields of the monomer.



$$(RO)_2P{-}P(OR)_2 + (CH_3)_3C{-}C(=O)Cl \longrightarrow (CH_3)_3C{-}\overset{O}{\overset{\|}{C}}{-}P(OR)_2 + (RO)_2PCl$$

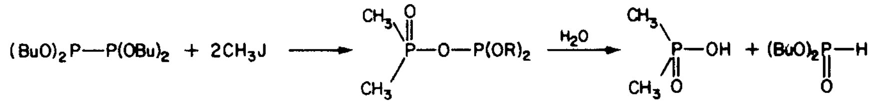
Alkylation of tetraalkoxydiphosphines is a complicated process. We assumed that alkyl halides would either break the P–P bond and lead to compounds containing one atom of phosphorus or cause two independent Arbuzov rearrangements resulting in conservation of the P–P bond and evolution of two moles of alkyl halide product. However neither of the reactions occurred.



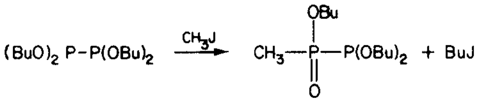
$$(RO)_2P{-}P(OR)_2 + CH_3J \xrightarrow[\not\;]{-2BuJ} BuO\overset{CH_3}{\underset{O}{P}}{-}\overset{CH_3}{\underset{O}{P}}OBu$$

Heating tetrabutoxydiphosphine with an excess of methyl iodide does result in two moles of butyl iodide and a two-phosphorus compound. The latter was extensively studied with chemical and spectral techniques.

To begin with the compound (isolated in a yield of 60%) is decomposed by water with spontaneous heating to give dumethylphosphonic acid (yield 60%) and dibutyl phosphite (yield 72%). The nmr ^{31}P spectra contain signals at −128 ppm and −21 ppm assignable to atoms of three- and five-coordinate phosphorus. These data suggest that the action of methyl iodide leads to a mixed anhydride of dimethylphosphonic and O, O-dibutyl phosphorus acids.

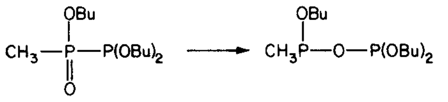


The process may be rationalized as follows: the first mole of methyl iodide causes the usual Arbuzov rearrangement in tetrabutoxydiphosphine giving the first mole of butyl iodide.



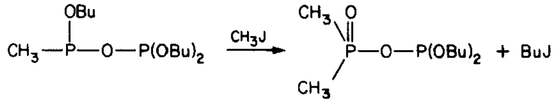
$$(BuO)_2P{-}P(OBu)_2 \xrightarrow{CH_3J} CH_3{-}\overset{OBu}{\underset{O}{P}}{-}P(OBu)_2 + BuJ$$

The polar P → O bond present in this compound lowers electron density on the adjacent three-coordinate phosphorus and thus facilitates nucleophilic attack of the oxygen on the spearhead, yielding the anhydride written below.



$$CH_3{-}\overset{OBu}{\underset{O}{P}}{-}P(OBu)_2 \longrightarrow CH_3\overset{OBu}{P}{-}O{-}P(OBu)_2$$

This anhydride contains two phosphorus atoms differing in their basicity. Methyl iodide at room temperature may cause one more Arbuzov rearrangement (the second one) leading to the mixed anhydride of dimethylphosphinic and O, O-dibutyl phosphorus acids and to the second mole of butyl iodide.



Consequently the action of methyl iodide on tetraalkoxydiphosphines causes three rearrangements in succession, two of them being of the Arbuzov type. The third rearrangement is a novel one. It is being studied at present in this laboratory on models of various kinds.

To sum up, I should like to emphasize that we have undertaken a study of thermal stability of organoelement O- and C-isomeric ketoenol derivatives as a function of the element E, the inductive effect of groups attached to the element, and, last but not least, of the substituent X at the central atom of the ketoenol triad. This has resulted in the discovery of more than twenty novel rearrangements of organic derivatives of silicon, germanium, tin, arsenic, antimony, and phosphorus. Some of these rearrangements have been described in this report.