Translated from *Uspekhi Khimii*, **43**, 1074-1101 (1974) U.D.C. 573.953 + 547.917 + 547.593.261

The Chemistry of Myoinositol

V.I.Shvets

The present state of the chemistry of myoinositol, a naturally occurring cyclitol, is discussed, with information on its stereochemistry, its physical and chemical properties, and the reactivity of the hydroxy-groups. The principal methods of preparation of various derivatives, in which the cyclitol structure is unaffected, are considered. Special attention is paid to phosphoric esters of myoinositol, which are structural units of inositol phosphatides, a most important class of naturally occurring phospholipids. Specific properties of the phosphoric esters are examined, together with problems of their stability and synthesis. A list of 169 references is included.

CONTENTS

I. Introduction 488
II. Stereochemistry of derivatives of myoinositol and their reactivity 488
III. Acetal derivatives of myoinositol and reactions based on 1(3),2-*O*-cyclohexylidene-*sn*-myoinositol 489
IV. Pentasubstituted derivatives of myoinositol 490
V. Phosphoric esters of myoinositol 494

I. INTRODUCTION

Myoinositol is the most widely occurring of the cyclitols (inositols, cyclohexanehexaols). Nine stereoisomeric inositols—neoinositol, *cis*-inositol, scylloinositol, myo-(*meso*-)inositol, (+)- and (−)-inositols, epi-inositol, mucoinositol, and alloinositol—are known[1]. All forms of inositols, with the exception of the (+)- and (−)-inositols, are *meso*-forms, but many of their derivatives may possess molecular asymmetry and hence exhibit optical activity. Naturally occurring optically active derivatives of myoinositol are known: (−)- and (+)-bornesitols (1- and 3-*O*-methyl-*sn*-myoinositols)†, (+)-ononitol (4-*O*-methyl-*sn*-myoinositol), (−)-liriodendritol (1,5-di-*O*-methyl-*sn*-myoinositol), galactin (3-*O*-α-D-galactopyranosyl-*sn*-myoinositol), phosphoinositides, and several other compounds have been isolated from bacterial, vegetable, and animal sources[1]. Myoinositol occurs widely in the vegetable kingdom as calcium salts of the hexaphosphoric ester (phytin)[1].

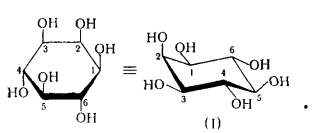
Inositols, in particular myoinositol, are suitable model compounds for the study of stereochemistry and conformational effects. Development of the chemistry of myoinositol has been stimulated also by its occurrence, as well as that of such derivatives as inosamines, in natural compounds—phospholipids, antibiotics, and several others.

Our interest in the chemistry of myoinositol arises from our prolonged concern with aspects of the synthesis of phosphoinositides and phosphoric derivatives of myoinositol, which raises the problem of the availability of definitely substituted derivatives of the latter. Each class of phosphoinositides—mono-, di-, and tri-phosphoinositides—requires its own methods of synthesis. Processes for obtaining triphosphoinositides are especially laborious, for no practicable routes are yet available; this contrasts with mono- and di-phosphoinositides, to whose synthesis definite approaches can be made.

Individual aspects of the chemistry and the biochemistry of myoinositol and its derivatives have been covered in several reviews and books[1,5-14]. The present Review does not deal with synthesis of the cyclitol structure of myoinositol, since this is an independent problem of intrinsic interest. Examples are the syntheses of derivatives of myoinositol and other cyclitols by the intramolecular aldol reaction of various compounds of D-glucose[15-21], by diene synthesis[22], by the hydroxylation of conduritols[23], etc. Research on the conversion of myoinositol derivatives into inosamines constitutes a separate field of investigation[24].

II. STEREOCHEMISTRY OF DERIVATIVES OF MYOINOSITOL AND THEIR REACTIVITY

Myoinositol (I) contains six hydroxy-groups—five equatorial and one axial[1]:



(I)

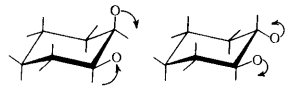
It is easy to predict by conformational analysis that the most stable conformation of myoinositol is the chair form (I), which possesses the smallest number of axial hydroxyls[25]. The chair conformation is consistent with such reactions of myoinositol and its derivatives as dehydrogenation, the formation of borate complexes, and acylation[25]. Physical data also support this conformation: derivatives exhibited an infrared absorption band at 873 ± 11 cm^{-1}, due to vibrations of equatorial C–H bonds[26]. The nuclear magnetic resonance spectra of myoinositol and its acetates[27] were also interpreted in terms of a chair conformation, and were fully consistent with the n.m.r. spectra of the corresponding hexachlorocyclohexanes[28]‡. The suggested conformation was supported also by X-ray diffraction[35] and by electron microscopy[36-38].

†A stereospecific nomenclature[2-4] is used in the Review for racemic and optically active asymmetrically substituted derivatives of myoinositol.

‡Several studies have recently been published[21,24,29-34] on the application of n.m.r. spectroscopy to the structural analysis of myoinositol and its derivatives.

Myoinositol is thermodynamically the most stable cyclitol, as is suggested by the calculated relative free energies (in kcal mole^{-1} at 25°C): myo 3.0, scyllo 3.2, (±) 3.55, (+) 4, neo 4.3, epi 4.9, allo 5.05, muco 5.1, and *cis* 8.05.[39] These values agree well with those determined from the equilibrium constants of the acid-catalysed epimerisation of isomeric inositols[40]. The possibility of the interconversion of myoinositol into other stereoisomers should always be taken into account in the preparation of various derivatives. These problems have been discussed in detail in reviews[1,14]. An example of the partial transition of myoinositol into scylloinositol is provided by the reduction of 2-myoinosose, obtained by oxidation of the axial hydroxyl[1]. Myoinositol hexa-acetate undergoes almost complete isomerisation into mucoinositol hexa-acetate when treated with liquid hydrogen fluoride[41], probably owing to the enhanced stability of intermediate acetyl-oxonium derivatives of the muco-form.

The reactivity of the hydroxyls in myoinositol is strongly dependent on the stereochemistry of the molecule, and is affected by steric hindrance. In this connection equatorial and axial substituents exhibit a difference in chemical behaviour, although the equatorial hydroxyls in myoinositol are not equivalent. But whereas differences between axial and equatorial groups in myoinositol[42] are well explained by conformational analysis and have been confirmed by numerous studies, the non-equivalence of the equatorial hydroxyls is not so usual, and each fact requires separate consideration. Attempts at such an approach have been made in reporting the chemistry of myoinositol. Many synthetic procedures, especially in the chemistry of phosphoinositides, have been based on these rules.



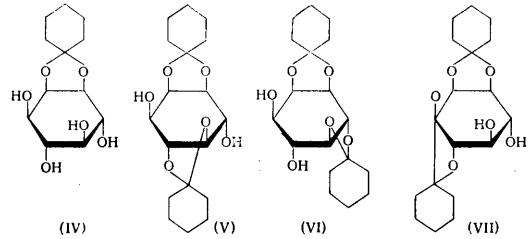
cis (II) *trans* (III)

The hydroxyls in myoinositol differ in reactivity also according as they are in *cis*- or *trans*-positions. In the undistorted chair form the distance between vicinal equatorial groups is the same as that between axial and equatorial *cis*-hydroxyls. It might have been expected, therefore, that the formation of cyclic acetals would occur equally readily with *cis*- and *trans*-hydroxyls. However, cyclisation involves formation of a new ring containing five coplanar atoms, and consequently the molecule is distorted in such a way that the two vicinal substitutents become quasi-coplanar. In all reactions requiring an approximately coplanar transition state, and not accompanied by migration of substituents, *cis*(*eq*, *ax*)-compounds react more rapidly than do *trans*(*eq*, *eq*)-compounds[43]. The chair conformation of the ring exhibits different relations towards the two types of distortion caused by bringing *cis*(*eq*, *ax*)- or *trans*(*eq*, *eq*)-substituents almost into coplanarity[36]. The former (II) is accompanied by levelling of the ring and increase in the endocyclic bond angles. Such distortion resembles incipient conformational inversion and requires no large consumption of energy. Formation of a new ring involving *trans*-hydroxyls is best explained in terms of a distorted conformation. Thus examination of hydrogen bonds has shown[44-46] that the effort to bring the two equatorial bonds (III) into the same plane entails a shortening of the interatomic distances, which distorts the chair form and therefore requires a large quantity of energy[47]. As a consequence, cyclisation takes place initially at the *cis*-hydroxyls (*ax*, *eq*), and then at the *trans*-hydroxyls (*eq*, *eq*) under more severe conditions[48]. These observations are confirmed by the formation of cyclic acetals of myoinositol.

III. ACETAL DERIVATIVES OF MYOINOSITOL AND REACTIONS BASED ON 1(3), 2-*O*-CYCLOHEXYLIDENE-*sn*-MYOINOSITOL

Studies of cyclic acetals of myoinositol are of interest for synthetic chemistry, besides the solution of stereochemical problems. Acetals have proved convenient protective groups in the chemistry of myoinositol. Originally an isopropylidene group was used to protect vicinal hydroxy-groups[43,49-55]. Myoinositol reacts with acetone in the presence of zinc chloride, and with 2,2-di(m)ethoxypropanes in the presence of toluene-*p*-sulphonic acid in dimethyl sulphoxide, to form isopropylidene derivatives. *cis*-Acetals are formed first[43,51], since they correspond more closely to coplanarity. The formation of acetals with a ketone requires that water be removed from the reaction medium. Acetone hinders the azeotropic removal of water, is unstable towards dehydrating agents, and causes side-reactions[48].

Cyclohexylidene derivatives were subsequently recommended for sugars and polyols, since they are obtained more simply than the corresponding acetonides, and moreover in the crystalline state[56]. Myoinositol is dissolved in a boiling mixture of cyclohexanone and benzene containing catalytic quantities of toluene-*p*-sulphonic acid, and water is removed by azeotropic distillation. The resulting formation of *O*-cyclohexylidene-*sn*-myoinositol derivatives —1(3), 2 (IV), 1(3), 2:4(6)5 (V), 1(3), 2:5, 6(4) (VI), and 1(3).2:3(1), 4(6) (VII)[48,57]



(IV) (V) (VI) (VII)

involved firstly the *cis*-hydroxyls (*ax*, *eq*) and then *trans*-hydroxyls (*eq*, *eq*).[48] Angyal showed[48] that a triacetal of myoinositol was formed, but this compound was not isolated.

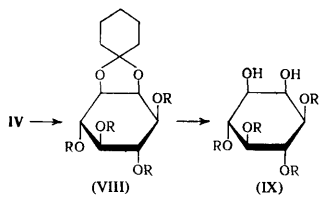
Cyclohexylidene derivatives of myoinositol are starting compounds for the preparation of phosphoinositides. A diphosphoinositide has been obtained from the diacetal (V).[58-60] Several syntheses of monophosphoinositides[61-65] have involved the use of 1(3), 4(6), 5, 6(4)-tetra-*O*-substituted derivatives of myoinositol obtained from the monoacetal (IV). Examples are the tetrabenzyl and tetra-acetyl compounds (IX: R = $C_6H_5CH_2$, CH_3CO) obtained by the benzylation or acetylation of (IV) followed by acid hydrolysis of the acetal protection (Scheme 1).[48,66] Other groups (toluene-*p*-sulphonyl (tosyl), methyl, allyl, etc.) are less suitable for these purposes, mainly because of the difficulty of their removal. Acetylation and benzylation of the acetal (IV) go to completion, so that differences in reactivity between the hydroxy-groups cannot be detected, although such conclusions may prove useful in the synthesis of polyphosphoinositides.

In this connection interesting results have been obtained for the tosylation of various derivatives of myoinositol. The action of tosyl chloride in pyridine on the mono-, di-, tri-, and tetra-tosylates (X–XVII, XIX, and XX) is represented by Scheme 2.[29] The degree of tosylation is determined by the quantity of the reagent: a large excess of tosyl chloride is required to obtain polytosyl derivatives of myoinositol. Gravimetric analysis of the tosylates obtained in various reactions leads to the reactivity sequence

1(3)-OH>4(6)-OH>5-OH>2-OH

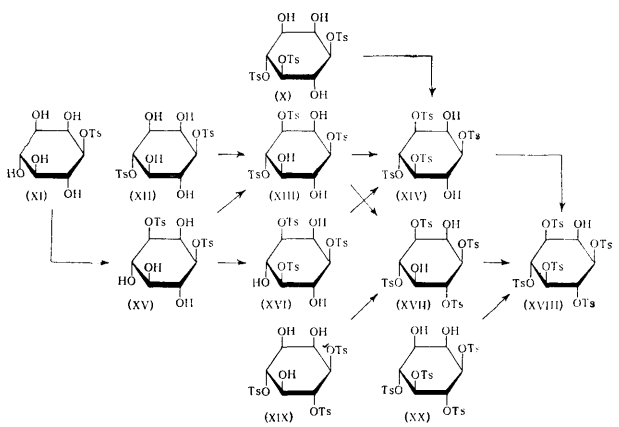
for the hydroxy-groups in this case.

Scheme 1



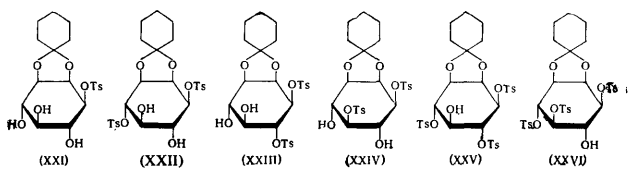
R = $C_6H_5CH_2$, CH_3CO

Scheme 2



Ts = p-$CH_3.C_6H_4.SO_2$

Similar results have been obtained for corresponding reactions with the monoacetal (IV):[30] several tosyl derivatives

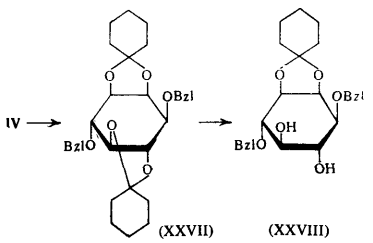


were prepared and used, after removal of the cyclohexylidene protection[31], to obtain polytosylates of myoinositol[29]. Similar reactivity of the hydroxy-groups in the monoacetal (IV) has been observed in benzoylation[33]. The derivatives (X), (XII), (XIII), (XXII), and (XXVI) are worthy of attention as starting materials for the preparation of di- and tri-phosphoinositides. However, the low yields of myoinositol tosylates, the difficulty of their isolation, and also the possibility of various transformations in work with tosyl groups[66,67] restrict the use of tosylation in the synthesis of polyphosphoinositides.

Several conclusions of the relative reactivity of the equatorial hydroxyls were drawn from an investigation of substitutions (S_N1 and S_N2) of the diacetals (V) and (VI) and their derivatives. Thus the benzylation[63,68,69], benzoylation[70], and phosphorylation[71] (S_N2) of (V) suggest that the 3(1)-hydroxyl is more reactive than the 6(4)-hydroxyl, despite the unfavourable conformational factors that the former is adjacent to a *cis*- and *trans*-acetal group, and the latter to a *trans*-group. The selectivity is due to the more strongly nucleophilic character of the 3(1)-hydroxyl. A similar phenomenon has been observed in the benzylation of (VI).[69] Selective benzoylation of the diacetal (V) formed the basis for a synthesis of a diphosphoinositide[60]. Nevertheless, these hydroxy-groups exhibit closely similar reactivity towards transesterification (S_N1).

With the diacetal (VI) this reaction showed that the 4(6)-hydroxy-group is more reactive than the 3(1)-hydroxyl, while 4 is the more active of the enantiotopic positions 4 and 6.[72,73] These hydroxyls behave similarly towards methylation[72,73]. The explanation is that position 4(6) is sterically more favourable (*trans*-OH, *trans*-acetal) than position 3(1) (*trans*-OH, *cis*-acetal).

Scheme 3



Bzl = $C_6H_5.CH_2$

Transesterification of 1(3), 4(6)-di-*O*-cyclohexylidene-*sn*-myoinositol (XXVIII) by the ethyl chloroacetate of D-mannose indicates that the 5-hydroxyl is more reactive than the 6(4)-group. Of the two most probable diastereomers the compound with a free 4-hydroxyl is formed preferentially[63]. Examination of the stability of the *cis*- and *trans*-cyclohexylidene groups in the diacetals (V)–(VII) revealed the possibility of selective removal of the *trans*-acetal protection as sterically the less favourable[57,63,68]. This provided a method for preparing (XXVIII)[63] (Scheme 3), from which compound the preparation of triphosphoinositides can be planned.

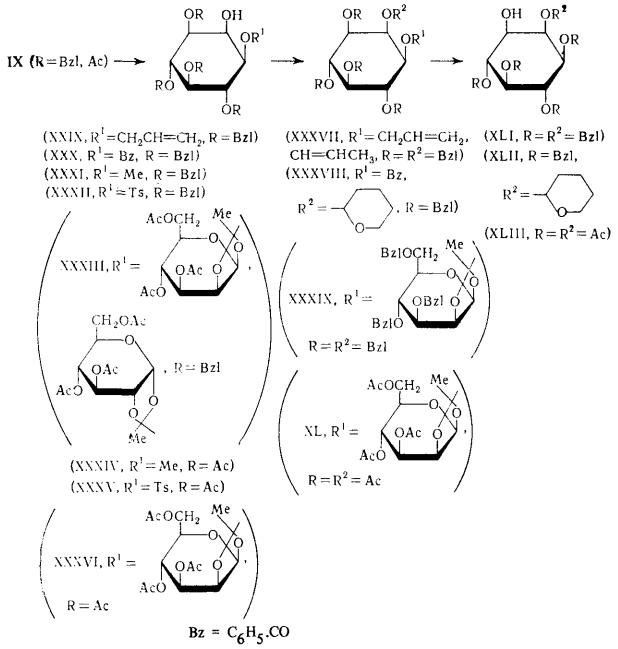
IV. PENTASUBSTITUTED DERIVATIVES OF MYOINOSITOL

A general method for obtaining monophosphoinositides is based on pentasubstituted derivatives of myoinositol having the free hydroxyl at the 3(1) position. It would therefore have been tempting to seek a selective protection for the axial hydroxyl in 1(3), 4(6), 5,6(4)-tetra-*O*-substituted derivatives. Unfortunately, it is impossible to

suggest such a group: substitution of 1(3), 4(6), 5,6(4)-tetra-*O*-substituted derivatives takes place predominantly at the 3(1) position. Benzylation [66], methylation [66], tosylation [31,74,75], acetylation [66], benzoylation [76], phosphorylation [62], and allylation [52] occur in this way. On the other hand, 2,3-dihydropyran and benzyloxymethyl chloride do not exhibit selectivity [77].

Reactions exhibiting selectivity towards an equatorial hydroxy-group can be assumed to depend on steric hindrance and to involve a transition state by an S_N2 substitution mechanism. If an ion is formed in the initial stage, on the other hand, the subsequent rapid interaction is less sensitive to steric hindrance, and such reactions (S_N1) therefore occur non-selectively. Results obtained for the transesterification of orthoacetates of D-mannose and D-glucose with 1(3), 4(6), 5,6(4)-tetra-*O*-benzyl-*sn*-myoinositol (IX: R = $C_6H_5CH_2$), [78,79] in which orthoesters of myoinositol isomeric with respect to the axial groups were isolated in considerable quantities, are significant in this connection. The absence of selectivity, despite steric hindrance to the introduction of an orthoester group at the 2-hydroxyl, becomes clear from an examination of the suggested S_N1 mechanism of transesterification [80], which is analogous to reactions with 2,3-dihydropyran and with benzyloxymethyl chloride [77].

Scheme 4

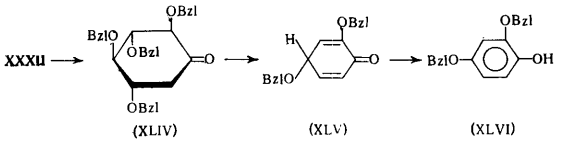


After the 3(1)-hydroxyl has been replaced, the problem is to protect the axial hydroxy-group and remove the protection from the 1(3)-hydroxyl (Scheme 4). The hydroxy-group attached to $C_{(2)}$ has been substituted by benzyl [52,61,62], acetyl [81], and tetrahydropyranyl [76] groups. 1(3), 4(6), 5,6(4)-Tetra-*O*-acetyl-*sn*-myoinositol (IX: R = CH_3CO) has not usually been employed in these syntheses, since the removal of methyl, acetyl, allyl, and tosyl groups entails deacetylation, although individual reactions [82] have been examined on this tetra-acetate. An exception is the orthoester carbohydrate protection, which makes it possible to acetylate completely the orthoester (XXXVI), and then remove the protective orthoester group without affecting the acetate groups [81]. Another factor restricting use of the tetra-acetate (IX), as well as the benzoyl derivatives to some extent, is acyl migration [83-85]. 1(3), 2,4(6), 5,6(4)-Penta-*O*-substituted derivatives of myoinositol have therefore been obtained mainly from the tetrabenzyl ether (IX: R = $C_6H_5CH_2$), from which the penta-acetate (XLIII) has also been prepared [86].

1. Tosylation–Detosylation Reactions

Tosylation of the compounds (IX: R = $C_6H_5CH_2$, CH_3CO) occurs selectively at the 3(1)-hydroxyl: tosyl chloride does not react with the sterically hindered 2-hydroxy-group [66,75]. Acetylation and benzylation of tosyl derivatives at the 2-hydroxyl (Scheme 4) followed by removal of the tosyl group might have given pentasubstituted derivatives of myoinositol with a free 1(3)-hydroxyl, but difficulties arise in such removal. Detosylation is effected with sodium amalgam in aqueous methanol at pH 5 to prevent side-reactions (deacetylation, acetyl migration, and formation of epoxides). The process takes place slowly, but varying the conditions leads to concurrent deacetylation [75].

Scheme 5



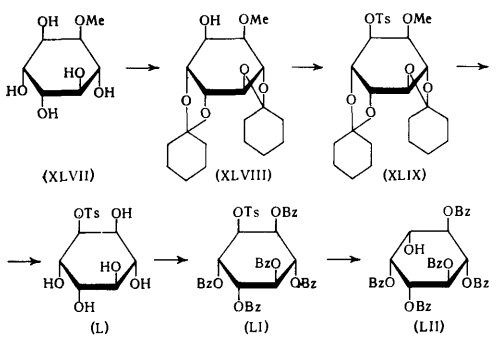
Attempts to benzylate 3(1), 4(6), 5,6(4)-tetra-*O*-benzyl-1(3)-*O*-tosyl-*sn*-myoinositol (XXXII) with benzyl chloride in the presence of alkali result in loss of the tosyl group with aromatisation of the ring. It was postulated that the reaction mechanism involved (Scheme 5) elimination of the tosyl group to give an unsaturated ketone (XLV), followed by aromatisation of the ring with formation of 2,4-dibenzyloxyphenol (XLVI). [66]

2. Methylation and Demethylation

Methyl ethers of cyclitols are of intrinsic interest, since they are widely represented in Nature [1]. They are used in the chemistry of myoinositol to establish the structure of its derivatives [71-73,78,79]. Methods of methylation are distinguished by standardisation of the conditions (methyl iodide and silver oxide) and are suitable for various derivatives of myoinositol [49,87], in which the 3(1)-hydroxyl is methylated first [66,74]. Other methods for methylating such compounds are also known (diazomethane and boron trifluoride) [88], when the 1(3)-hydroxyl is methylated more slowly than the 4(6)- and 5-groups, and the axial 2-hydroxyl does not react at all. [84]

Methyl ethers are little used as protection because of the severe conditions for demethylation by hydriodic and hydrobromic acids. Carbohydrate chemistry has recently seen the development of demethylation by means of boron trihalides (fluoride, chloride, and bromide), which form complexes with the ethereal oxygen, permitting nucleophilic cleavage of the O–CH_3 bond [89]. This method was first used in the chemistry of cyclitols by Gero [90] to prepare 1,2,4,5,6-penta-*O*-benzoyl-*sn*-myoinositol (LII) from natural quebrachitol, 2-*O*-methyl-(—)-inositol (XLVII) (Scheme 6). Cyclohexylidene and tosyl protective groups were employed in this preparation. Demethylation by boron trichloride was accompanied by removal of cyclohexylidene groups (XLIX → L). The tosylate (L) was benzoylated under the usual conditions, and the tosyl group was removed from (LI) by the action of sodium fluoride in dimethylformamide with inversion of the previously tosylated hydroxy-group.

Scheme 6



Since the initial quebrachitol (XLVII) is optically active, the pentabenzoate (LII) possesses the same property, but unfortunately only unnatural phosphoinositides, with the phosphoric residue at position 3, can be obtained from it. Another defect of the scheme is the relative unavailability of quebrachitol (XLVII). Boron tribromide has been used to remove methyl groups from pentatosylates of (–)-bornesitol (1-*O*-methyl-*sn*-myoinositol) and (+)-bornesitol (3-*O*-methyl-*sn*-myoinositol) [74,91].

3. Preparation of Penta-acyl Derivatives of Myoinositol. Acetyl Migration. Tetrahydropyranyl Protection. Acetolysis of Benzyl Ethers of Myoinositol

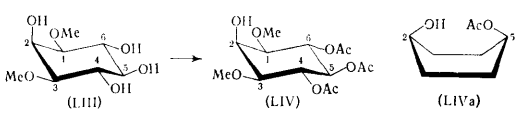
Acyl derivatives of myoinositol (acetates and benzoates) are well known. These groups are used to protect hydroxy-groups and also for the identification of derivatives. The simplicity with which acyl groups can be introduced and the great selectivity of the acylation of the 3(1)-hydroxyl attracted the attention of research workers, but these protections were then found to have substantial defects, so that they did not acquire general importance. Firstly, the ester link in derivatives of myoinositol is cleaved under conditions of hydrolysis and alcoholysis, so that it cannot be preserved during the removal of many other groups. Another disadvantage of acyl and especially acetyl groups is a tendency to migrate in the presence of bases [75,83,84].

Migration of acetyl groups in acetylated polyols has been observed previously [92–95]. In the chemistry of myoinositol attention was directed to this phenomenon in the methylation and tosylation of acetylated derivatives [49,85,96]. It is noteworthy that migration occurs when methyl iodide and silver oxide are used, but not when methylation is effected with diazomethane and boron trifluoride [83,84]. Migration is almost equally probable in *trans*- and *cis*-directions. The conformational factors responsible for the direction of these processes have not yet been determined [83,84].

The conditions governing acetyl migration have been studied in the methylation of 1(3), 4(6), 5,6(4)-tetra-*O*-acetyl-*sn*-myoinositol (IX: R = CH_3CO) and the 1(3), 3(1), 4(6), 5,6(4)-penta-*O*-acetyl derivative by the action of methyl iodide in the presence of silver oxide [83,84]. The presence of water is found to accelerate migration, which can be diminished to 25% by the addition of an anhydrous calcium sulphate, but cannot be completely suppressed because of the water produced in this method of methylation. The polarity of the solvent also influences the rate of the process: replacing dimethylformamide by chloroform in the methylation of the tetra-acetate (IX: R = CH_3CO) diminishes migration, but also lowers the yield of the methylated product. Raising the temperature accelerates methylation of the equatorial hydroxy-groups, but also increases *trans*-migration and methylation of the axial hydroxyl.

In order to avoid *trans*-migration and limit *cis*-migration in the methylation of 1(3), 4(6), 5,6(4)-tetra-*O*-acetyl-*sn*-myoinositol (IX: R = CH_3CO) it is advisable to use neutral silver oxide, a solvent of low polarity, a small content of methyl iodide, and a low temperature. However, methylation is incomplete under these conditions, and affects predominantly the equatorial position. Changing the reaction conditions in order to increase the yield entails increased migration.

Scheme 7



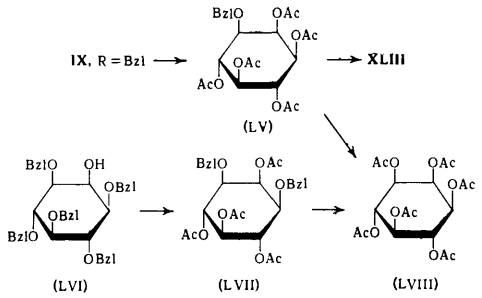
In view of possible transfers of acetyl groups round the ring, it was of interest to examine whether *trans*-ring migration—through adjacent *trans*-groups—will occur. To settle this question Angyal chose as model compound 1(3), 3(1)-di-*O*-methyl-*sn*-myoinositol (LIII, Scheme 7). [49] The axial hydroxyl remained free when this compound was acetylated, as the nuclear magnetic resonance spectra indicated that the main product was 4(6), 5,6(4)-tri-*O*-acetyl-1(3),3(1)-di-*O*-methyl-*sn*-myoinositol (LIV). The stability of the compound (LIV) in aqueous pyridine solution indicates that *trans*-ring migration is absent. These results also confirmed that myoinositol derivatives, in the present case (LIV), exist in the chair form, since in the boat form (LIVa) the 5-acetyl group is situated in a favourable position for migration to the $C_{(2)}$ atom.

Less study has been made of the behaviour of other ester derivatives of myoinositol. A benzoyl group has

been introduced at the equatorial group in 1(3), 4(6), 5,6(4)-tetra-*O*-benzyl- and -acetyl-*sn*-myoinositols (IX: R = $C_6H_5CH_2$ and CH_3CO respectively)[76,70,97] (Scheme 4). The product (XXX) was then used to obtain the 1(3), 2,4(6), 5,6(4)-penta-*O*-substituted derivative (XLII). The tetrahydropyranyl group was suggested for protecting the 2-hydroxyl in (XXX)[76]. This group had previously been used to protect primary, secondary, and tertiary alcohols[98], and several examples of its application in carbohydrate chemistry are known[99-101]. Having been the first to use it in the chemistry of myoinositol, Angyal[77] discovered the possibility of its selective removal by acid methanolysis in the presence of isopropylidene groups[102]. Unfortunately, the action of 2,3-dihydropyran is not distinguished by selectivity towards the 1(3)-hydroxyl[77]. A favourable aspect of this protection is the absence of acetyl migration when it is removed.

In spite of the difficulties caused by acetyl migration, the search for convenient synthetic methods of obtaining myoinositol penta-acetate (XLIII) was continued, since this compound forms a convenient starting point for the synthesis of an unsaturated monophosphoinositide. This problem was solved by the acetolysis of polybenzyl ethers of myoinositol[63,86,103]. Acetolysis of the tetrabenzyl ether (IX: R = $C_6H_5CH_2$) by acetic anhydride in the presence of perchloric acid at 18–20°C gives 1(3), 2,4(6), 5,6(4)-penta-*O*-acetyl-3(1)-*O*-benzylmyoinositol (LV) in 57% yield, which increases to 83% when the reaction is conducted at 0°C (Scheme 8). Acetolysis of the pentabenzyl derivative (LVI) involves formation of 2,4(6), 5,6(4)-tetra-*O*-acetyl-1(3),3(1)-di-*O*-benzyl-*sn*-myoinositol (LVII)[86].

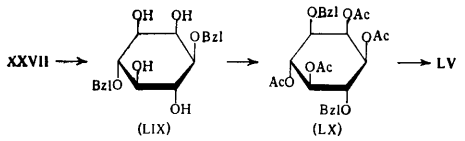
Scheme 8



The acetolysis of benzyl ethers of myoinositol (IX: R = $C_6H_5CH_2$) and (LVI) depends on steric factors. The 1(3)- and 2-benzyl groups are acetolysed more slowly than the corresponding 4(6)- and 5-groups, but this difference disappears with rise in temperature, and all benzyl groups are removed with formation of the hexa-acetate (LVIII). Acetolysis involves addition of an acetyl ion to the ethereal oxygen atom, and its rate depends on the nature and the configuration of neighbouring groups[86]: the acetoxy-group exerts greater steric hindrance than does the benzyloxy-group, and *trans*-groups impede acetolysis to a smaller extent than do *cis*-groups. It becomes clear why benzyl groups at positions 1(3) and 3(1) in the compounds (IX: R = $C_6H_5CH_2$) and (LVI) having *cis*-acetyl groups undergo acetolysis slowly. Acetolysis of the hexabenzyl ether is less selective and gives several products, among which the 1(3)-monobenzyl and 1(3),3(1)-dibenzyl derivatives (LV) and (LVII) predominate[86], which confirms the suggested reaction mechanism.

A similar process occurs in the acetolysis of 1(3), 4(6)-di-*O*-benzyl-*sn*-myoinositol (LIX), obtained from the diacetal (IV) by benzylation (XXVII) followed by removal of the protective cyclohexylidene groups (Scheme 9)[63].

Scheme 9



Hydrogenolysis of (LV) yields 1(3), 2,4(6), 5,6(4)-penta-*O*-acetyl-*sn*-myoinositol (XLIII), whose isolation may entail acetyl migration. Thus even crystallisation of the penta-acetate (XLIII) may be accompanied by migration owing to contamination with bases, and is therefore conducted in the presence of traces of acid[83,86].

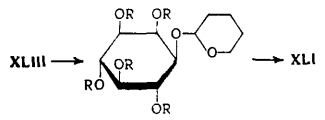
4. Pentabenzyl Ethers of Myoinositol. Allyl Protective Grouping

Benzyl ethers have found application as protective groups in the chemistry of cyclitols, in particular myoinositol, because they are stable in alkaline and acid media. They are obtained in good yields by the action of benzyl chloride or bromide in the presence of alkali[104], benzyl bromide in dimethylformamide in the presence of silver or barium oxide, and benzyl chloride in the presence of sodium hydride[105]. The benzyl group can be removed not only by catalytic hydrogenation but also by boiling with Raney nickel or reducing with metallic sodium in alcohol[66,106]. This makes the benzyl ethers convenient starting materials for obtaining monophosphoinositides. Their only disadvantage is that they cannot be used to obtain monophosphoinositides with unsaturated aliphatic acid residues.

The requirements for obtaining 1(3), 2,4(6), 5,6(4)-penta-*O*-benzyl-*sn*-myoinositol (XLI) are not satisfied by methyl, tosyl, or any ester group selectively introduced at the 3(1)-hydroxyl in the tetrabenzyl derivative (IX: R = $C_6H_5CH_2$). Allyl protection has since been successfully used for these purposes[52]. Allyl bromide, reacting mainly with the equatorial hydroxyl in the above compound (IX), gives a derivative (XXIX), which is benzylated to (XXXVII: $R^1 = CH_2.CH:CH_2$) and, after alkaline isomerisation of the allyl into the propenyl group and hydrolysis in an acid medium, is converted into (XLI)[52]. In the case of myoinositol derivatives containing acid-labile groups it has been suggested that the propenyl protection should be removed by (i) ozonolysis followed by alkaline hydrolysis, (ii) oxidation with alkaline permanganate, or (iii) the action of mercury(II) chloride in the presence of mercury[107-110]. A disadvantage of the allyl group is that it cannot be used in the presence of groups that are unstable to alkaline conditions, which applies in

particular to myoinositol derivatives with ester protecting groups. Furthermore, the conditions for isomerisation of the allyl into a propenyl group may cause aromatisation of the myoinositol ring[111].

Scheme 10



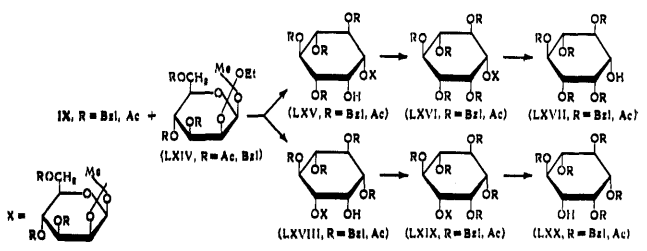
(LXI, R = Ac; LXII, R = H; LXIII, R = BzI)

Another route has recently been found[112] from the penta-acetate (XLIII) to the pentabenzyl ether (XLI). Reaction of the former with 2,3-dihydropyran gives 1(3), 2,4(6), 5,6(4)-penta-*O*-acetyl-3-*O*-tetrahydropyranyl-*sn*-myoinositol (LXI, Scheme 10), treatment of which with methanolic ammonia yields 1-*O*-tetrahydropyranyl-*sn*-myoinositol (LXII). Treatment of the latter with benzyl chloride in the presence of alkali converts it into the pentabenzyl derivative (LXIII), and removal of the oxanyl group by acid hydrolysis gives (XLI).

5. Orthoester Protective Group

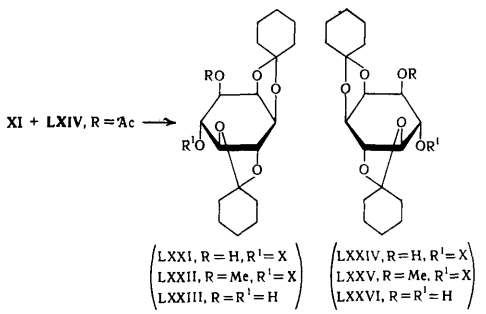
The carbohydrate orthoester group is beginning to find use in myoinositol chemistry[61,62,71-73,78,79,81,112-114]. Hitherto the main use of orthoesters has been based on their rearrangement into isomeric glycosides in the preparation of oligosaccharides[80]. The chief virtues of the orthoester group lie in the mild conditions of its introduction (transesterification with lower orthoacetates) and removal (acid hydrolysis)[80], which leave other groups unaffected. Furthermore, the diastereomeric orthoacetates of D-mannose and of myoinositol obtained from racemates of the latter differ in properties, and hence can be used to obtain optically active derivatives of an asymmetrically substituted myoinositol.

Scheme 11



D-Mannose orthoacetate (LXIV: R = CH_3CO, $C_6H_5CH_2$) has been used to prepare optically active pentabenzyl ethers and penta-acetates of myoinositol (LXVII, LXX: R = $C_6H_5CH_2$, CH_3CO—Scheme 11), which are initial compounds in the preparation of saturated and unsaturated monophosphoinositides[61,62,81,112,114]. A peculiarity of this reaction is that the 1-hydroxyl is more reactive than the 3-hydroxyl[78,81].

Scheme 12



D-Mannose orthoacetate (LXIV: R = CH_3CO) reacts with the diacetal (VI) to give the compounds (LXXI)–(LXXVI) (Scheme 12)[72,73], which, containing labile orthoester and *cis*- and *trans*-acetal groups, can be the starting points for the preparation not only of monophosphoinositides but also of di- and tri-phosphoinositides.

The orthoester protective group shows great promise in the chemistry of myoinositol, because of the simplicity of its introduction, the mild conditions of removal, and also the possibility of its use to obtain optically active derivatives of an asymmetrically substituted myoinositol.

V. PHOSPHORIC ESTERS OF MYOINOSITOL

1. Properties of Phosphoric Derivatives of Myoinositol

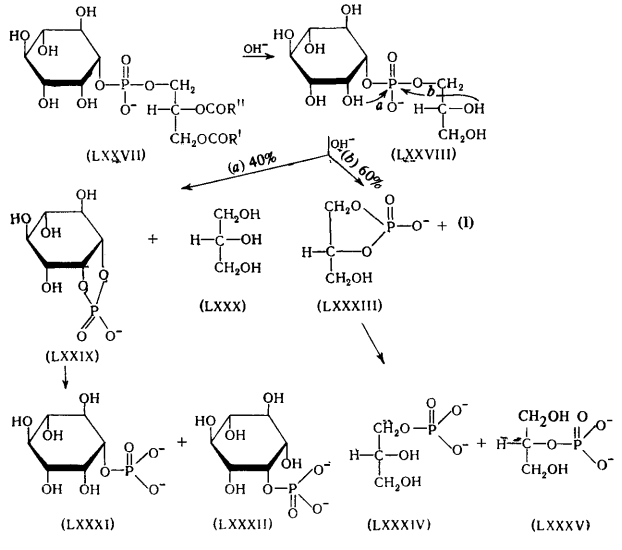
Phosphoric esters of myoinositol are polyfunctional compounds. The phosphoric groups in phosphoinositides are present in both monoesterified and diesterified forms; a triesterified form appears in the chemical reactions during preparation. Phosphoric esters of myoinositol are distinguished by lability depending on the presence of neighbouring groups. Study of the behaviour of these esters must take into account their capacity for various migrations[115-120], and therefore these properties should be allowed for in the preparation of phosphoinositides (phosphorylation, removal of protective groups).

Hydrolysis of Phosphoinositides

Diesterified phosphates of myoinositol are hydrolysed by acids and bases, the phosphates showing an appreciable tendency to cyclisation when vicinal hydroxyls are present (Scheme 13).[120-122] Such hydroxyls increase the rate of hydrolysis of phosphoric groups both in acid and in alkaline media, with formation of cyclic phosphates (LXXIX) and (LXXXIII) in the first stage. These reactions obviously involve transesterification, the cyclic phosphates being readily hydrolysed and forming the isomeric phosphates (LXXXI), (LXXXII), and (LXXXIV), (LXXXV). This is

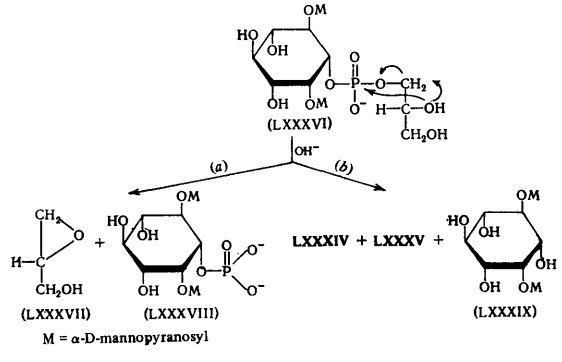
supported by results for the alkaline hydrolysis of the cyclic phosphate (LXXIX), when myoinositol 1-phosphate (LXXXI) and 2-phosphate (LXXXII) are formed to the extents of about 80–90% and 20–10% respectively, i.e. in the same proportions as in the alkaline hydrolysis of soya-bean phosphoinositides [122]. The ratio of these two phosphates shows that the bond at $C_{(2)}$ in the 1,2-cyclophosphate (LXXIX) is the more readily cleaved [122].

Scheme 13



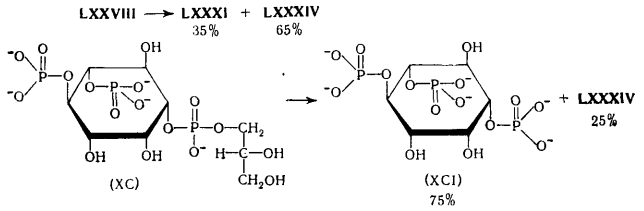
Cyclisation accompanying hydrolysis may involve functional groups both in *cis*(*ax*, *eq*) and in *trans*(*eq*, *eq*) positions. Stereochemical considerations indicate that a *cis*-diol cyclophosphate should be more stable than the *trans*-isomer, which was confirmed by Pizer and Ballou [122]. The action of dicyclohexylcarbodi-imide on *sn*-myoinositol 5-phosphate, in which the phosphate group is adjoined only by *trans*-hydroxyls, gives a series of unstable cyclophosphates, which then undergo several successive ring-openings and cyclisations, with the 1,2-cyclophosphate (LXXIX) as sole product of the reaction.

Scheme 14



The stability of deacylated dimannophosphoinositides (LXXXVI) to alkaline hydrolysis is somewhat puzzling [115–120]. The hydrolysis of these compounds is of considerable interest, since the vicinal hydroxyls attached to $C_{(2)}$ and $C_{(6)}$ are bound by a glycosidic bond with D-mannose and should not form cyclic phosphates. It might therefore have been expected that the only products of hydrolysis would be glycerophosphates, but a dimannoinositol phosphate (LXXXVIII) was also isolated on hydrolysis (Scheme 14). This fact can be explained by a different mode of degradation of the diesterified phosphate (LXXXVI), involving formation of epoxides (LXXXVII) (route *a*), which may compete with hydrolysis via intermediate formation of cyclic esters, which ultimately yield glycerophosphates (LXXXIV) and (LXXXV)—route (*b*).

Scheme 15



*Weights of hydrolysis products based on a mixture of isomers. *sn*-Myoinositol 2-phosphate and 2,4,5-triphosphate, as well as the 2-glycerophosphate, have been omitted from Scheme 15.

The ease of formation of cyclic phosphates depends very strongly on the degree of phosphorylation of the phosphoinositides [116–119]. In this connection it is interesting to compare the hydrolysis of mono- and tri-phosphoinositides (Scheme 15) [115–119,123]. Differences in the proportions of the corresponding hydrolysis products (LXXVIII) and (XC) may result from ionisation of the monoesterified phosphate groups in the triphosphoinositides, leading to distortion of the conformation of the myoinositol ring [124]. The 2-hydroxyl is then in a more favourable orientation for attack on the phosphorus, which is responsible for hydrolysis (route *a* in Scheme 13) with the formation of myoinositol triphosphate (XCI).

Migration of phosphate groups

Such migration was noticed in the isolation of glycerophosphates from lecithin and cephalin [125,126]. Hawthorne and Chargaff considered this process to be improbable in the myoinositol series in view of the large distance separating neighbouring hydroxy-groups in the chair conformation [127]. Migration of phosphate groups between vicinal hydroxy-groups in myoinositol phosphates was first observed by Posternak [128]. This phenomenon becomes appreciable at moderately low pH values [129]. The mechanism of such processes is analogous to migrations via cyclophosphates investigated in the alkaline hydrolysis of phosphoinositides (Scheme 13, route *a*) [121]. In myoinositol phosphates transfer of phosphate groups takes place when two vicinal *cis*-hydroxyls are present, whereas *trans*-migration is atypical [130].

Ballou et al.[122,131] investigated the migration of the phosphate group in *sn*-myoinositol 1-, 2-, and 5-phosphates, (-)-inositol 3-phosphate, and pinitol 4-phosphate in acid media. When 0.1 M solutions of the acid forms of myoinositol phosphates are heated to 90°C, interconversion of *sn*-myoinositol 1- and 2-phosphates is observed. The other compounds do not exhibit such properties, which indicates that autocatalytic migration of the phosphate group between *trans*-hydroxyls in hindered. It also appears possible[132] to hydrolyse monophosphoric esters of myoinositol at pH 4. Nevertheless, boiling 80% acetic acid leads to migration between the carbon atoms in positions 1(3) and 2, but not *trans*-migration; yet 1 *N* hydrochloric acid at 80–85°C causes both types of process. Under these conditions equilibrium is established between *sn*-myoinositol 1(3)- and 2-phosphates in 30 min, *trans*-migration is observed after 1 h, and all isomeric phosphates of myoinositol are detected after 8 h.[120,130,133] Thus under acid conditions transfers of phosphate groups took place between *cis*- and *trans*-positions, which governed migration round the ring.

Interconversions of myoinositol phosphates under alkaline conditions involve formation of an intermediate cyclic phosphate[134], as shown earlier. Absence of vicinal hydroxyls makes these processes more difficult owing to the low probability of formation of cyclophosphates through well separated hydroxyls, and also because of the stability of these cyclophosphates. Thus the cyclophosphate



obtained by phosphorylating *cis*-cyclohexane-1,3-diol, is not decomposed by 30% caustic soda at 100°C; ready degradation with the formation of phosphoric acid was appreciable only on treatment with 3 *N* hydrochloric acid at this temperature[134].

2. Synthetic Routes to Phosphoric Derivatives of Myoinositol

Preparation of monoesterified myoinositol phosphates

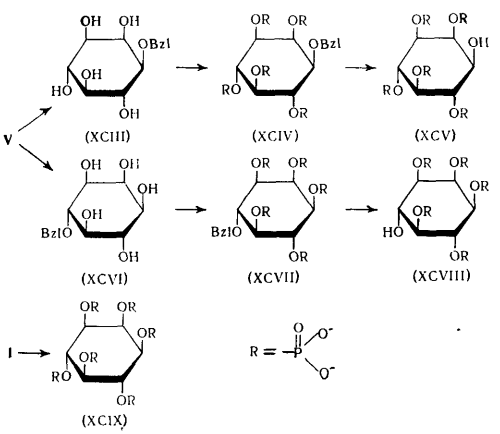
The phosphorylating agent most often used in the chemistry of monoesterified myoinositol phosphates is diphenyl phosphorochloridate, which is used at 0°C or in pyridine at 18–20°C. It is a strong phosphorylating agent, giving good yields of readily crystallisable triesterified phosphates. The phenyl groups are removed by hydrogenolysis in the presence of platinum catalysts. Phosphate migrations caused by the intrinsic acidity are avoided by isolating the myoinositol phosphates, obtained after removal of the protective groups, as their triethylammonium, cyclohexylammonium, and other salts. With as initial compounds myoinositol derivatives containing free hydroxyls at the positions to be phosphorylated, diphenyl phosphorochloridate has been successfully applied to the preparation of *sn*-myoinositol 2-phosphate[135], 1(3)-phosphate[49,52,71,112,131,136-138], 4(6)- and 5-phosphates[71,130] and 1(3), 4(6)-, 1(3),6(4)-, and 4(6),5-diphosphates[71,130]. It is interesting that, when this agent acts on D-mannose mono- and di-orthoacetates and on the diacetal (V) at 80–90°C, phosphorylation is accompanied[71] by replacement of orthoester by diphenyl phosphate groups (only phosphorylation takes place at 18–20°C), probably owing to nucleophilic attack on an orthoester oxygen atom by the activated phosphorus atom of the diphenyl phosphorochloridate with formation of a C–O–P bond. The phenomenon of removal of an orthoester group with simultaneous phosphorylation and probably acylation may find use in the synthesis of phosphoinositides.

Myoinositol monophosphates can be obtained also by the alkaline[139], acid[140], and enzymic[141-143] hydrolysis of phytin, and by the acid and alkaline hydrolysis of phosphoinositides[144,145].

The presence of a hydroxyl adjacent to the diphenoxyphosphinyloxy-group may lead to elimination of a phenyl group and migration of the phosphoric group with intermediate formation of a cyclic phosphate[118]. When the orientation of the vicinal hydroxyl is unfavourable to intramolecular phosphorylation, a bimolecular pyrophosphate may be formed. Hence the use of diphenyl phosphorochloridate for phosphorylating vicinal hydroxy-groups is not always justified.

A similar phosphorylating agent—bis-2,2,2-trichloroethyl phosphorochloridate—has recently been used to obtain monoesterified myoinositol phosphates[52]. Unlike a phenyl group, 2,2,2-trichloroethyl can be removed by the action of zinc in methyl alcohol[52]. This reagent has the same disadvantages as the diphenyl ester for obtaining polyphosphate derivatives. Dibenzyl and di-*p*-nitrobenzyl phosphorochloridates exerted a weak phosphorylating action on a secondary hydroxy-group in myoinositol[12].

Scheme 16

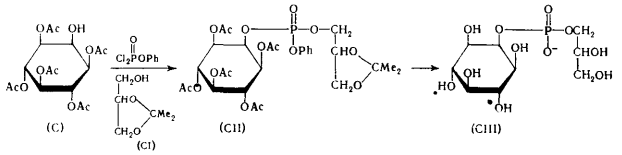


Angyal turned to polyphosphoric acid in the search for an agent for the polyphosphorylation of myoinositol derivatives[68]. However, application of this reagent to myoinositol compounds containing a benzyl, tosyl, or methyl protective group at position 1(3) results in the loss of such group with exhaustive phosphorylation. A convenient agent for these purposes was triethylammonium *N*-benzoylphosphoramidate[68], whose use completely eliminates the formation of cyclic phosphates, but involves experimental difficulties. Phytin (XCIX) and myoinositol pentaphosphates (XCV) and (XCVIII)—which may be products of the biosynthesis or decomposition of phytin—have been obtained by this method[146] (Scheme 16).

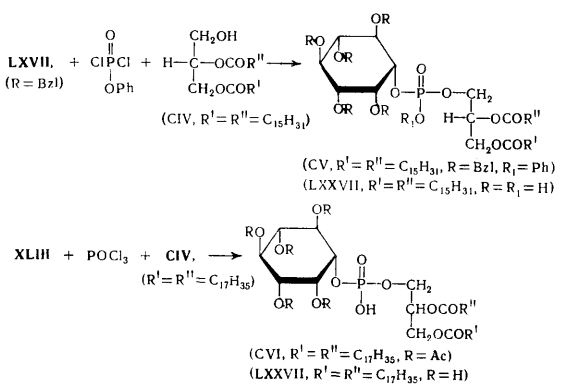
Preparation of diesterified myoinositol phosphates

Known methods of phosphorylation are used in myoinositol chemistry to form diesterified phosphate bonds[12]. Phosphorylation by means of polyfunctional chlorides of phosphoric acid presupposes the interaction of two different hydroxylated compounds followed by removal of protective groups. Thus Davies and Malkin[147] employed this method to prepare *sn*-myoinositol 2-*O*-glycerophosphate (CIII) by the interaction of *sn*-myoinositol 1(3),3(1),-4(6),5,6(4)-penta-acetate (C), phenyl phosphorodichloridate, and 1,2-*O*-isopropylideneglycerol (CI) (Scheme 17). A similar process was used to obtain the optically active monophosphoinositide (LXXVII) from the pentabenzyl derivative (LXVII: R = $C_6H_5CH_2$), phenyl phosphorodichloridate, and *sn*-glycerol 1,2-dipalmitate (CIV: R' = R" = $C_{15}H_{31}$) (Scheme 18)[61,62].

Scheme 17



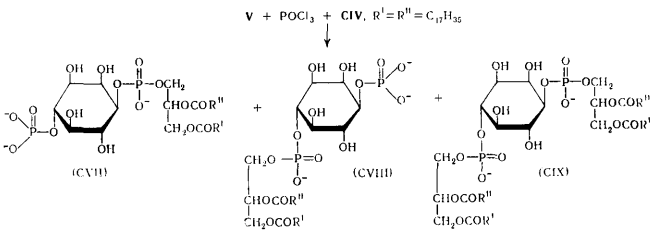
Scheme 18



Lyutik et al.[63] used phosphoryl chloride as phosphorylating agent (Scheme 18). This reacted with the 1,2-diglyceride (CIV: R' = R" = $C_{17}H_{35}$), and, without being isolated, the intermediate phosphorochloridate reacted further with myoinositol penta-acetate (XLIII). This method, unlike the previous method, can be used to obtain unsaturated monophosphoinositides. Another advantage is that the monophosphoinositide structure (CVI) is obtained as a diesterified phosphate—not the triesterified phosphate (CV)—which diminishes the number of stages in the synthesis.

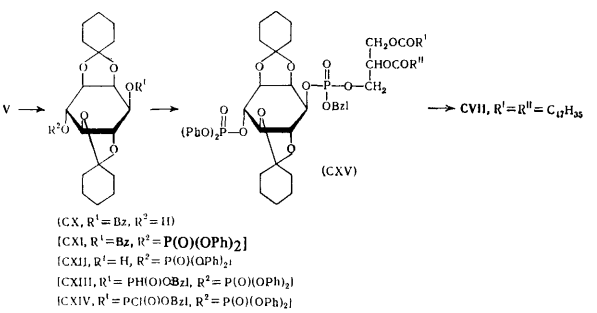
Phosphoryl chloride possesses not only advantages but also several disadvantages, which often prevent its use. Because of its polyfunctionality the phosphorylation of two hydroxylated compounds gives a large number of phosphorylated and also chlorinated products, which considerably lowers the yield of the required compound, and complicates its isolation[12].

Scheme 19



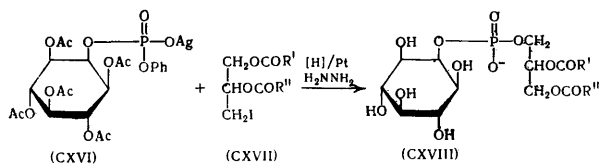
Phosphoryl chloride has been used also to produce the diesterified phosphate structure of more complicated phosphoinositides (Scheme 19)[58,59]. The above synthesis yielded not only the diphosphatidyl derivative (CIX) but also the diphosphoinositide positional isomers (CVII) and (CVIII), the latter (CVIII) having an unnatural structure. These isomers could not be separated.

Scheme 20



The above defect was overcome by using as starting material the diacetal benzoate (CX)[60], obtained by selective benzoylation of the diacetal (V) (Scheme 30)[70]. The compound (CX) was phosphorylated by means of diphenyl phosphorochloridate to form a monoesterified 4(6)-phosphate bond, and the benzoyl group was removed by the action of hydrazine hydrate (CX → CXI → CXII). A diesterified 1(3)-phosphate structure was formed by adding a phosphatidyl group by the method of mixed phosphoric anhydrides[12]: the phosphite (CXIII) was obtained by the action of the mixed anhydride of benzyl dihydrogen phosphite and diphenyl hydrogen phosphate on the derivative (CXII). The product was converted into the acid chloride (CXIV) by means of *N*-chlorosuccinimide, a new mixed anhydride was formed by the reaction of (CXIV) with diphenyl hydrogen phosphate, and this was condensed with the 1,2-diglyceride (CIV: R' = R" = $C_{17}H_{35}$) to obtain the protected diphosphoinositide (CXV), removal of the protective groups from which in the usual way gave the diphosphoinositide (CVII)[60].

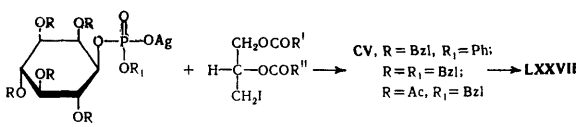
Scheme 21



(CXVI) (CXVII) (CXVIII)

The use of silver salts of substituted phosphoric acids for phosphorylation in the preparation of diesterified phosphates involves their reaction with halogen derivatives of the corresponding hydroxylated compounds. This method was first employed to obtain the unnatural monophosphoinositide (CXVIII) [148], by the action of 3-iodopropane-1,2-diyl distearate (CXVII) on the silver *sn*-myoinositol phosphate (CXVI)§ followed by removal of the protective groups (Scheme 21).

Scheme 22



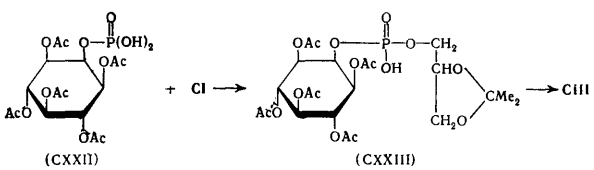
(CXIX, R = Bzl, R_1 = Ph) (CXVII, R' = R'' = $C_{15}H_{31}$;
(CXX, R = R_1 = Bzl) R' = $C_{11}H_{23}$, R'' = $C_{17}H_{33}$;
(CXXI, R = Ac, R_1 = Bzl) R' = $C_{15}H_{31}$, R'' = $C_{17}H_{33}$

The same method has been used to synthesise a natural monophosphoinositide [64,65,149] (Scheme 22), by treating the silver salts (CXIX)–(CXXI) with (CXVII). The silver salt (CXIX) was prepared by phosphorylating the pentabenzyl ether of myoinositol (XLI) with phenyl phosphorodichloridate, hydrolysing the product, and converting it into the potassium and then into the silver salt (CXIX) [52]. The silver salt (CXX) was synthesised by treating (XLI) with bis-2,2,2-trichloroethyl phosphorochloridate, removing the protective group, obtaining the dibenzyl ester by reaction with phenyldiazomethane, transforming to the sodium salt by anionic monodebenzylation, and converting to the silver salt (CXX) [149]. The silver salt (CXXI) was obtained similarly, except that myoinositol penta-acetate (XLIII) was phosphorylated with diphenyl phosphorochloridate, and the phenyl groups were then removed by hydrogenolysis [65]. This last salt (CXXI) was also prepared by treating (XLIII) with phosphoryl chloride and then with benzyl alcohol, subjecting the resulting triesterified phosphate to anionic monodebenzylation, and converting into (CXXI) [64]. The monophosphoinositide (LXXVII) containing unsaturated acid residues was obtained from (CXXI) [64,65].

The preparation of phosphoinositides by double decomposition between glycerol halogenohydrins and silver salts of phosphoric acids is distinguished by its selectivity and the high phosphorylation yields. However, it also involves many stages, as well as experimental difficulties in obtaining the starting materials, which often make it uncompetitive with other methods [12].

The reactions of monoesterified phosphates with hydroxylated compounds in the presence of condensing agents are also used to produce diesterified phosphate structures. The condensing agents act by preliminary activation of the monoesterified phosphate group [12]. Several of them are beginning to be used to obtain diesterified phosphate structures in the myoinositol series. Thus Ellis and Hawthorne synthesised the 2', 3'-dihydroxypropyl *sn*-myoinositol 1-phosphate (CIII) by condensing the phosphate (CXXII)¶ with 1,2-*O*-isopropylideneglycerol (CI) in the presence of dicyclohexylcarbodi-imide (Scheme 23) [150].

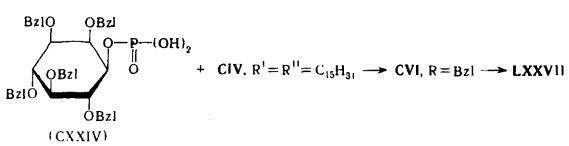
Scheme 23



(CXXII) (CXXIII)

2,4,6-Tri-isopropylbenzenesulphonyl chloride has been used to obtain the monophosphoinositide (LXXVII) from the phosphate (CXXIV) and the 1,2-diglyceride (CIV: R' = R'' = $C_{15}H_{31}$) (Scheme 24) [149]. The conversion of monoesterified into diesterified phosphates in the presence of condensing agents requires that excess of the hydroxylated compounds should be present: the use of stoichiometric quantities leads to the formation of pyrophosphate derivatives and hence a diminished yield of diesterified phosphates [150–159].

Scheme 24



(CXXIV)

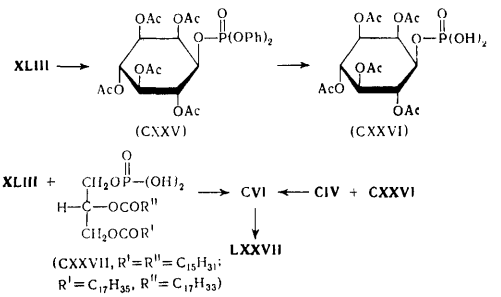
2,4,6-Trimethylbenzenesulphonyl chloride has been used in our laboratory to obtain mono- and di-phosphoinositides as optically active derivatives of natural structure or as diastereomeric mixtures (Scheme 25) [160]. Monophosphoinositides (LXXVII) have been obtained by the reaction of phosphatidic acids (CXXVII) with myoinositol penta-acetate (XLIII) or of the 1-phosphate of the penta-acetate

§The silver salt (CXVI) was prepared by phosphorylating the penta-acetate (C) with phenyl phosphorodichloridate, hydrolysing the product, isolating the potassium salt, and converting the latter into the silver salt (CXVI).

¶Compound (CXXII) was prepared by phosphorylating the myoinositol penta-acetate (C) with diphenyl phosphorochloridate and then removing the phenyl groups.

(CXXVI) with 1,2-diglycerides (CIV). A similar reaction was conducted with the phosphatidic acid (CXXVII) and the diacetal derivative (CXII) to obtain the diphosphoinositide (CVII: R' = R" = $C_{15}H_{31}$). This method is most promising for producing diesterified phosphate structures in the myoinositol series. Its virtue is that high yields of the products are obtained (almost uncontaminated with by-products) from readily available starting materials.

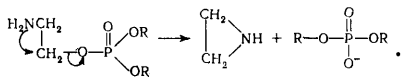
Scheme 25



Preparation of triesterified myoinositol phosphates

Various types of triesterified phosphates have already been mentioned as intermediates in the preparation of mono- and di-esterified structures. But their main interest lies in the hypothetical existence of triesterified glycerol phosphatides. It has been suggested that diesterified di- and tri-phosphoinositides are fragments of complicated lipid complexes, present in the animal brain, which may have the structure of triesters of phosphoric acid [161-165]. This hypothesis was first put forward by Collins [163]. Several hypothetical structures were suggested by Galanos and Kapoulos [164], who developed a technique for isolating lipid complexes from natural sources. According to the latter workers [164] myoinositol plays an important part in stabilising such complexes.

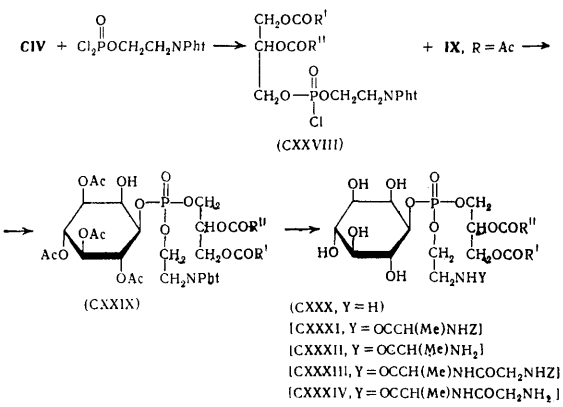
Nevertheless, other investigators [118] dispute the presence of phosphoric triesters in lipids because of instability. Reasons for the lability of triesterified myoinositol phosphates containing a vicinal hydroxyl have been discussed above. From theoretical considerations the corresponding triesters containing a neighbouring amino-group should also undergo hydrolysis with the formation of diesterified phosphate derivatives [118]:



Thus information on lipid complexes, as on triesterified phosphate structures, is inconsistent with theoretical views on the stability of such compounds studied on simple models. This problem requires further investigation, and one method may be to synthesise triesterified phosphate lipids.

Synthetic work has been done to obtain triesterified-phosphate glycerol phosphatides containing myoinositol (Scheme 26) [58,166-168]. The derivative (CXXVIII) was obtained by the action of 2-phthalimidoethyl phosphorodichloridate on the 1,2-diglyceride (CIV: R' = R" = $C_{17}H_{35}$) followed by condensation, without isolation, with the tetra-acetate (IX: R = CH_3CO), reaction occurring mainly at the equatorial hydroxyl in myoinositol [58,166]. Acetyl and phthaloyl groups were removed from the product (CXXIX) by hydrazinolysis. The resulting triesterified phosphate (CXXX) was used to synthesise phosphatido-peptides (CXXXII) and (CXXXIV) [58,167,168]—structural units in the hypothetical liquid complex of the bovine brain [164]—by condensation of the amino-group of the triesterified phosphate (CXXX) with *N*-benzyloxycarbonylalanine and *N*-benzyloxycarbonylglycylalanine followed by removal of the protective groups.

Scheme 26



The triesterified phosphate lipids—(CXXX), (CXXXII), and (CXXXIV)—are more labile than the corresponding diesterified-phosphate glycerol phosphatides [58,166-169], but their synthesis suggests that structures of this type may exist both in the free state and in natural lipids. Complexing with other natural compounds may restrict the degradation processes in triesterified phosphates studied on simple models. Final conclusions can be reached only after detailed investigation of this question.

REFERENCES

1. S. Angyal and L. Anderson, Adv. Carbohydrate Chem., **14**, 135 (1959).
2. B. A. Klyashchitskii, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Org. Khim., **5**, 192 (1969).
3. B. A. Klyashchitskii, V. I. Shvets, and N. A. Preobrazhenskii, Chem. Phys. Lipids, **3**, 393 (1969).
4. V. I. Shvets and R. P. Evstigneeva, Zhur. Org. Khim., **7**, 1550 (1972).
5. J. Hawthorne and P. Kemp, Adv. Lipid Res., **2**, 127 (1964).
6. J. Hawthorn, Vitamins and Hormones, **22**, 57 (1964).
7. "Cyclitols and Phosphoinositides", London, 1964–1966, Vols. 1 and 2.

8. B. A. Klyashchitskii, S. D. Sokolov, and V. I. Shvets, Uspekhi Khim., **38**, 740 (1969) [Russ. Chem. Rev., No. 4 (1969)].
9. "Cyclitols and Phosphoinositides—Chemistry, Metabolism, and Function", Ann. N. Y. Acad. Sci., 165, 509–819 (1969).
10. V. Ya. Dvorkin and D. A. Chetverikov, Uspekhi Sovrem. Biol., **70**, 397 (1970).
11. B. A. Klyashchitskii, V. I. Shvets, and R. P. Evstigneeva, Khim.-farm. Zhur., **5**, 7 (1971).
12. V. I. Shvets, Uspekhi Khim., **40**, 625 (1971) [Russ. Chem. Rev., No. 4 (1971)].
13. B. A. Klyashchitskii and V. I. Shvets, Uspekhi Khim., **41**, 1315 (1972) [Russ. Chem. Rev., No. 7 (1972)].
14. L. Anderson, Carbohydrate Chem. Biochem., **1A**, 520 (1972).
15. I. Grosheintz and H. Fischer, J. Amer. Chem. Soc., 70, 1476 (1948).
16. I. Grosheintz and H. Fischer, J. Amer. Chem. Soc., 70, 1479 (1948).
17. V. Brocca and A. Dansi, Ann. Chim. appl., **44**, 120 (1954).
18. T. Posternak, W. Schopfer, and R. Huguenin, Helv. Chim. Acta, **40**, 1875 (1957).
19. D. Kiely and H. Fletcher, J. Org. Chem., **39**, 1386 (1969).
20. V. D. Gusev, T. K. Mitrofanova, O. N. Tolkachev, and R. P. Evstigneeva, Khim. Prirod. Soed., 8 (1972).
21. J. Kovar and H. Baer, Canad. J. Chem., **51**, 1801 (1973).
22. C. Kowarski and S. Sarel, J. Org. Chem., **38**, 117 (1973).
23. N. Kurihara, H. Shibata, H. Saeki, and M. Nakajima, Annalen, **701**, 225 (1967).
24. T. Suami, S. Ogawa, S. Yanagida, and K. Nojima, Bull. Chem. Soc. Japan, **45**, 2593 (1972).
25. E. L. Eliel, H. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis" (Translated into Russian), Mir, Moscow, 1969, p. 419.
26. S. Barker, E. Bourne, R. Stephens, and D. Whiffen, J. Chem. Soc., 4211 (1954).
27. R. Lemieux, B. Kulling, H. Bernstein, and W. Schneider, J. Amer. Chem. Soc., 79, 1005 (1957).
28. S. Browstein, J. Amer. Chem. Soc., **81**, 1606 (1959).
29. T. Suami, S. Ogawa, and S. Oki, Bull. Chem. Soc. Japan, **44**, 2824 (1971).
30. T. Suami, S. Ogawa, T. Tanaka, and T. Otake, Bull. Chem. Soc. Japan, **44**, 835 (1971).
31. T. Suami, S. Ogawa, and S. Oki, Bull. Chem. Soc. Japan, **44**, 2820 (1971).
32. T. Suami, S. Ogawa, S. Oki, and K. Ohashi, Bull. Chem. Soc. Japan, **45**, 2597 (1972).
33. T. Suami, S. Ogawa, K. Ohashi, and S. Oki, Bull. Chem. Soc. Japan, **45**, 3660 (1972).
34. J. McConnel, S. Angyal, and J. Stevens, J. Chem. Soc., Perkin II, 2039 (1972).
35. J. Rabinowitz and J. Kraut, Acta Cryst., **17**, 159 (1964).
36. O. Hassel and B. Ottar, Acta Chem. Scand., **1**, 929 (1947).
37. O. Hassel, Research, **3**, 504 (1950).
38. O. Hassel, Quart. Rev., **7**, 221 (1953).
39. S. Angyal and D. McHugh, Chem. and Ind., 1147 (1956).
40. S. Angyal, P. Gorin, and M. Pitman, Proc. Chem. Soc., 337 (1962).
41. H. Paulsen and H. Höhne, Chem. Ber., **105**, 3445 (1972).
42. S. Angyal and J. Mills, Rev. Pure Appl. Chem., **2**, 188 (1952).
43. S. Angyal and C. Macdonald, J. Chem. Soc., 686 (1952).
44. L. Kuhn, J. Amer. Chem. Soc., **74**, 2492 (1952).
45. L. Kuhn, J. Amer. Chem. Soc., **76**, 4323 (1954).
46. K. Luhn, Spectrochim Acta, **17**, 650 (1961).
47. S. Angyal and R. Hoskinson, J. Chem. Soc., 2991 (1962).
48. S. Angyal, M. Tate, and S. Gero, J. Chem. Soc., 4116 (1961).
49. S. Angyal, P. Gilham, and C. Macdonald, J. Chem. Soc., 1417 (1957).
50. T. Posternak, Helv. Chim. Acta, **35**, 50 (1952).
51. S. Angyal and R. Hoskinson, J. Chem. Soc., 2985 (1962).
52. R. Gigg and C. Warren, J. Chem. Soc., 2367 (1969).
53. G. Domgschat, Naturwiss., **30**, 146 (1942).
54. F. Charalampous, J. Biol. Chem., **225**, 585 (1957).
55. M. Pitman, S. Angyal, and L. Anderson, Adv. Carbohydrate Chem., **14**, 155 (1959).
56. V. Micovic and A. Stojilikovic, Tetrahedron, **4**, 186 (1958).
57. S. Angyal, G. Irving, D. Rutherford, and M. Tate, J. Chem. Soc., 6662 (1965).
58. A. V. Luk'yanov, A. I. Lyutik, V. I. Shvets, and N. A. Preobrazhenskii, Dokl. Akad. Nauk SSSR, **165**, 121 (1965).
59. A. V. Luk'yanov, A. I. Lyutik, V. I. Shvets, and N. A. Preobrazhenskii, Khim. Prirod. Soed., 230 (1966).
60. S. P. Kozlova, N. B. Tarusova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., **39**, 2463 (1969).
61. B. A. Klyashchitskii, E. G. Zhelvakova, V. I. Shvets, R. P. Evstigneeva, N. A. Preobrazhenskii, Tetrahedron Letters, 578 (1970).
62. B. A. Klyashchitskii, E. G. Zhelvakova, V. V. Pimenova, V. I. Shvets, R. P. Evstigneeva, and N. A. Preobrazhenskii, Tetrahedron Letters, 41, 1386 (1971).
63. A. I. Lyutik, V. N. Krylova, S. P. Kozlova, B. A. Klyashchitskii, V. I. Shvets, R. P. Evstigneeva, E. S. Zhdanovich, Zhur. Obshch. Khim., 41, 1386 (1971).
64. Yu. G. Molotkovskii and L. D. Bergel'son, Dokl. Akad. Nauk SSSR, 198, 461 (1971).
65. J. G. Molotkovsky and L. D. Bergelson, Chem. Phys. Lipids, **11**, 135 (1973).
66. S. Angyal and M. Tate, J. Chem. Soc , 6949 (1965); S. Angyal and T. Stewart, Austral. J. Chem., **20**, 2117 (1967).
67. S. Angyal and T. Stewart, Proc. Chem. Soc., 331 (1964).
68. S. Angyal and A. Russell, Austral. J. Chem., **22**, 391 (1969).
69. B. A. Klyashchitskii, E. B. Nesterchuk, and V. I. Shvets, Zhur. Obshch. Khim., **42**, 2586 (1972).
70. N. B. Tarusova, V. S. Grosheva, S. P. Kozlova, R. B. Teplinskaya, and N. A. Preobrazhenskii, Zhur. Org. Khim., **4**, 967 (1968).
71. S. P. Kozlova, I. S. Pekarskaya, B. A. Klyashchitskii, V. I. Shvets, and R. P. Evstigneeva, Zhur. Obshch. Khim., **42**, 702 (1972).
72. B. A. Klyashchitskii, A. K. Starostina, V. I. Shvets, and R. P. Evstigneeva, Dokl. Akad. Nauk SSSR, **195**, 102 (1970).
73. B. A. Klyashchitskii, A. K. Starostina, L. F. Linberg, V. I. Shvets, and R. P. Evstigneeva, Zhur. Org. Khim., 7, 492 (1971).
74. E. G. Zhelvakova, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Org. Khim., 6, 62 (1970).

75. S. Angyal, P. Gilham, and G. Melrose, J. Chem. Soc., 5252 (1965).
76. T. P. Zubkova, Z. Ya. Khrapkova, I. K. Sarycheva, and N. A. Preobrazhenskii, Zhur. Org. Khim., **4**, 2226 (1968).
77. S. Angyal and S. Gero, J. Chem. Soc., 5255 (1965).
78. B. A. Klyashchitskii, G. D. Strakhova, V. I. Shvets, S. D. Sokolov, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., **40**, 236 (1970).
79. B. A. Klyashchitskii, A. E. Stepanov, V. I. Shvets, R. P. Evstigneeva, and N. A. Preobrazhenskii, Zhur. Org. Khim., **7**, 487 (1971).
80. N. K. Kochetkov, A. Ya. Khorlin, and A. F. Bochkov, Tetrahedron, **23**, 693 (1967).
81. A. E. Stepanov, O. O. Tutorskaya, B. A. Klyashchitskii, V. I. Shvets, and R. P. Evstigneeva, Zhur. Obshch. Khim., **42**, 709 (1972).
82. J. Davies and T. Malkin, Nature, **184**, 789 (1959).
83. S. Angyal and G. Melrose, J. Chem. Soc., 6494 (1965).
84. S. Angyal and G. Melrose, J. Chem. Soc., 6501 (1965).
85. L. Anderson and A. Landel, J. Amer. Chem. Soc., **76**, 6130 (1954).
86. S. Angyal and M. Randall, J. Chem. Soc. (C), 919 (1967).
87. R. Shah and F. Owens, J. Label Compounds, **6**, 333 (1970).
88. M. Neeman, M. Caserio, J. Roberts, and W. Johnson, Tetrahedron, **6**, 36 (1959).
89. S. Allen, T. Bonner, E. Bourne, and N. Saville, Chem. and Ind., 630 (1958).
90. D. Mercier, J. Barnett, and S. Gero, Tetrahedron, **25**, 5681 (1969).
91. E. G. Zhelvakova, O. G. Ul'yanova, V. I. Shvets, and N. A. Preobrazhenskii, Khim. Prirod. Soed., 163 (1970).
92. E. Fischer, Ber., **53**, 1621 (1920).
93. H. Ohle, Ber., **57**, 403 (1924).
94. J. Sugihara, Adv. Carbohydrate Chem., **8**, 2 (1963).
95. W. Bonner, J. Org. Chem., **24**, 1388 (1959).
96. R. Kuhn, H. Trischmann, and J. Löw, Angew. Chem., **67**, 32 (1955).
97. T. Suami, T. Lichtenthaler, and S. Ogawa, Bull. Chem. Soc. Japan, **39**, 170 (1966).
98. J. McOmie, Adv. Org. Chem., **3**, 218 (1963).
99. H. Khorana, A. Turner, and J. Vizsolyi, J. Amer. Chem. Soc., **83**, 686 (1961).
100. M. Smith, D. Rammler, J. Goldberg, and H. Khorana, J. Amer. Chem. Soc., **84**, 420 (1962).
101. A. Belder, P. Garegg, and B. Lindberg, Acta chem. Scand., **16**, 623 (1962).
102. B. Baker and H. Sachder, J. Org. Chem., **28**, 2132 (1963).
103. H. Burton and P. Praill, J. Chem. Soc., 522 (1951).
104. G. Zemplen, Z. Crüros, and S. Angyal, Ber., **70**, 1848 (1937).
105. M. Tate and C. Bishop, Canad. J. Chem., **41**, 1801 (1963).
106. C. McCloskey, Adv. Carbohydrate Chem., **12**, 137 (1957).
107. J. Gigg and R. Gigg, J. Chem. Soc. (C), 82 (1966).
108. R. Gigg, and C. Warren, J. Chem. Soc. (C), 1903 (1968).
109. R. Gigg and C. Warren, J. Chem. Soc., 2205 (1965).
110. R. Gigg and C. Warren, Tetrahedron Letters, 1683 (1967).
111. P. Gent and R. Gigg, J. Chem. Soc. (C), 2253 (1970).
112. B. A. Klyashchitskii, V. V. Pimenova, A. I. Bashkatova, E. G. Zhelvakova, S. D. Sokolov, V. I. Shvets, R. P. Evstigneeva, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., **40**, 2482 (1970).
113. B. A. Klyashchitskii, G. D. Strakhova, V. I. Shvets, S. D. Sokolov, and N. A. Preobrazhenskii, Dokl. Akad. Nauk SSSR, **185**, 106 (1969).
114. V. I. Shvets, B. A. Klyashchitskii, A. E. Stepanov, and R. P. Evstigneeva, Tetrahedron, **29**, 231 (1973).
115. H. Hendrickson, Ann. N. Y. Acad. Sci., **165**, 668 (1969).
116. M. Kai and J. Hawthorne, Ann. N. Y. Acad. Sci., **165**, 761 (1969).
117. R. Dawson, Ann. N. Y. Acad. Sci., **165**, 782 (1969).
118. D. Brown, Ann. N. Y. Acad. Sci., **165**, 687 (1969).
119. D. Brown, G. Hall, and R. Letters, J. Chem. Soc., 3547 (1959).
120. Y. Lee and C. Ballou, J. Biol. Chem., **239**, 1316 (1964).
121. D. Brown, G. Hall, and H. Higson, J. Chem. Soc., 1360 (1958).
122. F. Pizer and C. Ballou, J. Amer. Chem. Soc., **81**, 915 (1959).
123. D. Brown and J. Stewart, Biochim. Biophys. Acta, **125**, 413 (1966).
124. S. Angyal, Quart. Rev., **11**, 212 (1957).
125. E. Baer and M. Kates, J. Biol. Chem., **175**, 79 (1948).
126. E. Baer and M. Kates, J. Biol. Chem., **185**, 615 (1950).
127. J. Hawthorne and E. Chargaff, J. Biol. Chem., **206**, 27 (1954).
128. T. Posternak, Helv. Chim. Acta, **41**, 1891 (1958).
129. D. Brown and A. Todd, Nature, **177**, 1124 (1956).
130. S. Angyal and M. Tate, J. Chem. Soc., 4122 (1961).
131. G. Kildour and C. Ballou, J. Amer. Chem. Soc., **80**, 3956 (1958).
132. J. Baddiley, J. Buchanan, and R. Letters, J. Chem. Soc., 1000 (1958).
133. T. Posternak, Helv. Chim. Acta, **42**, 390 (1959).
134. D. Brown and H. Higson, J. Chem. Soc., 2034 (1957).
135. B. Iselin, J. Amer. Chem. Soc., **71**, 3822 (1949).
136. C. Ballou and L. Pizer, J. Amer. Chem. Soc., **81**, 4745 (1959).
137. C. Ballou and L. Pizer, J. Amer. Chem. Soc., **82**, 3333 (1960).
138. J. G. Molotkovsky and L. D. Bergelson, Tetrahedron Letters, 4791 (1971).
139. A. Desjobert, Bull. Soc. Chim. Biol., **36**, 1293 (1954).
140. L. Anderson, J. Biol. Chem., **18**, 441 (1914).
141. M. McCornick and H. Carter, Biochem. Prep., **2**, 65 (1952).
142. S. Posternak and T. Posternak, Helv. Chim. Acta, **12**, 1165 (1929).
143. D. Brown and G. Hall, J. Chem. Soc., 357 (1959).
144. J. McKibbin, J. Biol. Chem., **220**, 537 (1956).
145. R. Dawson and J. Eichberg, Biochem. J., **96**, 634 (1965).
146. D. Cosgrove, Rev. Pure Appl. Chem., **16**, 209 (1966).
147. J. Davies and T. Malkin, Nature, **184**, 789 (1959).
148. J. Davies and T. Malkin, Chem. and Ind., 1155 (1959).
149. P. Gent and R. Gigg, Tetrahedron Letters, 2575 (1970).
150. R. Ellis and J. Hawthorne, Nature, **184**, 790 (1959).
151. P. Gilham and H. Khorana, J. Amer. Chem. Soc., **80**, 6212 (1958).

152. H. G. Khorana, "Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest" (Translated into Russian), Mir, Moscow, 1964, p. 146.
153. F. Cramer and G. Weimann, Chem. and Ind., 46 (1960).
154. H. Staab, H. Schaller, and F. Cramer, Angew. Chem., 71, 736 (1959).
155. H. Staab, Angew. Chem., 68, 754 (1956).
156. J. Moffat and H. Khorana, J. Amer. Chem. Soc., 83, 649 (1961).
157. R. Lohrmann and H. Khorana, J. Amer. Chem. Soc., 88, 829 (1966).
158. R. Aneja, J. Chadha, and A. Davies, Biochim. Biophys. Acta, 218, 102 (1970).
159. A. P. Kaplun, M. A. Kabanova, A. I. Lyutik, V. I. Shvets, and R. P. Evstigneeva, Zhur. Obshch. Khim., 43, 1839 (1973).
160. V. I. Shvets, Doctoral Thesis, Moscow Institute of Fine Chemical Technology, 1973.
161. J. Folch and F. LeBaron, Canad. J. Biochem. Physiol., 34, 305 (1956).
162. T. Malkin and A. Poole, J. Chem. Soc., 3470 (1953).
163. F. Collins, Nature, 188, 297 (1960).
164. D. Galanos and V. Kapoulas, Biochim. Biophys. Acta, 98, 278, 293, 331 (1965).
165. J. Davenport, Nature, 210, 198 (1966).
166. A. V. Luk'yanov, A. I. Lyutik, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 36, 1029 (1966).
167. A. V. Luk'yanov, A. I. Lyutik, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 36, 1031 (1966).
168. A. I. Lyutik, A. V. Luk'yanov, E. S. Zhdanovich, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 38, 2251 (1968).
169. V. I. Shvets, M. K. Petrova, R. B. Teplinskaya, N. V. Arkhangel'skaya, Ziyad Kafai al'-Azzavi, E. V. Golubkova, E. G. Ivanova, and N. A. Preobrazhenskii, Zhur. Org. Khim., 5, 2033 (1969).

Lomonosov Moscow Institute
of Fine Chemical Technology