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Non-standard Phosphorus-containing Derivatives of Carbohydrates

E.E.Nifant'ev and I.P.Gudkova

The review deals with the analogues of natural carbohydrate phosphates modified in the phosphorus-containing fragment. Synthetic pathways leading to compounds which are of greatest interest owing to their chemical properties and their behaviour in certain enzymatic reactions have been examined.
The bibliography includes 110 references.

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I. INTRODUCTION

Numerous studies on the synthesis and chemical properties of phosphorus-containing carbohydrate derivatives and their applications in biochemical studies have been published. As a rule sugar mono-, di-, and tri-phosphates or phosphoramidates were investigated. Such substances are either natural products or their close analogues, differing in detailed features of the ester groups.

However, there exists another group of phosphorus-containing carbohydrate derivatives consisting of derivatives of phosphorus-containing acids which have not been detected hitherto in animal and plant organism. The importance of these substances (we shall call them "non-standard phosphorus-containing derivatives of carbohydrates")† is evident, since they can be widely used to investigate many questions of sugar metabolism at a molecular level and to elucidate the structure of the active centres in the corresponding enzymes. Moreover, some of the above types of compounds are of interest for the synthetic chemistry of carbohydrates.

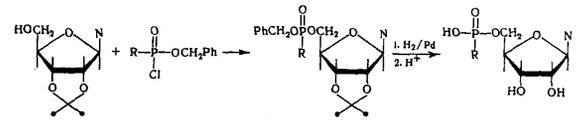
The non-standard phosphorus-containing carbohydrate derivatives were begun to be investigated mainly recently and in the literature there are no reviews dealing with their chemistry. Bearing this in mind, we undertook the writing of the present review, which covers the literature mainly up to the end of 1970: the first section deals with problems of the chemistry of phosphorus(V) acid derivatives and the second with phosphorus(III) acid derivatives. Each section begins with a description of phosphorylated pentoses.

II. DERIVATIVES OF PHOSPHORUS(V) ACIDS AND CARBOHYDRATES

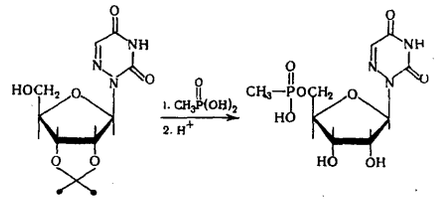
Among other non-standard phosphorus-containing carbohydrate derivatives, the phosphonic analogues of natural phosphates have been most widely investigated both chemically and biochemically and therefore the first subsection of the first section will be devoted to them. Alkylphosphoric, phosphoramidic, and phosphorothioic acid esters of carbohydrates and some of their derivatives containing quinquevalent phosphorus will be considered next.

1. Carbohydrate Phosphonates‡

The phosphonates of natural sugars were obtained for the first time in 1951 by Todd[3], who described analogues of adenosine 5'-phosphate, and uridine 5'-phosphate containing phenyl- and ethyl-phosphonic acid residues instead of the orthophosphoric acid residue. These esters were synthesised by phosphorylating 2',3'-*O*-isopropylideneadenosine and 2',3'-*O*-isopropylideneuridine by the corresponding phosphonochloridic acid with subsequent elimination of the protecting groups:



Subsequently the synthesis of nucleoside phosphonates was investigated by Holý[4]. By allowing 2',3'-*O*-isopropylidene-6-azauridine to react with pyridinium methylphosphonate in the presence of dicyclohexylcarbodi-imide, he obtained 6-aza-uridine 5'-methylphosphonate:

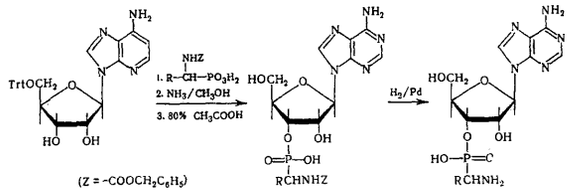


When 5'-*O*-acetylazauridine is used as the starting material, 6-azauridine 2'(3')-methyl-phosphonates are formed.

† One should bear in mind that the term "non-standard phosphorus-containing carbohydrate derivatives" is to some extent arbitrary. Recently phospholipids[1] and an antibiotic[2] belonging to the class of phosphonic acids have been found in natural products and therefore it now appears quite likely that phosphonates and other unusual sugar derivatives will be detected among products of plant and animal origins.

‡ This subsection will also deal with the esters of other acids with C–P bonds containing two or three phosphorus atoms. Such acids, which do not have generally accepted names as yet, will be combined under the term "phosphonic" just as orthophosphoric, pyrophosphoric, and triphosphoric acids are frequently referred to as "phosphoric" acids.

Žemlička and Chladek[5] obtained by this procedure the phosphonic analogues of 2′(3′)-*O*-alanyl- and 2′(3′)-*O*-phenylalanyl-adenosines in which the carboxy-group of the aminoacyl residue was replaced by the H–O–P=O group:

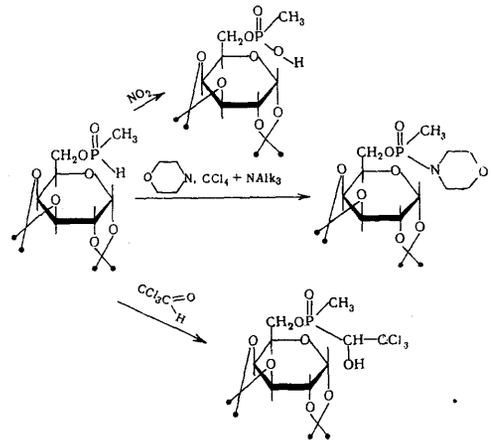


(Z = -COOCH$_2$C$_6$H$_5$)

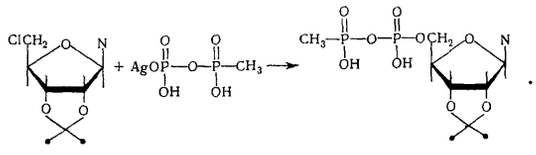
According to preliminary data, α-aminophosphonates of nucleosides inhibit the biosynthesis of certain peptides; in this respect they behave similarly to the antiobiotic chloramphenicol.

Comparison of the above two methods of synthesis of nucleoside phosphonates shows that the latter is preferable, since it is simpler, gives better yields of the desired compounds, and requires much more readily available phosphorylating compounds.

Carbohydrate phosphonates may be also obtained from the corresponding phosphonites. Thus 1,2;3,4-di-*O*-isopropylidenegalactose-6-methylphosphonite was oxidised to the corresponding methylphosphonate[6]. The same phosphonite was made to react successfully with morpholine and carbon tetrachloride to form a phosphonamidate, and with chloral to form 1,2;3,4-di-*O*-isopropylidenegalactose-6-βββ-trichloro-α-hydroxyethylmethylphosphinate:

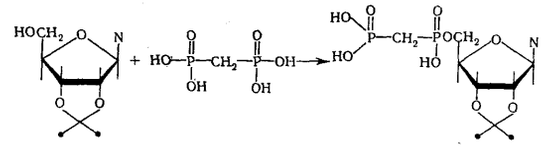


In the first half of the 1960's, the analogues of nucleoside pyrophosphates, in which one of the acid hydroxy-groups was replaced by a carbohydrate substituent, were investigated. Two methods were proposed for the synthesis of these compounds. The first consists of the interaction of a 5′-deoxy-5′-halogenonucleoside, the hydroxy-groups of which are protected, with a metal salt of the corresponding acid[7], for example:

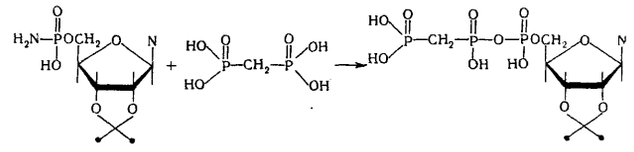


This investigation cannot be regarded as complete. The point is that the structures of the compounds obtained have not been proved. Indeed one can imagine the formation of two pyrophosphonate isomers in one of which the sugar is linked to the phosphate fragment of the acid residue and in the other to the phosphonate fragment. On the basis of general concepts concerning the electronic effects in the series of phosphorus-containing acids, one can postulate a greater probability of the formation of the second structure, while the authors chose the alternative structure without any explanation. The second method, which was investigated in greater detail, is based on the reaction of nucleotides with alkylphosphonic acids in the presence of dicyclohexylcarbodi-imide[8] or another condensing agent[9,10].

Analogues of nucleoside di- and tri-phosphates in which one of the oxygen bridges between the phosphorus atoms has been replaced by a methylene unit have also been described in the literature. It has been suggested that these nucleoside diphosphonates be obtained by the condensation of partly protected nucleosides with methylenediphosphonic acid in the presence of condensing agents[10], for example:



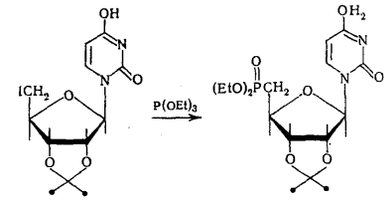
Myers et al. proposed two methods for the preparation of phosphonic analogues of adenosine triphosphate[10]. In the first, adenosine 5′-phosphoramidic acid is allowed to interact with methylenediphosphonic acid:



In the second method adenosine 5′-monophosphate is condensed with methylenediphosphonic acid under the influence of dicyclohexylcarbodi-imide. The first method gives a higher yield of the final product, while the second is simpler.

The compounds described above are of definite interest from the standpoint of biochemical studies of those reactions in which the dissociation of phosphoanhydride linkages is postulated[11,12].

Compounds in which there is a direct covalent bond between the phosphorus atom and the carbon atom of the main sugar chain are extremely interesting phosphonic analogues of natural phosphates. Such structures were obtained for the first time by the Arbuzov reaction. Bannister and Kagan synthesised in this way diethyl 5′-deoxyuridine 5′-phosphonate[13]:

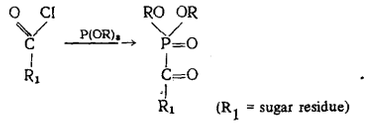


In the hydrolysis of the diethyl phosphonate under severe conditions, undertaken to eliminate the *O*-ethyl groups, the sugar molecule decomposed and the free phosphonic acid could not be isolated. Griffin and Burger reported[14] that this difficulty may be overcome by using specially

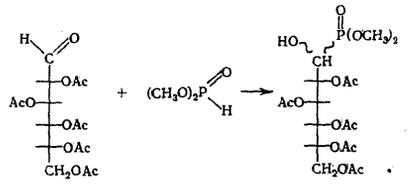
selected esters with a high chemical lability, for example benzyl phosphonates. However, it is difficult to achieve this reaction, since the required phosphonates are obtained from phosphites which enter into the Arbuzov reaction with difficulty. Thus, according to Holy's data, phosphites with 2-cyanoethyl, 2-chloroethyl, 2,2,2-trichloroethyl, and benzyl groups are not alkylated satisfactorily by halogenodeoxynucleosides. Therefore Holy suggests the use of tri-(2-benzoyloxyethyl) phosphite which gives a satisfactory result; however, in this case one has to employ a multistage procedure for the removal of protecting groups[15]. On the basis of the results of Maruszewska-Wieczorkowska et al.[17], Rammler et al.[16] suggest that the phosphite group be protected with allyl groups, which can be subsequently removed by catalytic hydrogenolysis.

Apart from riboside derivatives, derivatives of 6-halogeno-6-deoxyhexoses have been introduced into the Arbuzov reaction: 6-bromo-6-deoxytetra-acetylglucopyranose[14], 7-(2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-β-D-glucopyranosyl)theophylline[18], and 6-benzamido-9-(2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-β-D-glupyranosyl)purine[19]. In all these cases, substances differing sharply in hydrolytic stability from the corresponding phosphates were synthesised. It is significant that the phosphonic acids obtained are structurally very similar to the related hexose-ω-phosphates, but they possess a skeletal system of covalently linked atoms which is shorter by one unit.

Recently Zhdanov and coworkers[20] extended the Arbuzov reaction to aldonic acid chlorides and obtained a new type of sugar derivative in which the phosphorus atom is linked directly to the first carbon atom of the carbohydrate chain:

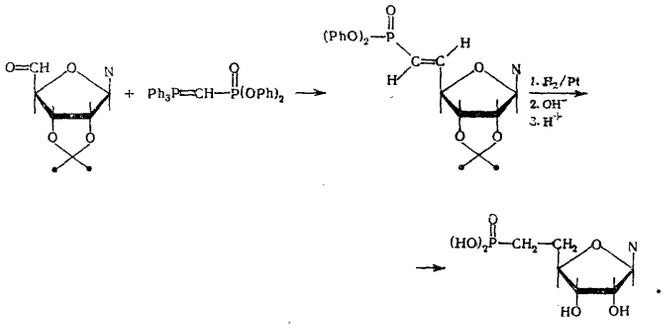


Apart from the Arbuzov reaction, other fundamental methods of the chemistry of organophosphorus compounds, in particular the Abramov and Wittig reactions, may be employed for the synthesis of the phosphonic analogues of sugar phosphates under discussion. Certain esters of phosphonic acids containing a hydroxy-group at the α-carbon atom (in relation to phosphorus) have been obtained by the Abramov reaction[21,22], for example:



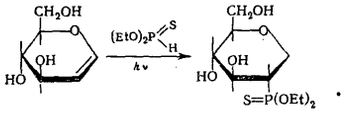
The authors suggest that the products be employed as insecticides.

The Wittig reaction makes available compounds in which the phosphorus atom is joined to the polyol fragment of the carbohydrate residue by an ethylene link. Thus, when modified adenine- or uridine-nucleosides with an aldehyde group at the 5'-carbon atom react with the corresponding Wittig reagent, the following products are obtained after hydrogenation[23]:

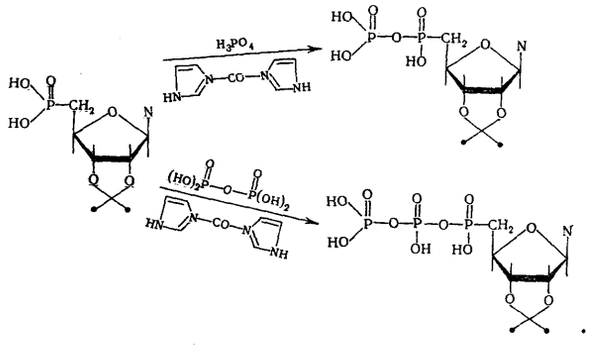


Phosphonic acid derivatives of carbohydrates containing a direct linkage between the phosphorus atom and a carbon atom in the sugar residue can also be synthesised by oxidising the corresponding phosphonous acids which have become available recently (see p. 858–859).[24]

There are literature data on the synthesis of a number of esters of the thioanalogues of the phosphonic acids under consideration. For this purpose, diethyl phosphorothioite was linked to unsaturated sugars[25], for example:



A method based on phosphonic acid derivatives of carbohydrates has been developed for the synthesis of phosphonate analogues of sugar diphosphates and triphosphates differing structurally from the esters with two and three phosphorus atoms already mentioned. The synthesis is carried out according to the following simple scheme[16] using inorganic phosphates and pyrophosphates in the presence of the usual condensing agents:



2. Carbohydrate Alkyl Phosphates

This subsection deals with compounds having the general formula nucl–O–P(=O)(–OR)–OR and nucl–O–P(=O)(–OR)–OH which are of direct interest for biochemical research. We shall not

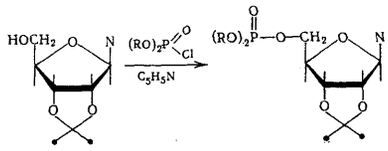
consider the numerous esters of this type which are used solely as intermediates in syntheses, for example, of benzyl, phenyl, and 2-cyanoethyl phosphate derivatives of sugars. The literature data on this problem have already been discussed[26].

Nucleoside dialkyl phosphates were obtained by the usual methods developed in the chemistry of organophosphorus compounds. The main problem, always arising in the extension of the phosphorylation procedures to carbohydrates, was the choice of suitable protecting groups.

Todd and coworkers[27] described the synthesis of the dimethyl ester of uridine 3′-phosphate by treating the corresponding acid with diazomethane. Szer and Shugar[28] extended their method to the synthesis of the dimethyl esters of uridine 5′-phosphate and cytidine 5′-phosphate. Later the reaction with diazomethane was investigated in detail for several mononucleotides[29] and *N*-aminoacid derivatives of nucleotides[30]. It was shown that not only the phosphate fragment but also the heterocyclic ring is methylated, the latter pathway being preferred.

Probably this side reaction also occurred in the earlier investigations[27,28].

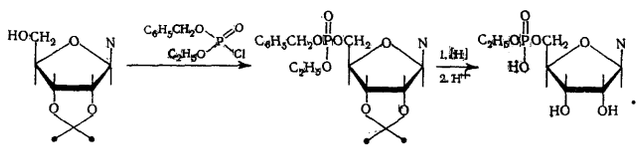
Montgomery et al.,[31] Libman and Heidelberger[32], and later Šorm[33] investigated another method of synthesising alkyl nucleoside 5′-phosphates. It consists of the interaction of 2′,3′-isopropylidenenucleosides with dialkyl phosphorochloridates in the presence of pyridine:



We shall now consider the monoalkyl esters of nucleotides. In a number of studies it has been stated that the desired compounds are formed on partial hydrolysis of the corresponding neutral esters[27,28,31-33]. Probably this procedure is of no preparative value, since under the conditions of such treatment the bond linking the phosphorus atom to the sugar residue is the first to dissociate.

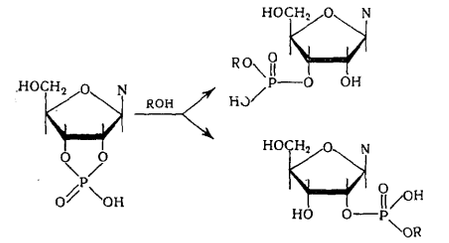
An unsuccessful attempt to obtain the methyl ester of uridine 5′-phosphate by treating the nucleoside with methyl phosphorodichloridate in the presence of pyridine has been described. In this case the main reaction product was the nucleotide. When ethyl phosphorodichloridate is employed, a mixture of products is obtained[34].

The monoethyl esters of adenosine and uridine 5′-phosphates were obtained by the reaction of 2′,3′-*O*-isopropylidenenucleosides with benzyl ethyl phosphorochloridate and subsequent elimination of the isopropylidene and benzyl protecting groups[35]:

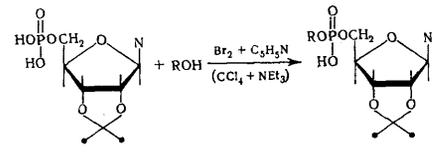


Another method of synthesising alkyl nucleoside 5′-phosphates consists of the treatment of a mixture of the alcohol and the nucleotide with carbodi-imide[33,36]. Despite the weak nucleophilic properties of alcohols compared with those of the phosphate anion, a large excess of the alcohol ensures that the reaction takes place in the required direction.

Alcoholysis of nucleoside 2′:3′-cyclicphosphates by primary alcohols, catalysed by both bases[37] and acids[38] (the latter is preferable), leads to a mixture of alkylnucleoside 2′- and 3′-phosphates:



An interesting method for the preparation of nucleoside esters with monoalkylphosphoric acids is the oxidative phosphorylation proposed by Todd[39]. The synthesis is carried out according to one of two variants—using bromine in pyridine as the oxidising system or carbon tetrachloride and triethylamine:

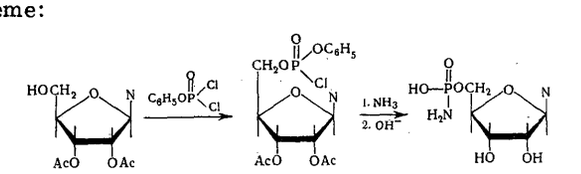


The alkyl esters of nucleotides are of interest in the study of certain problems in molecular biology. Thus it has been shown that they increase the permeability of cell membranes to nucleotide analogues[32]. Moreover alkyl esters of nucleotides have been used in the synthesis of highly specific chemical modifying agents for nucleic acids[40].

3. Carbohydrate Phosphoramidates

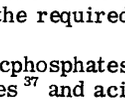
Numerous studies have been devoted to the phosphoramidates of various sugars. In the present review we have excluded from consideration those compounds with a P–N bond which are of purely synthetic importance. Data concerning the very interesting aminoacid derivatives of nucleotides have also been omitted, since the latter were considered recently in detail in a review by Shabarova and Prokof'eva[41].

The first study on the synthesis of the relevant compounds[42] was carried out according to the following scheme:



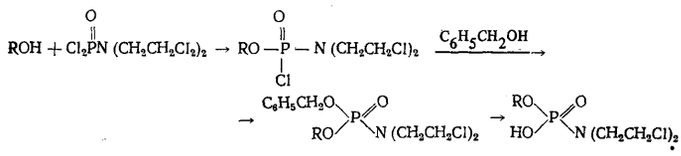
A more effective single-stage method of synthesis of the required amides, based on the condensation of nucleotides with ammonia in the presence of dicyclohexylcarbodiimide, was developed somewhat later[43]. Adenosine, uridine, cytidine, and guanidine phosphoramidates were obtained in high yields by this general method[43,44]. The piperidide and morpholide derivatives of nucleotides were synthesised similarly[45].

Several examples of the synthesis of phosphoramidate derivatives of monoses[46] with the general formula



are also known. The following

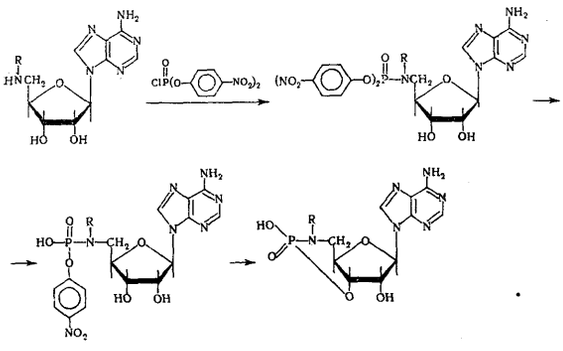
scheme is employed. Partly protected sugars are phosphorylated with an excess of an acid dichloride—*NN*-bis-(dichloroethyl)phosphoramidic dichloride; next the phosphoramidochloridate, which is the primary product, is converted by treatment with benzyl alcohol into an asymmetric diesteramide which yields the required compound after the removal of the protecting groups:



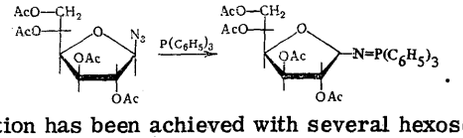
Derivatives of ribose, fructose, and glucose were used as the carbohydrate components. It is suggested that, owing to the presence of the carbohydrate residue, these compounds can readily penetrate the cell, where, under the influence of phosphatase and phosphoamidase, they split off bis-β-chloroethylamine, which suppresses the growth of malignant cells.

In addition to the methods for the preparation of sugar phosphoramidates described above, yet another procedure for their synthesis, based on the corresponding amides of acids containing phosphorus(III), may be mentioned. Thus 1,2;3,5-di-*O*-isopropylidineglucofuranose-6-(*NNN'N'*-tetramethyl)phosphorodiamidite is readily oxidised by oxygen, nitric oxide, and nitrogen dioxide[47]. 2,3,4,6-Tetra-*O*-acetylglucopyranose 1-(*NNNN'*-tetramethyl)phosphorodiamidite was oxidised under similar conditions[48].

Several compounds in which the nitrogen of the amide group in the phosphoramidates is linked directly to a carbon atom in the sugar ring have been described. Starting with 5'-amino-5'-deoxynucleosides and di-*p*-nitrophenyl phosphorochloridate, Jastorff and Hettler[49] obtained 50–85% yields of nucleoside phosphoramidate diesters[49]. Later the 5'-amide analogue of adenosine, converted subsequently into 3':5'-cyclicphosphoramidate, was obtained by a similar procedure[50]:



In conclusion of this subsection, mention should be made of compounds which are only indirectly related to the phosphoramidates discussed above as regards their structures. These are sugar derivatives of phosphine imide, for which a synthesis involving the treatment of the sugar azide with triphenylphosphine has been proposed[51]:

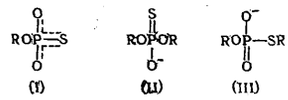


The reaction has been achieved with several hexoses. The final products are obtained in high yields.

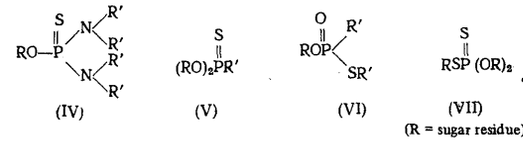
4. Sugar Phosphorothioates

In studies of enzymatic reactions at a molecular level using analogues of natural sugar phosphates, the phosphorothioates should be investigated first, since they involve minimal structural changes but differ significantly in one feature. Unfortunately, certain difficulties arise in their synthesis and this is why they have been comparatively little investigated hitherto.

The nucleoside phosphorothioates described in the literature can be represented by three types of general formulae:

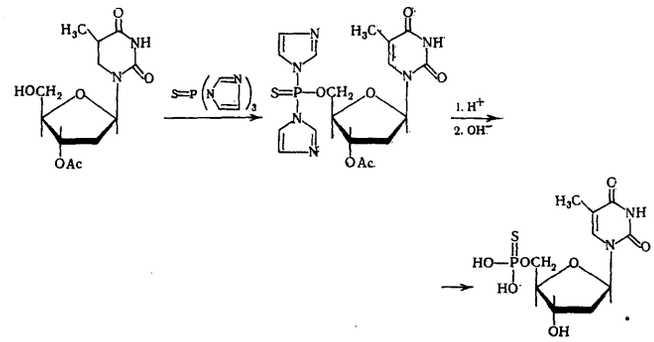


In addition, compounds with the following structures have been obtained from hexoses:



The methods of synthesising sugar phosphotothioates in the sequence (I)–(VII) specified above will be discussed below.

Nucleoside phosphorothioates were first obtained by Eckstein in 1966.[52] He phosphorylated 3'-*O*-acetyl-2'-deoxythymidine with tri-imidazolylphosphine sulphide:



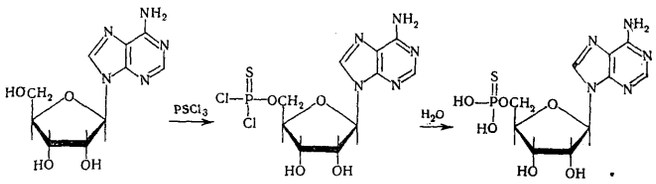
Somewhat later other investigators synthesised a series of nucleoside 5'-phosphorothioates using the same phosphorylating agent[53].

Eckstein employed tri-imidazolylphosphine sulphide to synthesise 2':3'-cyclic phosphorothioates from 5'-*O*-acetyluridine[54]. However, the desired product was isolated in a yield of 12% only. Moreover, the reaction was complicated by a side process involving the formation of 5'-*O*-acetyluridine 2':3'-cyclicphosphate.

Uridine 2':3'-cyclicphosphorothioate is interesting as a substrate for pancreatic ribonuclease[55].

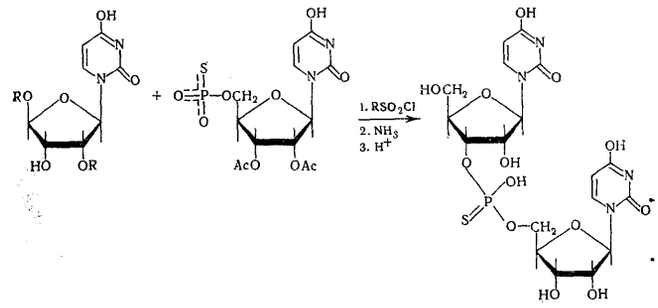
It is stated in the literature that tri-imidazolylphosphine sulphide employed as a phosphorylating agent gives satisfactory results only in the synthesis of the 5'-analogues of nucleotides. The attempts to synthesise the 3'-isomers were unsuccessful[56].

Phosphorus thiochloride was also used for the synthesis of nucleoside phosphorothioates. Thus adenosine 6′-phosphorothioate was obtained in a high yield by this procedure[57]:



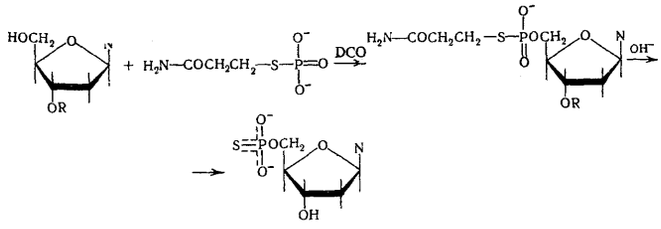
However, when phosphorus thiochloride was used in the phosphorylation of 2′,3′-*O*-isopropylideneinosine, the desired product was isolated in a relatively low yield after the removal of the isopropylidine protecting group[58].

It has been reported that nucleoside 5′-phosphorothioates are themselves effective phosphorylating agents. By treating 2′,5′-di-*O*-ethoxyethyluridine with 2′,3′-di-*O*-acetyluridine 5′-phosphorothioate, Eckstein achieved the synthesis of diuridine-3′,5′-phosphorothioate[59]:



In this reaction tri-isopropylbenzenesulphonyl chloride was employed as an activator.

Unfortunately the carbodi-imide method, which has been developed satisfactorily in the chemistry of nucleotides, could not be extended for a long time to the synthesis of phosphorothioates because the intermediate complex of the phosphorothioate and dicyclohexylcarbodi-imide decomposes with formation of dicyclohexylthiourea[60]. Cook et al. found a way of obviating this difficulty by employing in the carbodi-imide synthesis an inorganic phosphorothioate with a protected thio-group. Initially ethyl phosphorothioate was employed in the synthesis of sugar phosphorothioates[61]. However, subsequently it was suggested that the 2-carbamoylethyl protecting group, which is labile in an alkaline medium and can be readily removed at the end of the synthesis, be employed[62].

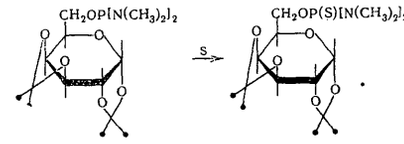


Nucleoside 3′ as well as 5′-phosphorothioates were obtained in this way in high yields.

The use of the 2-carbamoylethyl protecting group in this synthesis is analogous to the employment of the commoner 2-cyanoethyl protecting group in nucleotide synthesis. The reason for the above modification is that the authors were unable to synthesise 2-cyanoethyl phosphorothioates.

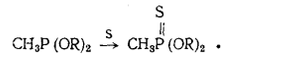
Carbohydrate phosphorothioates as well as phosphoramidates can be synthesised from the corresponding phosphorus(III) compounds.

Compounds with trico-ordinate phosphorus are known to combine readily with sulphur. This reaction has been carried out with 2,3;5,6-di-isopropylidinemannofuranose 1-(*NNN′N′*-tetramethyl)phosphorodiamidite[48], 1,2;3,5-di-isopropylideneglucofuranose 6-(*NNN′N′*-tetramethyl)phosphorodiamidite, and 1,2;3,4-di-isopropylidenegalactopyranose 6-(*NNN′N′*-tetramethyl)phosphoramidite[47], for example:



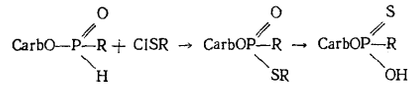
Glycosyl phosphoramidites react with sulphur on fusion of the starting materials and non-glycosidic sugar phosphoramidites react with spontaneous heating simply on mixing the components. In both cases the reaction gives high yields. Thus it is easy to obtain from readily available phosphorodiamidites the closest analogues of natural products—phosphoramidothioates. The biochemical properties of glucose 6-(*NNN′N′*-tetramethyl)phosphorodiamidothioate were investigated in a number of enzymatic reactions and it was shown that the compounds behave like the natural glucose-6-phosphate when acted upon by a number of glycolytic enzymes. However, the rates of its reactions are lower[63].

The addition of sulphur to disugar methylphosphonites has also been achieved[64]:



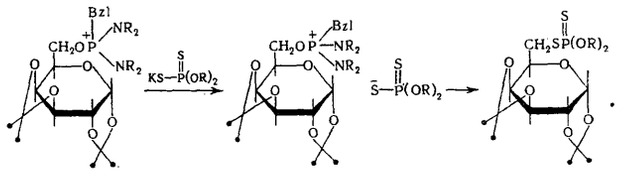
It has been shown that on heating the phosphonothioates [phosphonothionates?] thus synthesised partly isomerise to phosphonothiolates.

It has been suggested that phosphonothiolates, in which sulphur is present as a thiol group, be synthesised by treating partial sugar phosphonite esters with sulphenyl chlorides; the esters can be converted also into the corresponding phosphonothionates[6]:



The synthesis of acid phosphonamidothioates from phosphonamidites has also been described[65]. In this case the thione–thiol isomerisation does not take place.

Dialkyl sugar phosphorodithioates were obtained very recently by replacing the halogen anion by a phosphorodithioate anion in quasiamidophosphonium compounds with subsequent decomposition via the mechanism of the Arbuzov reaction[66]:



A characteristic feature of these compounds is the position of the sulphur atom between the phosphorus atom and the carbohydrate skeleton of the molecule.

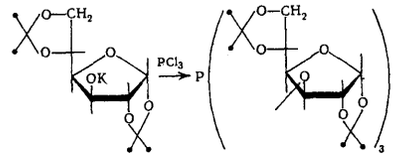
III. DERIVATIVES OF PHOSPHORUS(III) ACIDS AND CARBOHYDRATES

In recent years studies were begun in a number of laboratories on the synthesis and chemical properties of derivatives of phosphorus(III) acids and carbohydrates. These substances appear to be very promising as intermediates for the preparation of a wide variety of non-standard phosphorus-containing derivatives of carbohydrates, natural phosphates, and numerous dephosphorylation products. This assessment is due primarily to the high chemical reactivity of derivatives of tervalent phosphorus acids and sugars and also the fact that they are obtained under milder conditions and usually in higher yield than the corresponding phosphorus(V) acids. There is no doubt that the analogues of natural carbohydrate phosphates containing phosphorus(III) acid residues are of independent interest for biochemical research. Studies on those lines have already begun [63,67-69]. Certain facts now suggest that phosphites and other phosphorus(III) acid derivatives are formed in organisms as metabolic intermediates from a number of sugar phosphates and phosphoramidates.

In this review we shall consider the derivatives of phosphorus(III) acids and carbohydrates in the following order: neutral and acid phosphites and phosphoramidites and neutral and acid phosphonites, phosphonamidites, and phosphinites.

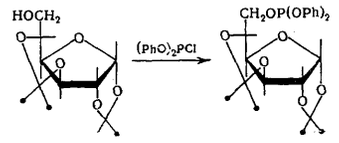
1. Neutral Phosphites

In the first studies on the synthesis of neutral sugar phosphites, acid chlorides were employed as phosphorylating agents. The phosphorylation of the potassium alkoxide derivatives of diacetoneglucose with phosphorus trichloride was reported in 1934. For a 3:1 reactant ratio, the formation of a neutral phosphite was postulated [70]:

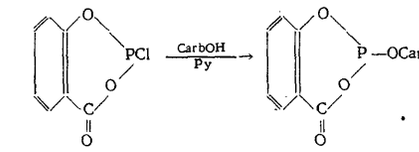


Unfortunately the yield of the reaction product, the methods of its purification, and necessary evidence for the individuality and structure of the trisugar phosphites are not included in the above report.

Later attempts were made to employ phosphorochloridite esters for the phosphorylation of carbohydrates. Thus the reaction between 1,2;3,5-di-isopropylideneglucofuranose and diphenyl phosphorochloridite has been described [71]:

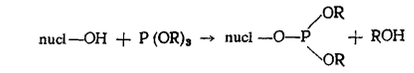


Later Tanaka published data on the preparation of diacetoneglucose-6-phosphite and diacetone galactose-6-phosphite using bis-(2,4-dichlorophenyl)phosphorochloridite as a phosphorylating agent [72]. The same investigator drew attention to the desirability of choosing cyclic phosphorochloridites, for example salicyl phosphorochloridite [73]:



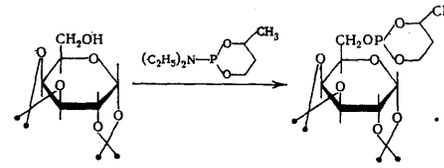
One may suppose that the phosphorochloridite method described has not found wide application because it suffers from disadvantages such as the instability of the initial reactants and the occurrence of side reactions. It is significant that phosphorochloridites cannot be used in the synthesis of glycosyl phosphites. Like other glycoside esters, they should be decomposed by amine hydrochlorides, which are formed as side products in the phosphorylation reactions [74], with formation of glycosyl halides.

Neutral phosphite esters have been proposed as phosphorylating agents for carbohydrates. In a series of studies by Czech chemists, a transesterification reaction for the synthesis of nucleoside phosphites has been described [75-81]. They employed triethyl and triphenyl phosphites as the transesterifying components:

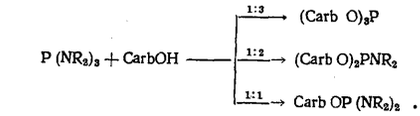


On treatment with triphenyl and triethyl phosphites, ribonucleosides yield nucleoside mono-, di-, and triphosphites and possibly also cyclicphosphites and dinucleoside phosphites. On subsequent hydrolysis, all these substances decompose to dihydrogen phosphite esters. Ribonucleosides with protected 2′- and 3′-hydroxy groups yield 5′-phosphites on transesterification with neutral phosphites [75-79].

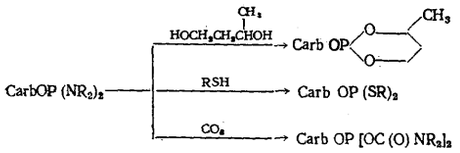
The transesterification method appears to be promising for the chemistry of sugars and nucleosides. However, recently the range of its applications has been restricted owing to the appearance of a new method—the alcoholysis of phosphoramidites [82,83]. This reaction has important advantages in syntheses: it is achieved under mild conditions, it does not involve the liberation of corrosive side products, and the starting materials are readily available. The method can be illustrated by the following example [84]:



An interesting variant of this reaction is phosphorylation of sugar derivatives with phosphorous hexa-alkyltriamides. In this case, depending on the reactant ratio, it is possible to obtain one of three types of compounds [65,84]:



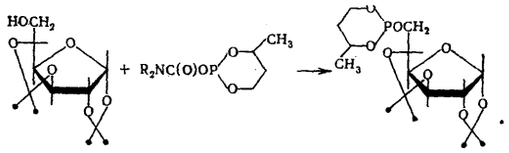
Phosphorodiamidites are valuable intermediates for the preparation of new phosphite derivatives. Thus, they readily react with alcohols[85], aminoalcohols[86], mercaptans[87], and carbon dioxide[88] and are converted into new phosphoramidite esters, phosphorothioite esters, phosphite esters, and carbamoyl phosphites. In particular, the following reactions have been achieved:



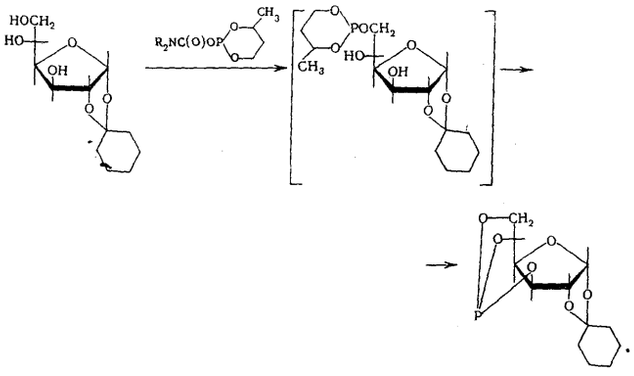
The phosphoramidites can be converted into monosugar phosphites by hydrolysis and acidolysis[89].

The synthesis of phosphites and phosphoramidites involving the alcoholic sugar hydroxyls was described above. The synthesis of glycosyl phosphites was achieved using phosphoramidous acids and their esters[48].

Sugar acyl phosphites[90], particularly carbamoyl phosphites[90], react under even milder conditions than the phosphoramidites, for example:

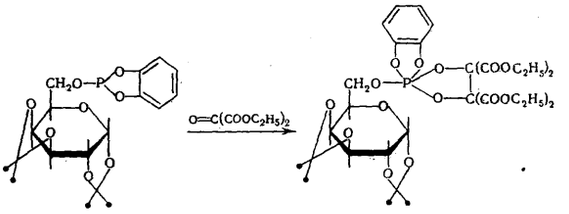


1,3-Butylene *NN*-dimethylphosphoramidite and 1,3-butylene dimethylcarbamoyl phosphite were investigated in a reaction with 1,2-cyclohexylideneglucofuranose[92]. In the phosphorylation with the carbamoyl phosphite, the reaction takes place at room temperature with formation of a bicyclic phosphite. Probably the first stage involves the formation of the sugar 1,3-butylene phosphite, which undergoes spontaneous transesterification to 1,2-cyclohexylideneglucofuranose 2,5,6-phosphite as a result of the specific properties of the carbohydrate phosphite system:



The structure of the bicyclic phosphite was demonstrated by synthesis involving the phosphorylation of 1,2-cyclohexylideneglucose with phosphorous hexaethyltriamide[92].

In the preview section of the review it was already mentioned that neutral sugar phosphites and phosphoramidites serve as starting materials for the synthesis of the corresponding phosphorus(V) derivatives. In addition, other reactions involving them have been achieved. Thus, alkylation, leading to a wide variety of deoxysugar derivatives[66,93], and the reaction with mesoxalic esters[94] deserve mention:

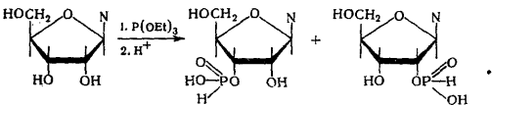


2. Acid Phosphites

It has been suggested that sugar dihydrogen phosphite esters be synthesised by the reaction of the sugar with phosphorous acid in the presence of dicyclohexylcarbodiimide as the condensing agent. This method was employed for the first time in 1961 by Todd[95]. Subsequently Holý et al.[96] developed on this basis a preparative synthesis for certain nucleoside phosphites.

A second method for the preparation of mononucleoside phosphites involves the hydrolysis of Menshutkin acid chlorides of the type $ROPCl_2$, formed when specially protected nucleosides are treated with phosphorus trichloride[97,98]. The problem of whether the phosphorodichloridite esters enter into various side reactions before treatment with water still remains uninvestigated. Therefore it is difficult to assess the preparative value of the method.

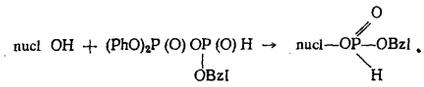
It has been suggested that mononucleoside phosphites be obtained by the hydrolysis of the corresponding neutral phosphites[76-78]. Initially 2′(3′)-phosphites were obtained from nucleosides with a protected 5′-hydroxy-group[76]. However, subsequently it was reported that nucleoside 2′(3′)-phosphites can be synthesised by the reaction of unprotected ribonucleosides with triethyl phosphite[78]:



The authors suggest that such selectivity of the secondary hydroxyl in the presence of a free primary hydroxyl is due to the formation of the thermodynamically more favourable 2′:3′-cyclic phosphite structure the hydrolysis of which leads to the acid phosphite. However, the formation of such cyclic esters is possible only when *cis*-hydroxy-groups are present. Thus all the acid phosphites which may be expected on hydrolysis of the cyclic phosphites, presumed to be formed via the transesterification of the alkyl phosphites with the *cis*-hydroxy-groups of the sugar, were obtained from lyxose, xylose, and arabinose[79]. Moreover, it is asserted that ribonucleosides with protected 2′,3′-hydroxy-groups as well as 2′-deoxyribonucleosides altogether fail to be phosphorylated by triethyl phosphite under the chosen conditions.

A synthesis of monosugar phosphites by the acidolysis and hydrolysis of the corresponding phosphorodiamidites has been proposed[85,89].

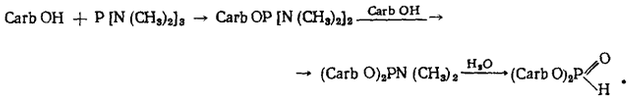
For the synthesis of monohydrogen phosphite esters, Todd proposed the method of mixed anhydrides requiring the use of the *O*-benzylphosphorous-*OO*-diphenylphosphoric anhydride:



Ribonucleosides containing blocking groups at the 2',3'- and 3',5'-hydroxyls and also 5'-protected 2'-deoxyribonucleosides are usually introduced into this reaction.

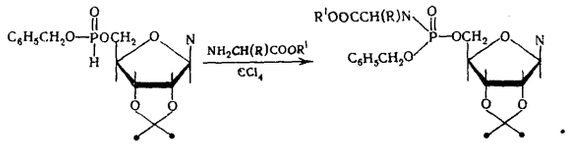
Nucleoside benzyl phosphites are synthesised in connection with the solution of a wide variety of chemical problems and such synthesis has become fairly common[26]. However, its further applications are restricted by the low availability of phosphorylating agents which can only be obtained by a fairly complex procedure.

Monohydrogen phosphite esters containing one or two sugar residues are formed on hydrolysis or acidolysis of the corresponding phosphoramidites, which are in turn obtained via a two-stage phosphorylation procedure[85], for example:



Acid phosphites of carbohydrates are very interesting synthetically. Dihydrogen phosphite esters have been suggested as intermediates in the synthesis of phosphates. Nitrogen dioxide[85], hexachloroacetone[76], and mercury(II) chloride[98] have been used as oxidising agents. Monohydrogen esters are readily converted into the corresponding phosphorochloridates by treatment with *N*-chlorosuccinimide and similar reagents[100]. Such phosphorochloridates are highly reactive and are readily converted into a wide variety of carbohydrate derivatives.

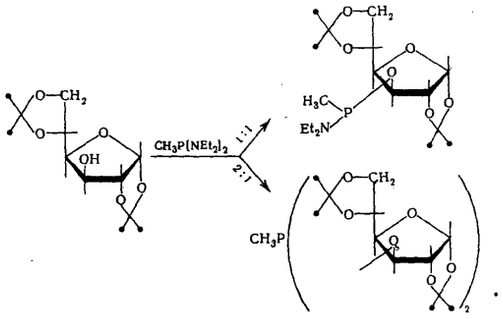
Benzyl nucleoside phosphites react with amines in the presence of carbon tetrachloride to form phosphoramidates[101]. This reaction was employed by Prokof'ev, Shabarova, and coworkers to synthesise compounds containing the phosphoramidate linkage between a nucleotide and an aminoacid[102-104], for example:



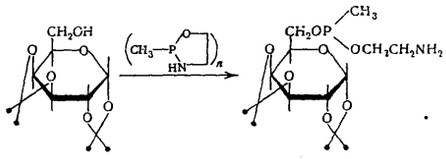
3. Neutral Phosphonites and Phosphonamidites

The alcoholysis of methylphosphonite esters and methylphosphonamidous acids has been suggested as a method of phosphorylating carbohydrates. Thus isopropylidineadenosine can be converted into an asymmetric phosphonite by treating it with diphenyl methylphosphonite[105] and diacetonehexoses can be converted into the corresponding methylphosphonamidites by reaction with methylphosphonous tetraethyldiamide[65].

With a 2 : 1 reactant ratio, disugar methyl phosphonites are formed[65], for example:



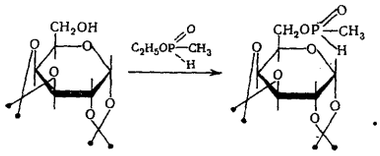
The following synthesis has been suggested for asymmetric phosphonites containing the ethanolamine residue:



Carbohydrate phosphonites and phosphonamidites are highly reactive. They are readily oxidised, combine with sulphur to form the corresponding phosphorus(V) derivatives[65,85], and enter into the Arbuzov reaction with formation of deoxysugars[93]. Phosphonamidites also react with a wide variety of reagents containing a mobile hydrogen, becoming converted into other sugar phosphonites[6,65].

4. Acid Phosphonites

Acid phosphonites of protected monoses have been obtained by the transesterification of phosphonites and by the alcoholysis of amides. The transesterification method has been used to prepare 1,2;3,4-di-isopropylidenegalactose 6-methylphosphonite by treating the sugar with ethyl methylphosphonite[6]:

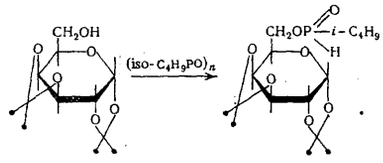


The reaction takes place under severe conditions (170°C, 7h). In the alcoholysis of amides, the phosphorylation takes place under milder conditions. The reaction temperature is reduced (110°C) and the yield of the final product increases.

Acid phosphonites can also be obtained by the acidolysis and hydrolysis of the corresponding phosphonamidite esters[89].

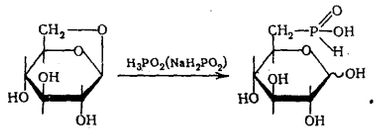
Acid carbohydrate phosphonites can be obtained under the mildest conditions by the interaction of protected sugars with anhydrides of the type $(R-PO)_n$.[106] The

reaction is not accompanied by the formation of side products and takes place at room temperature on simple mixing of the reactants:



Both alcoholic and glycosidic hydroxyls can be phosphorylated in this way. However, the anhydrides themselves are extremely labile. They polymerise rapidly with formation of unreactive products.

Among phosphorus(III) acid derivatives, analogues of natural phosphates with a direct covalent bond between the phosphorus atom and the carbon atom of the main sugar chain have also been obtained. Such phosphonous acids have been synthesised by the opening of the ring in 1,6-anhydrohexoses with hypophosphorous acid or its mixture with sodium hypophosphite[24]:



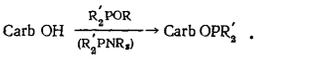
This reaction has been achieved with 1,6-anhydroglucose and 1,6-anhydrogalactose.

The above method of synthesis of phosphonous acids is particularly valuable because it makes it possible to avoid the laborious procedures involving the introduction and removal of protecting groups.

Phosphorous acid has also been investigated in the reaction with laevoglucosan, but in this case a product with a phosphorus-carbon bond was not isolated.

5. Carbohydrate Phosphinites

Two methods have been proposed for the synthesis of carbohydrate phosphinites: using phosphinite esters[107] and phosphinous amides[84,107] as phosphorylating agents:



These substances have been less thoroughly investigated than the phosphites and phosphonites owing to the experimental difficulties in their synthesis. Nevertheless, it has been shown that sugar phosphinites enter into a wide variety of substitutive phosphorylations leading to halogenodeoxy-[84,107-109] and mercaptodeoxy-derivatives[110] of sugars.

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Faculty of Chemistry,
Lomonosov Moscow State
University