U.D.C. 547.953.1

Advances in the Synthesis of Glycerol Phosphatide Esters

V.I.Shvets

CONTENTS

I. Introduction	330
II. Synthesis of glycerophosphatides from 1,2-diglyceride structures	330
III. Synthesis of glycerophosphatides by the acylation of substituted glycerophosphoric acids	336
IV. Synthesis of complex glycerophosphatides	337
V. Methods of synthesis of optically active phosphoinositides	338

A survey is given of the present position in the synthesis of glycerol phosphatide esters—phosphoric esters in which the glycerol residue is esterified—some of the principal representatives of the biologically important class of substances, the lipids. The main principles and recent advances are discussed in the synthesis of classical glycerol phosphatide diesters of the type of cephalins, lecithins, phosphatidylserines, cardiolipins, phosphatidylglycerols and their amino-acid derivatives, etc., and also complex phosphatides containing amino-acids, peptides, and sugars. Special attention is paid to the synthesis of optically active unsymettrically substituted myoinositols, which include such glycerol phosphatides as mono-, di-, and tri-phosphoinositides and complexes based on them. The list of references includes 246 items.

I. INTRODUCTION

During the past twenty years the chemistry of the important natural compounds the lipids, including that of glycerol phosphatide esters, has made great advances, with the possibility of finally determining the structure of the principal classical glycerophosphatide esters—phosphatidic acids, phosphatidylaminoethanols (cephalins), phosphatidylcholines (lecithins), phosphatidylserines, phosphoinositides of various types (mono-, di-, and tri-phosphoinositides) phosphatidylglycerols, diphosphatidylglycerols (cardiolipins), amino-acid derivatives of phosphatidylglycerol, etc.[1,2]

To a considerable extent this enabled the problem of studying the part played by glycerophosphatides in processes occurring in the living cell (membrane processes, the chain of electron transfer, the transmission of nerve impulses, metabolic mechanisms, etc.) to be raised to the molecular level, which promises in the near future to solve many fundamental questions of biology where an important role is assigned to glycerophosphatides[3].

Synthetic work in the field of glycerophosphatides has made one of the principal contributions to their chemical investigation. The main lines of these researches were shown in several reviews[4-12], which were devoted to individual aspects of the synthetic chemistry of glycerophosphatides and hence did not give a complete picture. Furthermore, most of them almost completely ignore work in the Soviet Union on the synthesis of glycerophosphatides, which is being widely developed at the present time and in many respects has enriched considerably our knowledge of their chemistry. These were the main reasons for publishing the present Review.

The synthesis of glycerophosphatides reached its present level in effect only during the past decade in connection with the widespread introduction into the chemistry of lipids of physicochemical methods for purifying and identifying organic compounds and establishing their structure. In this sense an important part in the advances of recent years has been played by adsorption, paper, thin-layer, and gas–liquid chromatography, infrared spectroscopy, and recently mass spectroscopy, nuclear magnetic resonance (n.m.r.), and optical rotatory dispersion.

Nowadays the synthesis of diester glycerophosphatides such as cephalins, lecithins, and phosphatidylserines—which are often termed classical—presents no difficulty, largely owing to recent advances in the synthesis of triester glycerophosphatides[13-15], phosphatidopeptides[16-21], and other complex glycerophosphatides[22-26], papers on whose isolation from natural sources have begun to appear.

The methods now used for the preparation of glycerophosphatides consist in the successive building up of individual structural parts of the molecule (phosphoric esters of the nitrogen bases and amino-acids, aliphatic acids, etc.) from various derivatives of unsymmetrically substituted glycerol.

All the methods which have been described for synthesising glycerophosphatides can be divided into two broad groups: (1) synthesis from 1,2-diglyceride structures presupposes the initial production of the 1,2-diglyceride part of the molecule, so that in this case the introduction of aliphatic acids into a substituted glycerol molecule precedes phosphorylation; (2) the synthesis from glycerophosphoric esters is characterised by the opposite sequence of esterification and phosphorylation.

II. SYNTHESIS OF GLYCEROPHOSPHATIDES FROM 1,2-DIGLYCERIDE STRUCTURES

This group of preparations includes two independent methods. A common feature is the initial production of a 1,2-diglyceride structure either in the form of a 1,2-diacyl-*sn*-glycerol† or as a 1,2-diacyl-3-deoxy-3-iodo(or bromo)-*sn*-glycerol. Phosphoric ester bonds are formed with the first group of compounds by well known methods of phosphorylation[27], and with the second group by reaction with the silver salts of substituted phosphoric acids[28].

† The nomenclature of optically active unsymmetrically substituted glycerol derivatives conforms to the IUPAC–IUB rules—European J. Biochem., 2, 127 (1967).

1. Synthesis of 1,2-Diglycerides

The preparation of 1,2-diglycerides presents considerable difficulties, owing to the greater reactivity of the 1,3-hydroxy-groups of glycerol in comparison with the 2-hydroxyl, and also because of the ease of migration of acyl groups from the 2-position to the 1- and 3-positions[29]. Therefore many of the earlier published syntheses of 1,2-diglycerides did not yield pure compounds but mixtures of 1,2- and 1,3-diglycerides. These facts have necessitated special approaches to the preparation of 1,2-diglycerides which would avoid these difficulties.

One approach is the temporary protection of the 3-hydroxyl. The methods used most frequently have been benzyloxycarbonyl[30], trityl[31-35], benzyl[39], oxanyl[34,37], ethoxyethyl[34], and 2,2,2-trichloroethoxycarbonyl[38,39] protection. The 3-*O*-derivatives of glycerol were esterified either in stages or exhaustively, and at the last stage the protecting group was removed by catalytic hydrogenolysis[30-32,36] or mild acid hydrolysis, excluding migration of the aliphatic acid radicals[33-35,38,39]. This yielded 1,2-diglycerides containing the same or different acids. The problem of the selective introduction of different aliphatic acid radicals and also the possibility of obtaining highly unsaturated 1,2-diglycerides will be specially considered in subsequent sections.

Another approach to the preparation of 1,2-diacylglycerols consists in using 2-monoglycerides obtained by removing benzylidene protecting groups by catalytic hydrogenolysis[40,41] or mild hydrolysis with boric acid[42,43] of the corresponding acyl derivatives of 1,3-*O*-benzylideneglycerol. 2-Monoglycerides are selectively esterified to 1,2-diglycerides. The method makes it possible to obtain racemic 1,2-diglycerides of any structure and degree of unsaturation.

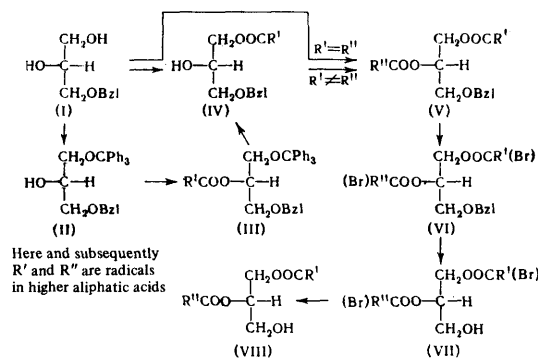
None of the above methods is universally applicable: with some of them it is impossible (or possible in only a few cases) to obtain 1,2-diglycerides containing the radicals of highly unsaturated aliphatic acids[30-32,36], which are widely distributed in natural sources and are of the greatest biological value[1,2]; other methods are unsuited to the preparation of optically active 1,2-diacyl-*sn*-glycerols[30-33,37,44-47], in the form in which they are involved in various biological processes in the living cell[1,2].

Further discussion of synthetic approaches to 1,2-diglycerides will be arranged to show which methods are most suitable for the preparation of saturated and unsaturated 1,2-diacyl-*sn*-glycerols containing the same and different acid radicals. These compounds have been prepared most often by the benzyl method, which was proposed for saturated 1,2-diglycerides[36].

Hydrogenation of ethylenic double bonds in acyl radicals during the preparation of unsaturated 1,2-diglycerides, which would occur on catalytic debenzylation (VI) → (VII), is avoided by preliminary protection with bromine (V) → (VI). Debenzylation is followed by debromination with zinc dust (VII) → (VIII), which restores the original double bonds, without change in their configuration, to give the 1,2-diacyl-*sn*-glycerols (VIII)[48-57] (Scheme 1).

Diglycerides containing different acid radicals can be prepared in two ways, distinguished by the methods used to introduce aliphatic acids into the 1- and 2-positions—(i) acylation in stages (I) → (IV) → (V)[51,52,54,56,57] [direct esterification (I) → (V) yields diglycerides containing the same acid radicals[48,50,52,55]], and (ii) preliminary protection of the 1-hydroxyl with a trityl radical (I) → (II), which, after introduction of an aliphatic acid radical on the 2-hydroxyl (II) → (III), is removed by means of hydrogen chloride with migration of the acyl radical from the 2- to the 1-position (III) → (IV), this being followed by esterification of the freed 2-hydroxyl (IV) → (V).[49,53,54]

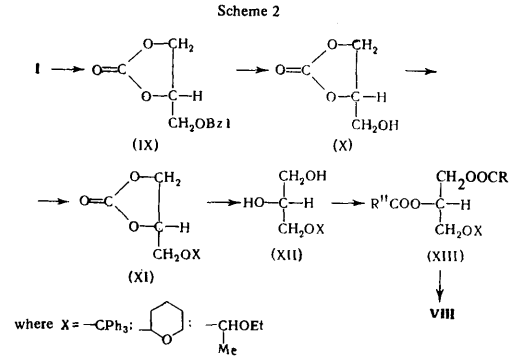
Scheme 1



With highly unsaturated aliphatic acids such as linoleic and linolenic acids the benzyl method of preparing diglycerides has considerable limitations[50-57], and it is entirely unsuitable for the preparation of 1,2-diacyl-*sn*-glycerols containing still more highly unsaturated acid radicals, e.g. from arachidonic acid. This is because a large quantity of bromine introduced at the double bonds in the aliphatic acid leads to difficulties in debenzylation owing to poisoning of the catalyst, and also because of the poor solubility of the bromides which are formed. Several attempts have been made recently to modify the benzyl method of preparing 1,2-diglycerides with the aim of applying it to obtain 1,2-diacyl-*sn*-glycerols of any degree of unsaturation.

The first of these attempts consists in replacing the benzyl protection in 3-*O*-benzyl-*sn*-glycerol (I) by a trityl, an oxanyl, or an ethoxyethyl group (I) → (XII). These groups are easily removed by mild acid hydrolysis of compounds of type (XIII)—obtained by the esterification of 3-*O*-derivatives of *sn*-glycerol (XII)—with the formation of 1,2-diglycerides (VIII) (Scheme 2).[34]

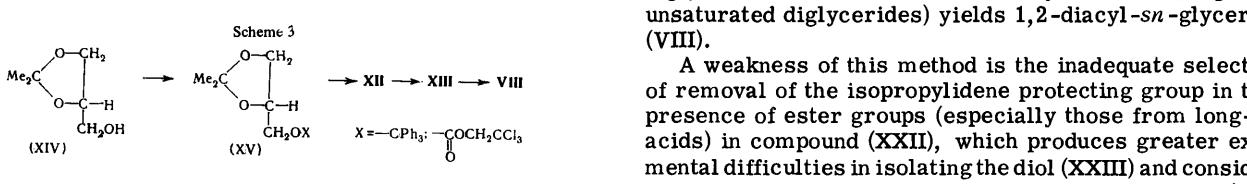
Scheme 2



Other papers[35,38,39] also propose replacing the benzyl group in 3-*O*-substituted glycerol (XII) by groups more suitable for the preparation of highly unsaturated 1,2-diglycerides, such as trityl[35] and 2,2,2-trichloroethoxycarbonyl[38,39] (the former is removed by chromatography on

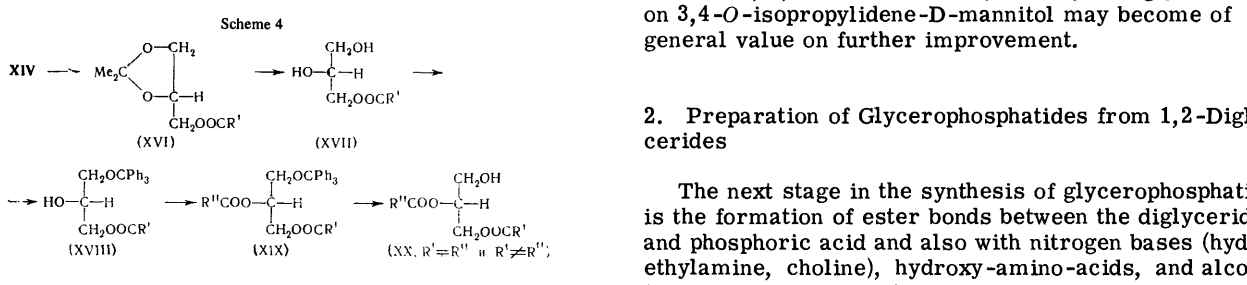
silicic acid[33], and the latter with zinc in acetic acid[38,39]) (Scheme 3).

Scheme 3



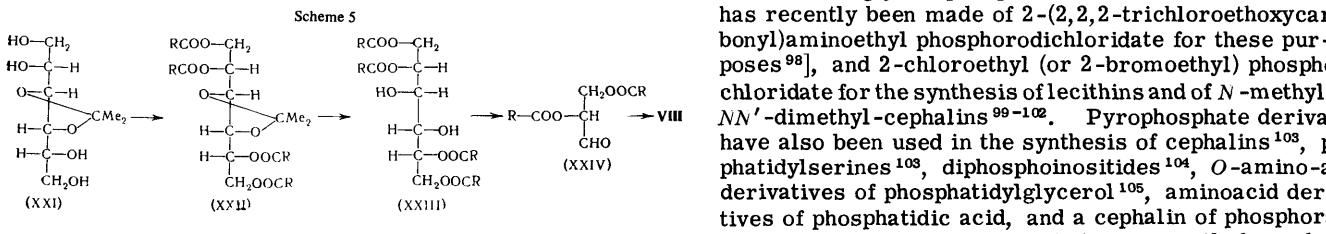
The chief difficulty in these syntheses is to remove isopropylidene protecting groups‡ in the presence of trityl and 2,2,2-trichloroethoxycarbonyl groups (XV) → (XII): in the first case[35] this is achieved by the action of trichloroacetic acid, and in the latter case with boric acid[38,39]. Since both isopropylidene and the two other protective groups[35,38,39] are sensitive to acid hydrolysis, although in differing degrees, it is difficult to rely on complete selectivity of removal of the acetal group, which considerably diminishes the potentialities of this method.

Scheme 4



Attempts to replace benzyl by trityl protecting groups had been made earlier (Scheme 4).[56,58] The diglycerides were prepared from 1,2-*O*-isopropylidene-*sn*-glycerol (XIV), which was converted into the 3-monoglyceride (XVII), then subjected to tritylation and complete acylation (XVII) → (XVIII) → (XIX), and after removal of the trityl protecting group under mild conditions[33] converted, as was to be expected, into the enantiomer of the natural diglyceride, 2,3-diacyl-*sn*-glycerol (XX). The preparation of 1,2-diacyl-*sn*-glycerols by this method from L-mannitol as starting material (D-mannitol was used in the other preparations) was impracticable because of the great shortage of L-mannitol.

Scheme 5



Finally, a new method has recently been suggested for preparing 1,2-diacyl-*sn*-glycerols[59], in which the starting material is 3,4-*O*-isopropylidene-D-mannitol (XXI), which is obtained from D-mannitol via the intermediate formation of 1,2 : 3,4 : 5,6-tri-*O*-isopropylidene-D-mannitol (Scheme 5).[60] Esterification converts (XXI) into the tetra-acyl derivative (XXII). After mild acid hydrolysis of the acetal protecting group the diol (XXIII) is oxidised with lead tetra-acetate to the 1,2-diacyl-*sn*-glyceraldehyde (XXIV). Reduction of (XXIV) with hydrogen in the presence of Raney nickel (for the preparation of saturated diglycerides) or with sodium tetrahydroborate (to give unsaturated diglycerides) yields 1,2-diacyl-*sn*-glycerols (VIII).

A weakness of this method is the inadequate selectivity of removal of the isopropylidene protecting group in the presence of ester groups (especially those from long-chain acids) in compound (XXII), which produces greater experimental difficulties in isolating the diol (XXIII) and considerably diminishes the overall yield of the diglyceride (VIII).

Summarising this Section, we can say that, in spite of the great amount of work on the preparation of 1,2-diacyl-*sn*-glycerols, no method can be suggested at the present time which would be universally applicable to products of any structure and degree of unsaturation. Nevertheless, some specialisation of methods is possible. The benzyl method is the most suitable for obtaining saturated and slightly unsaturated diglycerides. The carbonate method is to be recommended for the preparation of highly unsaturated diglycerides. Finally, methods based on 3-*O*-trityl- or 3-*O*-2′,2′,2′-trichloroethoxycarbonyl-*sn*-glycerols and on 3,4-*O*-isopropylidene-D-mannitol may become of general value on further improvement.

2. Preparation of Glycerophosphatides from 1,2-Diglycerides

The next stage in the synthesis of glycerophosphatides is the formation of ester bonds between the diglycerides and phosphoric acid and also with nitrogen bases (hydroxyethylamine, choline), hydroxy-amino-acids, and alcohols (glycerol, myoinositol).

Phosphorylation is most often effected with phenyl phosphorodichloridate[61-74] and phosphoryl chloride[39,57,75-93] in the cases of saturated and unsaturated compounds respectively. Use of the latter agent lowers the yield of the final glycerophosphatides owing to formation of a large quantity of by-products. Compounds of the required structure are isolated from the complicated reaction mixture mostly by chromatography on silicic acid.

There are several modifications of phosphorylation, which make it possible to achieve unambiguous results in certain particular cases. Thus 2-phthalimidoethyl phosphorodichloridate has been used for the synthesis of cephalins and triester glycerophosphatides[13-15,21,44,47,55,58,94-97] [use has recently been made of 2-(2,2,2-trichloroethoxycarbonyl)aminoethyl phosphorodichloridate for these purposes[98]], and 2-chloroethyl (or 2-bromoethyl) phosphorochloridate for the synthesis of lecithins and of *N*-methyl- and *NN*′-dimethyl-cephalins[99-102]. Pyrophosphate derivatives have also been used in the synthesis of cephalins[103], phosphatidylserines[103], diphosphoinositides[104], *O*-amino-acid derivatives of phosphatidylglycerol[105], aminoacid derivatives of phosphatidic acid, and a cephalin of phosphoramide type[24,26]. Interesting methods have recently been developed for producing bonds of the type P—O—nitrogen base (the latter is usually aminoethanol). Among them are the reactions of phosphatidic acids with aziridine and its derivatives[106,107], and also with nitrogen bases in the presence of trichloroacetonitrile[39], 2,4,6-tri-isopropylbenzenesulphonyl chloride[108], and dicyclohexylcarbodiimide[109]. This last reagent has also been used to obtain phosphatidylglycerol and dipyrophosphatidic acid from phosphatidic acid[93,100].

In order to ensure an unambiguous result of phosphorylation, all the functional groups, other than the hydroxyls

‡ See next paragraph (Editor of Translation).

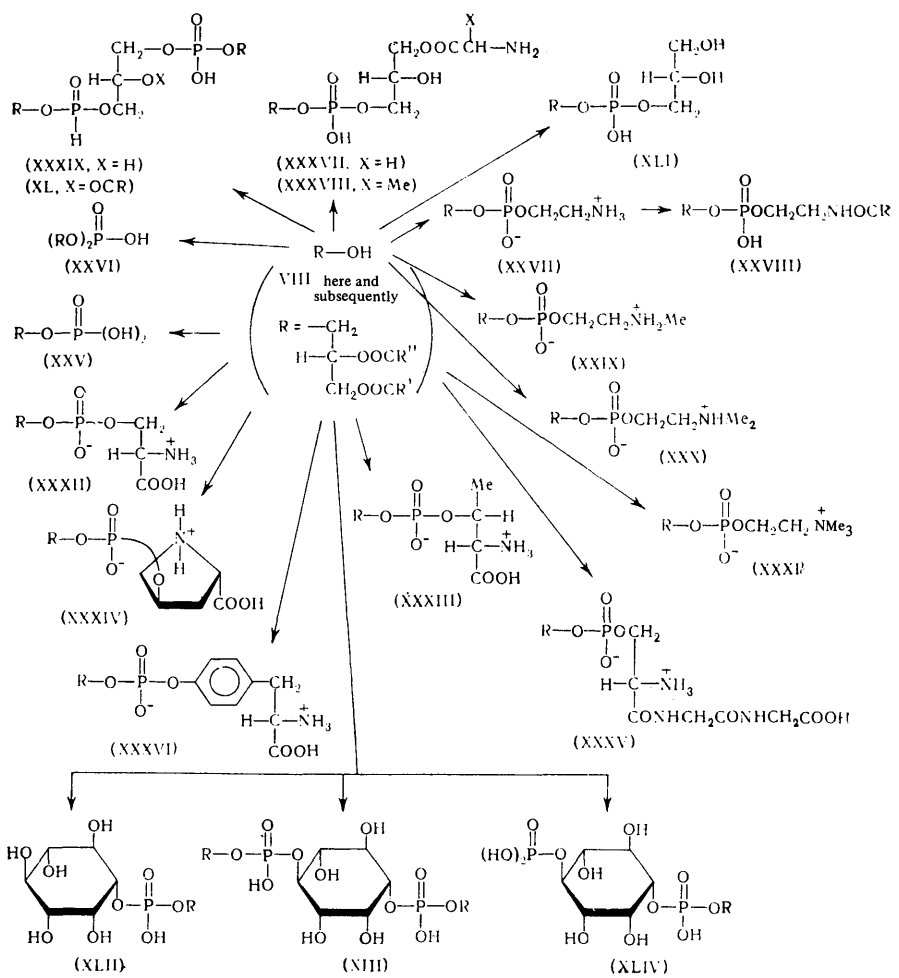
to be phosphorylated, in the nitrogen bases, hydroxy-amino-acids, glycerol, and myoinositol are blocked with protective groups. Amino-groups are protected with benzyloxycarbonyl [13,14,19,25,64,66-72,85], phthaloyl [13-15,44,45,47,55,58,77,78,84,86,94-97,105], t-butoxycarbonyl [39,81,83,90,91,109], methoxybenzyloxycarbonyl [92], 2,2,2-trichloroethoxycarbonyl [98], and γ-chlorobutyroyl [87] groups. The carboxy-groups of the amino-acids are blocked with benzyl [15,24,26,66,67,69,70,103], t-butyl [83,86,90], and phthalimidomethyl [81,87,92] protecting groups; and the hydroxyl of glycerol and myoinositol with benzyl [73,88,105,111-113], t-butyl [91], isopropylidene [75], cyclohexylidene [104,114], acetyl [13,16,21,115], benzoyl [104,116,117], toluene-*p*-sulphonyl [118,119], and oxanyl [111,116] groups.

Protective benzyloxycarbonyl, benzyl, and toluene-*p*-sulphonyl groups are removed in the last stages of hydrogenolysis, which excludes their application to the preparation of unsaturated glycerophosphatides. However, the methods which have appeared for the mild electrochemical removal of these groups will undoubtedly enable the limitations on their protective use to be overcome [20,120,121]. The conditions under which the remaining protective groups are eliminated enables them to be recommended for the preparation of both saturated and unsaturated glycerophosphatides. Thus phthaloyl, phthalimidomethyl, acetyl, and benzoyl groups are split off by mild hydrazinolysis, t-butyl, t-butoxycarbonyl, methoxybenzyloxycarbonyl, γ-chlorobutyroyl, isopropylidene, cyclohexylidene, and oxanyl groups by mild acid hydrolysis; and the 2,2,2-trichloroethoxycarbonyl radical with zinc in acetic acid.

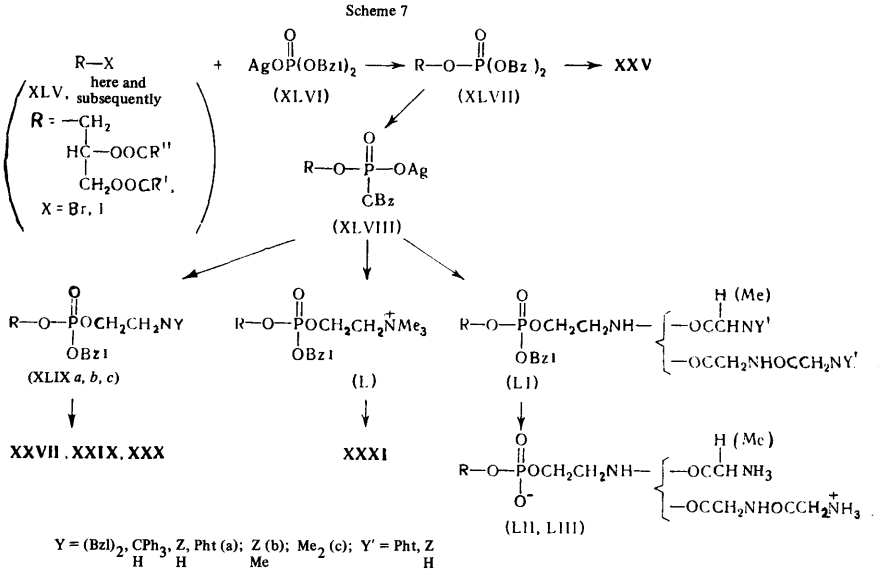
The wide choice of means of protection and phosphorylating agents enables glycerophosphatides of any structure to be obtained, provided that such structure was present in the initial diglycerides and also in the second structural unit of the phosphatide (nitrogen base, hydroxy-amino-acid, glycerol, myoinositol, etc.).

As is shown by Scheme 6, many glycerophosphatides have now been prepared, including phosphatidic acids (XXV) and diphosphatidic acids (XXVI), [65,75,76,82,89,92,93,110,122,123] cephalins (XXVII), [39,44,45,47,55,58,63,64,77,78,84,85,94-98,103,107-109] on the basis of which have recently been obtained *N*-acyl-cephalins (XXVIII), [124] *N*-methylcephalins (XXIX), [68,101,108] *NN'*-dimethylcephalins (XXX), [57,101,108] lecithins (XXXI), [61,62,79,80,99,100,102] phosphatidylserines (XXXII), [66,81,83,89,87,130] and also several phosphatides containing threonine (XXXIII), [70] hydroxyproline (XXXIV), [69,92] and serylglycylglycine (XXXV). [97] Effectively the same methods have been used to obtain the highly unsaturated compounds phosphatidyltyrosine (XXXVI), [90] *O*-amino-acid derivatives of phosphatidylglycerol (XXXVII) and (XXXVIII), [73,91,105]

Scheme 6



Scheme 7



cardiolipin and its acyl derivatives (XXIX) and (XL),[88,89] phosphatidylglycerols (XLI),[75,88,110] and also racemic monophosphoinositides (XLII)[115] and diphosphoinositides of various structures (XLIII) and (XLIV)[104,114] (the preparation of optically active phosphoinositides will be discussed separately).

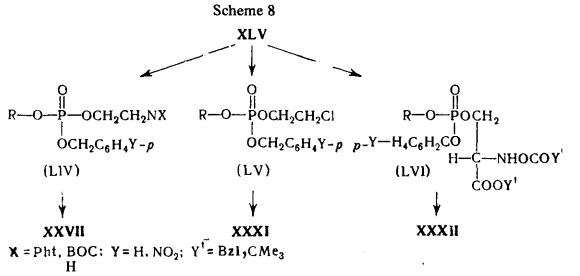
This method has also been used to prepare several modified glycerophosphatides containing 2-aminopropan-1-ol,[72] 2-amino-2-methylpropan-1-ol,[71] α-methylcholine[74], and certain cytotoxic groups[125].

3. Preparation of Glycerophosphatides based on 1,2-Diacylhalogenohydrins of *sn*-Glycerol

The preparation of 1,2-diacylhalogenohydrins of *sn*-glycerol presents considerably fewer difficulties than that of 1,2-diglycerides. They are prepared from 1,2-*O*-isopropylidene-*sn*-glycerol (XIV) in a series of stages, the last of which is esterification. Replacement of the hydroxyl by a halogen (iodine, bromine) is accomplished by the use of toluene-*p*-sulphonyl derivatives as intermediates[28,126-130]. Phosphoric ester bonds are then produced by the reaction of 1,2-diacylhalogenohydrins of *sn*-glycerol with silver salts of substituted phosphoric acids[28].

The synthesis can be effected in two ways. In the first case (Scheme 7) the reaction of 1,2-diacylhalogenohydrins of *sn*-glycerol (XLV) with silver dibenzyl phosphate (XLVI) yields dibenzyl phosphatidates (XLVII), which after anionic monodebenzylation with sodium iodide, lithium fluoride, or a similar reagent[131] are converted into alkali-metal salts, and then into the silver benzyl phosphatidates (XLVIII). These last products react with halogeno-derivatives of nitrogen bases to form protected glycerophosphatides (XLIX)–(LI). The benzyl group (sometimes *p*-nitrobenzyl is used instead) is removed by catalytic hydrogenolysis or by further anionic debenzylation, which in this case can be conveniently accomplished with a tertiary base such as *N*-methylmorpholine. The same groups are used to block amine and carboxyl functions as in the preparation of glycerophosphatides from 1,2-diglycerides. The benzyl[132-134] and trityl[135] groups are also used to protect amino-groups. This variant has proved most convenient for preparing several phosphatidic acids (XXV),[28,130,136-140] cephalins (XXVII),[128,132-135,141] *N*-methylcephalins (XXIX),[135] *NN'*-dimethylcephalins (XXX),[142] lecithins (XXXI),[127,128,143-145] and also phosphatidopeptides (LII) and (LIII).[17-20] Series of lysophosphatides such as lysocephalins and lysolecithins have been obtained similarly[146,147].

Scheme 8



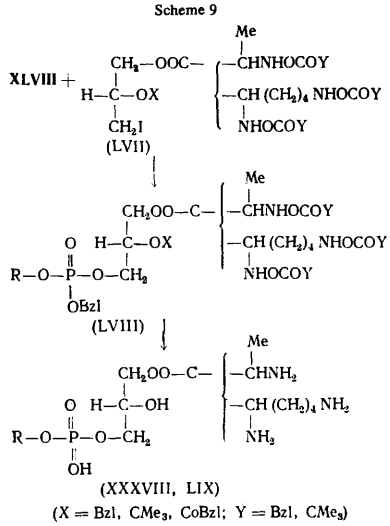
In the second form of the method (Scheme 8) molecules of protected glycerophosphatides (LIV)–(LVI) are produced by condensing the 1,2-diacylhalogenohydrin of *sn*-glycerol (XLV) with a silver salt of a substituted phosphoric acid in which a phosphoric ester bond has already been established with a nitrogen base or with serine.

Differences in principle between these methods are slight. The latter variant has found application also in the synthesis of cephalins (XXVII),[129,127,148-153] lecithins (XXXI),[154] and also, in contrast to the first variant, to obtain phosphatidylserines (XXXII).[126,155,156] This method of synthesis has proved especially convenient for obtaining highly unsaturated phosphatides[148-154,156], amino-groups being protected by means of the t-butoxycarbonyl group[151,156], and the carboxyl function by means of a t-butyl group[156].

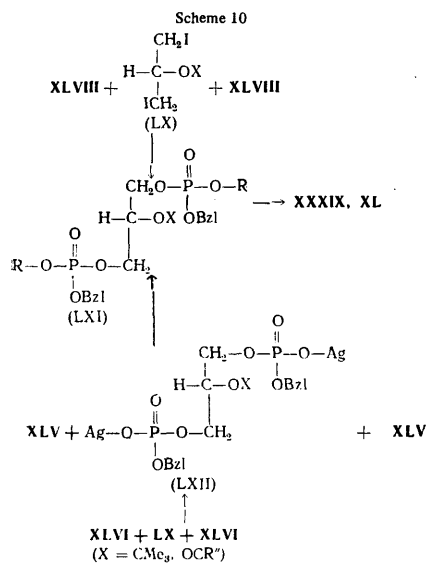
Double decomposition between derivatives of glycerol iodohydrin and silver salts of phosphoric acids is widely used in the preparation of *O*-amino-acid derivatives of phosphatidylglycerol. The method has found application in obtaining both unsaturated[91,157,158] and saturated compounds with individual parts of the molecule differing in configuration[159-161]. It consists in condensing silver benzyl phosphatidates (XLVIII) with glycerol iodohydrins

protected in the 2-position and esterified in the 1- or 3-position with protected amino-acids (LVII). As usual, the protected groups are removed at the last stage: (LVIII) → (XXXVIII), (LIX) (Scheme 9).

Scheme 9



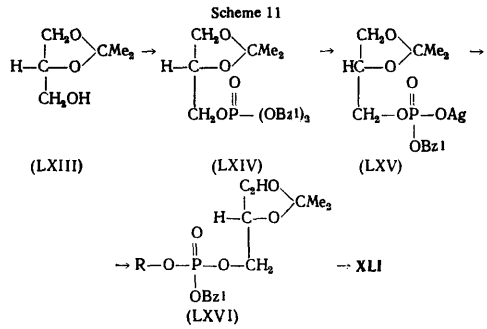
Scheme 10



The same principle forms the basis of a synthesis of cardiolipin (XXXIX) and its *O*-acyl derivatives (XL) [162,163] (Scheme 10). The molecular structures (LXI), containing three glycerol residues linked by phosphoric acid, were produced either by the reaction of two molecules of silver benzyl phosphatidate (XLVIII) with 2-*O*-t-butyl(or acyl)-1,3-deoxy-1,3-di-iodoglycerol (LX) or by combining two molecules of 1,2-diacyliodohydrins of *sn*-glycerol (XLV) with the disilver salt of 2-*O*-t-butyl(or acyl)glycerol 1,3-bis(benzyl phosphate) (LXII), obtained by the reaction of (LX) with silver dibenzyl phosphate (XLVI) followed by partial debenzylation and conversion into the corresponding silver salt (LXII). The protecting groups were removed in the usual way as the final stage: (LXI) → (XXXIX), (XL).

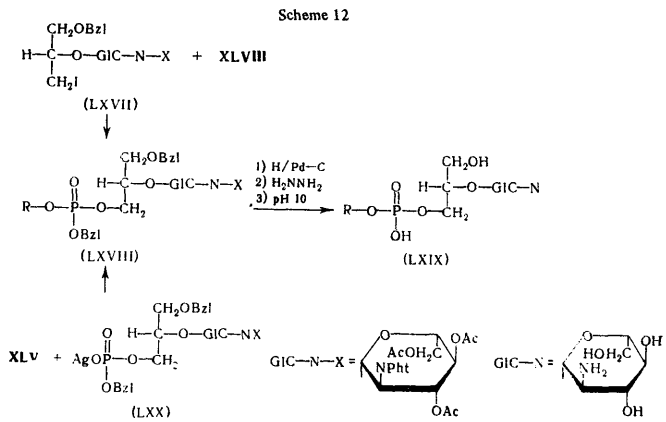
Phosphatidylglycerol (XLI) has been synthesised by a similar method [164] (Scheme 11).

Scheme 11



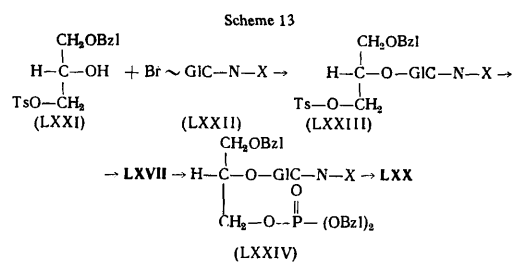
During recent years the present method has been used for the preparation of several glycolipids. The first synthetic work on these lines was concerned with a glucosamine derivatives of phosphatidylglycerol (LXIX) [22]—a glycolipid found in *Bacillus megatherium* [23,165] (Scheme 12).

Scheme 12



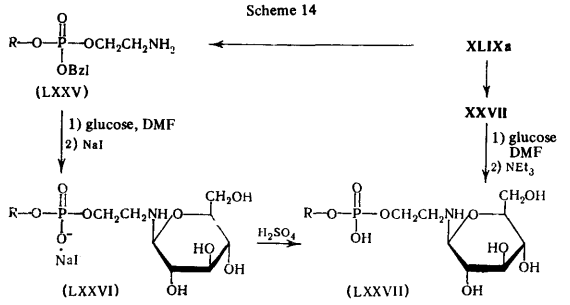
A glycosidic bond between the anomeric hydroxyl of the glucosamine and the 2-hydroxyl of glycerol was formed by the Koenigs–Knorr reaction of the corresponding glycerol derivatives (LXXI) and the glucosamine bromide (LXXII). The product (LXXIII) was converted by well known methods into the halogenohydrin (LXVII) and the silver salt (LXX), which were used as the chief intermediates in the synthesis of a glucosamine derivative of phosphatidylglycerol (LXIX) (Scheme 13).

Scheme 13



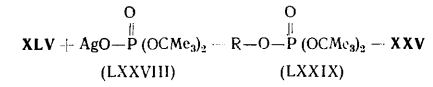
Another example is the synthesis of the *N*-glycoside of aminoethyl phosphatidate (LXXVII) [166] based on synthetic cephalin (XXVII) [135] (Scheme 14).

Scheme 14



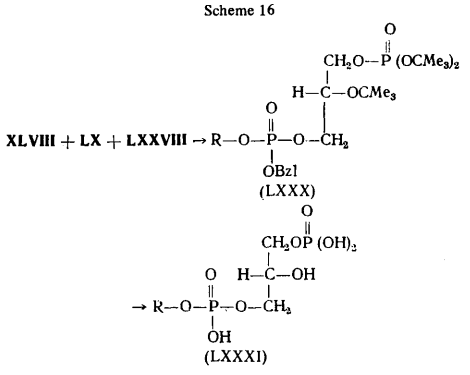
A further development of the method is to use silver di-t-butyl phosphate (LXXVIII) as phosphorylating agent in cases in which phosphoric monoesters are to be prepared, because of the ease of removal of a t-butyl group with hydrogen chloride (Scheme 15). Thus phosphatidic acid (XXV) has been obtained by the reaction of 1,2-diacyliodohydrin of *sn*-glycerol (XLV) with the above silver salt (LXXVIII). [167]

Scheme 15



The same silver salt (LXXVIII) has been used for the synthesis of phosphatidyl glycerophosphate (LXXXI) [167] by condensation with silver benzyl phosphatidate (XLVIII) and glycerol di-iodohydrin (LX) followed by removal of the protecting group (Scheme 16).

Scheme 16



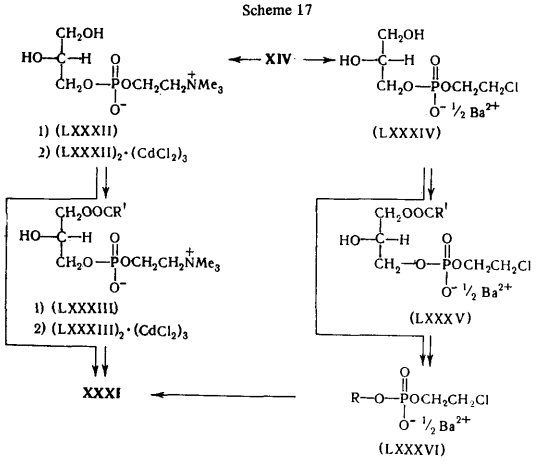
The method of preparing phosphatides by double decomposition of various glycerol halogenohydrins with silver salts of derivatives of phosphoric acids is distinguished from syntheses based on 1,2-diacyl-*sn*-glycerols by its directional character and hence by higher yields of reactions involving the formation of phosphoric ester bonds. However, it is also characterised by many stages and serious experimental difficulties in obtaining many of the starting materials, which often prevent it from competing with the preparation of phosphatides from 1,2-diglycerides.

III. SYNTHESIS OF GLYCEROPHOSPHATIDES BY THE ACYLATION OF SUBSTITUTED GLYCEROPHOSPHORIC ACIDS

The first group of methods for synthesising glycerophosphatides is characterised by several stages, which often diminishes its preparative possibilities. The second type of synthesis, in which the sequence of phosphorylation and acylation is reversed compared with the first group, enables diester glycerophosphatides to be obtained by a shorter route and in high yields directly from 1,2-*O*-isopropylidene-*sn*-glycerol (XIV).

It must be borne in mind that the esterification of glycerophosphoric esters of protected aminoethanol, choline, and serine occurs with considerable difficulty and yields mainly lysophosphatides [62,168,169]. During recent years, however, methods have been found which have permitted the selective or exhaustive esterification of glycerophosphoric esters of nitrogen bases [145,169-192]. The starting material mostly used for this purpose in the synthesis of lecithins (XXXI) has been either the cadmium complex of 3-*sn*-glycerylphosphorylcholine 2(LXXXII).$.3CdCl_2$ [145,169,171-177,179] or barium chloroethyl 3-*sn*-glyceryl phosphate (LXXXIV), [170,178] both obtainable by accessible methods from 1,2-*O*-isopropylidene-*sn*-glycerol (XIV). The compounds—(LXXXII), 2(LXXXII).$3CdCl_2$, (LXXXIII), 2(LXXXIII).$3CdCl_2$, (LXXXIV), and (LXXXV)—were acylated either selectively or exhaustively with aliphatic acid chlorides [169-179] or by enzymatic esterification [180,181]. In the case of the cadmium complexes [145,169,171-177,179] this immediately yields lecithins (XXXI) or lysolecithins (LXXXIII) depending on the degree of esterification. When the barium salts (LXXXIV) and (LXXXV) are used [170,173], the quaternary ammonium group of the lecithins (XXXI) is introduced by reaction between the acylated barium salt (XXXVI) and trimethylamine (Scheme 17).

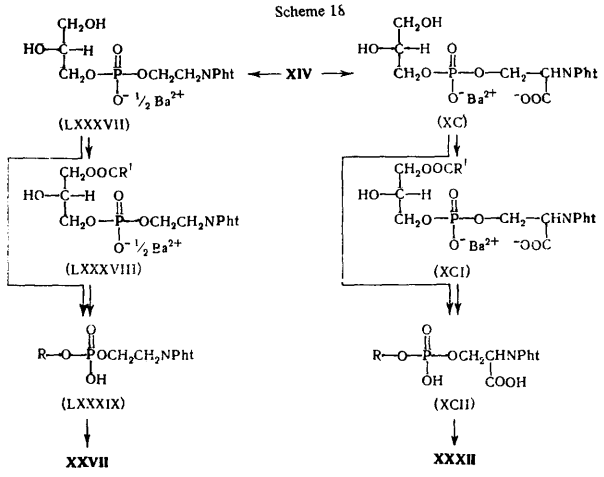
Scheme 17



In the synthesis of cephalins (XXVII) [182-185] and phosphatidylserines (XXXII) [186] from 1,2-*O*-isopropylidene-*sn*-glycerol (XIV) barium 3-*sn*-glyceryl *N*-phthaloylaminoethyl phosphate (LXXXVII) and the corresponding *N*-phthaloylserine salt (XC) are obtained. These are converted by stepwise esterification—(LXXXVII) → (LXXXVIII) → (LXXXIX) or (XC) → (XCI) → (XCII)—or complete esterification—(LXXVII) → (LXXXIX) or (XC) → (XCII)—into phthaloyl derivatives of cephalin (LXXXIX) or

phosphatidylserine (XCII), from which the protective groups are removed by mild hydrazinolysis (XXVII) or (XXXII) (Scheme 18). A similar principle has been used to obtain an unsaturated phosphatidylserine from barium glyceryl *N*-methoxybenzyloxycarbonylserine phosphate or the phthalimidomethyl ester[187].

Scheme 18



Besides being shorter than the first group of methods, the present route for the synthesis of glycerophosphatides has the advantage of being universally applicable for the preparation of phosphatides containing either saturated or unsaturated aliphatic acids.

Attempts have been made at the direct acylation of glycerophosphoric esters of nitrogen bases by means of acid anhydrides. Although the first work of this type[188] has only historic significance, later investigations on the acylation of 3-*sn*-glycerophosphate[189], 3-*sn*-glyceryl-phosphoryl-*N*-phthaloylaminoethanol[190] obtained by saponifying natural cephalins and then protecting the amino-group with a phthaloyl group, and 3-*sn*-glyceryl-phosphorylcholine[191,192] with aliphatic acid anhydrides in the presence of their tetraethylammonium salts can make full claim to preparative use.

IV. SYNTHESIS OF COMPLEX GLYCEROPHOSPHATIDES

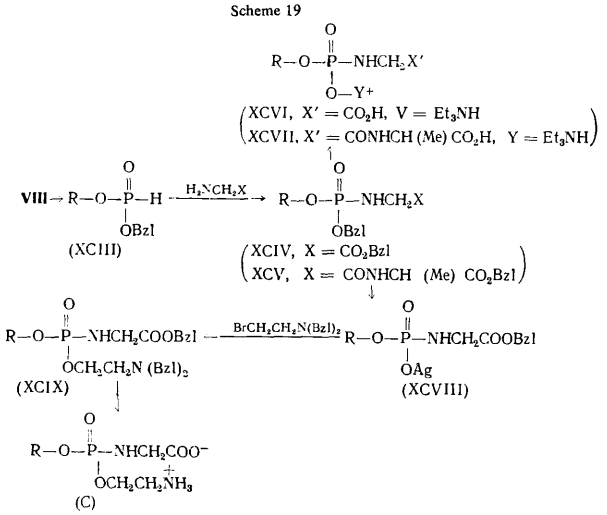
All the papers discussed have been concerned mainly with the synthesis of the so called classical diester glycerophosphatides. An exception is provided by the syntheses of amino-acid derivatives of certain phosphatides (XXXIII), (XXXIV), (XXXVI)–(XXXVIII), and (LIX)[69,70,73,90-92,105,157-161], phosphatidopeptides (XXXV), (LII), and (LIII),[16-21,67] the glucosamino-derivative of phosphatidylglycerol (LXIX),[22] and an *N*-glycoside of phosphatidylaminoethanol (LXXVII);[166] the need to discuss them in preceding Sections was dictated solely by methodological considerations. These compounds cannot be included among classical glycerophosphatides. Phosphatides which contain, besides the traditional structural units, amino-acids, peptides, carbohydrates, etc. are often termed complex phosphatides, and perhaps classical glycerophosphatides are fragments of these complex lipid structures, which are present in natural tissues and are easily decomposed in the course of isolation[193-199]. Another feature of these compounds is presumably a triester structure of the phosphate portion[193-199]. Progress in the synthesis of classical glycerophosphatides has enabled a close approach to be made to obtaining certain classes of complex phosphatides. The chief researches on these lines, other than the few discussed in the previous Sections, will be described below.

Among the most widely distributed complex phospholipids are amino-acid and peptide derivatives of glycerophosphatides. Besides the amino-acid derivatives of phosphatidylglycerol (XXXVII), (XXXVIII), and (LIX), phosphatidylpeptides based on cephalins and phosphatidylserines (XXXV), (LII), (LIII), and also cardiolipin[199] we may assume the possibility of the covalent addition of amino-acids and peptides to the phosphoric acid in glycerophosphatides by means of phosphoramide and acyl–phosphate bonds. Definite indications of the possibility of such complex formation have now been obtained[200].

1. Synthesis of Amino-acid and Peptide Derivatives of Phosphatidic Acid and Phosphatidylaminoethanol of Phosphoramide and Acyl Phosphate Types

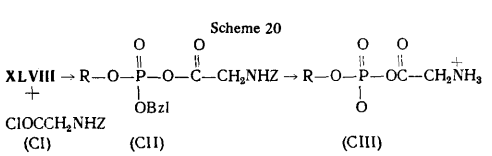
Phosphatidylamino-acids (XCVI)[24] and phosphatidylpeptides (XCVII)[24] containing a phosphoramido-bond are obtained (from 1,2-diglycerides) by a method widely used in the chemistry of nucleotide amino-acids and peptides[201] with synthetic procedures characteristic of glycerophosphatides. In order to obtain (P→N)-glycylphosphatidylaminoethanol (C) the corresponding protected derivative of phosphatidic acid (XCIV) is converted, by the methods described in Section II, into the silver salt (XCVIII), from which the cephalin (XCIX) is formed[26] (Scheme 19).

Scheme 19



A glycine derivative of phosphatidic acid of acyl phosphate type (CIII) is formed by reaction of silver benzyl phosphatidate (XLVIII) with *N*-benzyloxycarbonylglycyl chloride (CI) followed by removal of the protective groups (CII) → (CIII)[25] (Scheme 20).

Scheme 20

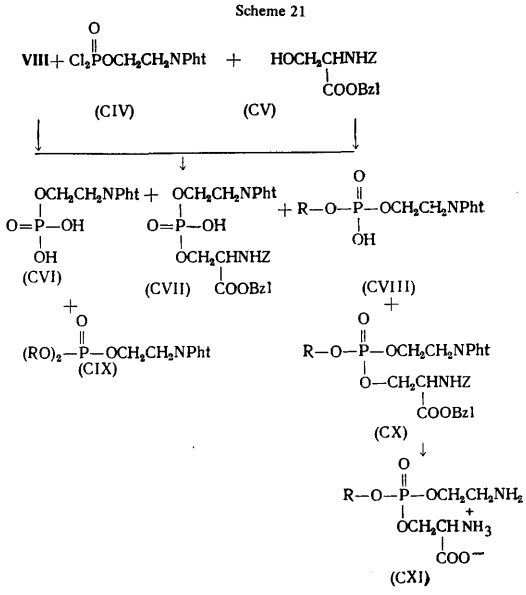


Investigations of the properties under comparable conditions of classical glycerophosphatides and of amino-acid and peptide derivatives of phosphatidic acid and phosphatidylaminoethanol—(XCVI), XCVII), (C), and (CIII)—have shown[24-26] the lower hydrolytic stability of the latter compounds. Both acyl–phosphatide and phosphoramide bonds are labile even in weakly acid media. Study of the structure and properties of the synthetic amino-acid and peptide derivatives of glycerophosphatides—(XCVI), (XCVII), (C), and (CIII)—suggests that such complex formation may occur in natural lipoproteins, but the exceptional lability of these structures creates serious difficulties in their isolation from natural sources in the native state, so that the question of the presence of compounds of this type in natural lipid–protein complexes is still a matter of controversy.

2. Synthesis of Triester Phosphatides and Phosphatidopeptides

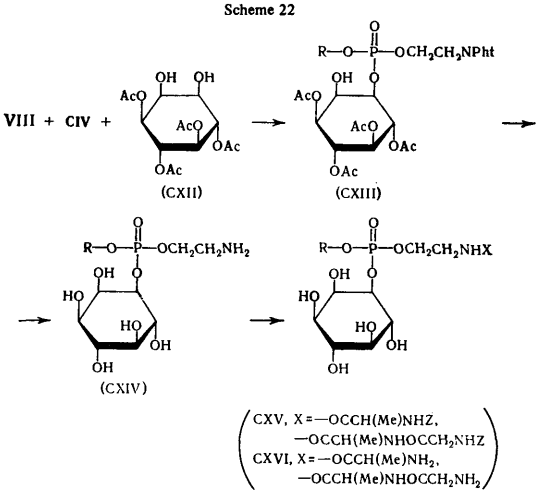
The preparation of triester phosphatides and phosphatidopeptides has been based on the method of synthesising diester glycerophosphatides from 1,2-diglycerides. Aminoethylphosphatidylserine (CXI)—a triester glycerophosphatide assumed to be present in the microsomes of brain tissue[202,203]—has been synthesised by reaction among the 1,2-diglyceride (VIII), 2-phthalimidoethyl phosphorodichloridate (CIV), and the dibenzyl ester of *N*-carboxyserine (CV), with subsequent removal of the protective groups (CX) → (CXI) [15] (Scheme 21). The course of the reaction is ambiguous, being accompanied by the formation of a series of phosphoric mono-, di-, and tri-esters (CVI)–(CIX), as a consequence of which the yield of aminoethylphosphatidylserine (CXI) after removal of the protective groups does not exceed 2–3%.

Scheme 21



The 1-*O*-aminoethylphosphatidylmyoinositol structure (CXIV) has been formed similarly[13]. The synthetic triester (CXIV) has been used to obtain phosphatidopeptides (CXVI) [16,21]—structural units in the lipid complex of ox brain[198]—by condensation of the amino-group in the aminoethyl residue of (CXIV) with the azides of *N*-benzyloxycarbonyl-alanine and -glycylalanine followed by removal of the protective groups by known methods (CXV) → (CXVI) (Scheme 22).

Scheme 22



Study of the stability of the synthetic triester phosphatides—(CXI), (CXIV), and (CXVI)—has shown that they are labile compared with the cephalins, phosphatidylserines, and phosphatidylinositols which they contain[13,15,16,21], this being fully consistent with published data[193-199] on the properties of triester phosphatides. The triester (CXIV) and (CXVI) containing myoinositol are considerably more stable than the triester (CXI),[13,15,16,21] which is supported by the assumed special role of myoinositol in the formation and functioning of complex phosphatides and phosphatidopeptides[198].

V. METHODS OF SYNTHESIS OF OPTICALLY ACTIVE PHOSPHOINOSITIDES

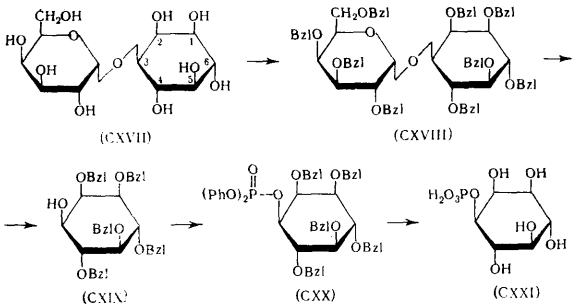
The problem of obtaining optically active phosphoinositides requires special consideration (all those mentioned hitherto were synthesised in optically inactive form). In naturally occurring phosphoinositides the myoinositol molecule is asymmetrically substituted in the 1-equatorial position by the phosphatidyl radical, and hence possesses optical activity. This has been proved both for inositophosphatides of simple structure[204-208] and for the complexes[209-212].

The problem of synthesising optically active phosphoinositides is in essence a particular case of the wider problem of obtaining optically active myoinositol derivatives. At the present time there are two approaches to a solution—(1) the use of natural substances (galactin, quebrachitol, bornesitol, etc.), in which molecular asymmetry is already established, for their further conversion into optically active asymmetrically substituted myoinositols of specified structure; and (2) the resolution of racemic asymmetrically substituted myoinositols, prepared from myoinositol itself, into enantiomers.

1. First Method

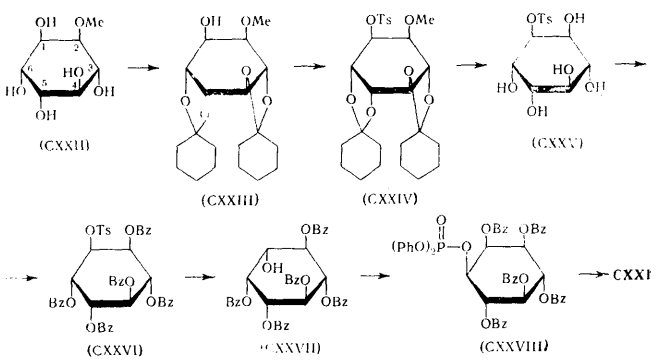
In 1959 Ballou reported[207] the synthesis of optically active *sn*-myoinositol 3-phosphate§. The starting material was galactin, which was completely benzylated (CXVII) → (CXVIII); methanolysis with 1% hydrochloric acid led to cleavage of the α-glycosidic bond in the nonabenzylgalactin (CXVIII); the resulting 1,2,4,5,6-penta-*O*-benzyl-*sn*-myoinositol (CXIX) was phosphorylated with diphenyl phosphorochloridate; and after removal of the protective groups *sn*-myoinositol 3-phosphate (CXXI) was isolated (Scheme 23).

Scheme 23



Gero[117] has recently proposed another route to the optically active 3-phosphate (CXXI), starting from quebrachitol (2-*O*-methyl-(−)-inositol) (CXXII). This was converted into 3,4 : 5,6-di-*O*-cyclohexylidenequebrachitol (CXXIII), which was then transformed into 3,4 : 5,6-di-*O*-cyclohexylidene-2-*O*-methyl-1-*O*-tosyl-(−)-inositol (CXXIV). The latter after elimination of the methyl group with boron trichloride gave 1-*O*-tosyl-(−)-inositol (CXXV). After benzoylation (CXXV) → (CXXVI) and removal of the tosyl group with inversion of the configuration of the 3-hydroxyl the product was 1,2,4,5,6-penta-*O*-benzoyl-*sn*-myoinositol (CXXVII), which was converted by the methods described by Ballou[207] into *sn*-myoinositol 3-phosphate (CXXI) (Scheme 24).

Scheme 24

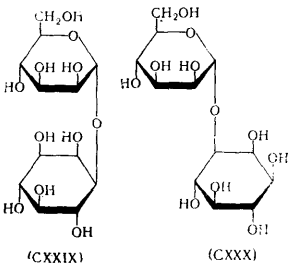


However, these syntheses[117,207,215] possess extremely serious limitations, and hence cannot be recommended for obtaining optically active phosphoinositides of natural structure. Apart from the difficult availability of galactin and quebrachitol, which are isolated from vegetable sources inaccessible in the Soviet Union, the many stages in the syntheses, and the low yields of optically active asymmetrically substituted myoinositols, a further significant defect must be mentioned. It is readily observed that the application of asymmetrically substituted myoinositols, obtained from galactin and quebrachitol, to the synthesis of optically active phosphoinositides will yield phosphatides containing the phosphatidyl group at the 3-position of myoinositol, i.e. of unnatural configuration.

The method of obtaining 2,3,4,5,6-penta-*O*-tosyl-*sn*-myoinositol from (−)-bornesitol (1-*O*-methyl-*sn*-myoinositol),[118,119] based on its exhaustive tosylation with subsequent removal of the methyl group with boron tribromide, does not possess this disadvantage. However, attempts to prepare phosphatidylinositol from 2,3,4,5,6-penta-*O*-tosyl-*sn*-myoinositol have encountered insuperable difficulties[118].

2. Second Method

Purely chemical methods for obtaining the two series of optically active derivatives of myoinositol have not been developed hitherto because of the great difficulty of resolving their racemic mixtures. Isolated papers have been published on unsuccessful attempts at separation[113]. Nevertheless, mention must be made of Angyal's work[216] on the preparation of mannosylmyoinositols, which were obtained in low (4.5%) yield by the Koenigs–Knorr reaction¶ and separated by crystallisation into two diastereomers—1- and 3-*O*-α-D-mannopyranosyl-*sn*-myoinositols



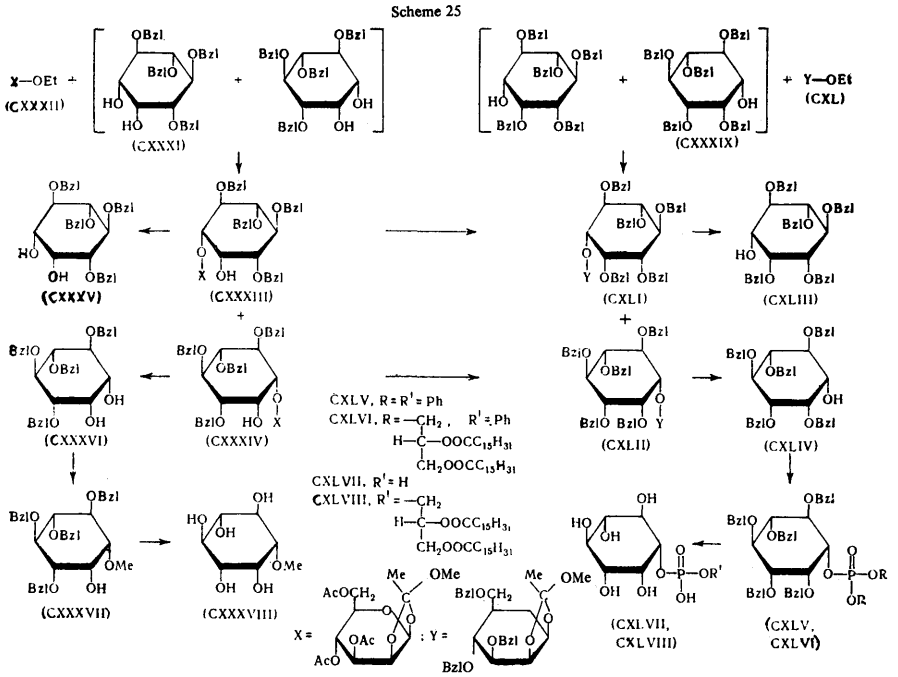
Use of the orthoester method of glycosylation[217] to form a glycosidic bond enabled the yield of diastereomeric mannosylmyoinositols (CXXIX) and (CXXX) to be raised considerably (to 10–12%).[218] The mannoside (CXXIX) might have served as initial compound for obtaining optically active 1-*O*-substituted derivatives of myoinositol, but this was prevented by its low yield in the main reaction.

A procedure has been developed recently in our laboratory for separating racemates of asymmetrically substituted myoinositols via the diastereomeric orthoacetates with D-mannose[219], which has opened a path to obtaining optically active phosphoinositides. Transesterification of 1,4,5,6-tetra-*O*-benzylmyoinositol (CXXXI) with D-mannose orthoacetate (CXXXII) gave the diastereomeric orthoesters (CXXXIII) and (CXXXIV), which were separated by crystallisation or by chromatography. Acid hydrolysis of these orthoesters yielded 1,4,5,6- and 3,4,5,6-tetra-*O*-benzyl-*sn*-myoinositols (CXXXV) and (CXXXVI). The absolute configuration of these products was established by conversion of (CXXXVI) into the methyl ether (CXXXVIII), which was compared with specimens of (+)- and (−)-bornesitols[220] (Scheme 25).

§ Our proposed nomenclature[213,214] is used for optically active myoinositol derivatives.

¶ The Koenigs–Knorr reaction has been used also to prepare galactin in 2.1% yield. In this case the diastereomers were separated by seeding with crystalline natural galactin[216].

Scheme 25



An attempt to use 3,4,5,6-tetra-*O*-benzyl-*sn*-myoinositol (CXXXVI) to synthesise the monophosphoinositide was unsuccessful owing to the presence of vicinal hydroxy-groups in (CXXXVI), which made it necessary to seek ways of synthesising the corresponding pentabenzyl derivatives. 2,3,4,5,6-Penta-*O*-benzyl-*sn*-myoinositol (CXLIV) was obtained from 1,2,4,5,6-penta-*O*-benzylmyoinositol (CXXXIX)[111,113,221] by the method developed for separating 1,4,5,6-tetra-*O*-benzylmyoinositol (CXXXI)[221] (Scheme 25).

Since the orthoesters (CXLI) and (CXLII) have very similar physicochemical properties and are therefore difficult to separate, the synthesis of the pentabenzyl ethers (CXLIII) and (CXLIV) was modified[222]. The orthoesters (CXXXIII) and (CXXXIV), easily obtained by the transesterification of 1,4,5,6-tetra-*O*-benzylmyoinositol (CXXXI),[220] were taken as starting materials. In this case formation of the orthoacetate with D-mannose was used both the resolve racemic compounds and to protect temporarily the 1- and 3-hydroxyls in myoinositol. The stability of the orthoester grouping under alkaline conditions was exploited by exhaustively benzylating (CXXXIII) and (CXXXIV) to (CXLI) and (CXLII), and hydrolysing in the usual way to the pentabenzyl ethers (CXLIII) and (CXLIV). Application of the new carbohydrate orthoester protection enabled optically active pentabenzyl ethers of myoinositol to be obtained in preparative quantities (Scheme 25).

2,3,4,5,6-Penta-*O*-benzyl-*sn*-myoinositol (CXLIV) has been used as starting material for the directed synthesis (Scheme 25) of the structural unit of all phosphoinositides—*sn*-myoinositol 1-phosphate (CXLVII)[221]—which proves to be identical with the *sn*-myoinositol 1-phosphate isolated from soya-bean phosphatides[207].

These investigations culminated in the first chemical synthesis of an optically active phosphatidylinositol[222,223] (Scheme 25). To obtain the monophosphoinositide (CXLVIII) the pentabenzyl ether (CXLIV) was condensed with 1,2-dipalmitoyl-*sn*-glycerol and phenyl phosphorodichloridate to give a compound (CXLVI) which on hydrogenation yielded phosphatidylinositol (CXLVIII). The properties of the synthetic phosphatidylinositol (CXLVIII) were closely similar to those of monophosphoinositides isolated from various natural sources[224,225].

---o0o---

During preparation of the manuscript for press several papers have been published on the synthesis of glycerophosphatides and their structural units.

A new method has been developed for the synthesis of 1,2-diacyl-*sn*-glycerols from *sn*-glycerol 1,2-carbonate[226,227], obtained by a shorter route than the existing method[34] from 3,4-*O*-isopropylidene-D-mannitol. The preparation of 1,2-diglycerides by the direct esterification of this last compound[59], which was unsuitable for compounds containing higher aliphatic acid radicals, has been freed from this defect[228].

The natural glycolipids[229]—mannosyl and glucosyl diglycerides[230]—have been synthesised from the diglycerides obtained[226-228]. Galactosyldiglycerides have been prepared from 2,5-*O*-methylene-D-mannitol[231]. This same compound has been the starting material for a new synthesis of 1,2-diacyl-*sn*-glycerols undertaken in our laboratory, by means of which saturated and unsaturated 1,2-glycerides containing the same and different acid radicals can be obtained.

No fundamentally new work on the synthesis of nitrogen-containing glycerophosphatides has appeared recently, although several papers make a definite contribution to the further development of synthetic methods. Thus the use of 2,4,6-tri-isopropylbenzenesulphonyl chloride as condensing agent to produce a phosphoric ester bond[108] has been extended to the phosphatidyl derivative of L-threonine[232], this synthesis comprising initially the formation of the glycerophosphoric structure and then introduction of ester radicals by means of Lapidot's method using aliphatic acid anhydrides[189].

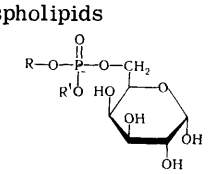
Several papers have appeared on the direct acylation of 3-*sn*-glycerylphosphorylcholine. Thus the cadmium complex of the 1-substituted compound has been used for exhaustive esterification of the 2-position with ^{14}C-labelled oleic acid[233]. Aneja and Chadha[234] have investigated the

mechanism of the esterification of 3-*sn*-glycerylphosphorylcholine by higher aliphatic acid chlorides. The formation of lecithin is shown to be accompanied by that of several more polar secondary products, which has a considerable effect on the overall yield of lecithin[6]. One of them is lysolecithin, and another—previously regarded as a cyclic lysolecithin[6]—is a mixture of isomeric monoacyldeoxychloroglycerylphosphorylcholines, the secondary products being formed from a common intermediate compound.

Among methodological papers mention must be made of the development of the mild removal, by means of zinc in acetic acid, of the phthalimidomethyl group[235], which is widely used for blocking the carboxyl function of amino-acids in the synthesis of phosphatidylserines and phosphatidylhydroxyprolines[81,87,92].

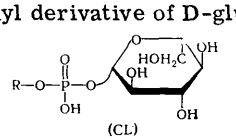
A series of syntheses of certain modified glycerophosphatides was designed to prepare materials for the investigation of enzymatic reactions with phosphatides, the part they play in the formation of biological membranes, etc. Thus, for the purpose of studying lipid–protein interactions by means of electron spin resonance spectroscopy in the investigation of lipolytic enzymes, *O*-(1,2-distearoyl-*sn*-glycerol-3-phosphoryl)-3′-oxymethyl-2′,2′,5′,5′-tetramethylpyrrolidine 1′-oxide has been synthesised by reaction between the corresponding phosphatidic acid and 3-hydroxymethyl-2,2,5,5-tetramethylpyrrolidine 1-oxide in the presence of 2,4,6-tri-isopropylbenzenesulphonyl chloride[236]. 3-Palmitoyl-*sn*-glyceryl-1-phosphorylcholine (lysolecithin of unnatural structure)[237] and also 2,3,4,5-tetrastearoyl-1,6-diphosphorylcholine-D-mannitol (an analogue of lecithin of unnatural structure)[238] have been prepared from 3,4-*O*-isopropylidene-D-mannitol and D-mannitol itself by methods which leave much to be desired from the viewpoint of the present-day chemistry of the glycerophosphatides. The glycerophosphatides obtained were investigated as substrates for phospholipases and acyltransferases. Similar methods have been used to obtain analogues of lysolecithins based on trimethylene glycol[239], which have been examined as components of artificial membranes.

Several papers deal with the synthesis of new glycerophosphatides. Thus the method of silver salts has been used for diester and triester glycophospholipids, which are assumed to be present in natural sources[196–198]. The synthetic glycophospholipids



(CXLIX, R′ = H, $CH_2CH_2NH_2$)

contain D-galactose attached by an ester link to the phosphatidyl group[240,241]. The same method has been used to obtain a phosphatidyl derivative of D-glucose



(CL)

but in this case the phosphatidyl group is attached at the anomeric hydroxyl (CL).[242]

In the field of the synthesis of phosphoinositides the resolution has been accomplished of racemic 1,2:5,6-di-*O*-cyclohexylidenemyoinositol[243], and each of the enantiomers—of 1,2:5,6- and 2,3:4,5-di-*O*-cyclohexylidene-*sn*-myoinositols—can be used as principal starting material for obtaining di- and tri-phosphoinositides and also other members of this class of phosphatides. Attempts to separate 1,2:4,5-di-*O*-cyclohexylidenemyoinositol into enantiomers[244], and also to use D-glucose orthoacetate instead of D-mannose orthoacetate for the resolution[244], have been unsuccessful.

Molotkovskii[245] has accomplished the synthesis of racemic phosphatidylinositol with unsaturated acids using 1,2,4,5,6-penta-*O*-acetylmyoinositol as inositol component. A phosphoric diester bond was formed by reaction of the 1,2-diacyl-3-deoxy-3-iodoglycerol with silver benzyl 1,2,4,5,6-penta-*O*-acetylmyoinositol phosphate.

Gigg and his coworkers[246] have examined in detail the possibility of producing a racemic phosphatidylinositol structure using—(1) the reaction of a 1,2-diacyl-3-deoxy-3-iodoglycerol with various silver phosphates containing 1,2,4,5,6-penta-*O*-benzylmyoinositol attached by a phosphoric ester bond, with subsequent removal of the protective groups by hydrogenolysis and anionic debenzylation; and (2) the reaction of 2,3,4,5,6-penta-*O*-benzylmyoinositol 1-phosphate (obtained by phosphorylation of the corresponding penta-substituted myoinositol with bis-2,2,2-trichloroethyl phosphorochloridate, the protective groups being removed with zinc dust in methanol) with a 1,2-diglyceride in the presence of 2,4,6-tri-isopropylbenzenesulphonyl chloride. The latter method is shown to have considerable advantages over the former.

REFERENCES

1. D. Hanahan, "Lipide Chemistry", New York, 1960.
2. G. Ansell and J. Hawthorne, "Phospholipids", Amsterdam, 1964.
3. E. M. Kreps, "Fosfolipidy Kletochnykh Membran Nervnoi Sistemy v Razvitii Zhivotnogo Mira" (Phospholipids of Cell Membranes of the Nervous System in the Evolution of the Animal World), Nauka, Leningrad, 1967.
4. P. Verkade, Bull. Soc. chim. France, 1993 (1963).
5. G. Haas, "Glycerophosphatides, Their Chemical Synthesis and Application in Lipid Biochemistry", Utrecht, 1963.
6. L. Deenen and G. Haas, Adv. Lipid Res., 2, 167 (1964).
7. E. Baer, J. Amer. Oil Chem. Soc., 42, 257 (1965).
8. L. Deenen and G. Haas, Ann. Rev. Biochem., 35, 157 (1966).
9. L. D. Bergel'son, Uspekhi Sovrem. Biol., 64, 355 (1967).
10. E. Baer, Trans. Roy. Soc. Canada, 20, 231 (1967).
11. P. Verkade, Farmaco Ed. scient., 23, 149 (1968).
12. B. A. Klyashchitskii, S. D. Sokolov, and V. I. Shvets, Uspekhi Khim., 38, 740 (1969) [Russ. Chem. Rev., No. 4 (1969)].
13. A. V. Luk'yanov, A. I. Lyutik, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 36, 1029 (1966).
14. M. A. Grun-Grzhimailo, L. V. Volkova, G. A. Serebrennikova, and N. A. Preobrazhenskii, Zhur. Org. Khim., 3, 650 (1967).
15. 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).
16. A. V. Luk'yanov, A. I. Lyutik, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 36, 1031 (1966).

17. S. Ya. Mel'nik, M. A. Miropol'skaya, and G. I. Samokhvalov, Zhur. Obshch. Khim., 36, 1095 (1966).
18. S. Ya. Mel'nik, M. A. Miropol'skaya, and G. I. Samokhvalov, Zhur. Obshch. Khim., 37, 320 (1967).
19. S. Ya. Mel'nik, M. A. Miropol'skaya, and G. I. Samokhvalov, Zhur. Obshch. Khim., 37, 2452 (1967).
20. S. Ya. Mel'nik, V. G. Mairanovskii, M. A. Miropol'skaya, and G. I. Samokhvalov, Zhur. Obshch. Khim., 38, 1495 (1968).
21. A. I. Lyutik, A. V. Luk'yanov, E. S. Zhdanovich, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 38, 2251 (1968).
22. M. Gurr, P. Bonsen, J. Kamp, and L. Deenen, Biochem. J., 108, 211 (1968).
23. J. Kamp, P. Bonsen, and L. Deenen, Biochim. Biophys. Acta, 176, 298 (1969).
24. M. K. Petrova, V. I. Shvets, V. A. Dachkovskaya, and N. A. Preobrazhenskii, Zhur. Org. Khim., 5, 1198 (1969).
25. M. K. Petrova, V. I. Shvets, M. M. Voevodina, N. G. Kolosova, L. G. Natalkina, and N. A. Preobrazhenskii, Zhur. Org. Khim., 5, 1489 (1969).
26. M. K. Petrova, S. D. Bakalo, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Org. Khim., 5, 1883 (1969).
27. D. M. Brown, Adv. Org. Chem., 3, 79 (1963).
28. L. Hessel, I. Morton, A. Todd, and P. Verkade, Rec. Trav. chim., 73, 150 (1954).
29. D. Buchnea, Chem. Phys. Lipids, 1, 113 (1967).
30. B. Daubert and C. King, J. Amer. Chem. Soc., 61, 3328 (1939).
31. P. Verkade, W. Cohen, and A. Vroege, Rec. Trav. chim., 59, 1123 (1940).
32. A. Doerschuk, J. Amer. Chem. Soc., 74, 4202 (1952).
33. L. T. Dorofeeva, E. I. Kovshev, L. V. Volkova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 33, 2883 (1963).
34. J. Gigg and R. Gigg, J. Chem. Soc. (C), 431 (1967).
35. Yul. G. Molotkovskii, L. F. Nikulina, and L. D. Bergel'son, Khim. Prirod. Soed., 210 (1969).
36. G. Sowden and H. Fischer, J. Amer. Chem. Soc., 62, 3244 (1940).
37. L. Krabisch and B. Borgström, J. Lipid Res., 6, 156 (1965).
38. F. Pfeiffer, C. Miao, and J. Weisbach, J. Org. Chem., 35, 221 (1970).
39. S. Rakhit, J. Bagli, and R. Deghenghi, Canad. J. Chem., 47, 2906 (1969).
40. M. Bergmann and N. Carter, Z. physiol. Chem., 191, 211 (1930).
41. B. Stimmel and C. King, J. Amer. Chem. Soc., 56, 1724 (1934).
42. G. Martin, J. Amer. Chem. Soc., 75, 5482 (1953).
43. V. I. Shvets, G. G. Zapesochnaya, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., Sbornik "Sintez Prirodnykh Soedinenii, Ikh Analogov i Fragmentov" (Synthesis of Natural Compounds, their Analogues, and Fragments), 1965, p. 16.
44. N. A. Boroslovskii, G. I. Samokhvalov, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 31, 1143 (1961).
45. N. A. Boroslovskii, G. I. Samokhvalov, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 32, 135 (1962).
46. L. V. Volkova, V. I. Shvets, S. F. Ryzhenkova, N. B. Varvarina, I. V. Smolovik, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 32, 1764 (1962).
47. V. I. Shvets, S. F. Morozova, L. V. Volkova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 35, 554 (1965).
48. E. Baer and D. Buchnea, J. Biol. Chem., 230, 447 (1958).
49. D. Buchnea and E. Baer, J. Lipid Res., 1, 405 (1961).
50. V. I. Shvets, L. V. Volkova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 31, 2181 (1961).
51. V. I. Shvets, L. V. Volkova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 32, 2474 (1962).
52. V. I. Shvets, L. V. Volkova, E. E. Lukashenko, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 32, 2479 (1962).
53. V. I. Shvets, L. V. Volkova, V. V. Vasil'eva, L. M. Filonova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 33, 1848 (1963).
54. L. V. Volkova, V. I. Shvets, V. S. Khandkarova, S. F. Ryzhenkova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 33, 1848 (1963).
55. L. T. Dorofeeva, O. N. Tolkachev, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 33, 2880 (1963).
56. V. I. Shvets, L. T. Dorofeeva, L. V. Volkova, M. A. Grun-Grzhimailo, I. S. Shmidt, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 34, 3303 (1964).
57. L. V. Volkova, V. I. Shvets, L. T. Dorofeeva, S. I. Lobanova, N. V. Konstantinova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 35, 550 (1965).
58. L. T. Dorofeeva, T. V. Zharova, L. V. Volkova, O. N. Tolkachev, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 34, 2935 (1964).
59. V. I. Shvets, M. A. Kabanova, E. G. Zhelvakova, and N. A. Preobrazhenskii, Zhur. Org. Khim., 4, 597 (1968).
60. L. Wiggins, J. Chem. Soc., 13 (1946).
61. E. Baer and M. Kates, J. Amer. Chem. Soc., 70, 1394 (1948).
62. E. Baer and M. Kates, J. Amer. Chem. Soc., 72, 942 (1950).
63. T. Bevan and T. Malkin, J. Chem. Soc., 2667 (1951).
64. E. Baer, J. Maurukas, and M. Russell, J. Amer. Chem. Soc., 74, 152 (1952).
65. E. Baer, J. Biol. Chem., 198, 853 (1952).
66. E. Baer and J. Maurukas, J. Biol. Chem., 212, 25 (1955).
67. E. Baer, J. Maurukas, and D. Clarke, J. Biol. Chem., 228, 181 (1957).
68. E. Baer and S. Pavanaram, J. Biol. Chem., 236, 1269 (1961).
69. E. Baer and A. Zschocke, J. Biol. Chem., 236, 1273 (1961).
70. E. Baer and F. Eckstein, J. Biol. Chem., 237, 1449 (1962).
71. E. Baer and K. Rao, J. Biol. Chem., 238, 1941 (1963).
72. E. Baer and J. Blackwell, J. Biol. Chem., 238, 3591 (1963).
73. E. Baer and K. Rao, Canad. J. Biochem. Physiol., 44, 899 (1966).
74. E. Baer and B. Pal, Canad. J. Biochem. Physiol., 45, 309 (1967).
75. E. Baer and D. Buchnea, J. Biol. Chem., 232, 895 (1958).
76. E. Baer and D. Buchnea, Arch. Biochem. Biophys., 78, 294 (1958).
77. E. Baer and D. Buchnea, J. Amer. Chem. Soc., 81, 1758 (1959).
78. E. Baer and D. Buchnea, Canad. J. Biochem. Physiol., 39, 1471 (1961).
79. E. Baer and A. Kindler, Biochemistry, 1, 518 (1962).
80. V. I. Shvets, L. T. Dorofeeva, M. A. Grum-Grzhimailo, I. S. Shmidt, L. V. Volkova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 34, 3983 (1964).

81. D. Turner, M. Silver, E. Baczynski, N. Giordano, and J. Rodalewica, J. Lipid Res., 34, 3983 (1964).
82. V. I. Shvets, L. T. Dorofeeva, B. A. Klyashchitskii, and N. A. Preobrazhenskii, see Ref. 43, p. 23.
83. M. K. Petrova, V. I. Shvets, I. I. Gracheva, and N. A. Preobrazhenskii, see Ref. 43, p. 27.
84. L. V. Volkova, S. F. Morozova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 35, 84 (1964).
85. D. Rehbinder and D. Greenberg, Annalen, 681, 182 (1965).
86. V. I. Shvets, L. V. Volkova, A. I. Miroshnikov, S. F. Morozova, V. G. Grineva, V. A. Polyanskaya, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 36, 49 (1966).
87. D. Turner, M. Silver, and E. Baczynski, J. Medicin. Pharmaceut. Chem., 9, 771 (1966).
88. R. Saunders and H. Schwarz, J. Amer. Chem. Soc., 88, 3844 (1966).
89. V. I. Shvets, V. I. Chicherina, L. A. Malysheva, and N. A. Preobrazhenskii, Zhur. Org. Khim., 3, 1179 (1967).
90. V. I. Shvets, L. F. Pogrebnaya, A. A. Kraevskii, and N. A. Preobrazhenskii, Zhur. Org. Khim., 4, 971 (1968).
91. V. I. Shvets, S. M. Presnyakova, L. V. Malysheva, and N. A. Preobrazhenskii, Zhur. Vses. Khim. Obshch. Mendeleeva, 13, 112 (1968).
92. D. Turner, M. Silver, R. Holburn, and E. Baczynski, Lipids, 3, 228 (1968).
93. J. Berecoechea, M. Faure, and J. Anatol, Bull. Soc. Chim. biol., 50, 1561 (1968).
94. R. Hirt and R. Berchtold, Helv. Chim. Acta, 40, 1928 (1957).
95. V. I. Shvets, L. V. Volkova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 31, 2184 (1961).
96. V. I. Shvets, L. V. Volkova, S. F. Ryzhenkova, E. E. Lukashenko, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 33, 2876 (1963).
97. Yu. B. Pyatnova, I. K. Sarycheva, and N. A. Preobrazhenskii, see Ref. 43, p. 21.
98. F. Pfeiffer, S. Cohen, and J. Weisbach, J. Org. Chem., 34, 2795 (1969).
99. R. Hirt and R. Berchtold, Pharm. Acta Helv., 33, 349 (1958).
100. N. A. Bogoslovskii, G. I. Samokhvalov, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 32, 2210 (1962).
101. D. Shapiro and Y. Rabinsohn, Biochemistry, 3, 603 (1964).
102. H. Eibl, D. Arnold, H. Weltzien, and O. Westphal, Annalen, 709, 226 (1967).
103. D. Brown and P. Hammond, J Chem. Soc., 4232 (1960).
104. S. P. Kozlova, N. B. Tarusova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 39, 2463 (1968).
105. M. A. Grum-Grzhimailo, L. V. Volkova, M. I. Komakhina, and N. A. Preobrazhenskii, Zhur. Org. Khim., 4, 1157 (1968).
106. Yu. S. Tsizin and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 33, 2873 (1963).
107. R. Aneja, J. Chadha, A. Davies, and C. Rose, Chem. Phys. Lipids, 3, 286 (1969).
108. R. Aneja, J. Chadha, and A. Davies, Biochim. Biophys. Acta, 218, 102 (1970).
109. J. Barzilay and Y. Lapidot, Chem. Phys. Lipids, 3, 280 (1969).
110. M. Coulon-Morelec and D. Girand, Bull. Soc. Chim. biol., 47, 47 (1964).
111. B. A. Klyashchitskii, V. V. Pimenova, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 39, 1653 (1969).
112. B. A. Klyashchitskii, V. V. Pimenova, V. I. Shvets, S. D. Sokolov, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 39, 2373 (1969).
113. R. Gigg and C. Warren, J. Chem. Soc. (C), 2367 (1969).
114. A. V. Luk'yanov, A. I. Lyutik, V. I. Shvets, and N. A. Preobrazhenskii, Khim. Prirod. Soed., 230 (1966).
115. A. I. Lyutik, V. N. Krylova, E. S. Zhdanovich, and N. A. Preobrazhenskii, in "I Sovetsko-indiiskii Simpozium po Khimii Prirodnykh Soedinenii, Tezisy Dokladov" (First Soviet–Indian Symposium on the Chemistry of Natural Compounds, Abstracts of Papers), Tashkent, 1968, p. 42.
116. T. P. Zubkova, Z. Ya. Khrapkova, I. K. Sarycheva, and N. A. Preobrazhenskii, Zhur. Org. Khim., 4, 2226 (1968).
117. D. Mercier, J. Barnett, and S. Gero, Tetrahedron, 25, 5681 (1969).
118. E. G. Zhelvakova, O. G. Ul'yanova, V. I. Shvets, and N. A. Preobrazhenskii, Khim. Prirod. Soed., 163 (1970).
119. E. G. Zhelvakova, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Org. Khim., 6, 62 (1970).
120. V. G. Mairanovskii, A. Ya. Veinberg, and G. I. Samokhvalov, Zhur. Obshch. Khim., 38, 666 (1968).
121. V. G. Mairanovskii, A. Ya. Veinberg, and G. I. Samokhvalov, Zhur. Obshch. Khim., 38, 667 (1968).
122. E. Baer, J. Biol. Chem., 189, 235 (1951).
123. J. Uhlenbrock and P. Verkade, Rec. Trav. chim., 72, 395 (1953).
124. R. Aneja, J. Chadha, and J. Knaggs, Biochem. Biophys. Res. Comm., 36, 401 (1969).
125. S. G. Batrakov, Yul. G. Molotovskii, V. V. Dorogov, and L. D. Bergel'son, Zhur. Obshch. Khim., 37, 426 (1967).
126. T. Bevan, T. Malkin, and J. Tiplady, J. Chem. Soc., 3086 (1957).
127. T. Baylis, T. Bevan, and T. Malkin, J. Chem. Soc., 2962 (1958).
128. G. Haas and L. Deenen, Rec. Trav. chim., 80, 951 (1961).
129. G. Haas and L. Deenen, Rec. Trav. chim., 81, 215 (1962).
130. R. Bird and J. Chadha, Tetrahedron Letters, 4541 (1966).
131. L. Zervas and I. Dilaris, J. Amer. Chem. Soc., 77, 5354 (1955).
132. M. Hoefnagel, L. Stegerhock, and P. Verkade, Rec. Trav. chim., 79, 336 (1960).
133. M. Hoefnagel, L. Stegerhock, and P. Verkade, Rec. Trav. chim., 79, 605 (1960).
134. A. Veen and P. Verkade, Rec. Trav. chim., 79, 1085 (1960).
135. J. Billimoria and K. Lewis, J. Chem. Soc. (C), 1404 (1968).
136. T. Bevan, D. Brown, G. Gregory, and T. Malkin, J. Chem. Soc., 127 (1953).
137. J. Gielkens, M. Hoefnagel, L. Stegerhock, and P. Verkade, Rec. Trav. chim., 77, 656 (1958).
138. N. Stanacev and M. Kates, Canad. J. Biochem. Physiol., 38, 297 (1960).
139. G. Haas and L. Deenen, Rec. Trav. chim., 80, 1951 (1961).
140. M. Klepp and L. Schmid, Nahrung, 12, 41 (1968).
141. T. Malkin, Fette u. Seifen, 60, 930 (1958).

142. E. Baer and S. Pavanaram, J. Biol. Chem., 236, 2410 (1961).
143. G. Haas and L. Deenen, Tetrahedron Letters, 9, 1 (1960).
144. P. Verkade, Proc. k. ned. Akad. Wetenschap., 65B, 164 (1962).
145. P. Bird, G. Haas, C. Heemskerk, and L. Deenen, Biochim. Biophys. Acta, 98, 566 (1965).
146. A. Slotboom, G. Haas, and L. Deenen, Rec. Trav. chim., 82, 469 (1963).
147. G. Haas and L. Deenen, Biochim. Biophys. Acta, 106, 315 (1965).
148. V. M. Polyachenko, G. I. Samokhvalov, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 32, 396 (1962).
149. G. Haas, F. Daemen, and L. Deenen, Biochim. Biophys. Acta, 65, 260 (1962).
150. F. Daemen, G. Haas, and L. Deenen, Rec. Trav. chim., 81, 348 (1962).
151. F. Daemen, G. Haas, and L. Deenen, Rec. Trav. chim., 82, 487 (1963).
152. J. Maurukas, S. Kairys, and C. Holland, Biochemistry, 2, 397 (1963).
153. J. Chadha, Chem. Phys. Lipids, 2, 415 (1968).
154. Yul. G. Molotkovskii, T. Yu. Lazurkina, and L. D. Bergel'son, Izv. Akad. Nauk SSSR, Ser. Khim., 1784 (1969).
155. G. Haas and L. Deenen, Proc. k. ned. Akad. Wetenschap., 64C, 592 (1961).
156. G. Haas, H. Lutphen, P. Bonsen, and L. Deenen, Rec. Trav. chim., 83, 99 (1964).
157. P. Bonsen, G. Haas, and L. Deenen, Biochim. Biophys. Acta, 106, 93 (1965).
158. P. Bonsen, G. Haas, and L. Deenen, Biochemistry, 4, 1114 (1967).
159. Yul. G. Molotkovskii and L. D. Bergel'son, Izv. Akad. Nauk SSSR, Ser. Khim., 2321 (1967).
160. Yul. G. Molotkovskii and L. D. Bergel'son, Izv. Akad. Nauk SSSR, Ser. Khim., 2498 (1967).
161. Yul. Molotkovsky and L. Bergelson, Chem. Phys. Lipids, 2, 1 (1968).
162. G. Haas and L. Deenen, Rec. Trav. chim., 82, 1163 (1963).
163. G. Haas and L. Deenen, Rec. Trav. chim., 84, 436 (1965).
164. P. Bonsen, G. Haas, and L. Deenen, Chem. Phys. Lipids, 1, 33 (1966).
165. J. Kamp and L. Deenen, Chem. Phys. Lipids, 1, 86 (1966).
166. J. Billimoria and K. Lewis, Chem. and Ind., 1731 (1968).
167. P. Bonsen and G. Haas, Chem. Phys. Lipids, 1, 100 (1967).
168. D. Hanahan, J. Biol. Chem., 207, 879 (1954).
169. N. Tattrie and C. McArthur, Canad. J. Biochem. Physiol., 35, 1165 (1957).
170. E. Baer and D. Buchnea, J. Amer. Chem. Soc., 78, 232 (1956).
171. E. Baer and D. Buchnea, Canad. J. Biochem. Physiol., 37, 953 (1959).
172. F. Kögl, G. Haas, and L. Deenen, Rec. Trav. chim., 79, 661 (1960).
173. D. Hanahan and H. Brockerhoff, Arch. Biochem. Biophys., 91, 326 (1960).
174. G. Haas and L. Deenen, Tetrahedron Letters, 22, 7 (1960).
175. G. Haas and L. Deenen, Biochim. Biophys. Acta, 70, 469 (1963).
176. N. Tattrie and J. Bennett, Canad. J. Biochem. Physiol., 41, 1983 (1963).
177. V. I. Shvets, Laslo Antal, L. V. Volkova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 34, 1908 (1964).
178. V. I. Shvets, V. A. Klopova, and N. A. Preobrazhenskii, Khim. Prirod. Soed., 225 (1966).
179. A. Brandt and N. Lands, Biochim. Biophys. Acta, 144, 605 (1967).
180. H. Bosch, L. Golde, A. Slotboom, and L. Deenen, Biochim. Biophys. Acta, 152, 694 (1968).
181. H. Bosch, A. Slotboom, and L. Deenen, Biochim. Biophys. Acta, 176, 632 (1969).
182. E. Baer, Y. Suzuki, and J. Blackwell, Biochemistry, 2, 1227 (1963).
183. E. Baer and J. Blackwell, Biochemistry, 3, 975 (1964).
184. L. M. Bova, V. I. Shvets, F. Ya. Shutova, and N. A. Preobrazhenskii, Zhur. Org. Khim., 1, 1720 (1965).
185. V. I. Shvets, V. A. Klopova, and N. A. Preobrazhenskii, Khim. Prirod. Soed., 80 (1966).
186. V. I. Shvets, M. K. Petrova, G. A. Kazenova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 37, 1454 (1967).
187. D. Turner, M. Silver, and E. Baczynski, Lipids, 1, 439 (1966).
188. A. Avison, J. Chem. Soc., 732 (1955).
189. Y. Lapidot, J. Barzilay, and J. Hajdu, Chem. Phys. Lipids, 3, 125 (1969).
190. R. Aneja, J. Chadha, E. Cubero Robles, and R. Daal, Biochim. Biophys. Acta, 178, 439 (1969).
191. E. Cubero Robles and H. Jongh, Rec. Trav. chim., 86, 762 (1967).
192. E. Cubero Robles and D. Berg, Biochim. Biophys. Acta, 187, 520 (1969).
193. F. Collins, Nature, 188, 297 (1960).
194. F. Collins and V. Shotlander, Biochem. J., 79, 321 (1961).
195. D. Sinha and W. Gaby, J. Biol. Chem., 239, 3668 (1964).
196. D. Galanos and V. Kapoulas, Biochim. Biophys. Acta, 98, 278 (1965).
197. D. Galanos and V. Kapoulas, Biochim. Biophys. Acta, 98, 293 (1965).
198. D. Galanos and V. Kapoulas, Biochim. Biophys. Acta, 98, 313 (1965).
199. V. S. Chigirev, V. I. Shvets, and E. N. Bezinger, Dokl. Akad. Nauk SSSR, 181, 747 (1968).
200. A. Koning, Nature, 200, 1211 (1963).
201. Z. A. Shabarova, Doctoral Thesis, Moscow State University, 1965.
202. G. Porcellati, F. Jeso, and M. Malcovati, Life Sci., 5, 769 (1966).
203. G. Procellati, F. Jeso, M. Malcovati, and M. Biasion, Life Sci., 5, 1791 (1966).
204. L. Pizer and C. Ballour, J. Amer. Chem. Soc., 81, 915 (1959).
205. H. Brockerhoff and D. Hanahan, J. Amer. Chem. Soc., 81, 2591 (1959).
206. D. Brown, G. Hall, and R. Letters, J. Chem. Soc., 3547 (1959).
207. C. E. Ballou and L. Pizer, J. Amer. Chem. Soc., 81, 4745 (1959).
208. J. Hawthorne, P. Kemp, and R. Ellis, Nature, 185, 27 (1960).
209. H. Brockerhoff and C. E. Ballou, J. Biol. Chem., 236, 1907 (1961).
210. R. Dawson and J. Dittmer, Biochem. J., 81, 540 (1961).

211. C. Grado and C. E. Ballou, J. Biol. Chem., 236, 54 (1961).
212. D. Brown and J. Stewart, Biochim. Biophys. Acta, 125, 413 (1966).
213. B. A. Klyashchitskii, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Org. Khim., 5, 192 (1969).
214. B. A. Klyashchitskii, V. I. Shvets, and N. A. Preobrazhenskii, Chem. Phys. Lipids, 3, 393 (1969).
215. C. E. Ballou and L. Pizer, J. Amer. Chem. Soc., 82, 3333 (1960).
216. S. Angyal and B. Shelton, J. Chem. Soc. (C), 433 (1966).
217. N. Kochetkov, A. Khorlin, and A. Bochkov, Tetrahedron, 23, 693 (1967).
218. B. A. Klyashchitskii, V. I. Shvets, S. D. Sokolov, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 40, 1148 (1970).
219. B. A. Klyashchitskii, G. D. Strakhova, V. I. Shvets, S. D. Sokolov, and N. A. Preobrazhenskii, Dokl. Akad. Nauk SSSR, 185, 594 (1969).
220. B. A. Klyashchitskii, G. D. Strakhova, V. I. Shvets, S. D. Sokolov, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 40, 236 (1970).
221. 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).
222. B. A. Klyashchitsky, E. G. Zhelvakova, V. I. Shvets, R. P. Evstigneeva, and N. A. Preobrazhenskii, Tetrahedron Letters, 587 (1970).
223. E. G. Zhelvakova, B. A. Klyashchitskii, V. I. Shvets, R. P. Evstigneeva, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 40, 248 (1970).
224. G. Rouser, G. Kritchevsky, D. Heller, and E. Lieber, J. Amer. Oil Chem. Soc., 40, 425 (1963).
225. G. Colacicco and M. Rapport, J. Lipid Res., 8, 513 (1967).
226. E. G. Zhelvakova, V. A. Magnashevskii, L. I. Ermakova, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Org. Khim., 6, 1987 (1970).
227. E. G. Zhelvakova, G. V. Smirnova, V. I. Shvets, and N. A. Preobrazhenskii, Zhur. Org. Khim., 6, 1992 (1970).
228. E. G. Zhelvakova, Candidate's Thesis, Moscow Institute of Fine Chemical Technology, 1970.
229. W. Lenarz, Adv. Lipid Res., 4, 175 (1966).
230. G. V. Smirnova, A. I. Bashkatova, V. I. Shvets, and R. P. Evstigneeva, Zhur. Org. Khim., 6, 1756 (1970).
231. H. Wehrli and Y. Pomeranz, Chem. Phys. Lipids, 3, 357 (1969).
232. J. Moore and M. Szelke, Tetrahedron Letters, 4423 (1970).
233. A. Poulos, J. Lipid Res., 11, 496 (1970).
234. R. Aneja and J. Chadha, in "7-i Mezhdunar. Simp. po Khimii Prirodnykh Soedinenii, Tezisy Dokladov" (Seventh International Symposium on the Chemistry of Natural Compounds—Abstracts of Papers), 1970, p. 295.
235. D. Turner and E. Baczynski, Chem. and Ind., 1204 (1970).
236. R. Aneja and A. Davies, Chem. Phys. Lipids, 4, 60 (1970).
237. H. Eibl and O. Westphal, Annalen, 738, 161 (1970).
238. H. Eibl and O. Westphal, Annalen, 738, 174 (1970).
239. H. Eibl and O. Westphal, Annalen, 738, 170 (1970).
240. M. G. Luchinskaya, L. V. Volkova, V. A. Stupnikova, and N. A. Preobrazhenskii, Zhur. Obshch. Khim., 40, 915 (1970).
241. M. G. Luchinskaya, L. V. Volkova, A. S. Pyshkin, and N. A. Preobrazhenskii, Uch. Zap. MITKhT Lomonosova, 1, 72 (1970).
242. H. Verheij, P. Smith, P. Bonsen, and L. Deenen, Biochim. Biophys. Acta, 218, 97 (1970).
243. B. A. Klyashchitskii, A. K. Starostina, V. I. Shvets, and R. P. Evstigneeva, Dokl. Akad. Nauk SSSR, 195, 102 (1970).
244. V. I. Shvets, B. A. Klyashchitskii, and N. A. Preobrazhenskii, see Ref. 234, p. 293.
245. Yu. G. Molotkovskii, see Ref. 234, p. 291.
246. P. Gent, R. Gigg, and C. Warren, Tetrahedron Letters, 2575 (1970).

Lonomosov Moscow Institute of
Fine Chemical Technology