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Organophosphorus Compounds with an Active Methylene Group

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The review deals with the present state of the chemistry of organophosphorus compounds with an active methylene group: esters and nitriles of phosphonoacetic acids, phosphonoacetone, and other compounds in which the methylene group is linked directly to the P=O and any other electronegative group. Compounds of this type are analogues of acetoacetic, malonic, cyanoacetic, and phenylacetic esters, the importance of which for theoretical and synthetic organic chemistry is well known. The methods for the synthesis of phosphorus-containing compounds with an active methylene group are considered in the first part of the review, while their chemical properties associated with the mobility of the hydrogen atoms of the methylene group (alkylation, addition, condensation, P(O)-activated olefin formation, and certain other reactions) are dealt with in the second part.
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I. INTRODUCTION

The chemistry of organophosphorus compounds has been developing very rapidly recently. This is primarily due to the considerable theoretical and especially practical importance which organophosphorus compounds have acquired in various branches of the national economy and modern engineering. The applications of organophosphorus compounds as insecticides in agriculture, medicinal preparations (particularly for eye infections), extractants, flotation agents in mining, plasticisers and stabilisers for polymers, and antioxidants for lubricating oils and the manufacture of non-combustible fabrics and materials are well known. The range of practical uses of organophosphorus compounds increases every year. Among the numerous types of organophosphorus compounds those with an active methylene group are of great interest. The first representative of this class of compound—ethyl diethoxyphosphonoacetate—was obtained by A. E. Arbuzov and Dunin in 1914 by the Arbuzov rearrangement. They established for the first time that the hydrogen atoms of the methylene group may be substituted by sodium and the reaction of the sodio-derivative of the diethoxyphosphonoacetate ester with alkyl halides can yield alkyl derivatives. Since then a number of organophosphorus compounds with an active methylene group have been obtained by the Arbuzov and Michaelis–Becker reactions and other methods.

The hydrogen atoms of the methylene group linked to the phosphorus atom and any other electron-accepting group exhibit considerable mobility which is responsible for the capacity of these compounds to undergo alkylation, acylation, addition, condensation, P(O)-activated olefin formation, and halogenation reactions. Thus we see an analogy between these organophosphorus compounds and esters of ketoacids and dicarboxylic acids such as the acetoacetic and malonic esters, which have played an extremely important role in theoretical and synthetic organic chemistry. Problems associated with the structure and tautomerism of this type of organophosphorus compounds are also of definite interest. The present review is a first attempt at a general account of the extensive and interesting data available in world chemical literature on the synthesis, structure, and reactivity of organophosphorus compounds with an active methylene group. Soviet chemists have made a very large contribution to the development of this branch of the chemistry of organophosphorus compounds.

II. SYNTHESIS OF ORGANOPHOSPHORUS COMPOUNDS WITH AN ACTIVE METHYLENE GROUP

1. Derivatives of Phosphorylated Acetic Acid and Its Nitrile

Ethyl diethoxyphosphonoacetate was obtained for the first time by A. E. Arbuzov and Dunin more than half a century ago by the reaction of ethyl bromoacetate with triethyl phosphite[1]:

$$(C_2H_5O)_3P + BrCH_2COOC_2H_5 \rightarrow (C_2H_5O)_2P(O)CH_2COOC_2H_5 + C_2H_5Br.$$

Subsequently the Arbuzov–Dunin method was successfully used for the synthesis of the ethyl esters of higher dialkoxyphosphonoacetic acids[2–7] and phosphonoacetic esters containing unsaturated substituents both at the phosphorus atom and in the carboxy-group[8–10].

The fully esterified alkylphosphonous and dialkylphosphinous acids enter into the Arbuzov rearrangement with esters of halogenoacetic acids more vigorously than trialkyl phosphites[11–15]. After the reaction of the ethyl esters of dialkylphosphinous acids with iodoacetic ester, Razumov and Zabusova isolated crystalline intermediates of the quasiphosphonium type, in accordance with the first step of the Arbuzov reaction[16]:

$$R_2POC_2H_5 + ICH_2COOC_2H_5 \rightarrow \left[R_2P\begin{matrix}OC_2H_5\\CH_2COOC_2H_5\end{matrix}\right]^+ I^-.$$

Their stability depends on the nature of the groups joined to the phosphorus atom. On storage and on heating, the products decompose in accordance with the second step of the Arbuzov reaction, forming ethyl iodide and dialkylethoxycarbonylmethylphosphine oxide[17,18]:

$$\left[R_2P\begin{matrix}OC_2H_5\\CH_2COOC_2H_5\end{matrix}\right]^+ I^- \rightarrow R_2P(O)CH_2COOC_2H_5 + C_2H_5I.$$

The reactions of phosphorus and dialkylphosphinous acids with alkyl- and aryl chlorothioloacetic acids follow

two pathways: via the classical mechanism of the Arbuzov rearrangement and with formation of alkenyl esters of phosphorus acids, i.e. via the Perkow mechanism[19-22]:

$$R_2POC_2H_5 + ClCH_2COSC_2H_5 \rightarrow \begin{cases} \rightarrow R_2P(O)CH_2COSC_2H_5 \\ \rightarrow R_2P(O)-O-C(SC_2H_5)=CH_2 \end{cases}.$$

Nylen successfully used the Michaelis–Becker method for the preparation of phosphonoacetic esters. Thus ethyl diethoxyphosphonoacetate was obtained in high yield by the reaction of sodium diethyl phosphite with ethyl chloroacetate[23,24]:

$$(C_2H_5O)_2PONa + ClCH_2COOC_2H_5 \rightarrow (C_2H_5O)_2P(O)CH_2COOC_2H_5 + NaCl.$$

A large number of various phosphonoacetic acid esters[25-31] and dialkylcarboxymethylphosphine oxides[32] were obtained by this method, usually referred to as the Michaelis–Becker–Nylen method. Phosphonoacetic acid esters can be obtained by the reaction of dialkylphosphorous acids themselves with diazoacetic ester[33,34]:

$$(C_2H_5O)_2POH + N_2CHCOOC_2H_5 \rightarrow (C_2H_5O)_2P(O)CH_2COOC_2H_5.$$

Apart from the above general methods, a number of specific reactions leading to the formation of phosphorylated derivatives of carboxylic acids of the type of tertiary phosphine oxides have been described. The starting materials in these reactions are the chlorides of phosphinous acids. Dialkylalkoxycarbonylmethylphosphine oxides have been obtained by the addition of α-halogeno-substituted acid esters to dialkylchlorophosphines with subsequent hydrolysis of the addition products[35,36]:

$$R_2PCl + HalCH_2COOR' \rightarrow \left[R_2P(Cl)(Hal)-CH_2COOR' \right] \xrightarrow{H_2O} R_2P(O)CH_2COOR'.$$

In the method proposed by Lutsenko and coworkers dialkylchlorophosphines, alkyldichlorophosphines, and aryldichlorophosphines are allowed to react with trichlorostannylacetic acid[37,38]:

$$\rangle P-X + R'_3SnCH_2COOR \rightarrow \rangle P-CH_2COOR + R'_3SnX.$$

The alkoxycarbonylmethylphosphines and di(alkoxycarbonylmethyl)phosphines are oxidised further by atmospheric oxygen with formation of the corresponding phosphine oxides.

Phosphorylated acids may be obtained also by the oxidation of the corresponding phosphorylated aldehydes by peracetic acid[39]:

$$\begin{matrix} R \\ R' \end{matrix}\rangle P(O)CH_2CHO \xrightarrow{CH_3COOOH} \begin{matrix} R \\ R' \end{matrix}\rangle P(O)CH_2COOH.$$

They are converted by esterification into esters of dialkylphosphonoacetic acids.

The first example of phosphonoacetonitriles was obtained in 1952 by Dawson and Burger[40] as a result of the reaction between chloroacetonitrile and triethyl phosphite[40]:

$$(C_2H_5O)_3P + ClCH_2CN \rightarrow (C_2H_5O)_2P(O)CH_2CN + C_2H_5Cl.$$

The method based on the Arbuzov rearrangement was successfully employed subsequently also for the synthesis of phosphorylated acetonitriles[19,41-43]. The reactions of trialkyl phosphites with chloroacetamide and its substituted derivatives leads to the formation of phosphonoacetamide or its *N*-alkyl and *N*-aryl derivatives[2,3,19,21,44-52]:

$$(RO)_3P + ClCH_2CON\begin{matrix} R' \\ R'' \end{matrix} \rightarrow (RO)_2P(O)CH_2CON\begin{matrix} R' \\ R'' \end{matrix} + RCl.$$

Apart from phosphites, phosphoroamidites and esters of phenylphosphonous acid were employed in these reactions[49].

2. Phosphorylated Ketones

The Arbuzov rearrangement was used as the first synthetic procedure for esters and other derivatives of β-ketophosphonic acids, which are phosphorus analogues of the corresponding derivatives of β-ketocarboxylic acids. A. E. Arbuzov and Razumov obtained diethoxyphosphonoacetophenone in 1934 by the reaction of triethyl phosphite with ω-bromoacetophenone[25]. In a similar reaction with bromoacetone Razumov and Petrov established that two products are then formed, which they suggested are tautomers of diethoxyphosphonoacetone[54].

This problem was elucidated much later when Perkow[55] showed for α-halogenoaldehydes and then Pudovik[56,57] and Allen and Jonson[58] for α-halogenoketones that the reactions of esters of phosphorus(III) acids with α-halogenocarbonyl compounds can take place in two ways: with formation of ketophosphonates, unsaturated phosphoric acid esters, or both simultaneously; diethyl isopropenyl phosphate was isolated by one of the authors of this review[57]:

$$(RO)_3P + CCl_3CHO \rightarrow (RO)_2P(O)-O-CH=CCl_2,$$

$$(RO)_3P + BrCH_2COCH_3 \rightarrow (RO)_2P(O)CH_2COCH_3 + (RO)_2P(O)-O-C(CH_3)=CH_2.$$

The relative amounts of the ketophosphonic esters and unsaturated phosphates or phosphonates formed by the reaction of phosphites or phosphinites with α-halogenoketones are significantly influenced by the nature and amounts of halogen atoms and also by the structure of the halogenoketones and the reaction conditions. Pudovik and Aver'yanova showed that the relative yield of ketophosphonic esters increases appreciably on going from chloro- to bromo- and iodo-acetone[59].

With increase in the number of halogen atoms in the halogenoketone, the formation of ketophosphonates becomes more difficult and the yield of unsaturated phosphates increases. The reactions with asymmetric dichloro- and dibromo-acetones[56,60,61] and tribromoacetone[62] lead to the formation of unsaturated phosphates only.

Ketophosphonic esters are formed in high yields from primary monobromo-[62,64] and iodo-ketones[59,63]. When secondary and particularly tertiary[64] halogenoketones are employed, their yield is considerably reduced or they are not formed at all.

The yield of ketophosphonic esters is significantly affected also by the reaction temperature and the solvent. An increase of temperature favours the formation of the ketophosphonate[56,59]. When iodoacetone is allowed to react with triethyl phosphite in ethyl ether as solvent[59], the ketophosphonic ester is formed with a higher yield than, for example, in aqueous alcohol[63].

Mixed esters of phosphorous acid[61], phosphoroamidites[61], and esters of phenylphosphonous[59] and diphenylphosphinous[53,65] acids have been allowed to react with halogenocarbonyl compounds in order to synthesise various derivatives of ketophosphonic acids. The reactions of α-halogenoacetophenones with phosphites[25,66-69], mixed

phosphites[70,72], and diphenylphosphinous acid esters[53,65] take place similarly. In all cases both products—the phosphonate and vinyl phosphate—are formed in different proportions:

$$(RO)_3P + BrCH_2COC_6H_5 \rightarrow (RO)_2PCH_2COC_6H_5 + (RO)_2P(O)-O-C(C_6H_5)=CH_2.$$

The Michaelis–Becker reaction has been used for the synthesis of ketophosphonic esters. Nylen, who was the first to investigate the reactions of α-chloro- and α-bromo-acetones with sodium diethyl phosphite, concluded that they take place in a complex manner and did not obtain the ketophosphonic esters[24]. Subsequently B. A. Arbuzov and coworkers showed that this reaction leads to a mixture of products consisting of esters of β-ketophosphonic acids and epoxyphosphonic acids and unsaturated esters of phosphoric acid[64,67,73-83]. They suggest[78] that the reactions can involve both the α-carbon atom and the carbonyl group. In the first case the ester of a β-ketophosphonic acid is formed:

$$(RO)_2PONa + HalCH_2COR' \rightarrow (RO)_2PCH_2COR' + NaHal.$$

The reaction via the carbonyl group leads to the formation of a dipolar ion, which rearranges to an unsaturated phosphate or is stabilised as an epoxyphosphonic ester[78,84]:

$$(RO)_2PONa + ClCH_2COCH_3 \rightarrow$$

$$ClCH_2-C(CH_3)(ONa)-P(O)(OR)_2 \rightarrow {}^{+}CH_2-C(CH_3)(O^{-})-P(O)(OR)_2 \rightarrow (RO)_2P(O)-O-C(CH_3)=CH_2 \quad (RO)_2P(O)-C(CH_3)(O)-CH_2.$$

While α-chloro- and α-bromo-cyclohexanones and α-bromoacetophenone form with sodium diethyl phosphite mixtures of phosphoric and epoxyphosphonic acids[78], the reaction with chloro- and bromo-acetones leads to a mixture of esters of β-keto- and epoxy-phosphonic acids[76,79,85].

The esters of chloro- and trichloro-acetylphosphonic acids and diethoxyphosphonoacetyl- and diethoxyphosphonodichloroacetyl-phosphonic acids have been obtained by the reaction of sodium dialkyl phosphites with chloro- and trichloro-acetyl chlorides[86,87]:

$$(RO)_2PONa + ClCH_2COCl \rightarrow (RO)_2P(O)COCH_2Cl +$$

$$+ (RO)_2P(O)CH_2C(O)P(O)(OR)_2 + NaCl.$$

The above results show that esters of β-ketophosphonic acids are formed by the Michaelis–Becker reaction either in very low yields or not at all. Among other reactions leading to the formation of esters of β-ketophosphonic acids, the interaction of phosphorus pentachloride with enol acetates is of considerable interest. This reaction, developed by Lutsenko and Kirillov, leads to the formation initially of the chlorides of β-acetoxy- β-chloroalkylphosphonic acids, which are converted into diethoxyphosphonoacetone by treatment with alcohol[88]:

$$2PCl_5 + R-C(OCOCH_3)=CH_2 \rightarrow R-C(Cl)(OCOCH_3)-CH_2PCl_4PCl_5 \xrightarrow{SO_2}$$

$$\rightarrow R-C(Cl)(OCOCH_3)-CH_2P(O)Cl_2 + POCl_3 + 2SO_2Cl_2 \xrightarrow[C_5H_5N]{C_2H_5OH} (C_2H_5O)_2P(O)CH_2COCH_3.$$

Diethoxyphosphonoacetaldehyde[88,89] and diethoxyphosphonoacetophenone[90] were obtained by the same method.

The latter is also formed in the reaction between diazomethane and benzoylphosphonic ester[90]:

$$(C_2H_5O)_2P(O)COC_6H_5 + CH_2N_2 \rightarrow (C_2H_5O)_2P(O)CH_2COC_6H_5.$$

The reaction of trialkylstannylacetone with dialkylchlorophosphines gave dialkylacetonylphosphines, the oxidation of which leads to dialkylacetylmethylphosphines[91]:

$$R_2PCl + R'_3SnCH_2COCH_3 \rightarrow R_2PCH_2COCH_3 \xrightarrow{H_2O_2} R_2P(O)CH_2COCH_3.$$

Phosphorylated acetals have been obtained by the action of halogeno-substituted acetals on phosphorus(III) acid esters; their hydrolysis leads to phosphorylated aldehydes[40,92-94]:

$$R(R')P-OC_2H_5 + BrCH_2CH(OC_2H_5)_2 \rightarrow R(R')P(O)CH_2CH(OC_2H_5)_2 \xrightarrow{HCl}$$

$$\rightarrow R(R')P(O)CH_2CHO.$$

In order to investigate the tautomerism of the keto–enol type of β-ketophosphonic esters, B. A. Arbuzov and Vinogradova employed methods involving titration with bromine and ultraviolet, infrared, and Raman spectroscopy[64,74-76,95,96]. Phosphonoacetone and methylphosphonoacetone, which are the phosphorus analogues of acetoacetic and methylacetoacetic esters, contain a small amount of the enolic form[96]. They undergo appreciable enolisation only in an alkaline medium[97]. Titration with bromine of cyclohexanone-2-phosphonic acid in alcoholic solution revealed the presence of 9% of the enolic form and in hexane solution 60% of the enolic form was found[98,99]. Comparison of the effects of the carboxy- and phosphono-groups on the capacity for the formation of the enolic form led to the conclusion that there is a definite analogy in the behaviour of β-keto acids and their phosphorus analogues, with the difference that the β-ketophosphonic esters are less enolised. A complete parallelism is not, however, observed.

The structure of metal derivatives in the molecules of which the methylene group is located between the P = O and carbonyl groups was investigated by infrared, ultraviolet, and NMR spectroscopy[100]. The results indicate the presence in the anion of phosphonoacetone of an extended π-orbital system, which is also characteristic of the acetylacetone anion:

$$\left[(RO)_2P(O)-CH=C(O^{-})-CH_3\right].$$

3. Phosphorylated Alkanes

The first example of this class of compound—tetraethyl methylenediphosphonate—was obtained by Ford-Moore and Williams[101] by the reaction of methylene iodide with triethyl phosphite[101]. The yield of the diphosphonate in this reaction was, however, very low, since considerable amounts of diethyl iodomethyl- and ethyl-phosphonates are formed at the same time:

$$(C_2H_5O)_3P + CH_2I_2 \rightarrow (C_2H_5O)_2P(O)-CH_2-P(O)(OC_2H_5)_2 +$$

$$+ (C_2H_5O)_2P(O)CH_2I + (C_2H_5O)_2P(O)C_2H_5 + C_2H_5I.$$

The yield of the diphosphonate may be increased somewhat by using in the reaction an excess of trialkyl phosphite[102-104]. The yield of tetra-alkyl methylenediphos-

phonates is improved still further when the reaction is carried out in two consecutive stages[105]:

$$(C_2H_5O)_3P + CH_2I_2 \rightarrow (C_2H_5O)_2P(O)CH_2I + C_2H_5I,$$
$$(C_2H_5O)_2P(O)CH_2I + (C_2H_5O)_3P \rightarrow [(C_2H_5O)_2P(O)]_2CH_2 + C_2H_5I.$$

When an attempt was made to obtain tetra-alkyl methylenediphosphonates by the Michaelis–Becker reaction between methylene iodide or chloride and sodium diethyl or diallyl phosphite, instead of the neutral esters only the corresponding disodium salts were isolated[105-107]. The formation of salts of the acid esters is observed also in the reactions of sodium dialkyl phosphite with di-(α-bromomethyl) and di-(α-chloro methyl) esters[108-110]:

$$2(RO)_2PONa + HalCH_2—O—CH_2Hal \rightarrow (RO)_2P(O)CH_2OCH_2P(O)(OR)_2 + \text{(RO, NaO)}P(O)CH_2OCH_2P(O)\text{(OR, ONa)}.$$

The formation of salts of acid esters is due to the alkylation of sodium dialkyl phosphite by the phosphonates[111]. When sodium dialkyl phosphite is alkylated by alkyl halides, the neutral alkylphosphonic esters are formed initially in all cases. The salts of the acid esters are formed as a result of secondary processes due to the high reactivity of the neutral alkylphosphonic esters. It has been shown for the reaction of sodium diethyl phosphite with diethyl chloromethylphosphonate that the salt-like product is a mixture of sodium chloride and salts of the acid esters of ethyl- and chloromethyl-phosphonic and methylenediphosphonic acids[112]:

$$(C_2H_5O)_2PONa + ClCH_2P(O)(OC_2H_5)_2 \rightarrow [(C_2H_5O)_2P(O)]_2CH_2 + C_2H_5P(O)\text{(OC}_2H_5\text{, ONa)} +$$
$$+ ClCH_2P(O)\text{(OC}_2H_5\text{, ONa)} + \text{(C}_2H_5O\text{, C}_2H_5O)P(O)CH_2P(O)\text{(OC}_2H_5\text{, ONa)} + \text{(C}_2H_5O\text{, NaO)}P(O)CH_2P(O)\text{(OC}_2H_5\text{, ONa)}.$$

Nevertheless, despite the complexity of these reactions[112-114], tetra-alkyl methylenediphosphonates are formed in high yields compared with the analogous reactions of phosphites. Until recently, methylenediphosphine dioxides were very difficult to obtain. A number of methods using organometallic compounds have been proposed for their synthesis. Thus, reactions of methylenediphosphonic dichloride with Grignard reagents have been described[114,115]:

$$[Cl_2P(O)]_2CH_2 + 4RMgX \rightarrow [R_2P(O)]_2CH_2 + 4MgXCl,$$

and also reactions of dialkylchloromethylphosphines with halogenomagnesium derivatives of dialkylphosphinous acids[116]:

$$R_2P(O)CH_2Cl + R_2POMgX \rightarrow R_2P(O)CH_2P(O)R_2 + MgXCl,$$

and reactions of diphenylphosphinic chloride with the lithio-derivative of methyldiphenylphosphine oxide[117]:

$$(C_6H_5)_2P(O)CH_3 \xrightarrow{n\text{-}C_4H_9Li} (C_6H_5)_2P(O)CH_2Li \xrightarrow{(C_6H_5)_2P(O)Cl} (C_6H_5)_2P(O)—CH_2—P(O)(C_6H_5)_2.$$

Methylenediphosphine dioxides may be obtained by the oxidation of the corresponding methylenediphosphines, which are formed in the reaction between methylene chloride or bromide with sodium diphenyl phosphite[118] or dialkylhydroxymethylphosphine[119]:

$$2(C_6H_5)_2PNa + CH_2Cl_2 \rightarrow (C_6H_5)_2PCH_2P(C_6H_5)_2 +$$
$$+ 2NaCl \xrightarrow{O_2} (C_6H_5)_2P(O)CH_2P(O)(C_6H_5)_2,$$
$$2R_2PCH_2OH + CH_2Br_2 \rightarrow R_2PCH_2PR_2 \xrightarrow{O_2} R_2P(O)CH_2P(O)R_2.$$

Among other methods for the synthesis of methylenediphosphine dioxides, the addition of chlorodimethylphosphine to methylene bromide with subsequent hydrolysis of the addition product is interesting[36]:

$$(CH_3)_2PCl + CH_2Br_2 \rightarrow \left[(CH_3)_2P\underset{Br}{\overset{Cl}{CH_2}}P\underset{Br}{\overset{Cl}{(CH_3)_2}}\right] \xrightarrow{H_2O} [(CH_3)_2P(O)]_2CH_2.$$

as well as the reaction of chlorodiphenylphosphine with diazomethane, which leads ultimately to tetraphenylmethylenedip'osphine dioxide[120]:

$$(C_6H_5)_2PCl + CH_2N_2 \xrightarrow[-N_2,-2HCl]{H_2O} (C_6H_5)_2P(O)CH_2P(C_6H_5)_2 \rightarrow$$
$$\xrightarrow{KMnO_4} (C_6H_5)_2P(O)CH_2P(O)(C_6H_5)_2.$$

However, all the methods enumerated above have not found wide practical application because of the difficulty of obtaining the reactants employed in them and the low yields of the desired products. In 1962 Kabachnik and Medved' proposed a simpler method for the synthesis of methylenediphosphine dioxides by the condensation of chloromethyldiphenylphosphine oxide with ethyl diphenylphosphinite[121]:

$$(C_6H_5)_2P(O)CH_2Cl + C_2H_5OP(C_6H_5)_2 \xrightarrow[-C_2H_5Cl]{} (C_6H_5)_2P(O)CH_2P(O)(C_6H_5)_2.$$

Subsequently this method was successfully employed for the synthesis of a number of methylenediphosphine dioxides with alkyl and substituted aromatic groups[122,123] and also methylenediphosphonic acids[124].

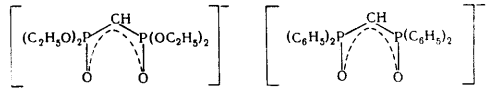
Similarly di(chloromethyl)phosphine and tri(chloromethyl)phosphine oxides and phosphorus(III) esters gave the corresponding phosphine oxides and phosphorus acid esters containing in the molecule several $\diagdown P(O)-CH_2\diagup$ groups[125-127]:

$$RP(O)(CH_2Cl)_2 + 2C_2H_5OPR'R'' \rightarrow \text{(R', R'')}P(O)—CH_2—\overset{R}{P}(O)—CH_2—P(O)\text{(R', R'')},$$
$$(ClCH_2)_3P(O) + 3R_2POC_2H_5 \rightarrow [R_2P(O)CH_2]_3P(O).$$

Certain compounds of this type, containing dialkoxyphosphono-groups, were hydrolysed to the corresponding acids[127], which proved to be extremely interesting and promising as complexones[128]:

$$CH_3P(O)(CH_2Cl)_2 + 2(C_2H_5O)_3P \rightarrow CH_3P(O)[CH_2P(O)(OC_2H_5)_2]_2 \xrightarrow{\text{conc. HCl}}$$
$$\rightarrow (HO)_2P(O)—CH_2—\underset{CH_3}{P}(O)—CH_2—P(O)(OH)_2.$$

In the study of the structure of sodio- and potassio-derivatives of tetraethoxydiphosphonomethane and tetraphenylmethylenediphosphine dioxide by infrared and NMR spectroscopy, Cotton and coworkers[129] in the first case and Kabachnik and coworkers[130] in the second showed that the anions of these compounds have a structure with delocalised π bonds:



4. Phosphorylated Alkenes

The esters of allylphosphonic acid are readily obtained by the Arbuzov rearrangement when allyl chloride or bromide reacts with trialkyl[131] and triallyl[132] esters of phosphorous acid:

$$(RO)_3P + BrCH_2CH=CH_2 \rightarrow (RO)_2P(O)CH_2CH=CH_2 + RBr.$$

The reaction of alkyl halides with esters of allylphosphonous acid gives esters of alkylallylphosphinic acids[132,134]:

$$(RO)_2PCH_2CH{=}CH_2 + R'X \rightarrow \begin{matrix} RO \\ R' \end{matrix}\!\!>\!P(O)CH_2CH{=}CH_2 + RX.$$

Phosphonic esters can also be synthesised by the Michaelis–Becker reaction. However, Pudovik's investigation showed that the reactions of salts of dialkylphosphorous acids with halogenoallyl compounds do not always take place unambiguously. The reactions of allyl bromide, crotyl chloride[135,136], cinnamyl chloride[137,138], and 1-chloro-5-methoxypent-2-ene with sodium diethyl phosphite in benzene solutions and in the presence of an excess of diethylphosphorous acid leads to the formation of diethyl alkenylphosphonates[131,139,140]. The reactions with secondary halogenoallyl isomers take place with the allyl rearrangement[135,139,141–143]:

$$\left.\begin{matrix}(C_2H_5O)_2PONa + RCH{=}CHCH_2Cl \\ (C_2H_5O)_2PONa + RCHClCH{=}CH_2\end{matrix}\right\rangle \rightarrow (C_2H_5O)_2P(O)CH_2CH{=}CHR.$$

When stoichiometric proportions of the reactants are used and the reaction is carried out without a solvent, the allylphosphonic esters undergo prototropic isomerisation to thermodynamically more stable substituted vinylphosphonic esters, to which diethylphosphorous acid adds subsequently. This results in a mixture of esters of phosphonic and diphosphonic acids[139]:

$$(RO)_2P(O)CH_2CH{=}CHR \xrightarrow{C_2H_5O^-} (RO)_2P(O)CH{=}CHCH_2R \rightarrow$$

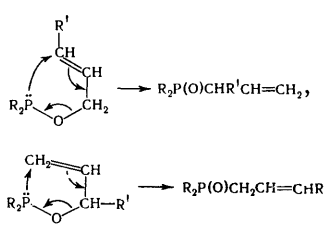
$$\xrightarrow[(RO)_2PONa]{(RO)_2POH} (RO)_2P(O)\underset{\displaystyle CH_2R}{\underset{|}{CH}}{-}CH_2P(O)(OR)_2.$$

The thermal rearrangement of allyl esters of phosphorous acid[144–146] leading to allylphosphonic esters and the similar rearrangements of alkyl-, dialkyl-, aryl-, and diaryl-phosphinous acids are very interesting reactions[147]. When the diallyl ester of ethylphosphonous acid is replaced by the allyl ester of diethylphosphinous acid, the rate of thermal rearrangement increases.

The isomerisation of the allyl esters of phenylphosphonous and diphenylphosphinous acids takes place much more readily. On vacuum distillation alone, the allyl ester of diphenylphosphinous acid isomerises to allyldiphenylphosphine oxide[147,148]:

$$(C_6H_5)_2POCH_2CH{=}CH_2 \rightarrow (C_6H_5)_2\underset{\displaystyle O}{\underset{\|}{P}}CH_2CH{=}CH_2.$$

The thermal isomerisation of α- and γ-substituted allyl esters takes place with inversion of the allyl radicals[145]. For these reactions, Pudovik and Aladzheva proposed an intramolecular mechanism with intermediate formation of five-membered cyclic transition states[145]:



Esters of propargylphosphonic acids with similar structures are difficult to obtain[149]. Gordon and Griffin showed that the reaction of propargyl bromide with sodium diethyl phosphite leads to the formation of a mixture of 1-propynylphosphonate, 2-propynylphosphonate, and allenylphosphonate[150]:

$$(C_2H_5O)_2PONa + BrCH_2C{\equiv}CH \rightarrow (C_2H_5O)_2P(O)C{\equiv}C{-}CH_3 +$$

$$+ (C_2H_5O)_2P(O)CH_2C{\equiv}CH + (C_2H_5O)_2P(O)CH{=}C{=}CH_2.$$

The content of 2-propynylphosphonate in the mixture is less than 1% according to NMR data. Similar results were obtained when an attempt was made to prepare 2-propynylphosphonate by the Arbuzov rearrangement[150,151].

5. Derivatives of Substituted Methylphosphonic Acids containing Aryl, Carbocyclic, and Heterocyclic Groups

Methods based on the Arbuzov rearrangement and the Michaelis–Becker reaction have been successfully employed to synthesise the esters of unsubstituted and ring-substituted benzylphosphonic acids[84,152–154] and alkyl(aryl)benzylphosphinic acids[155,156]:

$$\left.\begin{matrix}(C_2H_5O)_3P + ClCH_2C_6H_4{-}R \\ (C_2H_5O)_2PONa + ClCH_2C_6H_4{-}R\end{matrix}\right\rangle \xrightarrow[-NaCl]{-C_2H_5Cl} (C_2H_5O)_2P(O)CH_2C_6H_4{-}R.$$

The second method was used to prepare unsubstituted benzylphosphonates[156–159] and benzylphosphonates with alkyl[157], ethoxycarbonyl, and cyano-groups[154] in the benzene ring. The sodium salts of ethylphosphonous[160], benzylphosphonous[161], and diphenylphosphinous acids[162] can also be successfully employed in these reactions. Sodium diethylphosphorothioite reacts with benzyl chloride to form diethyl benzylphosphonothionate[163]. When it was heated with ethyl bromide, *OS*-diethyl benzylphosphonothiolate was obtained[164]:

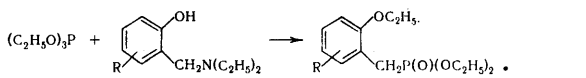
$$(C_2H_5O)_2PSNa + ClCH_2C_6H_5 \rightarrow (C_2H_5O)_2P(S)CH_2C_6H_5 + NaCl,$$

$$(C_2H_5O)_2P(S)CH_2C_6H_5 + C_2H_5Br \rightarrow \begin{matrix} C_2H_5O \\ C_2H_5S \end{matrix}\!\!>\!P(O)CH_2C_6H_5.$$

A modified Michaelis–Becker method, in which benzyl acetate is used in the reaction with sodium diallyl phosphite instead of benzyl chloride, has been successfully employed for the synthesis of diallyl benzylphosphonate[165]:

$$(CH_2{=}CHCH_2O)_2PONa + CH_3COOCH_2C_6H_5 \rightarrow (CH_2{=}CHCH_2O)_2P(O)CH_2C_6H_5 + CH_3COONa.$$

Esters of ethoxybenzylphosphonic acids are formed in the reaction between diethylaminomethylphenols and triethyl phosphites[166]:



An interesting method for the synthesis of substituted tribenzylphosphine oxides has been developed by Kirsanov and coworkers; it is based on the reaction of substituted benzyl chlorides with red phosphorus and iodine with subsequent treatment of the reaction products with sodium sulphite. Dibenzylphosphinic and benzylphosphonic acids are formed in these reactions in small amounts in addition to substituted tribenzylphosphine oxides[167]:

$$P + ClCH_2C_6H_4{-}R + I_2 \xrightarrow{Na_2SO_3} (R{-}C_6H_4CH_2)_3P(O) +$$

$$+ RC_6H_4CH_2P(O)(OH)_2 + (R{-}C_6H_4CH_2)_2P(O)OH.$$

The synthesis of methylphosphonic acids with carbocyclic and heterocyclic substituents has been achieved by the reaction of trialkyl phosphites and sodium dialkyl phosphites with a wide variety of carbocyclic[168] and heterocyclic derivatives of methyl halides[169–174]. α-Furyl-[169], α-tetrahydrofuryl-[169,170], α-thienyl-[171],

α-pyridyl-[172], and phthalimidomethyl-phosphonates[173,174], and phosphonates containing polycyclic substituents[157,168,175] were obtained.

6. Esters of Halogenomethyl-, Aminomethyl-, Hydroxymethyl-, and Alkoxymethyl-Phosphonic Acids

Esters of chloromethylphosphonic acids can be readily obtained by the reaction of chloromethylphosphonic dichloride with alcohols[112,176,177]. The dichlorides themselves became available after the discovery and development by Kabachnik and Shepeleva of the reaction between phosphorus trichloride and paraformaldehyde[176]:

$$PCl_3 + CH_2O \rightarrow ClCH_2P(O)Cl_2,$$
$$ClCH_2P(O)Cl_2 + 2\,ROH \rightarrow (RO)_2P(O)CH_2Cl + 2\,HCl.$$

A number of diarylchloromethylphosphine oxides[122,123] and the chlorides of alkyl- and aryl- chloromethylphosphinic acids were obtained similarly by the reaction of diarylchlorophosphines and alkyl- and aryl-dichlorophosphines with paraformaldehyde:

$$(R{-}C_6H_4)_2PCl + CH_2O \rightarrow (R{-}C_6H_4)_2P(O)CH_2Cl.$$

While the esters of bromomethyl-[101,179,180] and iodomethyl-phosphonic acids[30,101,105,180] and the free acids themselves[180] have been described in fair detail, the esters of fluoromethylphosphonic acid were difficult to obtain until recently. The reactions of the fluorides of dialkylphosphorous acids with diazomethane[158] or of the sodium salts of dialkylphosphorous with bromofluoromethane have been suggested for their synthesis[181]:

$$(RO)_2P(O)F + CH_2N_2 \rightarrow (RO)_2P(O)CH_2F + N_2,$$
$$(RO)_2PONa + BrCH_2F \rightarrow (RO)_2P(O)CH_2F + NaBr.$$

A simple method for the preparation of the chloride of di(chloromethyl)phosphinic acid, consisting in the reaction of phosphorus pentachloride with di(hydroxymethyl)phosphinic acid, was recently developed by Ivanov and coworkers[182]:

$$(HOCH_2)_2P(O)OH + 3\,PCl_5 \rightarrow (ClCH_2)_2P(O)Cl + 3\,HCl + 3\,POCl_3.$$

Numerous derivatives of di(chloromethyl)phosphinic[183] and di(chloromethyl)phosphinothionic acids[184-187] have been obtained from this acid chloride by substituting the chlorine at the phosphorus atom. These reactions may be represented by the following general equation:

$$(ClCH_2)_2P(O)Cl + RX \rightarrow (ClCH_2)_2P(O)X + RCl,$$

where X = OH, OAlk, OAr, $N(Alk)_2$, and others.

A number of methods have been proposed for the synthesis of aminomethylphosphonic acids and their various derivatives. When aqueous ammonia acts upon the esters of chloro- or iodo-methylphosphonic acids under severe conditions, the monoester of aminomethylphosphonic acid is formed. Its hydrolysis yielded the free aminomethylphosphonic acid[177]:

$$(C_2H_5O)_2P(O)CH_2Cl + NH_3 \xrightarrow{100^\circ} NH_2CH_2P(O)\begin{matrix}OC_2H_5\\OH\end{matrix} \xrightarrow{H_2O} NH_2CH_2P(O)(OH)_2.$$

Acid esters of dialkylaminomethylphosphonic acids may be obtained also as a result of the partial hydrolysis of the diesters[188]:

$$R_2NCH_2P(O)(OR')_2 + H_2O \rightarrow R_2NCH_2P(O)\begin{matrix}OR'\\OH\end{matrix}.$$

An *N*-substituted aminomethylphosphonic acid was obtained by the reaction of benzoyl chloride with aminomethylphosphonic acid[177]:

$$NH_2CH_2P(O)(OH)_2 + C_6H_5COCl \rightarrow C_6H_5CONHCH_2P(O)(OH)_2.$$

In 1952 Kabachnik and Medved'[189,190] and somewhat later Fields[191] developed a simple method for the preparation of esters of α-aminoalkylphosphonic acids by the condensation of aldehydes and ketones with dialkylphosphorous acids and ammonia or amines[189-191]:

$$(RO)_2P(O)H + \rangle C{=}O + H{-}N\langle \rightarrow (RO)_2P(O){-}\underset{|}{C}{-}N\langle + H_2O.$$

The reactions of dialkylphosphorous acids with formaldehyde and primary amines or ammonia give, depending on the proportions of the initial reactants, mono-, di-, and tri-(dialkylphosphonomethyl)amines[191-193]. Tertiary aminomethylphosphine oxides were obtained from secondary phosphine oxides, formaldehyde, and the amines[194,195]:

$$(CNCH_2CH_2)_2P(O)H + CH_2O + (C_4H_9)_2NH \rightarrow (CNCH_2CH_2)_2P(O)CH_2N(C_4H_9)_2.$$

Also in 1952 Pudovik found that substituted aminophosphinic esters can be readily obtained in high yields by the addition of partially esterified phosphorus acids to Schiff bases[196-198]:

$$(RO)_2P(O)H + X{-}C_6H_4CH{=}NC_6H_4Y \rightarrow (RO)_2P(O)\underset{|}{C}HNHC_6H_4Y.$$
$$C_6H_4X$$

This reaction was subsequently extended to carbodiimides, dibenzylidenediamines, and polymeric Schiff bases[199,200].

Esters of aminomethylphosphonic and di(aminomethyl)-phosphinic acids are also formed by the reaction of alkyl hypophosphites with diethylaminomethyl esters and di(diethylamino)methane[201]:

$$ROP(O)H_2 + (C_2H_5)_2N{-}CH_2{-}N(C_2H_5)_2 \rightarrow ROP(O)[CH_2N(C_2H_5)_2]_2.$$

The reactions of trialkyl phosphites, diethyl phosphoroamidites, and phosphorous triamides with esters and ethers of aminomethanol and diethylaminoacetylnitrile give rise to esters and other derivatives of dialkylaminomethylphosphonic acids[202]:

$$(C_2H_5O)_3P + CNCH_2N(C_2H_5)_2 \rightarrow (C_2H_5O)_2P(O)CH_2N(C_2H_5)_2.$$

Böme and coworkers[203] showed that the reactions of aminoacetates with triethyl phosphite and diethyl phosphoroamidite take place even at room temperature forming the diethyl ester of dimethylaminomethylphosphonic acids and the ethyl ester of dimethylaminomethylphosphonoamidic acid:

$$(C_2H_5O)_3P + (CH_3)_2NCH_2OCOCH_3 \rightarrow (C_2H_5O)_2P(O)CH_2N(CH_3)_2.$$

The reactions of aminomethyl ethers with triethyl phosphite are not unambiguous. In the presence of acetic acid the C–O bond in the aminomethyl ether is broken and diethyl diethylaminomethylphosphonate is formed, while alkyl halides lead to the formation of diethylalkoxymethylphosphonates[204]:

$$(C_2H_5O)_3P + ROCH_2N(C_2H_5)_2 \rightarrow \begin{cases}(C_2H_5O)_2P(O)CH_2N(C_2H_5)_2\\(C_2H_5O)_2P(O)CH_2OR\end{cases}.$$

All these reactions take place with the substitution of amino-, acetate, and alkoxy-groups by a phosphono-group and have a common mechanism based on the Arbuzov rearrangement.

Similar reactions of *N*-hydroxymethylamides of acetic and benzoic acids with trialkyl phosphites lead to esters of acetamido- and benzamido- methylphosphonic acids [209]:

$$(RO)_3P + R'CONHCH_2OH \rightarrow (RO)_2P(O)CH_2NHCOR' + ROH.$$

The reaction of the *N*-hydroxymethylamide of chloroacetic acid with triethyl phosphite is much more complicated, forming a mixture of products consisting of the ester, amide, and nitrile of diethoxyphosphonoacetic acid [51]:

$$(C_2H_5O)_3P + ClCH_2CONHCH_2OH \rightarrow (C_2H_5O)_2P(O)CH_2COOC_2H_5 + (C_2H_5O)_2P(O)CH_2CONH_2 + (C_2H_5O)_2P(O)CH_2CN.$$

The reaction of phosphorus trichloride with an *N*-hydroxymethylamide followed by hydrolysis of the products gave *N*-alkylaminomethylphosphonic acid [206,207]:

$$PCl_3 + RCONR'CH_2OH \rightarrow RCONR'CH_2OPCl_2 \rightarrow RCONR'CH_2P(O)Cl_2 \rightarrow RCONR'P(O)(OH)_2 \rightarrow NHR'CH_2P(O)(OH)_2.$$

When aminomethylphosphonic acid was acted upon by nitrous acid, hydroxymethylphosphonic acid was obtained [177]:

$$NH_2CH_2P(O)(OH)_2 + HNO_2 \xrightarrow{H_2O} HOCH_2P(O)(OH)_2.$$

Earlier hydroxymethylphosphonic acid had been synthesised by the hydrolysis of the intermediate formed in the reaction between phosphorus trichloride and paraformaldehyde [208]:

$$PCl_3 + (CH_2O)_3 \xrightarrow{H_2O} HOCH_2P(O)(OH)_2.$$

Similarly the reaction of phosphorus trichloride and benzaldehyde gave the dichloride of α-chlorobenzylphosphonic acid, the hydrolysis of which can yield both α-chlorobenzylphosphonic and α-hydroxybenzylphosphonic acids, depending on the conditions [209]:

$$PCl_3 + C_6H_5CHO \rightarrow \underset{Cl}{C_6H_5CHP(O)Cl_2} \xrightarrow{2H_2O} \underset{Cl}{C_6H_5CHP(O)(OH)_2} \xrightarrow[CH_3COOAg]{H_2O} \underset{OH}{C_6H_5CHP(O)(OH)_2}.$$

Abramov [210] showed for the first time that esters of hydroxymethylphosphonic acid are formed as a result of the addition of dialkylphosphorous acid to formaldehyde [211]. A large number of derivatives of both hydroxymethyl- and hydroxyalkyl-phosphonic acids have been obtained by the addition of partially esterified phosphorus acids to various carbonyl compounds.

Esters of alkoxymethylphosphonic [212], methylthiomethylphosphonic [213], and alkoxymethylphenylphosphinic [214] acids are formed in high yields when alkylchloromethyl and chloromethylthiomethyl ethers react with trialkyl phosphites and diethyl phenylphosphonite:

$$(RO)_3P + ClCH_2OR' \rightarrow (RO)_2P(O)CH_2OR' + RCl.$$

Depending on the conditions, the reaction of α-chloro- or α-bromo-methyl ethers with sodium dialkylphosphites gives rise either to esters of alkoxymethylphosphonic or an involatile mixture of ester salts [109,215,216]:

$$(RO)_2PONa + HalCH_2OCH_3 \rightarrow (RO)_2P(O)CH_2OCH_3 + \begin{matrix} RO \\ NaO \end{matrix}\!\!>\!P(O)-CH_2-OCH_3.$$

The sodium salt of diethylphosphinous acid reacts similarly with butyl chloromethyl ether [217].

III. REACTIONS OF ORGANOPHOSPHORUS COMPOUNDS WITH AN ACTIVE METHYLENE GROUP BASED ON THE MOBILITY OF ITS HYDROGEN ATOMS

The hydrogen atoms of the methylene group in organophosphorus compounds, located between two electron-accepting groups, become so mobile that the proton is readily eliminated with formation of carbanions even in reactions with weak organic bases.

A method has been proposed recently for a quantitative determination of mobile hydrogen atoms in compounds of this type [218]. It is a modification of the standard Chugaev–Tserevitinov method for the determination of mobile hydrogen and consists in the reaction of methylmagnesium iodide with the test compound. It was shown that, when the substituent X in the compound $>P(O)-CH_2-X^-$ is an electron-accepting group, both hydrogen atoms in the methylene group become mobile (esters and nitrile of diethoxyphosphonoacetic acid, diethoxyphosphonoacetone, and diethoxyphosphonoacetophenone). When the substituents X are various hydrocarbon residues or other groups without electron-accepting properties or with weak properties of this kind, only one hydrogen atom is mobile (esters of ethyl-, benzyl-, and propoxymethyl-phosphonic acids). Mobile hydrogen is found also in phosphonium salts of the type [219] $[(C_6H_5)_3\overset{+}{P}CH_2COAr]X^-$.

According to the data of Kabachnik and coworkers, the hydrogen atoms of the methylene group located between two diphenylphosphine oxide groups exhibit distinct proton mobility [220]. Thus tetraphenylmethylenediphosphine dioxide in aniline solution enriched with deuterium undergoes hydrogen isotope exchange at an appreciable rate even at room temperature. It has been confirmed by ^1H NMR that only the hydrogen atoms of the methylene group are involved in the isotope exchange.

Among the reactions of organophosphorus compounds with an active methylene group based on the mobility of the hydrogen atoms, the most important and the most interesting are the alkylation and acylation reactions, reactions involving addition to αβ-unsaturated compounds with activated multiple bonds, and reactions with carbonyl compounds.

1. Alkylation and Acylation Reactions

A. E. Arbuzov and Dunin [221–223] were the first to show that the reaction of alkyl halides with the sodio-derivative of diethoxyphosphonoacetic ester results in the formation of alkyl-substituted ethyl diethoxyphosphonoacetates [25,30,224–232]:

$$(C_2H_5O)_2P(O)CH_2COOC_2H_5 + Na \rightarrow (C_2H_5O)_2P(O)CH(Na)COOC_2H_5 \xrightarrow{+CH_3I} (C_2H_5O)_2P(O)\underset{CH_3}{CH}COOC_2H_5 + NaI.$$

Alkyl halides, esters of α-halogenocarboxylic acids, α-halogenoethers, and α-halogenoketones have been used as alkylating agents in the alkylation of esters of diethoxyphosphonoacetic acid [230]. Pudovik and coworkers [233] showed that the alkylation of diethoxyphosphonoacetic ester with isomeric butadiene hydrochlorides gives in both cases the same product, corresponding to the structure of the primary chloride—the ester of but-2-enyldiethoxyphosphonoacetic acid. The reaction with the secondary chloride takes place with complete allyl rearrangement:

$$(C_2H_5O)_2P(O)\underset{COOC_2H_5}{CH}-Na + ClCH_2CH=CHCH_3 \rightarrow (C_2H_5O)_2P(O)\underset{COOC_2H_5}{CHCH_2CH}=\underset{CH_3}{CH}.$$
$$(CH_3CHClCH=CH_2)$$

Apart from the alkylation of diethoxyphosphonoacetic esters, the alkylation of diethoxyphosphonoacetone [74,76,97,231,232] and diethoxyphosphonoacetonitrile [41,230] has been investigated in fair detail. The alkylation of diethoxyphosphonoacetone can be achieved fairly readily when its

sodio-derivative is acted upon both by alkyl halides[74,76,231] and the ethyl esters of bromoacetic and α-bromo-propionic acids and bromoacetone[230]:

$$(C_2H_5O)_2P(O)CH(Na)COCH_3 + BrCH_2COCH_3 \rightarrow (C_2H_5O)_2P(O)\underset{\underset{COCH_3}{|}}{C}HCH_2COCH_3 + NaBr.$$

The alkylation of diethoxyphosphonoacetonitrile with alkyl halides takes place most readily when its potassio-derivative in ether–dioxane solution is employed. In this case alkyl iodides are the most effective[41]:

$$(C_2H_5O)_2P(O)CH_2CN + K + RI \rightarrow (C_2H_5O)_2P(O)\underset{\underset{CN}{|}}{C}H-R + KI.$$

In the alkylation of the esters and nitrile of diethoxyphosphonoacetic acid and of diethoxyphosphonoacetone with equimolar amounts of alkylating agents, monoalkylation products were obtained in all cases. However, when propargyl bromide acts upon sodio- or potassio-derivatives of the ethyl ester or nitrile of diethoxyphosphonoacetic acid, a mixture of products of the substitution of one and two hydrogen atoms for a propargyl group is formed[234]. Evidently the introduction of a third electron-accepting group increases the mobility of the remaining hydrogen atom to such an extent that even with an equimolar ratio of the initial reactants the dialkylation product is formed preferentially:

$$(RO)_2P(O)CH_2COOC_2H_5 + BrCH_2C{\equiv}CH \rightarrow$$

$$(RO)_2P(O)\underset{\underset{COOC_2H_5}{|}}{C}H-CH_2C{\equiv}CH + (RO)_2P(O)\underset{\underset{COOC_2H_5}{|}}{C}(CH_2C{\equiv}CH)_2.$$

The dialkylation products of esters of diethoxy-[225], diethyl-[16], and diphenyl-phosphonoacetic acids[16] were obtained by the action of alkyl halides on the sodio- or potassio-derivatives of the corresponding monoalkylated products:

$$R_2P(O)\underset{\underset{COOC_2H_5}{|}}{C}R'(Na) + R''Hal \rightarrow R_2P(O)\underset{\underset{COOC_2H_5}{|}}{C}(R')(R'') + NaHal.$$

Among other organophosphorus compounds with an active methylene group, diethyl 2-pyridylmethylphosphonate[235] and tetraethyl methylenediphosphonate[100,102] were alkylated with alkyl bromides:

$$(C_2H_5O)_2P(O)-CH_2-\langle\text{pyridine-N}\rangle + K + RBr \rightarrow (C_2H_5O)_2P(O)\underset{\underset{R}{|}}{C}H-\langle\text{pyridine-N}\rangle + KBr.$$

The alkylation of the diphosphonate takes place with much more difficulty[236]. The reaction of butyl bromide with the potassio-derivative of tetraethoxydiphosphonomethane gave butyl(tetraethoxydiphosphono)methane in a yield of only about 15%[102]:

$$(C_2H_5O)_2P(O)CH_2P(O)(OC_2H_5)_2 + K + C_4H_9Br \xrightarrow[-KBr]{} [(C_2H_5O)_2P(O)]_2CH-C_4H_9.$$

In the alkylation of metallated derivatives of methylenediphosphine dioxides with alkyl iodides, it was shown that sodium iodide is firmly retained by the alkylated dioxide[237–239]. A tetrasubstituted product was obtained in the alkylation with allyl bromide of ethyl dimethylenetriphosphonate, which has two active methylene groups, as a result of the successive substitution of their mobile hydrogen atoms[125].

The acylation of organophosphorus compounds with an active methylene group has been investigated in less detail. It has not proved possible to obtain *C*-acylated products from diethoxyphosphonoacetic ester by the action of acetyl chloride on the alkali metal salts[240]. However, when the ethoxymagnesium salt of diethoxyphosphonoacetic ester was employed, ethyl diethoxyphosphonoacetoacetate (II) was obtained in a good yield:

$$(C_2H_5O)_2P(O)\underset{\underset{COOC_2H_5}{|}}{C}HMgOC_2H_5 + CH_3COCl \rightarrow \underset{(I)}{(C_2H_5O)_2P(O)\underset{\underset{COOC_2H_5}{|}}{\overset{\overset{COCH_3}{/}}{C}}-MgCl} +$$

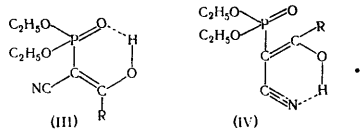
$$+ C_2H_5OH \xrightarrow{acid} \underset{(II)}{(C_2H_5O)_2P(O)CH\begin{matrix}\diagup COCH_3\\ \diagdown COOC_2H_5\end{matrix}}.$$

Diethoxyphosphonomalonic ester is obtained similarly.

The acylation of diethoxyphosphonoacetonitrile is achieved by the reaction of its potassio-derivative with the chlorides of acetic, propionic, n-butyric, and benzoic acids[241]:

$$(C_2H_5O)_2P(O)CH_2CN + K + RCOCl \rightarrow (C_2H_5O)_2P(O)CH\begin{matrix}\diagup COR\\ \diagdown CN\end{matrix}.$$

The authors suggest on the basis of infrared spectroscopy that the *C*-acyl derivatives of diethoxyphosphonoacetonitrile can have structures (III) or (IV):



(III) (IV)

The preferred structure is (III), in which the formation of a hydrogen bond involving the P=O group is postulated, since the displacement of the P=O absorption band is much greater (by 90 cm^{-1}) compared with the band due to the CN-group (by 50 cm^{-1}).

Recently it proved possible to formylate dialkoxyphosphonoacetonitriles[242]:

$$(RO)_2P(O)CH_2CN \xrightarrow{Na+HCOOCH_3} (RO)_2P(O)CH\begin{matrix}\diagup CHO\\ \diagdown CN\end{matrix}.$$

The formylation of the esters of dialkoxyphosphonoacetic[243], benzylphosphonic[244], and dibenzylphosphinous[245] acids has also been described:

$$(C_2H_5O)_2P(O)CH_2C_6H_5 + HCOOCH_3 \rightarrow (C_2H_5O)_2P(O)\underset{\underset{CHO}{|}}{C}H-C_6H_5 + CH_3OH.$$

However, in the last case the reaction takes place in a more complex manner: instead of the expected product, dibenzylhydroxymethylphosphine oxide and an enol are formed[245]:

$$(C_6H_5CH_2)_2P(O)H + 2HCOOR \rightarrow (C_6H_5CH_2)_2P(O)CH_2OH + \langle\text{cyclic enol}\rangle.$$

2. Addition Reactions

Reactions involving the addition of partially esterified phosphorus acids and organophosphorous compounds with an active methylene group to unsaturated electrophilic compounds, which were first achieved by Pudovik, serve as the basis of a new method for the synthesis of various derivatives of phosphonic and phosphinic acids[246].

The addition of diethoxyphosphonoacetic ester to the nitrile and the methyl ester of acrylic acid takes place readily in the presence of a small amount of sodium

ethoxide. Products of addition to one and two molecules of the unsaturated compound have been isolated[224,231,247]:

$$2\,(C_2H_5O)_2P(O)CH_2COOC_2H_5 + 3\,CH_2=CHX \xrightarrow{C_2H_5ONa}$$

$$(C_2H_5O)_2P(O)\underset{\displaystyle COOC_2H_5}{\underset{|}{C}}HCH_2CH_2X + (C_2H_5O)_2P(O)\underset{\displaystyle COOC_2H_5}{\underset{|}{C}}(CH_2CH_2X)_2,$$

where X = CN or $COOCH_3$. The addition of homologues of diethoxyphosphonoacetic ester—methyl and butyl diethoxyphosphonoacetates—to electrophilic compounds—acrylonitrile, methyl acrylate, and methyl methacrylate—also takes place readily[224,247]:

$$(C_2H_5O)_2P(O)\underset{\displaystyle COOC_2H_5}{\underset{|}{CH}}(C_4H_9) + CH_2=CHCN \rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle COOC_2H_5}{\underset{|}{C}}(C_4H_9)-CH_2CH_2CN.$$

When alkylalkoxy-, dialkyl-, and diphenyl-phosphonoacetic acids and their homologues, in which the methylene group is less reactive, were added to unsaturated compounds, the potassio-derivatives of the esters were employed[248]:

$$R_2P(O)CH_2COOC_2H_5 + CHR'=CR''X \xrightarrow{R_2P(O)CH(K)COOC_2H_5} R_2P(O)\underset{\displaystyle COO_2H_5}{\underset{|}{C}}HCHR'CHR''X,$$

Later the addition of phosphonoacetic esters to nitroisopentene, ethyl vinyl sulphone[249], divinyl sulphone, and *p*-di-(β-nitrovinyl)benzene[250] to esters of maleic[251], cinnamic[231], crotonic[252], and propynylphosphonic[253] acids, and also unsaturated polyesters[254] was achieved. The esters of αβ-unsaturated carboxylic acids can be arranged in the following sequence in terms of their reactivity in reactions involving the addition of diethoxyphosphonoacetic ester: acrylates > crotonates > methacrylates > cinnamates[247].

The addition of diethoxyphosphonoacetone and its homologues to acrylonitrile[255], methyl acrylate, diethyl maleate, diethyl acetylenedicarboxylate, and ethylideneacetone[231] has been achieved. In most cases these reactions take place with greater difficulty and are accompanied by very small heat change. In order to drive the reactions to completion, the reaction mixtures must be heated for a long time.

The addition of diethoxyphosphonoacetonitrile and its homologues[41,247,256] takes place much more readily compared with that of diethoxyphosphonoacetic ester and diethoxyphosphonoacetone:

$$(C_2H_5O)_2P(O)CH_2CN + CH_2=CRCOOCH_3 \rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle CN}{\underset{|}{C}}HCH_2CHRCOOCH_3 +$$

$$+ (C_2H_5O)_2P(O)\underset{\displaystyle CN}{\underset{|}{C}}(CH_2CHRCOOCH_3)_2.$$

Diethoxyphosphonoacetonitrile is somewhat more reactive and ethyl diethoxyphosphonoacetate somewhat less reactive than dibutylphosphorous acid, as shown by experiments on "competing addition" and confirmed by the results of a kinetic study of the addition of a number of organophosphorus compounds with a mobile hydrogen atom to acrylonitrile. The introduction of an alkyl residue into the methylene group of diethoxyphosphonoacetic ester results in a lowering of its reactivity in addition reactions[257].

The addition of (alkylsulphonyl)methyldiphenylphosphine oxide[258] and butyl (ethylsulphonyl)methylphenylphosphinate[259] to acrylonitrile has also been achieved:

$$(C_6H_5)_2P(O)CH_2SO_2R + CH_2=CHCN \rightarrow (C_6H_5)_2P(O)CH\begin{cases}SO_2R\\ CH_2CH_2CN\end{cases}.$$

When benzylphosphonic ester was added to acrylonitrile and ethyl acrylate, it proved impossible to isolate the addition product in a pure form[260]; in the reaction with ethyl cinnamate the addition product was isolated and characterised[261]:

$$(C_2H_5O)_2P(O)CH_2C_6H_5 + C_6H_5CH=CHCOOC_2H_5 \xrightarrow[70°,\ 1.5\ h]{C_2H_5ONa} (C_2H_5O)_2P(O)\underset{\displaystyle C_2H_5OOC-CH_2-CH-C_6H_5}{\underset{|}{CH}}-C_6H_5.$$

The addition of dialkyl esters of allylphosphonic acid to methyl acrylate yields the methyl esters of 3-(dialkoxyphosphono)pentene-3-carboxylic acid. The addition products formed initially, in the presence of sodium alkoxide, undergo prototropic isomerisation[262]:

$$(RO)_2P(O)CH_2CH=CH_2 + CH_2=CHCOOCH_3 \xrightarrow{RONa}$$

$$\rightarrow CH_2=CH-\underset{\displaystyle CH_2CH_2COOCH_3}{\underset{|}{CHP}}(O)(OR)_2 \xrightarrow{RONa} CH_3CH=\underset{\displaystyle CH_2CH_2COOCH_3}{\underset{|}{CP}}(O)(OR)_2.$$

In the presence of sodium ethoxide, diethyl allylphosphonate is converted into a dimeric product—1,3-di(diethoxyphosphono)-2-methylpent-3-ene[263]. Evidently the first stage in this reaction is prototropic isomerisation of the allylphosphonic ester to the diethyl ester of propenylphosphonic acid, which then adds on a second molecule of the allylphosphonic ester at the double bond. In the presence of alkoxide anions, the addition products undergo further prototropic isomerisation with formation of the final products[262]:

$$(RO)_2P(O)CH_2CH=CH_2 \overset{RO^-}{\rightleftarrows} (RO)_2P(O)CH=CHCH_3,$$

$$(RO)_2P(O)CH_2CH=CH_2 + CH_3CH=CHP(O)(OR)_2 \xrightarrow{RO^-}$$

$$\rightarrow CH_2=\underset{\displaystyle CH_3CHCH_2P(O)(OR)_2}{\underset{|}{CHP}}(O)(OR)_2 \xrightarrow{RO^-} CH_3CH=\underset{\displaystyle CH_3CHCH_2P(O)(OR)_2}{\underset{|}{CP}}(O)(OR)_2.$$

The possibility of the prototropic isomerisation of allylphosphonic esters to the propenyl isomers has been demonstrated by Ionin and Petrov for diethyl allylphosphonate and its methyl-, chloromethyl-, and phenyl-substituted derivatives[137]:

$$R-\underset{\displaystyle R'}{\underset{|}{C}}=CHCH_2P(O)(OC_2H_5)_2 \leftrightarrows R-\underset{\displaystyle R'}{\underset{|}{CH}}-CH=CHP(O)(OC_2H_5)_2.$$

Analysis of infrared, ultraviolet, and NMR (^1H and ^{31}P) spectroscopic data established that the isomerisation goes to completion only in the case of the allylphosphonic ester. Crotylphosphonic ester isomerises to the extent of 25% and cinnamylphosphonic ester does not isomerise at all. In the case of γ-chlorocrotylphosphonic ester the chlorine is replaced by an ethoxy-group without isomerisation. The above data led to the conclusion that the diethoxyphosphono-group interacts very weakly with a double bond. Conjugation with this group is less stable than hyperconjugation between a methyl group and a double bond. The conjugation between a double bond and a benzene ring is incomparably more favourable than the possible conjugation of this bond with a diethoxyphosphono-group[137].

Recently Kirilov and coworkers found that the ethyl esters of diethoxy- and di-isopropoxy-phosphonoacetic acids and diethoxyphosphonoacetonitrile add to the C=N double bonds of Schiff bases—benzylideneaniline, benzylidene-*p*-chloroaniline, etc.[264] The reactions take place in the presence of aluminium chloride, sodamide, and sodium alkoxides. The yields of the addition products are 30–60% and depend on the catalyst; the highest yields were obtained with aluminium chloride[265]:

$$(RO)_2P(O)CH_2X + C_6H_5CH=N-C_6H_4-R \rightarrow (RO)_2P(O)CH(X)CH(C_6H_5)NHC_6H_4-R,$$

where X = $COOC_2H_5$ or CN.

3. Condensation and P(O)-activated Olefin Synthesis

Condensation reactions. The possibility of the condensation of organophosphorus compounds having an active methylene group with aldehydes was demonstrated for the first time by Pudovik and Lebedeva in 1953. By heating diethoxyphosphonoacetic ester with benzaldehyde in acetic anhydride solution, they obtained the diethyl ester of α-ethoxycarbonyl-β-phenylvinylphosphonic acid[255]:

$$(C_2H_5O)_2P(O)CH_2COOC_2H_5 + C_6H_5CHO \xrightarrow{(CH_3CO)_2O} (C_2H_5O)_2P(O)C(=CHC_6H_5)COOC_2H_5 + 2CH_3COOH.$$

Later in the condensation of diethoxyphosphonoacetic ester with benzaldehyde under somewhat different conditions and in the presence of piperidine the yield of the condensation product was greatly increased[266,267]. The product of the condensation of benzaldehyde with two moles of diethoxyphosphonoacetic ester was also obtained in low yield[266].

Diethoxyphosphonoacetic ester reacts with aliphatic aldehydes and in particular formaldehyde under milder conditions, in methanol solution in the presence of piperidine. The esters of α-ethoxycarbonylvinylphosphonic acid have been obtained by this method[268]:

$$(C_2H_5O)_2P(O)CH_2COOC_2H_5 + CH_2O \rightarrow (C_2H_5O)_2P(O)C(=CH_2)COOC_2H_5 + H_2O.$$

The synthesis of esters of α-alkoxycarbonyl- and α-cyanovinylphosphonic acids by the condensation reaction has significant advantages both as regards yields and the availability of the starting materials over the methods for the preparation of these compounds described previously[264,270].

In the presence of piperidine, diethoxyphosphonoacetonitrile readily condenses with both aliphatic[271-273] and aromatic aldehydes[42,274]:

$$(C_2H_5O)_2P(O)CH_2CN + CH_2O \rightarrow (C_2H_5O)_2P(O)C(=CH_2)CN + H_2O.$$

In the presence of ammonium acetate and acetic acid, reaction with ketones also take place[275]:

$$(C_2H_5O)_2P(O)CH_2CN + RR'CO \rightarrow (C_2H_5O)_2P(O)C(=CRR')CN + H_2O.$$

Recently we showed that diethoxyphosphonoacetone[274,276,277] and diethoxyphosphonoacetophenone[278,279] are also capable of condensing with aliphatic and aromatic aldehydes. The reactions occur in benzene or toluene solutions in the presence of piperidine with simultaneous azeotropic distillation of the water formed:

$$(C_2H_5O)_2P(O)CH_2COCH_3 + R{-}C_6H_4CHO \xrightarrow{-H_2O} (C_2H_5O)_2P(O)C(=CHC_6H_4{-}R)COCH_3.$$

The reactions of aldehydes with dialkoxyphosphonoacetophenones are of considerable theoretical interest[279]. We established that the reaction with *p*-nitrobenzaldehyde can involve simultaneously either condensation or P(O)-activated olefin formation:

$$(RO)_2P(O)CH_2COC_6H_5 \overset{\text{base}}{\rightleftharpoons} (RO)_2P(O)\bar{C}HCOC_6H_5 + BH^+, \quad (V)$$

$$(RO)_2P(O)\bar{C}HCOC_6H_5 + R'CHO \rightleftharpoons (RO)_2P(O)CH(O^-)CHR'COC_6H_5 \quad (VI)$$

$$(VI) \overset{H^+}{\underset{A}{\rightleftharpoons}} (RO)_2P(O)C(H)(OH)CHR'COC_6H_5 \quad (VII)$$

$$(VII) \rightleftharpoons (RO)_2P(O)C(=CHR')COC_6H_5 \quad (IX)$$

$$(VI) \overset{B}{\rightleftharpoons} (RO)_2P(O^-)(O)CH(C_6H_5)CHR' \quad (VIII)$$

$$(VIII) \rightarrow (RO)_2P(O)O^- + C_6H_5COCH{=}CHR'. \quad (X)$$

The carbonion (V), formed when a basic reagent acts upon the organophosphorus compound with an active methylene group, interacts further with the carbonyl compound and is converted into the anion (VI). Both stages are common to the condensation and P(O)-activated olefin formation reactions. By combining with a proton, the anion (VI) is converted into the alcohol (VII) and its dehydration gives the condensation product (IX) (pathway *A*). The P(O)-activated olefin formation reaction (pathway *B*) probably takes place via the intermediate formation of an unstable four-membered cyclic product or transition state (VIII) (by analogy with the Wittig reaction); the bond redistribution in (VIII) leads to a phosphoric acid and an unsaturated ketone.

The rate and mode of this complex and multistage reaction depend both on the nature and amount of the catalysts and solvents employed and on the structure of the organophosphorus compounds and aldehydes[279].

Tetraethoxydiphosphonomethane, which has a less active methylene group, condenses with benzaldehyde only after prolonged heating of the reactants in xylene with simultaneous azeotropic distillation of the water formed[280]:

$$[(C_2H_5O)_2P(O)]_2CH_2 + C_6H_5CHO \rightarrow C_6H_5CH{=}C[P(O)(OC_2H_5)_2]_2 + H_2O.$$

Organophosphorus compounds with an active methylene group can be arranged in the following sequence in terms of their relative reactivities in condensation reactions with aldehydes[274]:

$$(C_2H_5O)_2P(O)CH_2CN > (C_2H_5O)_2P(O)CH_2COCH_3 > (C_2H_5O)_2P(O)CH_2COOC_2H_5 > (C_2H_5O)_2P(O)CH_2P(O)(OC_2H_5)_2.$$

Phosphonium salts also condense with aldehydes; thus dyes analogous to styryl dyes have been obtained by the condensation of phosphonium salts with *p*-dimethylaminobenzaldehyde[281]:

$$[(C_6H_5)_3\overset{+}{P}CH_2C(=O)C_6H_5]\,Cl^- + (CH_3)_2NC_6H_4CHO \xrightarrow{(CH_3CO)_2O,\ 130^\circ} (C_6H_5)_3\overset{+}{P}(Cl^-)CH{=}CHC_6H_4N(CH_3)_2 \cdot COC_6H_5.$$

The P(O)-activated olefin formation reaction. The P(O)-activated olefin formation reaction,

discovered by Horner in 1958, is characteristic of and specific to organophosphorus compounds with an active methylene group. It is of great preparative importance in organic chemistry, since it permits the syntheses of a wide variety of unsaturated hydrocarbons and their various derivatives.

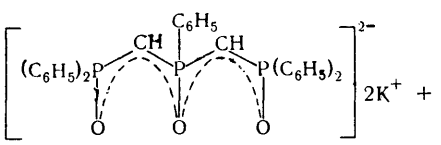
The use of reagents for the P(O)-activated synthesis of olefins is more effective than the Wittig reaction involving various phosphoranes. In relation to carbonyl compounds and in particular to ketones, reagents for P(O)-activated olefin synthesis are more reactive by virtue of their more pronounced nucleophilic properties compared with phosphoranes. The isolation of olefins is greatly facilitated when the P(O)-activated olefin formation method is employed. The unsaturated compounds obtained can be readily separated from the readily water-soluble alkali metal salts of alkylphosphoric acids, while in the Wittig reactions it is necessary to resort to special procedures for the separation of the olefin from triphenylphosphine oxide. Moreover, reagents for P(O)-activated olefin synthesis are more readily available than the Wittig reagents.

A detailed review has been published on the P(O)-activated olefin formation reaction in organic synthesis [282]. Here we shall confine ourselves to a discussion of studies which have been published recently and in which diphosphono-derivatives were used as for P(O)-activated olefin synthesis reagents. Reactions of this type are of considerable interest also because they permit a fairly simple synthesis of various unsaturated organophosphorus compounds.

The possibility of synthesising vinylphosphonates by the P(O)-activated olefin formation reaction was first demonstrated by Wadsworth and Emmons [283]. They obtained the diethyl ester of β-phenylvinylphosphonic acid by the reaction of tetraethoxydiphosphonomethane with benzaldehyde in the presence of sodium hydride [283]:

$$[(C_2H_5O)_2P(O)]_2CH_2 + C_6H_5CHO \xrightarrow{NaH} (C_2H_5O)_2P(O)CH{=}CHC_6H_5.$$

Similarly, even with the potassio-derivative of tetraphenylmethylenediphosphinedioxide, Kabachnik and coworkers obtained also unsaturated phosphine oxides [130]. Phosphine oxides with two unsaturated substituents may be obtained by using in the reaction with aldehydes the dipotassio-derivative of pentaphenyldimethylenetriphosphine trioxide [127]:



$$+\ 2C_6H_5CHO \xrightarrow{-2(C_6H_5)_2P(O)OK} (C_6H_5CH{=}CH)_2P(O)C_6H_5.$$

The P(O)-activated olefin formation reaction permits the synthesis of organophosphorus compounds with a substituent at the phosphorus atom containing several conjugated double bonds. For example, cinnamaldehyde is allowed to react for this purpose with the potassio-derivative of tetraethoxydiphosphonomethane [284]:

$$[(C_2H_5O)_2P(O)]_2CHK + C_6H_5CH{=}CHCHO \rightarrow (C_2H_5O)_2P(O)CH{=}CHCH{=}CHC_6H_5.$$

Diphosphonomethane derivatives in which the hydrogen has been replaced by another group readily enter into the P(O)-activated olefin formation reaction. Thus esters of unsaturated phosphonic acids containing the dimethylamino-group at the α-carbon atom have been obtained from di(diethoxyphosphono)dimethylaminomethane [285]:

$$[(C_2H_5O)_2P(O)]_2CHN(CH_3)_2 + RCHO \rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle N(CH_3)_2}{\underset{|}{C}}{=}CHR.$$

Unsaturated ketophosphonic esters were obtained by Normant by the reaction of carbonyl compounds with the sodio-derivative of 2-ethoxy-1,3-diphosphonopropene [265]:

$$(C_2H_5O)_2P(O)CH{=}\underset{\displaystyle OC_2H_5}{\underset{|}{C}}{-}CH_2P(O)(OC_2H_5)_2 \xrightarrow{+NaH+>C=O}$$

$$\rightarrow (C_2H_5O)_2P(O)CH{=}\underset{\displaystyle OC_2H_5}{\underset{|}{C}}{-}CH{=}C< \leftrightarrow (C_2H_5O)_2P(O)CH_2COCH{=}C<.$$

$\alpha\beta$-Unsaturated phosphines and phosphine sulphides have been obtained with the aid of the P(O)-activated olefin formation reaction [286]. In this case compounds containing simultaneously ter- and quinque-valent phosphorus atoms or diphenylphosphine oxide and diphenylphosphine sulphide groups were used in this case as reagents for P(O)-activated olefin synthesis:

$$(C_6H_5)_2P{-}CH_2{-}P(O)(C_6H_5)_2 + RCHO \rightarrow (C_6H_5)_2P{-}CH{=}CHR + (C_6H_5)_2\overset{\displaystyle O}{\overset{\|}{P}}OH,$$

$$(C_6H_5)_2\overset{\displaystyle S}{\overset{\|}{P}}{-}CH_2{-}\overset{\displaystyle O}{\overset{\|}{P}}(C_6H_5)_2 + RCHO \rightarrow (C_6H_5)_2P(S)CH{=}CHR + (C_6H_5)_2\overset{\displaystyle O}{\overset{\|}{P}}OH.$$

4. Reactions of Other Types

Among other reactions of organophosphorus compounds with an active methylene group in which the methylene hydrogen atoms are involved, bromination, chlorination, and azo-coupling reactions are known.

The bromination of diethoxyphosphonoacetone and diethoxyphosphonoacetaldehyde with elemental bromine takes place readily and rapidly in ethereal solution [40]:

$$(C_2H_5O)_2P(O)CH_2COCH_3 + Br_2 \rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle Br}{\underset{|}{C}}HCOCH_3 + HBr.$$

Chlorination of diethoxyphosphonoacetone with sulphuryl chloride gave a high yield of α-chlorodiethoxyphosphono-acetone [287]. When an excess of chlorine is allowed to react with dialkoxyphosphonoacetonitriles with simultaneous ultraviolet irradiation of the reaction mixture, both hydrogen atoms are substituted [288]:

$$(RO)_2P(O)CH_2CN + 2Cl_2 \xrightarrow[25-30^\circ]{h\nu} (RO)_2P(O)CCl_2CN + 2HCl.$$

Without ultraviolet irradiation, the chlorination does not take place but at a higher temperature not only the methylene group but also the alkoxy-group and the phosphorous atoms are chlorinated.

The azo-coupling of aromatic diazo-compounds with diethoxyphosphonoacetic ester, diethoxyphosphonoacetone, and diethoxyphosphonoacetonitrile has been achieved. The reactions were carried out under mild conditions in the absence of catalysts [289]:

$$(C_2H_5O)_2P(O)CH_2X + ClN_2C_6H_4R \rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle X}{\underset{|}{C}}H{-}N{=}NC_6H_4R + HCl,$$

where X = $COOC_2H_5$, $COCH_3$, or CN.

There are data showing that the reaction of diethylamino-aniline with organophosphorus compounds having an active methylene group in the presence of silver bromide leads to

the formation of azomethylene dyes containing the phosphono-group[290]:

$$(C_2H_5O)_2P(O)CH_2COR + H_2N{-}C_6H_4{-}N(C_2H_5)_2 + 4\,AgBr \rightarrow$$

$$\rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle COR}{\underset{|}{C}}{=}N{-}C_6H_4{-}N(C_2H_5)_2.$$

However, later it was shown that in the case of diethoxyphosphonoacetophenone the yields of dyes in this reaction are very low and they cannot be isolated in a pure form[291,292].

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