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Derivatives of trivalent phosphorus in the synthesis of glycerophosphatides and related phospholipids

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Abstract. The review is devoted to the analysis of one of the new trends in phospholipid synthesis. An attempt is made to demonstrate the likely usefulness of studies designed to establish an interdisciplinary field combining the interests and possibilities of the chemistry of lipids and the chemistry of trivalent phosphorus. The bibliography includes 218 references.

I. Introduction

Natural glycerophospholipids and their synthetic analogues, in the molecules of which phosphorus-containing functional groups have been modified, constitute a large group of compounds with a complex structure. Since many of these substances are very important for the development of physicochemical biology as well as certain modern branches of medicine and engineering, much attention is being devoted nowadays to their synthesis.[1–10]

Among other problems solved in the synthesis of glycerophospholipids and their analogues, the most difficult is that of the formation of the phosphorus-containing unit in these complex polyfunctional systems. For a long time, only pentavalent phosphorus reagents have been used in all the world research centres for the synthesis of phospholipids; we may note that a similar strategy was applied also in the synthesis of nucleic acids and certain other phosphorus-containing natural products. This situation can be accounted for by the relatively ready availability of pentavalent phosphorus-containing reagents, the knowledge of the compounds at the time, and the fact that their application in fine organic synthesis appeared evident. Nevertheless, these reagents frequently suffered from significant disadvantages. Thus they ensured only low rates of phosphorylation and exhibited a tendency to alkylate the electrolytes present in the reaction system and to undergo other side reactions. Furthermore, only a narrow range of synthetic possibilities is associated with pentavalent phosphorus-containing reagents.

In view of the foregoing, a trend has gradually arisen in the chemistry of phospholipids to change over to reagents containing trivalent phosphorus, which differ from the corresponding oxidised forms by a much higher phosphorylating capacity, better preparative results, and more extensive design possibilities. A very important factor is that specialists working actively in the chemistry of trivalent phosphorus have begun to be involved during the recent period in the study of problems in the chemistry of phospholipids of current interest. They were able to find a series of novel and fruitful solutions during a comparatively short period.

The first results of studies by methods from the chemistry of trivalent phosphorus in the synthesis of glycerophosphatides and their phosphorothioate, phosphoroselenoate, and other analogues were compiled and discussed by the authors of the present review at the beginning of the 1980s.[11,12] In the subsequent period, the interest in this problem increased sharply and a need therefore arose to return to this topic in order to survey the authors' own and literature data and to deduce the trends which have reliably arisen.

Analysis of the scientific facts published during recent years demonstrates not only quantitative but also qualitative changes in the overall series of studies being prosecuted. This factor necessitated a revision of the previous structure used in considering the available data. In the present review, we have differentiated two main problems. The first involves the phosphorylation of glycerol derivatives and related polyols using trivalent phosphorus-containing reagents. Here one may include also certain other reactions of trivalent phosphorus derivatives leading to the introduction of the phosphoryl functional group into the glycerol system. The second involves the conversion of the phosphites obtained into natural phospholipids or their analogues via reactions involving trivalent phosphorus atoms.

II. Phosphorylation of glycerol and related oligool derivatives by trivalent phosphorus reagents

The introduction of trivalent phosphorus reagents into the synthetic chemistry of lipids was initially problematical for several reasons. Thus reliable information concerning the use of phosphorous acid and other trivalent phosphorus acid derivatives for the phosphorylation of polyfunctional systems was lacking in the literature. There was also no experience in the identification and isolation of glycerophosphatides and related compounds with a complex structure. Finally, one had to be on one's guard against the ready disproportionation of asymmetric glycerophosphites similar to that occurring in studies with the simplest asymmetric phosphites.[13] In view of the foregoing, in the first stages of the investigation predominantly model systems were used, in which the necessary methodological problems were worked out. 1,2-*O*-Isopropylideneglycerol and other similar acetals were usually employed as models of this kind. A very

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important factor is that subsequently a rational procedure was found for the conversion of these acetals,[14-16] as well as cyclic orthoesters[17] and oxazolidines,[18] into phospholipid systems.†

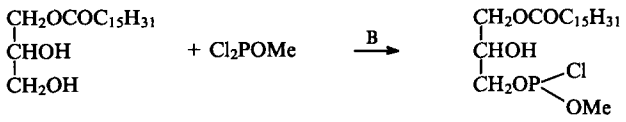
Various derivatives of tricoordinate phosphorus and hydrophosphoryl compounds were used as phosphorylating agents in the studies carried out.[21] Since each of the classes of these two types of reagents frequently exhibited significant chemical characteristic features, in the present review we have endeavoured to discuss topically the published data and to demonstrate the characteristics of the most important phosphorylating agents.

1. Phosphorylation by neutral derivatives of phosphorous acid

a. Phosphorylation by acid chlorides

In the synthesis of the simplest neutral esters of phosphorous acid, phosphorus trichloride and phosphorochloridites are usually employed as phosphorylating agents. These substances have been used also in the phospholipid synthesis. Thus diarylglycerols[22] and diacylglycerols[23-25] were treated with phosphorus trichloride to form glycerophosphorodichloridites. Unfortunately, the products of these reactions could not be isolated in a pure form and they were hydrolysed to the corresponding primary phosphites. Difficulties with isolation were noted also in the phosphorylation of diacylglycerols by 2,6-di-*tert*-butyl-4-methylphenyl phosphorodichloridite[26] and dimethyl and diphenyl phosphorochloridites.[27,28] In these cases, the primary reaction products were immediately converted by oxidation and subsequent hydrolysis (alcoholysis) into the corresponding phosphates. Unfortunately we must note that the use of phosphorochloridites for the synthesis of complex lipid systems has not always been carried out using well-founded schemes and in a number of instances was not accompanied by the demonstration of the structure. Thus the interaction of α-monopalmitoylglycerol with methyl phosphorodichloridite has been described.[27] The authors specify the mode of monophosphorylation, involving the formation of an alcohol-acid chloride (Scheme 1).

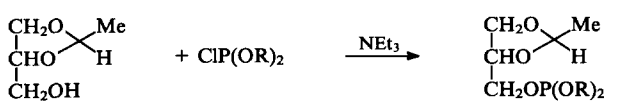
Scheme 1



It is most likely that such a product should either cyclise with formation of a 1,3,2-dioxaphosphorinane or should be converted into an oligophosphite. Therefore the probability that the above acid chloride exists for any [significant] period and then phosphorylates an extraneous nucleophile, as claimed by the authors,[27] is low.

More definite results were achieved using phosphoromonochloridites. The first investigation on these lines was carried out by Arbuzov and Yarmukhametova,[29] who synthesised dialkyl glycerophosphites from 1,2- and 1,3-*O*-ethyleneglycerols and dialkyl phosphorochloridites (Scheme 2).

Scheme 2



It was subsequently shown that phosphorylation yields better results when phosphoramidochloridites[30-37] as well as the readily available and experimentally more convenient cyclic acid chlorides—alkylene phosphorochloridites,[38-51] alkylene phosphoramidochloridites,[52-54] alkylene phosphorodiamidous chlorides,[54] and salicyl phosphorochloridites[55]—are employed. In this case, it was possible to obtain in satisfactory yields a series of neutral phosphites and phosphoramidites of the acetal and diacyl derivatives of glycerol[38-50,52-55] and thioglycerol.[51]

There are literature data concerning the analogous syntheses of phospholipids from etriol [2-hydroxymethyl-2-ethylpropane-1,3-diol (Translator)],[56] pentaerythritol,[57] ascorbic acid,[58] glycols,[59-61] higher aliphatic alcohols,[62-65] sphingophospholipids,[66-68] and fragments of lipid A.[69]

The use of phosphorus trichloride and phosphorochloridites in fine organic synthesis is not always justified. When complex lipid systems are synthesised, the application of reagents the use of which involves the evolution of hydrogen chloride is risky, because in this case there is a possibility of isomerisation, degradation of labile bonds, and other unfavourable processes. Furthermore, certain phosphorochloridites, for example those containing benzyl groups, exhibit a tendency to undergo rearrangements; the employment of such reagents may lead to explosions.[70] In view of the foregoing, a trend has recently arisen to employ mild phosphorylating agents in the synthesis of polyfunctional phosphorus-containing natural products, including phospholipids.

b. Phosphorylation by esters

The first experiments on this problem were carried out with model phosphorylating agents—phosphinous acid esters containing only one phosphorylating functional group. It was established that phosphinites are readily and effectively transesterified by 1,2- and 1,3-alkylideneglycerols.[71] Subsequently triphenyl[72] and triethyl phosphites[14-16,73,75] were transesterified.

Scheme 3



R = $C_{17}H_{35}$.

Phosphorylation by triethyl phosphite has been used for 1,2-diacylglycerols (Scheme 3).[74]

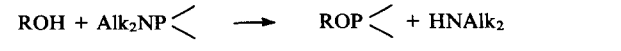
Transesterification has been used also for the synthesis of the phosphites of certain other polyols (see, for example, Petrov et al.[72]).

The transesterification method is also milder compared with the acid chloride method, but it too suffers from preparative disadvantages. Thus, in studies with partially acylated oligools, this procedure may be accompanied by side migrations, for example acyl migrations, owing to the high temperature of the main reaction. Investigators have therefore concentrated attention on the search for new phosphorylation procedures. The optimum procedure of this kind is examined below.

c. Phosphorylation by amides and amidoesters

Amides and amidoesters proved to be especially mild and convenient to use. Their employment ensured the maximum specificity and effectiveness of the phosphorylation reaction. We may also note that, when phosphoramides are used, amines are formed apart from the target esters. The amines can be readily evacuated from the reaction mixture and do not degrade the starting materials and reaction products (Scheme 4).[13]

Scheme 4

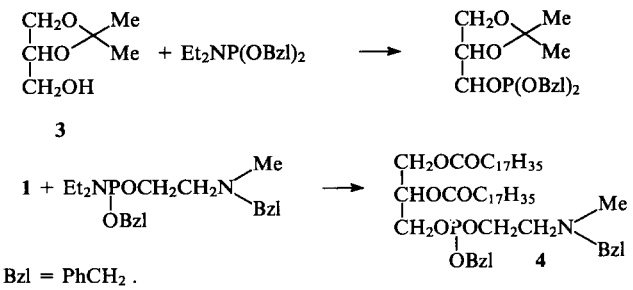


† In naming the phospholipids, we have employed, with some simplifications, the rules formulated by the IUPAC-IUB Commission on Chemical Nomenclature.[19,20]

We should draw attention to yet another factor. It has been shown that the rate of phosphorylation of nucleophiles by phosphorous acid amides can be regulated by catalysts. It has been proposed that amine hydrochlorides,[76,77] salts of dialkyldithiocarbamic acids,[78,79] and weak acids, for example tetrazole,[25,28,30–32,34–37,66–68,80–82] be used as catalysts of this kind. It has been stated that small amounts of added iodine have an activating effect in the phosphorylation reaction;[83–85] apparently hydrogen iodide and then its ammonium salts, which are in fact the catalysts, appear in the reaction mixture in such experiments.

Phosphoramides are used nowadays in syntheses of various lipid systems. Thus it has been suggested that phosphorous monoamides be used for the phosphorylation of glycerol acetals[26,74,86,87] and the corresponding esters[25,26,46,74,80,87] (Scheme 5).

Scheme 5

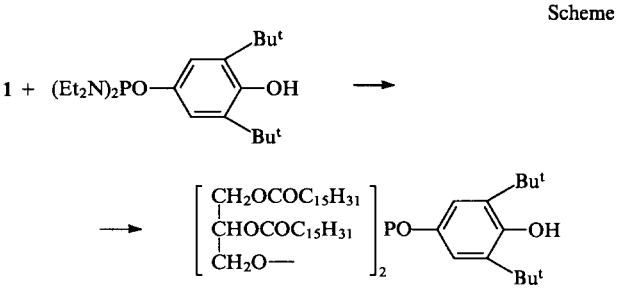


Bzl = $PhCH_2$.

The amides of cyclic phosphites and phosphoramidites are especially convenient to use and are promising for further reactions. A series of reactions with the amino-derivatives of phospholans,[88,89] phosphorinanes,[43,45,90] and phosphepans,[91,92] as well as oxazaphospholans[93–96] and oxazaphosphorinanes[52] have now been investigated.

Phosphorous diamides are even more widely used and it has been suggested that phosphomonoglycerides[26,74,86,87,97–102] and phosphodiglycerides[26,87] be obtained from them. We shall illustrate the latter possibility by the synthesis of a compound the structure of which includes a sterically hindered phenol fragment (Scheme 6).[26]

Scheme 6



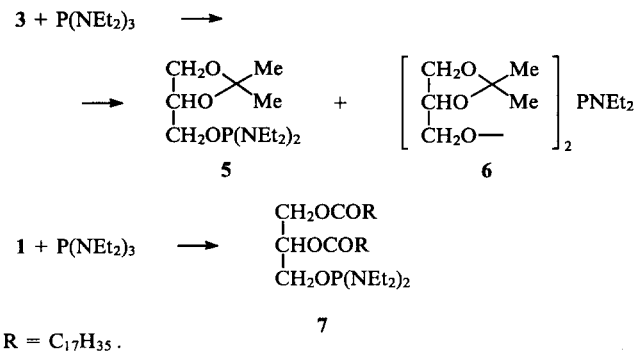
R = $C_{15}H_{31}$.

These and other similar compounds can be built into biological membranes and can protect the latter from homolytic oxidation.[103]

It has been suggested that phosphorous acid triamides be also employed as phosphorylating agents. Depending on the reactant ratio, it is possible to obtain in this case mono- or diglycerophosphoramidites (Scheme 7).[74,85,88,94,95,104,105]

In the course of the study of the phosphoramide method for the phosphorylation of diacylglycerols, fears arose concerning the possibility of acyl migrations. Indeed, as a strong nucleophile, the secondary amine produced should at least partially add to the carbonyl groups of the esters, which generally speaking can lead to rearrangements. Experimental data have confirmed the validity of such fears: in some

Scheme 7



R = $C_{17}H_{35}$.

experiments with 1,2- and 1,3-diacylglycerols isomerisations involving up to 10% of the starting materials were observed. Taking into account the foregoing considerations concerning the possible nature of the migrations, a study involving the search for optimum phosphorylation conditions was undertaken and it was observed that phosphorylation in a low vacuum (300 torr) makes it possible to achieve the timely evacuation of the amine produced and to protect the acylglycerol system against side reactions.[107]

Phosphorous acid amides have been used successfully in the synthesis of nonglycerol phospholipids—derivatives of ascorbic acid,[108] 1,1,1-tri(hydroxymethyl)alkanes,[18,56] pentaerythritol,[17,57,109] glycols,[78,79,83,110] fragments of lipid A,[69] and ceramide.[68,81,82]

The phosphoramidites and phosphorodiamidites of oligools have attracted attention not only in connection with their ready availability but also because they are convenient to use. They are optimum intermediates for the synthesis of a wide range of phospholipids, because they effectively phosphorylate the nucleophiles forming part of phospholipid systems—the choline, aminoalkyl, carbohydrate, acylglycerol, aminoacid, and other important synthons. This aspect of the problem will be considered below.

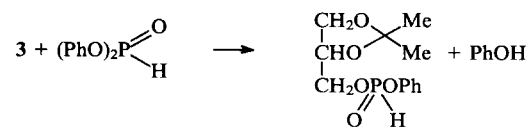
In conclusion of this section we shall deal with the problems of the stability of glycerophosphites and also with certain features of the experiments involving them. Depending on the molecular mass and nature of the glycerophosphites formed, the latter can be isolated by vacuum (high vacuum) distillation or chromatographically. However, in most cases this is superfluous. Bearing in mind the high phosphorylating capacities of trivalent phosphorus derivatives, the mild conditions, and hence the high effectiveness of the processes considered, it is useful to introduce glycerophosphites immediately into subsequent reactions without isolating them. An important preparative feature of glycerophosphites is noteworthy. In contrast to simple symmetric derivatives of phosphorous acid,[13] these compounds are thermally stable, i.e. are only poorly symmetrised on heating.

2. Phosphorylation by acid derivatives of phosphorous acid

a. Phosphorylation by diesters and diamides

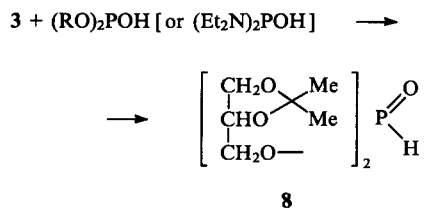
The possibility, in principle, of using the transesterification method for the synthesis of symmetrical and asymmetric disubstituted phosphites containing glycerol fragments in their structure has been demonstrated in the literature. Thus phenyl glycerophosphite has been synthesised from 1,2-*O*-isopropylideneglycerol **3** and diphenyl phosphite (Scheme 8).[72]

Scheme 8



Isopropylidenemetriol reacts similarly with diphenyl phosphite.[72] Subsequently the reaction was extended to aliphatic phosphites. The complete transesterification of dimethyl(ethyl) phosphite with 1,2-*O*-isopropylideneglycerol may serve as an example of the synthesis of symmetrical diglycerophosphites.[45,75,111,112] It was shown that the transesterification is accelerated by orthotitanic acid derivatives (Scheme 9).[112]

Scheme 9



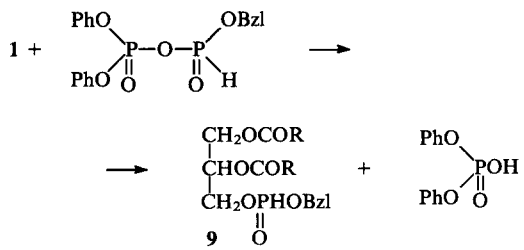
8

A similar result was obtained when phosphorus tetraethyldiamide was used.[111] Owing to the presence of two chiral centres and a pseudochiral centre in the molecule, the ^{31}P NMR spectra of diglycerophosphite **8** are relatively complex. It is noteworthy that the above compound was the first among hydrophosphoryl products in the molecules of which a pseudochiral phosphorus atom was detected.[75]

b. Phosphorylation by phosphorous acid monoesters

A promising method of synthesis of complex disubstituted phosphorous acid esters is based on the use of primary phosphites. The idea of this method is as follows. Primary phosphite salts, which are readily available and are convenient to use, are treated with strong electrophiles, usually the halides of organoelement and carboxylic acids. The alkyl phosphites are activated as phosphorylating agents as a result of the formation of mixed anhydrides. On contact with alcohols, the latter afford secondary phosphites. The practical application of the chlorides of organoelement acids was initiated by Corby et al. in relation to diphenyl phosphorochloridite.[113] This version of the phosphorylation method has been used in the chemistry of natural products, including lipids. As an illustration, we present the following example which resulted in the formation of benzyl 1,2-diacylglycerophosphite **9** (Scheme 10).[114–117]

Scheme 10



The application of carboxylic acid chlorides for the activation of monoalkyl phosphites has been proposed by Rogovin and the authors of the present review.[118,119] This version is apparently especially interesting for the chemistry of natural products.‡ It has already proved very useful in the synthesis of phosphorylated cellulose,[118,119] nucleic acids,[120–122] and sugar glycosyl phosphates.[123] At the present time, the above approach is one of the procedures in the chemistry of phospholipids for the phosphorylation of glycerols by primary phosphites of different nature and for the phosphorylation of the constituents of complex phospholipids by glycerophosphites (see Section III).

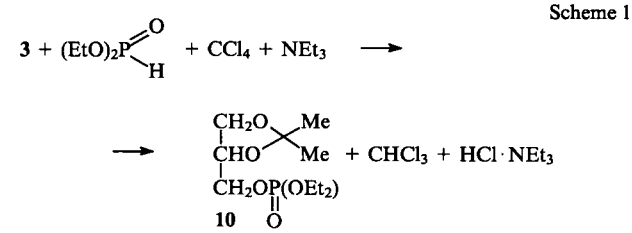
‡ This method is sometimes referred to in the literature, not entirely accurately, as the 'H-phosphonate' method. A more accurate term may be the 'hydrophosphoryl' method.

3. The use of trivalent phosphorus reagents for the oxidative introduction of phosphorus into the glycerol and related oligool systems

The direct phosphorylation reactions described above do not exhaust all the possibilities for the employment of trivalent phosphorus reagents in the synthesis of phosphoglycerol structures. Together with these reactions, studies have also been made on oxidation processes based on the use of phosphorous acid diesters and triesters, which made it possible to obtain glycerophosphates, glycerophosphorothiolates, and glycerophosphonates by a simple procedure.

The Todd–Atherton reaction is of great synthetic importance.[124] It has been studied in detail in relation to the phosphorylation of 1,2-*O*-isopropylideneglycerol **3** and 1,3-*O*-benzylideneglycerol by diethyl(methyl) phosphites in the presence of carbon tetrachloride.[14,15,74] As an example, we present the synthesis of diethyl 1,2-isopropylideneglycerophosphate **10** (Scheme 11).

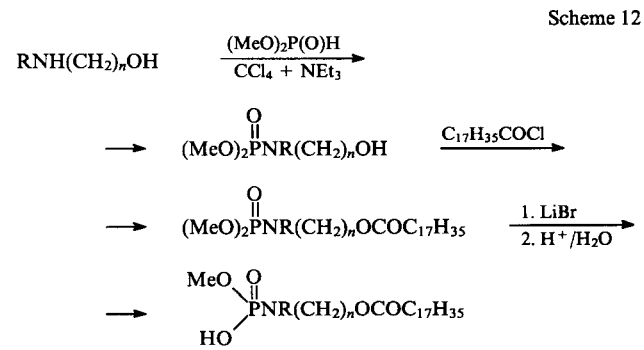
Scheme 11



The process is based on the use of readily available starting compounds, is carried out under mild conditions, and gives rise to high yields of the target products. In considering the Todd–Atherton reaction, one should bear in mind its extensive synthetic possibilities. We may point out that, in the oxidative phosphorylation of glyceroacetals and diacylglycerols, good results have been obtained not only with aliphatic but also with aromatic phosphites.[14] Furthermore, alkylene phosphites,[45] alkylene phosphorothioites,[40] and alkylene phosphoramidites[125] have been used in preparative practice. On the other hand, instead of glycerol derivatives it is possible to employ glycols and obtain diol phospholipids and their diphosphorus analogues.[56–61,126]

Important results have been achieved also in the phosphorylation of primary and secondary aminoalcohols.[127] This reaction made it possible to put forward a new strategy for the synthesis of the important, although nowadays little investigated, class of phospholipids (Scheme 12).

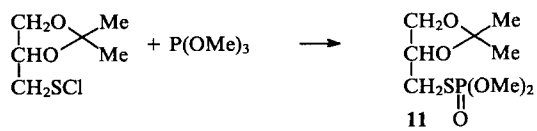
Scheme 12



n = 2, 3; R = H, Me.

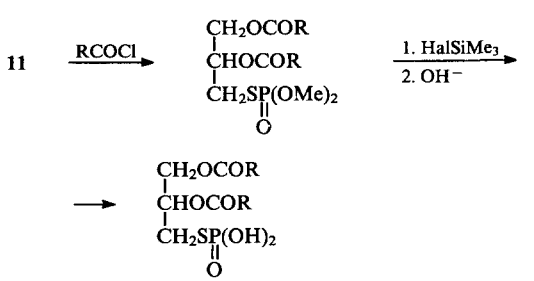
An elegant synthesis of lipids otherwise difficult to obtain, for example dimethyl 1,2-isopropylidenethioglycerophosphorothiolate **11**, has been described by Mlotkovska and Markovska,[128-130] who resorted to the reactions of sulfonyl chlorides derived from glycerol with neutral phosphites (Scheme 13).

Scheme 13



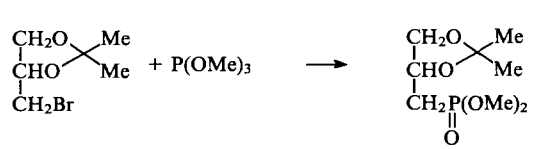
Analogues of natural phosphoglycerols can be readily obtained from such phosphoacetals.[14-16] In the molecules of phosphoglycerols, the glycerol residue is joined to the phosphorus atom via a labile thiol 'inset', which is of great interest for enzymological research for example (Scheme 14).[128]

Scheme 14



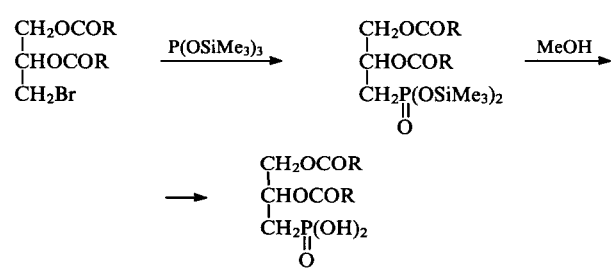
It has been suggested that the novel systems in the molecules of which the deoxyglycerol fragment is joined directly to the phosphorus atom be synthesised via the Arbuzov reaction (Scheme 15).

Scheme 15



Special reviews have been published on questions concerning the use of this reaction,[5,131,132] which makes it unnecessary to quote in detail the relevant studies in the present review. We shall only note the particularly good prospects for the use of trisilyl phosphites as the phosphorous component. This version of the reaction takes place particularly readily because of the high nucleophilicity of the silyl phosphites and makes it possible to obtain in the concluding stage the phosphono-analogues of phosphatidic acids by means of simple alcoholysis (Scheme 16).[133-135]

Scheme 16



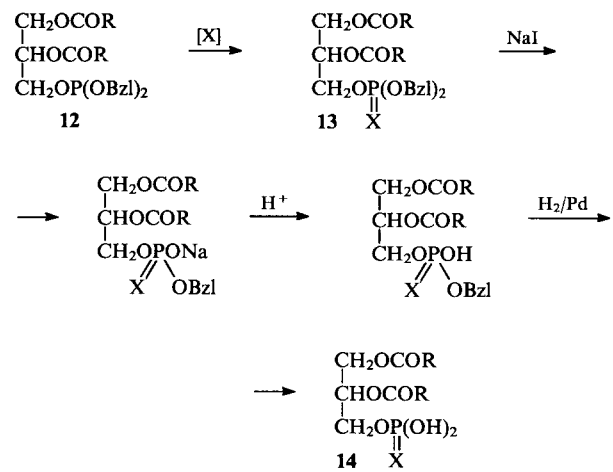
III. Synthesis of phospholipids from glycerophosphorous acid esters and amides

In this section, the literature data are discussed in three subsections. Each of them is devoted to the reactions of the most important classes of derivatives of glycerophosphorous acids which occur as key substances in lipid syntheses: neutral glycerophosphites, acid glycerophosphites, and glycerophosphoramidites. Sometimes the types of compounds considered are linked to one another by simple reactions which will be specially indicated.

1. Reactions of neutral glycerophosphites

In the first place, we shall consider the phospholipid syntheses based on neutral monoglycerophosphites.§ It has been suggested that the simplest of these compounds — acyclic esters — be used to synthesise phosphatidic acids.[74] Thus dibenzyl 1,2-diacylglycerophosphites **12** are oxidised¶ by nitrogen oxides or iodosobenzene with formation of the corresponding dibenzyl phosphates **13** (X = O), which were obtained previously via a much more complex scheme: by the reaction of the silver salts of dibenzylphosphoric acids with glycerol 1,2-diacylhalohydrins which are difficult to obtain and inconvenient to work with.[1,3,8,10] Dibenzyl phosphates **13** (X = O) are subsequently converted into the phosphatidic acids **14** (X = O). At the same time, it was shown that dibenzyl 1,2-diacylglycerophosphites **12** combine smoothly with sulfur and are converted into the phosphorothioates **13** (X = S), which are debenzylated to the thiophosphatidic acids **14** (X = S) (Scheme 17).

Scheme 17



R = $C_{15}H_{31}$, $C_{17}H_{35}$; X = O, S.

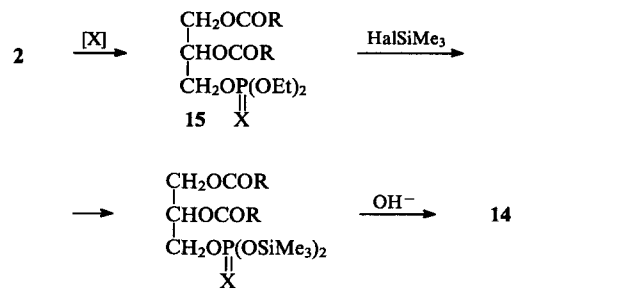
Another, apparently more promising version of the synthesis of phosphatidic acids **14** is based on the use of the glycerophosphates **2** with ethyl protecting groups in the phosphorus-containing functional group.[14-16,73] Diethyl 1,2-diacylglycerophosphites **2** are oxidised without complications to the phosphates **15** by a procedure similar to that used for the dibenzyl esters **12** already mentioned. Next the ethyl protecting groups are removed by silylation by a procedure similar to that used for the simplest phosphoric acid esters.[137-141]

§ Certain reactions of phosphoroamidites, in which only the valence state of the phosphorus atom changes, are also considered in this subsection. Subsection 3 is devoted to reactions involving the P–N bond.

¶ A method involving the selective development of trivalent phosphorus compounds in thin layer chromatography with the aid of a ninhydrin solution has been recommended for the monitoring of the oxidation reactions and also for the recognition of substances with similar R_f values.[136]

The scheme terminates with the hydrolysis of the trimethylsilyl derivatives of phosphatidic acids (Scheme 18).

Scheme 18



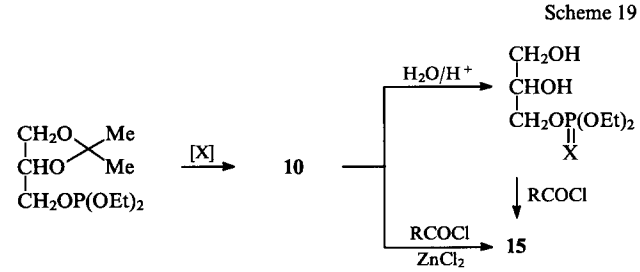
R = $C_{15}H_{31}$, $C_{17}H_{35}$; X = O, S.

The phosphatidic acids **14** have been obtained in a better yield (up to 56%) by using a solution of equimolar amounts of chlorotrimethylsilane and sodium iodide.

We may note that previously alkyl groups had already been considered for the temporary protection of acid hydroxyls in certain lipid syntheses. It was suggested that they be removed under severe conditions, for example by hydrolysis with lithium hydroxide, which involves considerable complications.[142,143] The new method—deethylation with the aid of halotrimethylsilanes—is carried out under mild conditions and ensures satisfactory yields of the lipids. It has therefore come to be widely used nowadays in many laboratories.[14-16,60,73,75,106,128,144-149]

The phosphatidic esters **15** can be obtained using diethyl (1,2-*O*-isopropylidene-3-glycero)phosphite by its oxidation or sulfurisation to phosphates (phosphorothioates) **10**, mild hydrolysis of the acetone protecting group, and acylation of the resulting phosphodiols.[14-16,73] Further progress on these lines was determined by the discovery of fundamentally new procedures for the acylation of the glycerophosphoacetals **10**, which markedly simplified the method of synthesis (Scheme 19).[14-16,73]

Scheme 19



The reaction presented in Scheme 19 (X = S) is an example of a convenient preparative method of synthesis of thiophosphatidic acids.

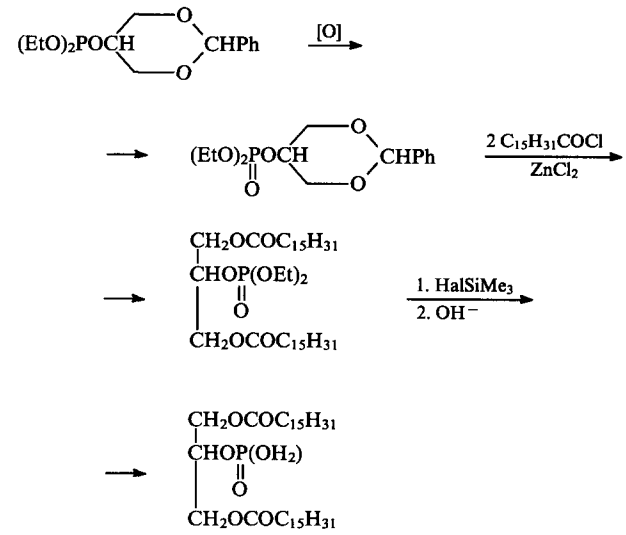
The version examined may be extended also to the synthesis of little investigated β-phosphatidic acids (Scheme 20).[14,15]

The series of studies on the acylation of 1,2- and 1,3-acetals with glycerols was completed by demonstrating the absence of acyl migrations in these decisive stages of the synthesis.[15]

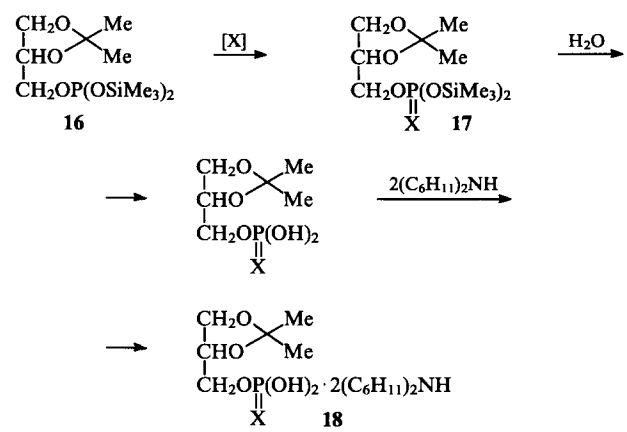
The new method for the acylation of glyceroacetals probably merits extensive use. It has already been applied successfully in the synthesis of a series of ester phospholipids.[14-16,26,45,56,57,73,75,87,91,92,106,109,128,150-155]

An even simpler version of the synthesis of phosphatidic acids, their thio-analogues, and also their previously unknown seleno-analogues is based on the use of the available bis(trimethylsilyl) 1,2-*O*-isopropylidene-3-glycerophosphite **16** (see below). This silyl phosphite was converted by oxidation (by the addition of oxygen, sulfur, and selenium) into the corresponding phosphates, phosphorothionates, and phosphoroselenonates **17**. Compounds **17** were isolated by high-vacuum distillation in yields up to 81%. Acid glycerophosphates and then their salts **18** were obtained by the hydrolysis of the neutral silyl esters **17** (Scheme 21).[106,156]

Scheme 20



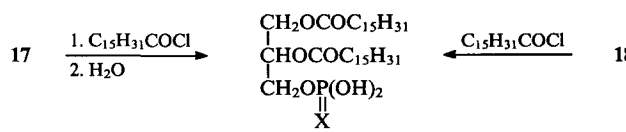
Scheme 21



X = O, S, Se.

The salts (or silyl phosphates) obtained are readily acylated and are converted ultimately into phosphatidic acids (Scheme 22).

Scheme 22



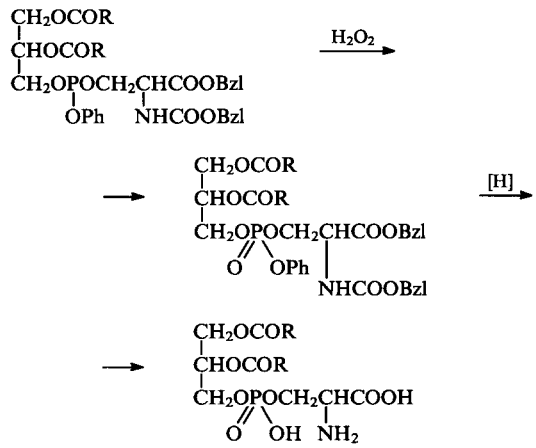
According to ^{31}P NMR data, thio- and seleno-phosphatidic acids exist in chloroform solutions in the thiono- and selenonophosphoryl forms. A similar conclusion concerning the structure of the seleno-acids was also reached from analysis of the direct $^{77}Se-^{31}P$ spin–spin coupling constants.

The method of synthesis of phosphatidic acids and their chalcogen analogues examined above was used to synthesise an optically active product—1,2-dipalmitoyl-*sn*-(3-glycero)-phosphate; in this case, the starting compound was 1,2-isopropylidene-*sn*-glycerol.[106]

The thionophosphatidic acids obtained in accordance with the schemes proposed immediately found applications in lipidology. Thus the use of a thionophosphatidic acid as a $^{31}P-\{^1H\}$ NMR probe (δ_P = 59 ppm) made it possible to investigate the polymorphic transformations of phosphatidic acids and of the phospholipid mixtures incorporating them.[157-161] Thionophosphatidic acids have also proved useful in the study of the permeability of bilayer lipid membranes in phase transitions and in the solution of other biophysical problems.[162-164] In connection with their spectroscopic characteristics, selenonophosphatidic acids (δ_P = 55 ppm) can also be used as ^{31}P NMR probes in the study of membranes. Additional information about the structure of the membranes can then be obtained by recording the satellites induced by the spin–spin splitting of the $^{31}P-^{77}Se$ signal. Selenonophosphatidic acids may be of interest as carriers which transfer selenium into biological membranes and also for the solution of other problems in physicochemical biology.[165,166]

The oxidative reactions of neutral glycerophosphites have been used in various laboratories also for the synthesis of diester phosphatides. Thus the oxidation of aminoalcohol and aminoacid glycerophosphites using hydrogen peroxide has been described (Scheme 23).[27,28]

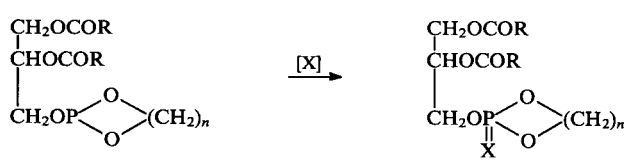
Scheme 23



As shown in the scheme presented above, the removal of the phenyl protecting group from the phosphate centre does not always yield satisfactory results. Therefore nowadays investigators usually select alternative solutions, including the formation of neutral glycerophosphites, the molecules of which contain β-cyanoethyl[60,69,167] or methyl[28,60,127] groups. After the oxidation of the phosphites to the corresponding neutral phosphates, these groups are readily and selectively removed by methods which have been thoroughly developed in the chemistry of nucleic acids.

The use of cyclic phosphites has proved particularly promising in oxidation reactions. They react smoothly and effectively with nitrogen oxide and dioxide, oxygen, ozone, iodosobenzene, sulfur, and selenium, forming cyclic phosphates, phosphorothionates, and phosphoroselenonates (Scheme 24).[41-46,47,49,51,88,150,168]

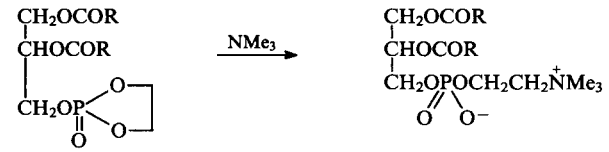
Scheme 24



n = 2, 3, 4; X = O, S, Se.

Owing to these processes, the attention of specialists in the chemistry of phospholipids has been fixed on cyclic phosphoglycerols. This trend proved to be extremely fruitful. It was established that the 1,3,2-dioxacyclanes synthesised are extremely useful alkyl donors, capable of novel reactions leading to conversion into most important classes of phospholipids. We shall illustrate the foregoing by a very simple synthesis of phosphatidylcholines (Scheme 25).[41,43,44,46,47,49,50,88,89,169,170]

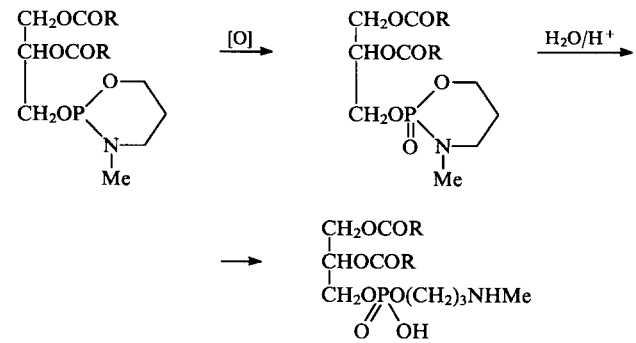
Scheme 25



Acetals can also be used in such reactions. They are converted into the required ester systems in the most convenient stages of the synthesis.[38-40,45,49,88,91,150,152-154,171,172] It is significant that alkylation has been used for the synthesis of nonglycerol phospholipids, for example diol,[59-61] etriol,[56,109] etc.[17,18,57,58,62,108,167] phospholipids.

The oxidation reactions of cyclic phosphoramidates[52,54,64,65,93,95,125,173-178] and cyclic phosphorodiamidates[54,63] have now been investigated. The phosphaza-derivatives of pentavalent phosphorus are also very promising for subsequent reactions. For example, they can be hydrolysed with formation of phosphatidylaminoalkanols, which are otherwise difficult to obtain and which are of great interest for lipidology (Scheme 26).[54,63]

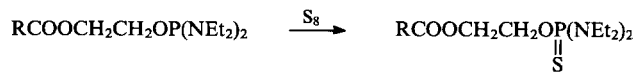
Scheme 26



The first studies on the use of cyclic phosphates and cyclic phosphoramidates in the synthesis of lipid systems were soon continued in various scientific centres and have been described in numerous publications which we shall not discuss in the present review.

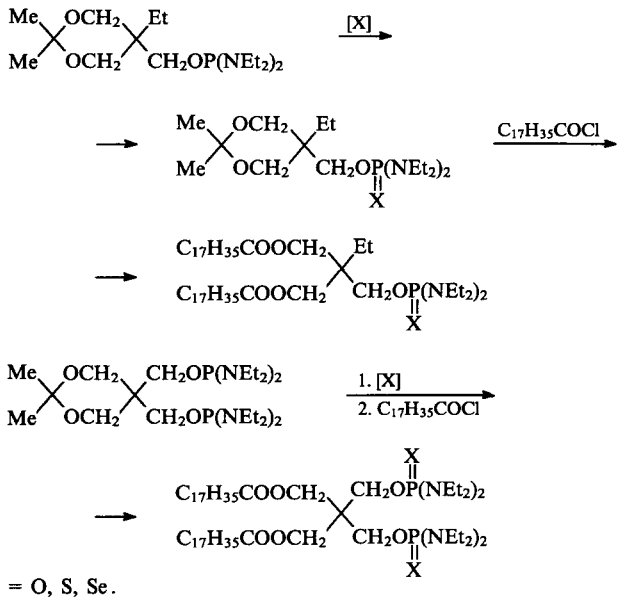
Oxidation reactions similar to those described above have been used also for the conversion of phosphites belonging to other classes of phosphorylated oligools. The phosphorodiamidites derived from monoacylglycols were sulfurised in this way (Scheme 27).[78,79,83,110]

Scheme 27



The possibilities in the use of etriol and pentaerylthritol phosphorodiamidites have been investigated in greater depth. Here is was possible to combine different new synthetic methods, for example those presented in Scheme 28.[56, 57, 109]

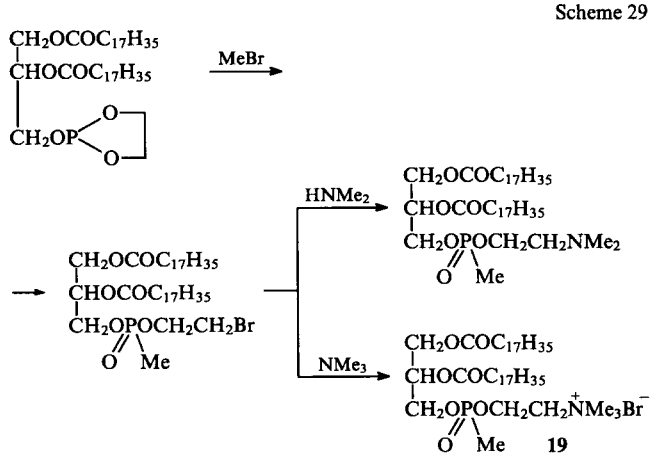
Scheme 28



X = O, S, Se.

A specific aspect of the use of cyclic glycerophosphatee is their involvement in the Arbuzov reaction. In this case, the main pathway in the process is the opening of the ring and the formation of the glycerophosphonate system. Attention should be drawn to the fact that phospholan glycerides react much more readily than phosphorinane glycerides, which can apparently be accounted for by the greater tendency of the five-membered ring to be opened in the second stage of the reaction. It has been suggested that the halo-derivatives formed initially be used for the preparation of the corresponding phosphonate analogues of phosphatidyldimethylethanolamine and phosphatidylcholine (Scheme 29).[39, 88]

Scheme 29



It is significant that, when the Arbuzov reaction is carried out, a second chiral centre—the phosphorus atom—is generated in the molecules of racemic glycerophosphonates. This results in the appearance of a mixture of two pairs of diastereoisomers, which are manifested separately in the $^{31}P-\{^{1}H\}$ NMR spectra.

It is noteworthy that a group of unique lipids **19**, having an electropositive molecular skeleton, have been obtained via the Arbuzov alkylation reaction. On the other hand, the natural products and synthetic compounds of this type obtained previously have an electronegative or neutral molecular skeleton. The lipids described are therefore of interest as carriers of biologically active compounds and also for the creation of selectively conducting membranes. For example, anion-selective channels were first detected in planar lipid bilayer membranes formed from compound **19**.[179]

For purposes of phospholipid chemistry, a study has been made of the interaction of the neutral phosphite of an important oligool (etriol) with carboxylic acid halides. Processes of this kind were investigated previously by Kabachnik, but he used trialkyl phosphites.[180] He showed that the phosphorus atom is subjected to electrophilic attack in the acylation reaction and that α-ketophosphonates are formed. It is very interesting that etriol phosphite behaves in an unusual way in the acylation reaction: electrophilic attack is directed not to the phosphorus atom but to an oxygen atom, which results in the formation of an ester with a phosphor(III)inane substituent (Scheme 30).[181]

Scheme 30

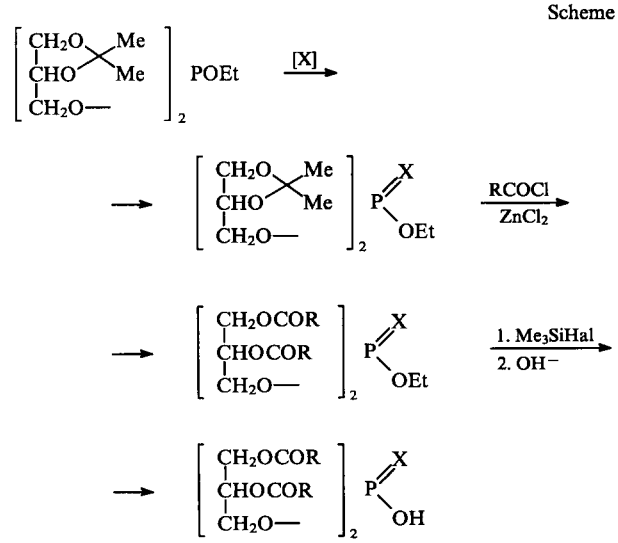


R = Me, $C_{17}H_{35}$.

Further reactions made it possible to obtain from this product unusual phospholipid compounds the molecules of which include a phosphorus-containing ring with a pentavalent phosphorus atom.

Neutral diglycerophosphites have also begun to be used for the synthesis of phospholipids. Thus a convenient method of synthesis of bisphosphatidic and previously unknown thiobisphosphatidic acids from ethyl diglycerophosphite has been developed with the aid of the fundamentally new synthetic solutions examined above [acylation of glycerol derivatives via the acetal bonds and the removal of the alkyl protecting groups by silylation and subsequent hydrolysis (Scheme 31)].[75]

Scheme 31



R = $C_{13}H_{27}$; $C_{17}H_{35}$; X = O, S; Hal = Br, Cl.

The influence of temperature and of the type of solvent on the effectiveness of the acylation of phosphobisglyceroketals and other stages of the synthesis was investigated in detail in the above study.

In the present review, we have already considered the acylation of phosphoglycerols the molecules of which contain only one glyceroketal fragment. The data illustrated by the last equation have significantly expanded the limits of the application of the new method of synthesis of ester derivatives of glycerol.

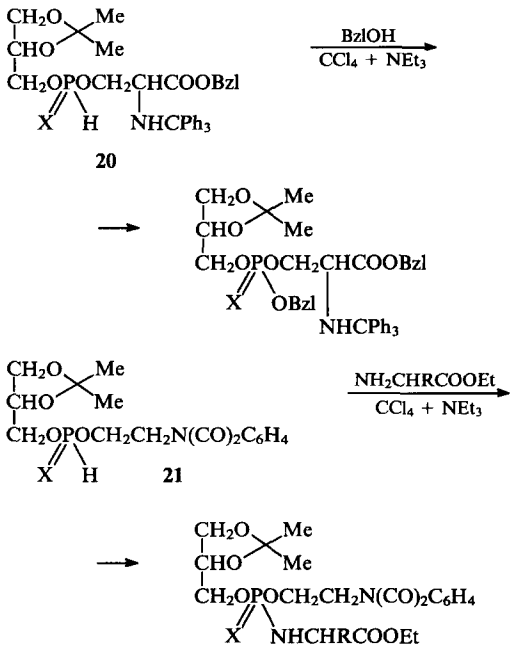
2. Reactions of acid glycerophosphites

The use of acid glycerophosphites has led to interesting prospects for phospholipid synthesis. Phosphorus as well as phosphorothious mono- and di-esters were usually assigned to this group of compounds.

Among these compounds, initially most attention was devoted to the diesters (secondary phosphites) which can be usefully subdivided into two groups—mono- and di-glyceroesters. We shall deal with these substances in the same sequence in considering their reactions.

Various types of secondary monoglycerophosphites are known at present: their molecules contain the residues of diacylglycerols, alkylglycerols, and the corresponding acetals. The structural characteristics of the systems listed above do not affect significantly their reactions, i.e. they all have the general properties of hydrophosphoryl compounds. Thus acetal systems enter widely into the Todd–Atherton oxidative phosphorylation.[124] As an example, one may quote the syntheses of lipids of different complexity: tri- and di-ester phosphoramidates based on isopropylideneglycerophosphites **20** and **21** (Scheme 32).[94,182–184]

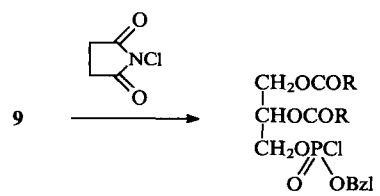
Scheme 32



R = H, Me; X = O, S.

When necessary, the Todd–Atherton reaction can be arrested in the intermediate stage involving the formation of phosphorochloridates.[104] It has been suggested that the phosphorochloridates be obtained also by chlorinating phosphites with *N*-chlorosuccinimide (Scheme 33).[114–117]

Scheme 33

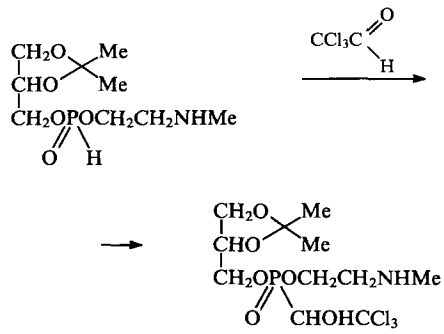


The phosphorochloridates obtained are usually employed without isolation to phosphorylate various nucleophiles, which affords, after debenzylation, phosphatidic acids, phosphatidylethanolamines, phosphatidylserines, phosphatide analogues of aminoacids phospholipids, and other important types of phospholipids.[114–117]

The oxidation reactions presented above began to be investigated also in relation to monoglycerophosphorothioites, which opens a simple path to the synthesis of neutral lipid phosphorothioates and phosphoramidothioates.[184,185]

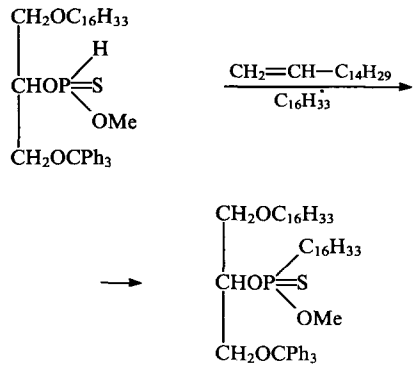
It has been suggested that α-hydroxyphosphonates be obtained from acid glycerophosphites by means of the Abramov reaction (Scheme 34).[174,186]

Scheme 34



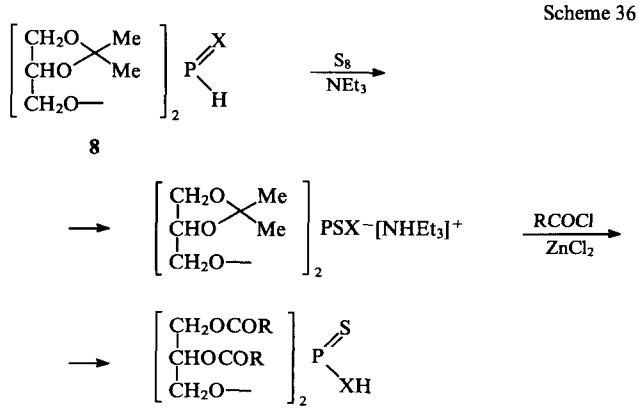
The phosphorus–carbon bond in the lipid systems can be formed also via the free-radical thiohydrophosphorylation of olefins for example (Scheme 35).[33]

Scheme 35



Secondary diglycerophosphites and their thio-analogues, represented by the 1,2-*O*-isopropylidene- and 1,3-*O*-benzylidene-derivatives, have been investigated in the Todd–Atherton oxidative phosphorylation reactions in greater detail than the monoglycerophosphites. A wide range of neutral ester diglycerophosphatides and thiophosphatides[104,111] and α- and β-bisphosphatidic acids[105] have been obtained from them. The thiophosphatides can also be obtained by direct sulfurisation (Scheme 36).[75]

Scheme 36

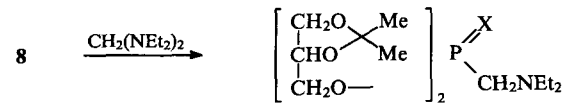


R = $C_{13}H_{27}$, $C_{17}H_{35}$; X = O, S.

Like the thio-analogues of other phospholipids, thiobisphosphatidic acids are promising substances in biochemical and biophysical research, since their resonance region in ^{31}P NMR spectroscopy is significantly different from that of natural phospholipids (δ_P = 65 and 97 ppm respectively).

The Kabachnik–Fields aminomethylation of diglycerophosphites, which makes it possible to obtain simply phospholipids belonging to the class of α-aminophosphonates and α-aminophosphonothioates, apparently merit much attention (Scheme 37).[48,104,185]

Scheme 37

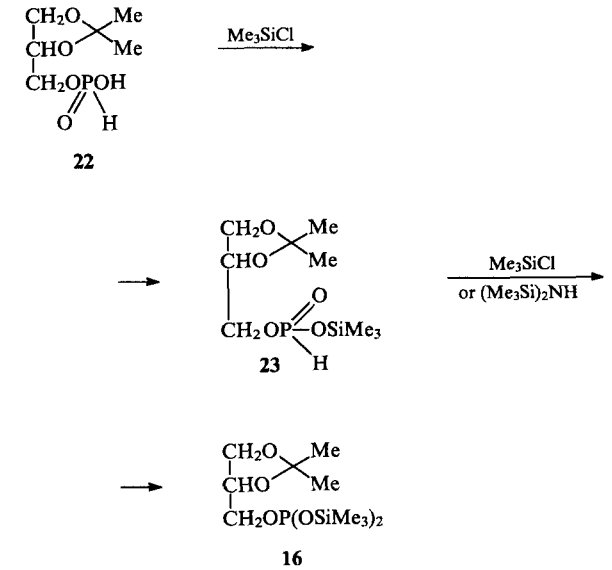


X = O, S.

The compounds obtained, which are effective chelating agents, can regulate the transport of certain metals in biological membranes. Furthermore, they can fix metals which are initiators of free-radical reactions in lipid compositions and thereby stimulate, when necessary, their oxidation and certain other reactions.

Studies on primary glycerophosphites from the standpoint of the interests of glycerophosphite chemistry are only just beginning. Nevertheless, here too important results have already been obtained and there are good prospects for the wide scale preparative application of these compounds. Thus it has been shown that 1,2-isopropylideneglycerophosphite **22** is readily converted into trimethylsilyl glycerophosphite **23** on treatment with chlorotrimethylsilane, while further silylation affords a satisfactory yield of bis(trimethylsilyl) glycerophosphites **16** (Scheme 38).[106,156]

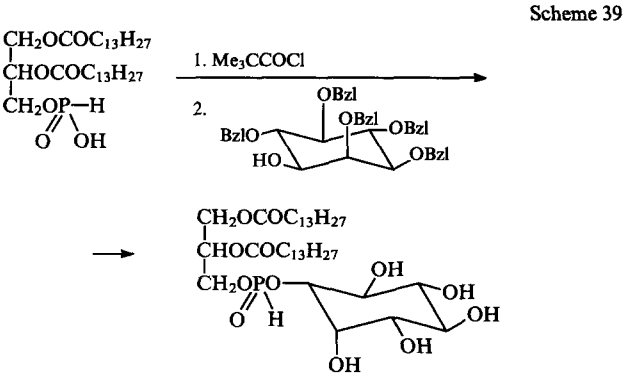
Scheme 38



As already stated in the discussion above, derivatives of tricoordinate phosphorus **16** are converted by means of simple reactions into phosphatidic acids and their thio- and seleno-analogues.

It has been suggested that primary glycerophosphites be made to react with pivaloyl chloride or other similar electrophiles to form highly reactive phosphorylating agents. The latter phosphorylate derivatives of aminoalcohols[23] and other biogenic nucleophiles,[23–25] which makes it possible to obtain rapidly valuable phosphite lipids (Scheme 39).

Scheme 39

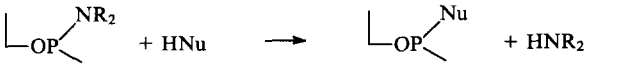


This and similar phosphites were oxidised or were introduced into other oxidation reactions, which made it possible to obtain effectively a wide variety of phospholipids and their chalcogen analogues. We may note that similar syntheses also of other types of complex phospholipids have been achieved, for example the synthesis of sphingophospholipids — dihydrosphingomyelin and its *N,N*-dimethyl analogues from the primary phosphite of 3-benzoylceramide.[68,81]

3. Reactions of phosphoramidites

Recent years have been marked by the active employment of the phosphoramidites of glycerol (and other polyols) in phospholipid syntheses. Extensive data have accumulated in this field, their amount increasing steadily as a result of the appearance of new ones. We have already considered above certain reactions of glycerophosphoramidites, for example oxidation, the addition of sulfur, and alkylation, i.e. processes involving only the trivalent phosphorus atom and sometimes the P–O fragment. In the present subsection, attention will be concentrated on the reactions involving the dissociation of one or two P–N bonds, i.e. on the phosphorylation of nucleophiles (Scheme 40).

Scheme 40



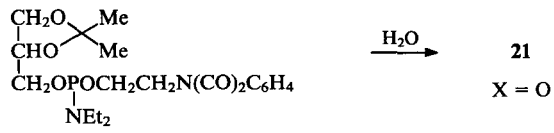
By virtue of the effectiveness and mildness of this reaction and its successful combination with the necessary 'routine' reactions (oxidation, removal of protecting groups, acylation, etc.), glycerophosphoramidites are readily converted into many complex substances, including those which are difficult to obtain by other popular methods of synthesis. We may note that the initial glycerophosphoramidites are readily available, are stable during storage, and are convenient to use. Thus they may prove to be valuable key products in the synthesis of phospholipids of different types.

The phospholipid syntheses from glycerophosphoramidites, described in the literature, have two aspects. The first of these concerns the phosphorylation of nucleophiles as a result of the selective removal of one amido-group or the successive removal of two amido-groups from the phosphorus atom. The second concerns the phosphorylation of bifunctional nucleophiles — glycols and aminoalcohols — with formation of cyclic phospha-compounds.

Natural diglycerophosphoramidites with different chemical structures can be selectively hydrolysed by cleaving only the P–N bond with the formation of the corresponding phosphites.[104,111,156]

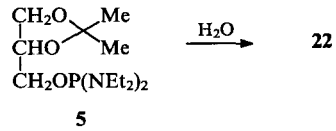
The hydrolysis of asymmetric phosphorus acid diesteramides is more complex (Scheme 41).[182–184]

Scheme 41



The diamides of glycerophosphorus acids are hydrolysed similarly. In this case, two phosphoramide bonds are cleaved and monosubstituted phosphites are formed, for example compound **11** (Scheme 42).[106, 156]

Scheme 42



The hydrolysis of phosphoramidites is accelerated by inorganic and organic acids and in this version is carried out without heating. This reaction is in fact the best method of synthesis of such acid phosphites.

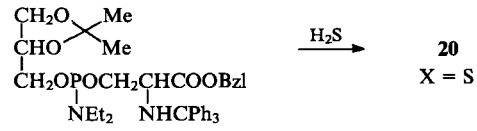
The sulfhydrolysis of glycerophosphoramides, which so far belongs to the class of little investigated reactions, also has considerable preparative prospects (Scheme 43).

Scheme 43



The cleavage of the P–N bond by treatment with hydrogen sulfide was discovered in the simplest of examples.[187, 188] Subsequently this reaction was investigated in more complex cases in our laboratory, where it was possible to introduce it into practical phospholipid syntheses.[40, 104, 184, 190] The possibilities of experiments with systems the structure of which includes acetal, ester, and trityl protecting groups were thus demonstrated (Scheme 44).[184]

Scheme 44



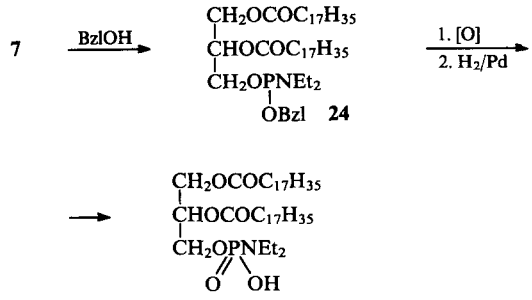
The thiohydrophosphoryl fragment in this and similar compounds exhibits a high chemical reactivity, for example in oxidative phosphorylation and in combining with sulfur.[40, 75, 104, 184, 185, 190]

Subsequently it was possible to achieve the sulfhydrolysis of phosphorous acid diamides accompanied by the cleavage of two P–N bonds, leading to the formation of phosphorodithioites which are difficult to obtain in other ways.[189] These compounds can be used to synthesise completely new types of phospholipids.

A special series of studies was devoted to the benzylolysis of glyercophosphoramidites and glycerophosphorodiamidites. These studies were mainly combined with those designed to obtain phosphatidic and other lipid acids. Thus it has been shown that the tetraethyldiamide derivative of 1,2-distearoylglycerol **7** is readily converted on treatment with two equivalents of benzyl alcohol into the neutral phosphite **12**, which is readily converted into the phosphatidic acid (see above).[74]

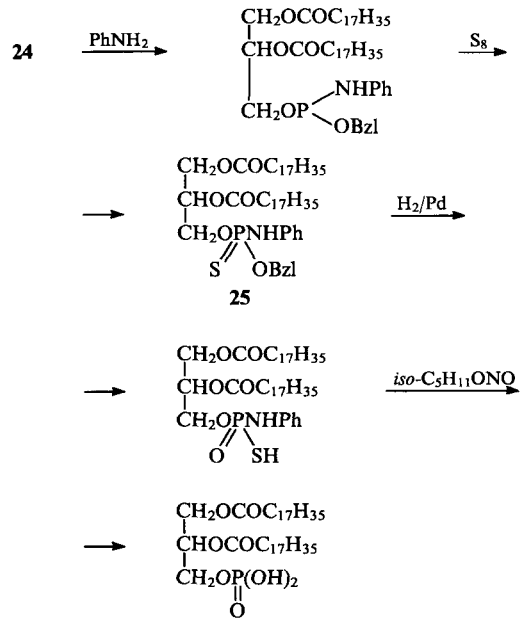
If the benzylolysis of the phosphorodiamidite **7** is carried out using an equivalent amount of alcohol, then selective monophosphorylation takes place. After oxidation and the removal of the protecting group, the product **24** was converted into an acid phosphoramidate—a representative of a rare class of phospholipids (Scheme 45).[74]

Scheme 45



Readily available and effective reagents—nitrogen(II) oxides and iodosobenzene—were used as oxidants in the schemes described above. Unfortunately they are not always convenient to use. A different way of converting glycerophosphoramidites into phosphatidic acids was therefore proposed. The idea of the synthesis consists in the fact that the benzyl glycerophosphorimidate, for example compound **24**, is transamidated with aniline† to form an anilide, which rapidly combines with sulfur, producing the neutral phosphoranilidothionate **25**. By means of a combined catalytic debenzylation and oxidative deamination, this compound is converted into a phosphatidic acid (Scheme 46).[99]

Scheme 46



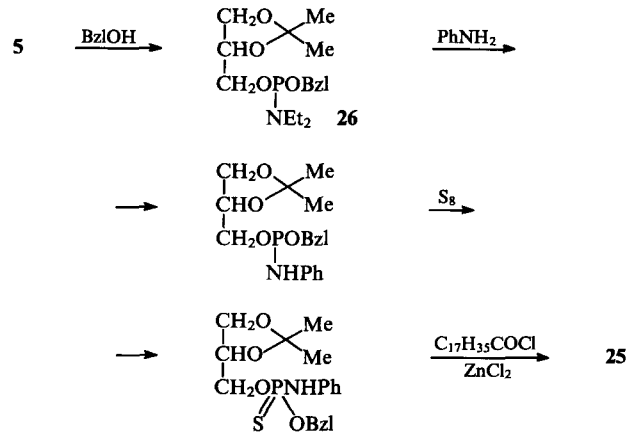
The somewhat longer synthesis in this case compared with the previous one is fully compensated by experimental convenient. It is also significant that the latter scheme affords good results when isopropylideneglycerophosphoramidites **5** are used as the starting materials (Scheme 47) (see over).[99]

Yet another factor is striking in the present instance: acylation of the acetals of the phosphorothioic derivative of glycerol is more effective than acylation of the corresponding phosphoryl product.[14, 16, 73] Thus yet another argument may be put forward in support of the second scheme.

Extremely varied and chemically significant syntheses of phospholipids consist in the stepwise interaction of glycerophosphorodiamidites with two different alcohols. The following strategy is often used in this case: instead of one of the amido-groups, an aminoalcohol, hydroxyaminoacid, substituted glycerol, carboyhydrate, or inositol residue, or one comprising

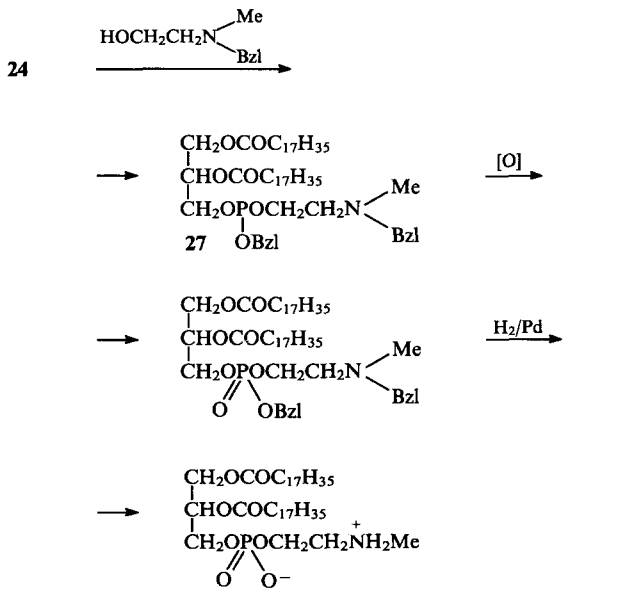
† The transamidation of the simplest phosphorous acid dialkylamides with aniline has been described.[191]

Scheme 47



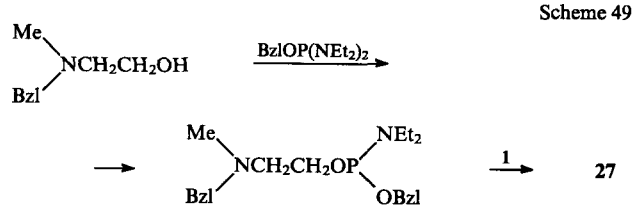
other important components of the complex natural lipids or related synthetic substances is introduced initially. Next, instead of the second amido-group, a new group protecting the hydroxyl is introduced. In many instances the opposite sequence of operations in the phosphorylation process is also employed. In some experiments primary phosphorylation of the alcohol component with subsequent condensation of the resulting phosphoromonoamidite and the glycerol derivative has been used too. All the syntheses listed above are terminated by oxidation processes, the removal of protecting groups, and, when necessary, a molecular reorganisation of the type involving the replacement of acetal fragments by ester fragments. We shall consider the most important data concerning these reactions. The use of glycerophosphoroamidites for the synthesis of phosphatidylaminoalcohols, for example phosphatidyl-*N*-methylethanolamine, has been described in detail in the literature,[46, 104, 175, 176, 182] For this purpose, the phosphatide **7** (a key compound) is converted by reaction with benzyl alcohol into the monoamide **24**, which is treated with benzylmethylethanolamine. After this the intermediate neutral phosphite **27** is oxidised and debenzylated twice (Scheme 48).[46]

Scheme 48



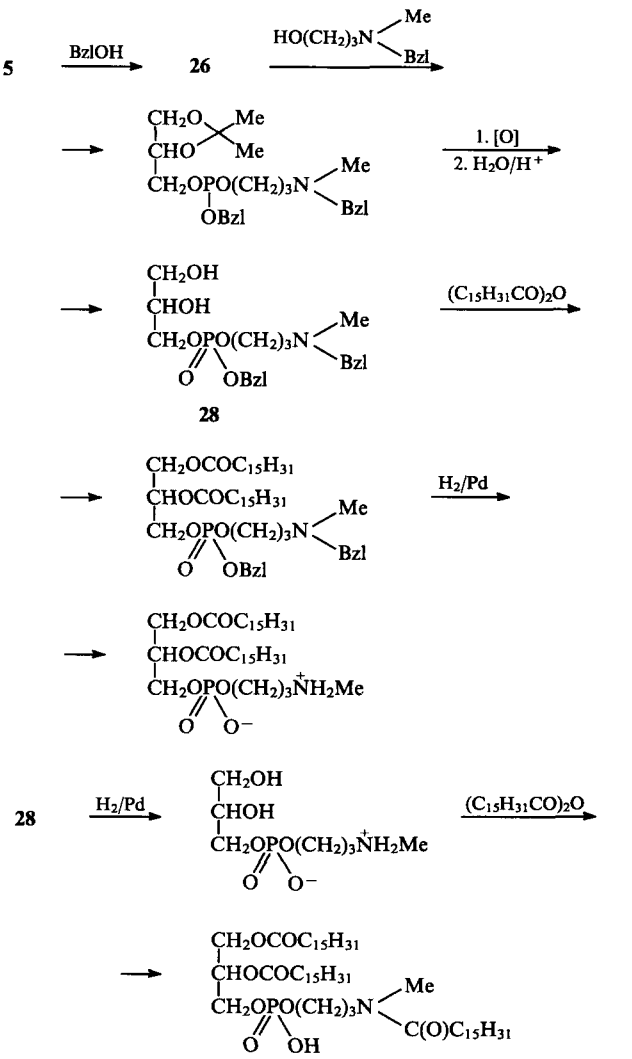
We may note that an alternative scheme, involving the initial phosphorylation of benzylmethylethanolamine with phosphorous acid diamine has certain preparative advantages (Scheme 49).[46]

Scheme 49



A fundamentally different method of synthesis of phosphatidylaminoalcohols presupposes the use of 1,2-*O*-isopropylideneglycerophosphorodiamidites **5** as the starting material. Experiments involving the hydrolysis of 1,2-isopropylideneglycerophosphate to the phosphate **28** unsubstituted in the glycerol residue and its subsequent acylation (Scheme 50) have been carried out for this purpose.[175, 176]

Scheme 50



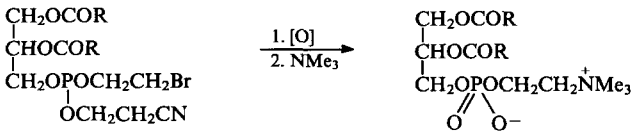
Unfortunately, nobody has investigated previously the possibility of using in this instance the acylation of a phosphorus-containing acetal with formation of ester systems, bypassing the diol stage.

In relation to the synthesis of the aminoalcohol lipids examined above, a number of workers have improved the classical scheme by a useful new feature—methyl phosphite derivatives were used as the reactants instead of benzyl phosphite derivatives. The former are readily oxidised to methyl phosphates, which exhibit an excellent methylating activity and readily lose the methyl group on treatment with, for example, ammonia in toluene or another nucleophile.[30–32]

Aminoalcohol derivatives of thiophosphatidic acids, including reactions where they were obtained as individual stereoisomers with chiral phosphorus atoms, have been obtained using this version of the synthesis.[32] These stereoindividual thiophospholipids are nowadays actively employed in biochemical research to elucidate the mechanism of the action of phospholipases.[32, 192–194]

There exists yet another version of the method described above. It differs by the use of neutral phosphites with a protecting β-cyanoethyl group. This protecting group is removed under milder conditions than the methyl group, which is the reason for the interest in the proposed modification. Phosphatidylcholine was obtained by this procedure. An additional advantage of the above scheme is the simultaneous occurrence of two reactions with trimethylamine: the removal of the cyanoethyl group and the formation of the ammonium group (Scheme 51).[60, 69, 80, 167]

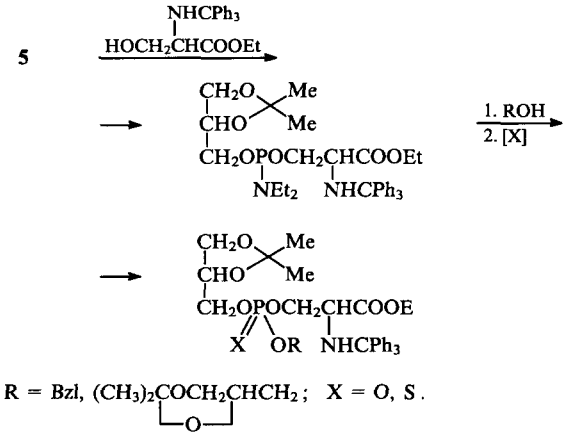
Scheme 51



The above schemes have also been used to synthesise sphingolipids.[66–68, 81, 82]

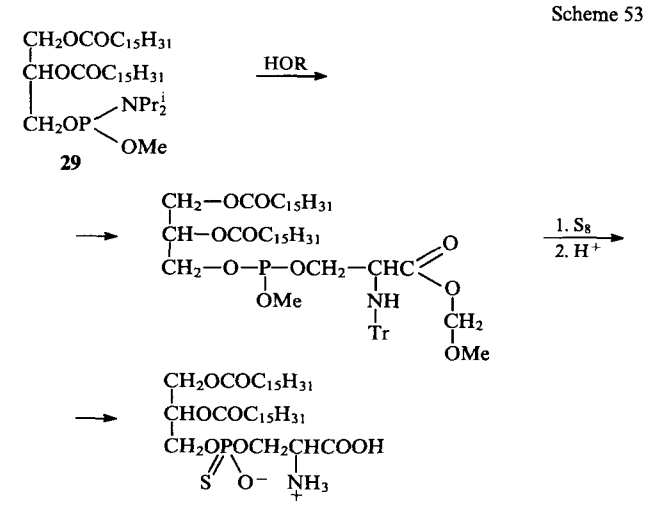
The phosphoroamidite method has been used to obtain models of lipids containing aminoacid, for example serine, residues (Scheme 52).[100, 183, 184]

Scheme 52



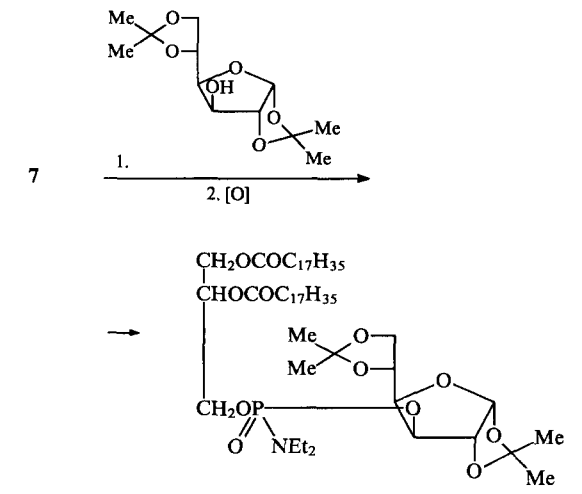
Similar reactions have been carried out also using *N,N*-diisopropyl-1,2-dipalmitoylglycerophosphoramidite **29** (Scheme 53).[35]

Scheme 53



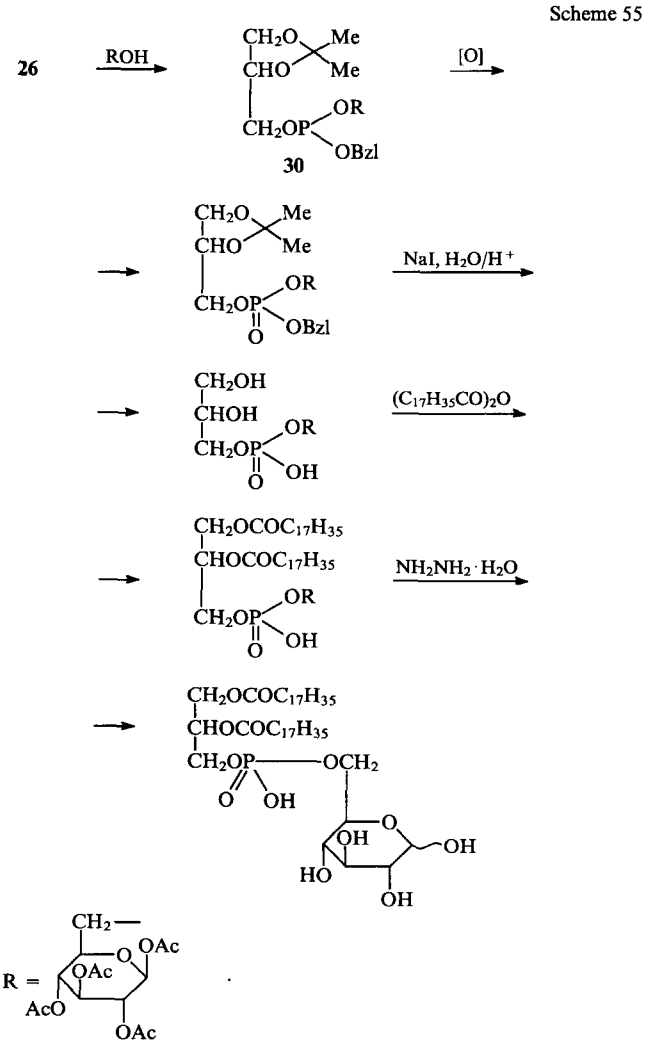
The use of glycerophosphoramidiates for the synthesis of carbohydrate-containing phospholipids, which have been recently attracting increasing attention, is especially valuable.[90, 195, 196] The reaction indicated in Scheme 54 indicates a simple path to these systems.[90, 96, 197, 198]

Scheme 54



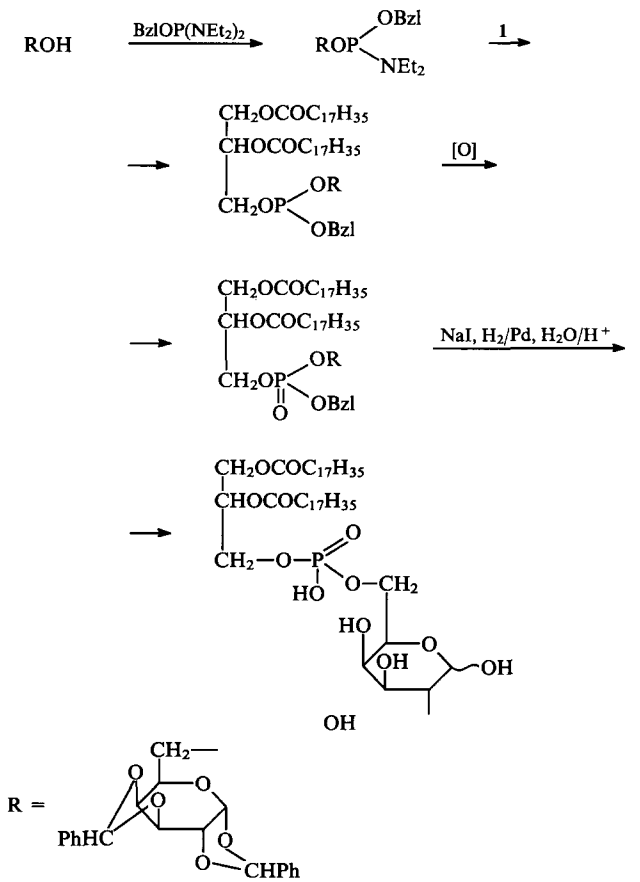
Another version of the synthesis of the complex lipid phosphatidyl-6-glucose is based on the employment of 1,2-*O*-isopropylideneglycerophosphoramidite **26** and 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose as the starting compounds (Scheme 55).[86]

Scheme 55



The asymmetric benzyl glyceroglycophosphite **30**, used in the above study, can be obtained also by the initial phosphorylation of the sugar with benzyl *N,N,N',N'*-tetraethylphosphorodiamidite and subsequent incorporation of the 1,2-*O*-isopropylidene-glycerol residue in the phosphorus unit. When a sugar with acetate protecting groups is used, this phos-phorylation sequence is less preferable, since it involves prolonged heating of the reaction mixture and this leads to appreciable charring and hence to a decrease in the yield of the asymmetric phosphite. On the other hand, the above method can be usefully employed in the synthesis of glycophospholipids based on stable benzylidene derivatives of sugars, for example, 1,2,3,4-di-*O*-benzylidene-α-D-galactopyranose, because in this case the labile diglyceride fragment is phosphorylated last and is less subject to thermal and chemical influences. A similar solution is used in the total synthesis of phosphatidyl-6-galactose (Scheme 56).[97]

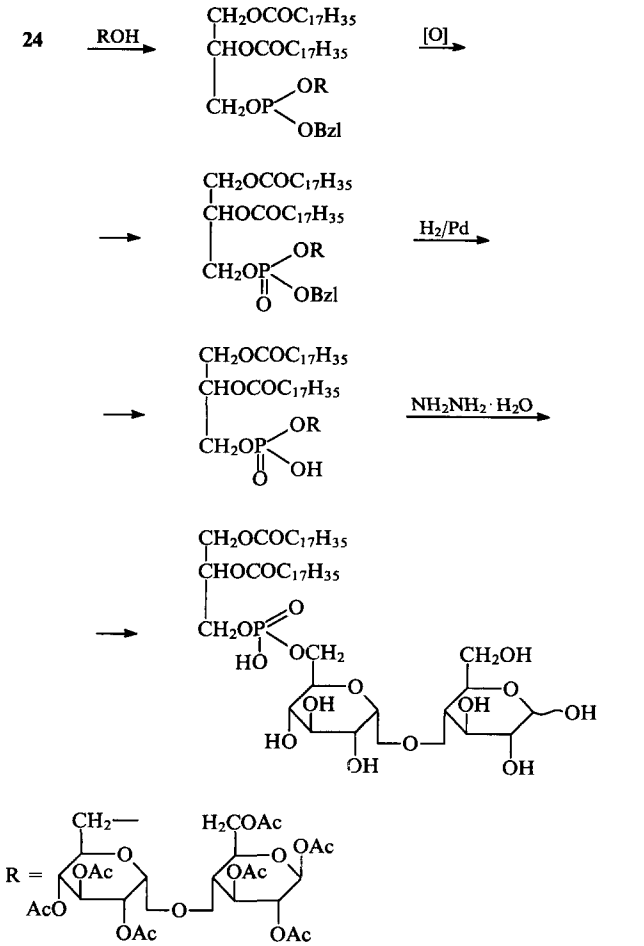
Scheme 56



The use of the synthetic ideas described above has led to the availability also of the very important disaccharide derivatives of glycerophospholipids.[199,200] We shall demonstrate this in relation to the synthesis of 6'-(1,2-distearoyl-3-glycerophospho)-maltose (Scheme 57).[198]

The methods of synthesis of glycophospholipids examined in the present subsection are distinguished by their simplicity. The main advantage of the 'phosphoramidite' method of synthesis of the phosphorus-containing unit compared with the commonest classical 'silver salt' method is the small number of stages. Thus, in order to phosphorylate a diglyceride or a partly protected carbohydrate with a free hydroxy-group by the 'silver salt' method, it is necessary to convert them in a preliminary step into halodeoxy-compounds. The yield of deoxy-derivatives usually does not exceed 50%. Furthermore, the alkyl dibenzyl phosphates used as phosphorylating agents must be converted by complex procedures into silver salts of monobenzyl phosphates.[1,195,196] The phosphoramidite method makes it

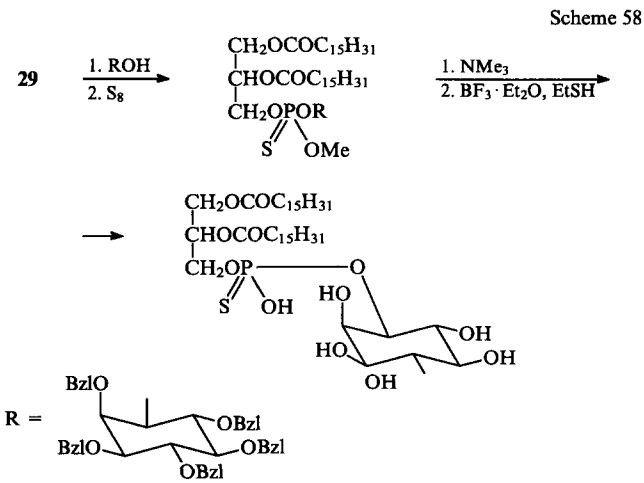
Scheme 57



possible to achieve directly the phosphorylation of diglycerides and of partly protected carbohydrates by phosphoramidites under mild conditions and with high yields in the decisive stages.

The phosphoramidite method has been recently used to synthesise inositylthiophosphatides. As in the synthesis of nitrogen- and carbohydrate-containing glycerophospholipids, in this case the synthesis is based both on the glycerophosphor-amidites **29** and myoinositol derivatives (Scheme 58).[34,36,37]

Scheme 58



The signals due to two diastereoisomers were detected in this instance in the $^{31}P-\{^{1}H\}$ NMR spectra for the optically active glycerol when a neutral phosphorothioate was used. These substances were resolved chromatographically. Their structure was demonstrated by enzyme analysis.

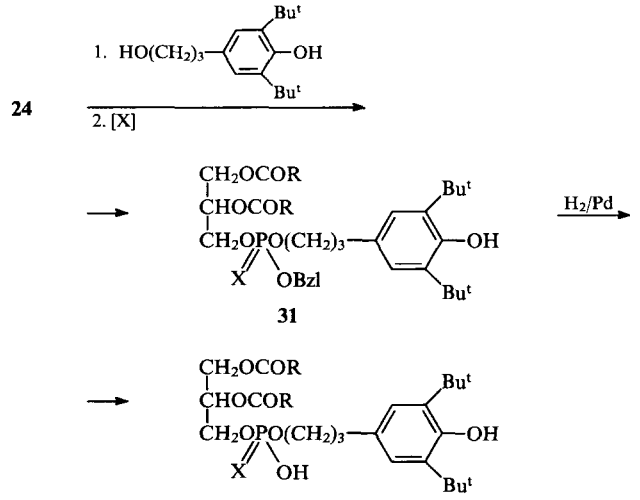
Neutral phosphoramidites with benzyl protecting groups, similar to those described above, have been used as the starting materials for the synthesis of the optically active natural phosphatidylinositol diphosphate and a fragment of a microbacterial phospholipid — phosphatidylmannomyoinositol.[101,102]

The phosphoramidite method has been used also to synthesise other related complex lipids, for example ceramide phosphoinositol and its thio-analogue,[68,81,82] and in addition diolphospholipids containing cholesterol and certain other steroids.[78,84,110]

The following aspect of the use of phosphoramidites has been applied to the synthesis of lipid antioxidants. Such compounds can be obtained by the chemical combination of sterically hindered phenols and phosphatidic acids. We may note that previously a number of investigators demonstrated in studies on the peroxide oxidation of lipids that natural inhibitors of radical reactions play a significant role in the regulation of this process. These natural bioantioxidants initially contain the residues of sterically hindered phenols as protecting groups.[201-206] It was of interest to investigate the regulation of the peroxide oxidation of lipids in the presence of synthetic anitoxidants which are also derivatives of sterically hindered phenols. Such studies have been carried out in different laboratories and, in the case where ionol was used, led to positive results.[201-204,206-210] Unfortunately ionol and its analogues are not chemically related to lipids, which prevents the ready transport of the antioxidants into the membrane.[206,211] Taking into account the foregoing, the synthesis was undertaken of membrane-addressed antioxidants containing phosphatide groups and residues of sterically hindered phenols: 2,6-di-(*tert*-butyl)-4-(γ-hydroxypropyl)phenol, 2,6-di(*tert*-butyl)-hydroquinone, and ionol.

In the search for a convenient preparative method of synthesis of phosphatidyl(hydroxalkyl)phenols, various synthetic procedures were investigated. One of the schemes employed included the phosphorylation of γ-hydroxypropylphenol by the phosphoramidites **24** (Scheme 59).[87]

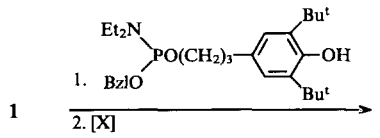
Scheme 59



R = $C_{15}H_{31}$, $C_{17}H_{35}$; X = O, S.

Of the two hydroxyls of the substituted phenols, the alcoholic hydroxyl reacts with the phosphoramidite.[212] In the second version, the key compounds **31** were obtained by phosphorylating 1,2-diacylglycerols **1** with benzyl γ-(di-*tert*-butylhydroxyphenyl)propyl *N,N*-diethylphosphoramidite (Scheme 60).

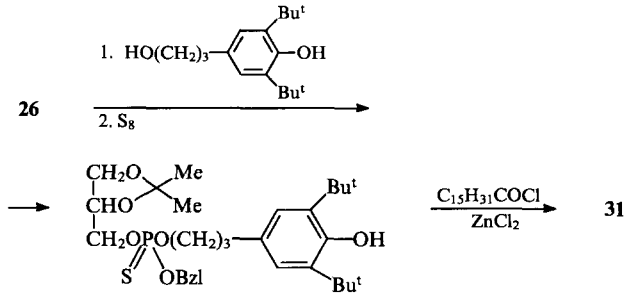
Scheme 60



R = $C_{15}H_{31}$, $C_{17}H_{35}$; X = O, S.

The lipid antioxidant has also been synthesised using the readily available 1,2-*O*-isopropylideneglycerophosphoramidite **26** instead of the phosphoramidite **24** as the starting compound (Scheme 61).

Scheme 61



The most important feature of the synthesis is the specificity of the acylation of the phenol-substituted phosphoacetal. It was shown that, on acylation with two moles of palmitoyl chloride, the phenolic hydroxyls are unaffected.

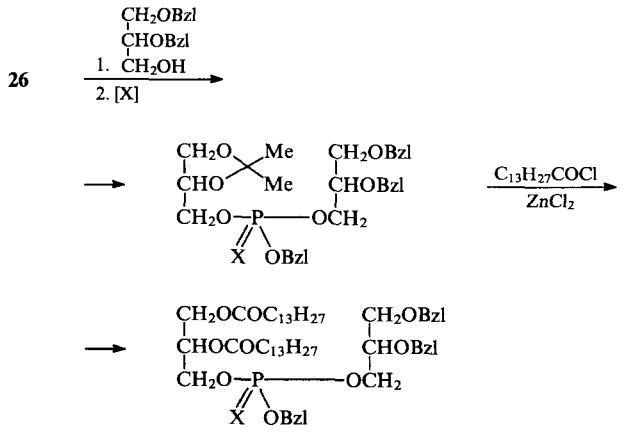
The synthesis of lipid antioxidants containing the 2,6-di-(*tert*-butyl)hydroquinone residue has also been investigated. The schemes presented above were used for this purpose.[26]

It was found that lipid antioxidants containing sterically hindered phenol residues have effective antioxidant properties.[103] There is therefore a prospect of formulating with the aid of these phospholipids (antioxidants) new problems in the study of the peroxide oxidation of membranes.

The phosphorylation of tocopherol, which is a carrier of antiradical properties, by *N,N,N',N'*-tetraalkylphosphorodiamidites is of definite interest for the synthesis of a new type of antioxidants.[78,83,110]

A very interesting fact was established in the search for lipid anitoxidants. It was found that certain glycerides containing phosphorothioic acid residues are also inhibitors of free-radical reactions.[103] Apparently, after a deeper investigation of such phosphorothioates, the procedures available in lipidology will be expanded by the inclusion of a new class of readily available antioxidants which are convenient to use.

Scheme 62



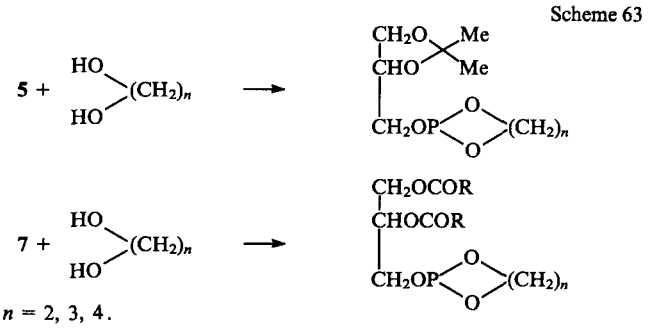
X = O, S.

We examined above the employment of monoglycerophosphoramidites for the synthesis of glycerophosphatides, the molecules of which contain one glycerol residue. We shall now proceed to the discussion of the syntheses of phospholipids containing two glycerol residues.[30,75,105] Thus phosphoramidites have been used to synthesis phosphatidylglycerols (Scheme 62) (see previous page).[75]

The neutral benzyl esters of phosphatide and thionophosphatide can be converted into phosphatidylglycerol (thiophosphatidylglycerol) by total debenzylation taking into account the results of other investigations.[1,3,8,10]

Another aspect of the synthetic application of glycerophosphoramidites concerns studies on the cyclophosphorylation of bifunctional nucleophiles, in the first place glycols (Scheme 63).

Scheme 63



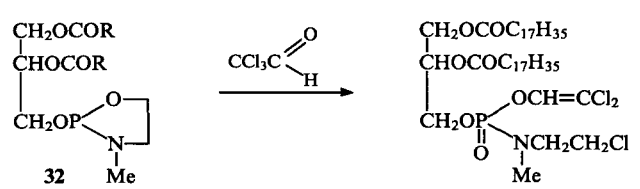
n = 2, 3, 4.

The choice of the diol has a considerable influence on the effectiveness of the cyclisation; 1,2- and 1,3-glycols react in accordance with the scheme presented and afford high yields of alkylene glycerophosphites (up to 70%).[46,88] Butane-1,4-diol is also converted into the expected glycero-1,3,2-dioxaphosphepan in 55% yield in the reaction with the diamine **5**. However, in this case a mixture of cyclic oligomers is formed simultaneously, but these can be readily separated from the target product.[91,92] It is of interest that the glycerophosphepan is a stable compound, while its analogues, containing chlorine, dialkylamino-groups, and other very simple substituents at the phosphorus atom, are very labile and readily oligomerise.[214-218] The last factor explains the low effectiveness of the synthesis of glycerophosphepans via an alternative scheme consisting in the phosphorylation of substituted glycerols by the chloro- and dialkylamino-phosphepans already mentioned.[91,92]

Glycerophospho(III)cyclanes are promising intermediates in the synthesis of different types of phospholipids. Data on this question have already been examined above in subsection 1 in the present section.

It has been suggested that cyclic glycerophosphoramidites — glycero-derivatives of oxazaphospholans[94,177,183] and oxazaphosphorinanes[52,175] — be synthesised via Scheme 63 but this time also using aminoalcohols.‡ These substances have already been used in oxidation reactions (see above) and in certain other syntheses. Thus treatment of glycerooxazaphospholans **32** with chloral in accorance with the Perkow procedure results in their conversion into unusual lipids belonging to the class of enol phosphates (Scheme 64).[95,186]

Scheme 64

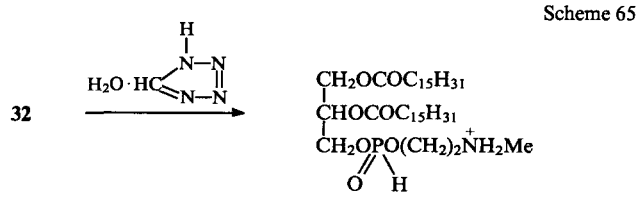


‡ The possibility of using also hydroxyaminoacid esters, for example serine, in such cyclisations has been demonstrated.[183]

The phosphorus centre in the molecules of enol glycerophosphates combines the structural features of the molecules of familiar alkylating ($\geq NCH_2CH_2Cl$) and phosphorylating [$\geq P(O)OCH=CCl_2$] preparations. Lipids, which contain such a functional group, can probably be regarded both as antitumour agents and as instruments for the study of the structures and functions of biological membranes. Phospholipids containing alkylating groups have also been obtained by the Arbuzov reaction between glycerophosphoramidites and methyl iodide.[186]

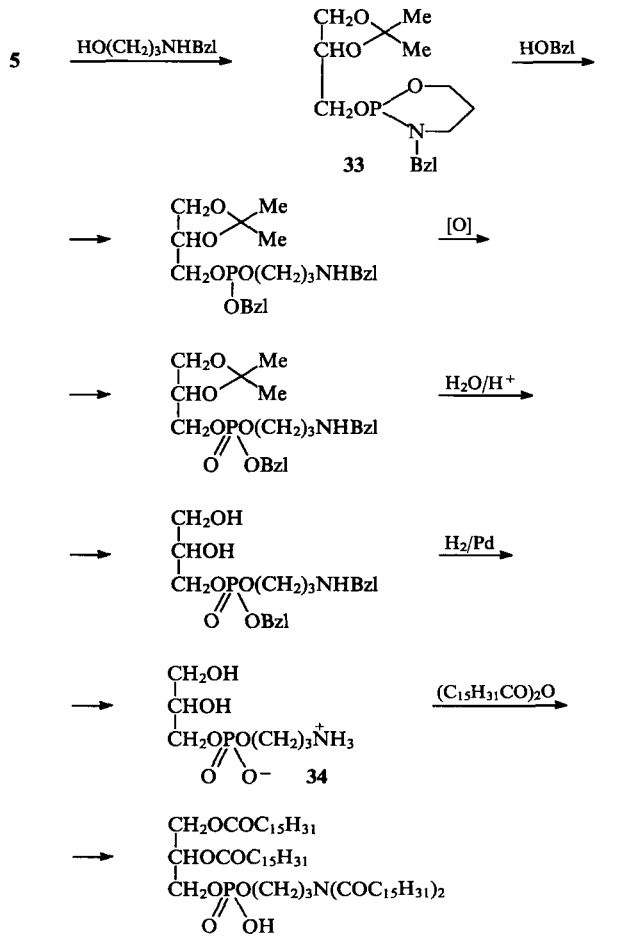
Another possible synthetic use of glycerophosphoramidites involves their reactions via the labile P—N bond. In this case, the fragment concealed by phosphorylation is immediately 'bared'. The simplest version of the cleavage of the P—N bond is acid hydrolysis, for example by monohydrates of sulfonic acids[52,173] or tetrazole,[53] and sulfhydrolysis,[185] which lead to hydrophosphoryl(thiohydrophosphoryl) analogues of phosphatidylaminoalcohols (Scheme 65).[53]

Scheme 65



The cyclic phosphoramidites examined above react satisfactorily also with alcohols of different chemical nature, which permits the solution of novel chemical problems. Thus the benzylolysis of glycerooxazaphosphorane **33** results in the formation of a neutral phosphite, the oxidation and deblocking of which lead to glycerophosphohomoethanolamine **34**. This

Scheme 66



polyfunctional product was acylated with palmitic acid anhydride, affording the tetrapalmitoyl derivative of a phospholipid which is difficult to obtain by other procedures (Scheme 66).[54, 176]

Alcoholysis can be used also to synthesise unusual neutral phosphites in the molecules of which the phosphorus atom is surrounded by residues of glycerol, aminoalcohols, and the reagent employed (carbohydrate, hydroxyaminoacid, glycerol derivative, etc.). The neutral phosphites obtained can be stabilised in either the phosphate or the phosphorothionate forms.[96, 184, 196] Such derivatives have been discussed in the literature in connection with the elucidation of the structures of natural complexes incorporating in their structure biopolymers and lipids.[8] Previously they were synthesised only by methods of classical phospholipid chemistry. The new suggestions based on the use of effective phosphorylation procedures apparently merit extensive use and can lead to progress in the study of such complex systems.

IV. Conclusion

The data presented have acquainted readers with the way in which the idea of replacing, in the intermediate stages of phospholipid syntheses, pentavalent phosphorus reagents by previously hardly used trivalent phosphorus reagents is applied. The application of this new synthetic strategy has entailed the vigorous utilisation of the possibilities of modern organophosphorus chemistry for the solution of problems in phospholipid chemistry of current interest and subsequently in membranology. On the other hand, further development of traditional studies on trivalent phosphorus derivatives has been greatly stimulated. All these factors suggest that a trend has arisen towards the establishment of a new interdisciplinary field of science.

Overall, the studies described demonstrate the necessity for their further expansion and deepening. Thus the absence of attempts to synthesis hypophosphite glycerolipids appears strange because all the previously investigated hypophosphites proved to be valuable key substances in the synthesis. Furthermore, hypophosphite glycerophospholipids as components of membranes can protect the latter against oxidation and other undesirable processes. The development of simple and effective methods of synthesis of glycerophosphites and similar compounds makes it necessary to undertake studies also on the corresponding metal complexes including transition metal complexes. Such coordination systems can play the role of a kind of carrier and can ensure the transport of metals into membranes. The distribution of metals in the lipid phases of membranes will clearly prove to be of fundamental importance since it will enable a series of important problems to be solved, for example that of the regulation of homolytic reactions in membranes or the binding to one another of individual lipid molecules as a result of the oxidative addition of C–H bonds to the metal.

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