Translated from *Uspekhi Khimii*, **55**, 1803-1833 (1986) U.D.C. 547.303/306

Alkyl Orthoesters and Their Applications in Organic Synthesis

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A systematic account is given of data characterising the chemical properties of alkyl esters of orthocarboxylic acids. The suggested reaction mechanisms are discussed and the extensive possibilities of the application of the orthoesters in the solution of various problems in organic synthesis are demonstrated.
The bibliography includes 91 references.

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I. INTRODUCTION

Inspection of the literature data of recent years shows that the interest in orthoesters, which are reactive chemical reagents, has not weakened and has stimulated the discovery of further new aspects of the application of these compounds. The aim of the present review is to give a systematic account of the data concerning the use of alkyl orthoesters in organic synthesis, which have been published during the period from 1971 to 1984 and which have not been included in earlier reviews.[1-6]

One of the fundamental works devoted to the synthesis and properties of orthoesters and their analogues is the book by De Wolfe[1] in which a profound analysis of all possible chemical reactions of orthoesters, thio-orthoesters, amidoacetals, ester-aminals, and orthoamides has been carried out and the proposed reaction mechanisms are discussed. A review by the same author, with an extensive coverage of the methods of synthesis of orthoesters, was published somewhat later.[2] One of the chapters in Bergstrom's book[3] is devoted to the chemistry of orthoesters, acetals, and ketals, attention being concentrated on the methods of synthesis of orthoesters and the mechanism of their hydrolysis.

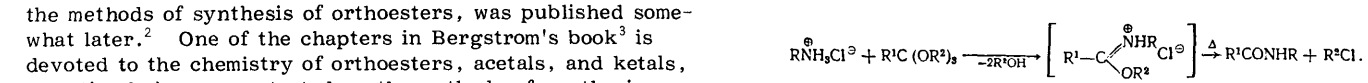
The Soviet literature on the synthesis and properties of orthoesters is represented by two reviews[4,5] and the chemistry of cyclic orthoesters is described in a collected volume.[6]

Since the modern methods of synthesis of orthoesters have been described in the above literature sources in adequate detail, the data on the hydrolysis of orthoesters have been analysed, and the data concerning the synthesis and behaviour of cyclic orthoesters have been surveyed, this review does not include the relevant sections.

II. INTERACTION OF ORTHOESTERS WITH NITROGEN-CONTAINING COMPOUNDS

1. Reactions with Primary and Secondary Amines

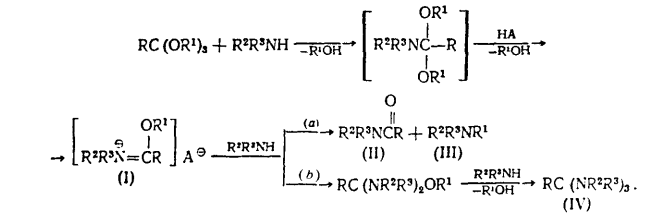
It has been shown[7] that alkyl orthoesters can be used successfully for the acylation of primary and secondary amines and aminoacid esters. The reaction is carried out by heating briefly (70–90 °C) the amino-component in the form of the hydrochloride (or another salt) with the alkyl orthoester. An alcohol, an alkyl halide, and the corresponding *N*-acyl derivative of the amino-component, whose yield in most cases exceeds 90%, are then formed. The nature of the products obtained suggests that the reaction takes place mainly via a stage involving the formation of imidoester salts, which undergo the "Pinner" cleavage to the amide and the alkyl halide at elevated temperatures:



It is noteworthy that the mechanism of the interaction of orthoesters with amides depends in most cases on whether the amino-group is in the free state or whether the salt of the amino-component is introduced into the reaction; it also depends on whether the salt has been formed with a weak or a strong acid.

It is known[1] that the acid-catalysed reactions of secondary amines with orthoesters can lead to the formation of three types of products: amidoacetals, ester-aminals, and orthoamides. The interaction of orthoesters with secondary amines of different types has been investigated in order to

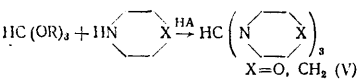
discover a convenient method for the synthesis of orthoamides.[8] It was shown that the yield of the latter depends mainly on the reactivity and structure of the initial amine and also on the type of the acid catalyst used in the reaction. For example, when weakly basic amines, such as *N*-alkylanilines, are acted upon by orthoesters, then orthoamides are either not formed at all (both in the absence of catalysts and in the presence of toluene-*p*-sulphonic acid) or are obtained in a low yield (in catalysis by hydrochloric or acetic acid). In the presence of acids the reaction can proceed via the following mechanism:



The changes in the ratios of the products (II), (III), and (IV), obtained in the presence of different acids have been explained[8] by the influence of the anion A^- on the structure of the intermediate complex (I).

The main products of the reactions of orthoformates with alkylanilines are *N*-alkylformanilides (II) and *NN*-dialkylanilines (III). *N*-Benzylmethylamine behaves analogously to *N*-alkylanilines, affording approximately equal amounts of *N*-benzyl-*N*-methylformamide and *N*-benzyl-*N*-ethylmethylamine in the reaction with triethyl orthoformate in the presence of toluene-*p*-sulphonic acid.

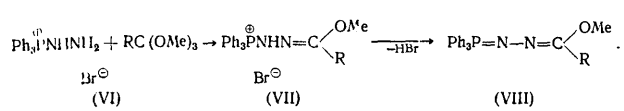
Acyclic secondary amines do not form appreciable amounts of orthoamides in their reactions with orthoesters under these conditions. Only the interaction of orthoesters with highly basic cyclic amines, such as morpholine, piperidine, and *N*-methylpiperazine led to the isolation of the corresponding orthoamides (V) in high yields regardless of the type of catalyst employed:



This method of synthesis of the orthoamides (V) is more convenient and more economical than those used previously,[9,10] although it does suffer from certain limitations: orthoamides are formed only from six-membered cyclic amines; it has not been possible to carry out similar reactions with pyrrolidine and hexamethyleneimine.

2. Reactions with Compounds Containing the Hydrazino-Group

The interaction of orthoesters with hydrazinotriphenylphosphonium bromide (VI) leads to a new method of synthesis of *syn*- and *anti*-α-methoxyalkylidenetriphenylphosphazines (VIII).[11] The attack by the orthoester on the hydrazino-group of the initial compound (VI) results in the formation of α-methoxyalkylidenetriphenylphosphazinium bromides (VII), which can be readily converted into the corresponding phosphazines (VIII) via dehydrobromination:

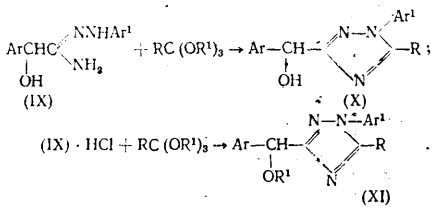


The thermal or photochemical decomposition of compound (VIII) leads to the formation of α-alkoxycarbenes, which have been little investigated hitherto.

3. Reactions with Amino-components Accompanied by Cyclisation

Alkyl orthoesters are finding increasing applications in the synthesis of a wide variety of heterocyclic derivatives. The reaction involving the formation of triazoles from orthoesters and aryl-substituted hydrazones of carboxylic acids has been known for a long time.[12] Studies on the mechanisms of the analogous reactions and side processes are being continued.

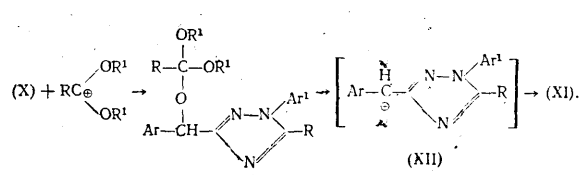
It has been shown[13] that the reactions of alkyl orthoesters with the *N*-arylamidrazones of mandelic acid (IX) (in the form of a free base) lead to the formation of 1,3,5-trisubstituted triazoles (X), the hydroxy-group in the side chain remaining unchanged. If the hydrochloride of the amidrazone (IX) is used as the initial compound, the corresponding triazole (XI) with an alkylated hydroxy-group is obtained:



The corresponding monochloro-compound (IXa, Ar = o-C_6H_4Cl) reacts with the orthoester, both in the form of a free base and in the form of a hydrochloride, to form only a triazole of type (X) with an unsubstituted hydroxy-group.

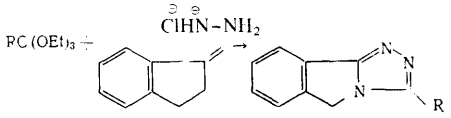
Under the influence of acid (HCl), the orthoesters are apparently converted into the corresponding dialkoxycarbonium ions, which are known to be strong alkylating agents. In the presence of acids, the hydroxy-group in the side chain of triazole is therefore alkylated, while in the absence of acid it remains unaltered. This hypothesis has been confirmed by the fact that the product (X) is converted quantitatively into compound (XI) in solutions of orthoesters after the addition of acids. The monochloro-derivative (IXa) is not alkylated, probably owing to steric factors.

The same workers[14] traced analogous reactions of the optically active *N*-arylamidrazones of mandelic acid in the presence and absence of inorganic acids. In the absence of acids, the reaction proceeds stereospecifically: the dextrorotatory amidrazone forms a dextrorotatory triazole. The reactions with the hydrochlorides of the optically active amidrazones result in the formation of a racemic triazole alkylated at the hydroxy-group. It has been suggested that, as a result of the attack on the hydroxy-group of triazole by the dialkoxycarbonium ion, the cation (XII) is formed as an intermediate. Further reactions of this cation lead to the racemate (XI):



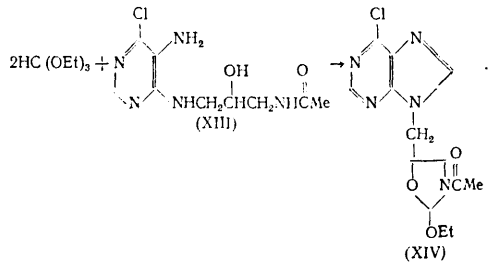
In certain cases the reaction between the orthoester and the amino-component is possible only in the presence of acid. For example, the reaction of ethyl orthoacetate or ethyl

orthoformate with the hydrochloride of 1-hyrazinoisoindolenine proceeds solely as a result of the formation of dialkoxycarbonium ions.[15] Its product is a triazoloindole:



In the absence of acid, the orthoesters are passive in relation to hydrazinoisoindolenines.

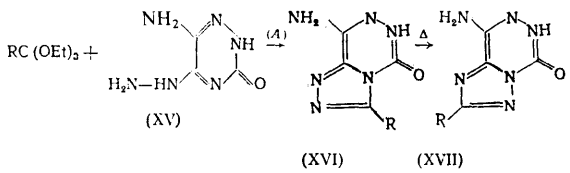
It is known that, on reaction with 5-amino-4-hydrazinopyrimidines, the orthoesters give rise to *N*-aminoimidazolopyrimidines.[16] The reaction between orthoformate and diaminopyrimidine (XIII) is of the same type:[17]



(XIII) (XIV)

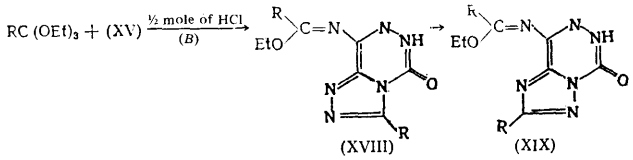
However, four active groups of the initial compound (XIII) participate simultaneously in this reaction, which results in the formation of two new rings: the imidazole and oxazolidine rings. The disubstituted purine (XIV) formed is used as the intermediate in the synthesis of an acyclic analogue of puromycin.

The reaction of orthoesters with 6-amino-5-hydrazino-1,2,4-triazin-3-one (XV) does not take place unambiguously.[18] The course of this reaction is influenced by several factors: the temperature conditions, the presence of acid in the reaction mixture, and even its amount. It is noteworthy that, at room temperature in the absence of acid, the orthoesters do not interact with compound (XV). When the orthoesters are refluxed with compound (XV) without added acid [version (*A*)], cyclisation takes place initially with formation of compound (XVI), the primary amino-group not being involved. Subsequently, as a consequence of an intramolecular rearrangement, the product (XVI) is converted into the more stable compound (XVII):



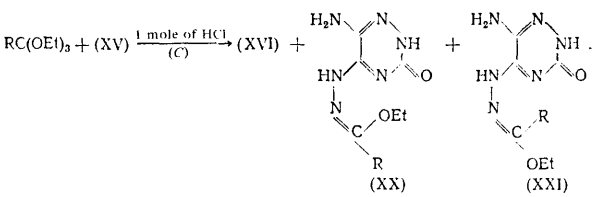
(XV) (XVI) (XVII)

At room temperature in the presence of a certain amount of hydrochloric acid [version (*B*)], a mixture of products (XVIII) and (XIX) was obtained. It was noted that compound (XVIII) gradually isomerises to compound (XIX):



(XVIII) (XIX)

When the reaction was carried out without heating in the presence of an equimolar amount of acid [version (*C*)], three products were isolated: (XX), (XXI), and (XVI). The quantitative stereoisomer ratio (XX):(XXI) in the mixture was 2:1:



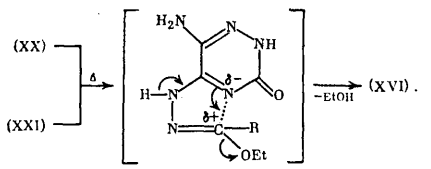
(XX) (XXI)

If more than one equivalent of hydrochloric acid is introduced into the mixture of the initial reactants at room temperature [version (*D*)], then only the product (XVII) is obtained.

In contrast to other orthoesters, orthoformate reacts with the initial compound (XV) to form products of type (XVI) and (XVII) regardless of whether the acid is present in an excess or deficiency.

We shall now consider the proposed reaction mechanism.

Version (*A*). In the absence of acid, the reaction mixture must be heated for the reactants to react. The orthoester molecule reacts with the hydrazino-group of compound (XV) as the most reactive nucleophilic centre. This results in the initial formation of the products (XX) and (XXI), which cyclise with simultaneous elimination of an alcohol [transition state (XXII)]. Heating promotes the occurrence of this process, which ultimately leads to the formation of compound (XVI):



(XXII)

Version (*B*). When concentrated hydrochloric acid is introduced into the reaction mixture, more active electrophiles, dialkoxycarbonium ions, appear in the reaction sphere. They can apparently interact not only with the hydrazino-group but also with the less reactive, in the given instance, amino-group of the initial compound (XV). The products of this reaction are compounds (XVIII) and (XIX).

Thus, in the presence of acid, which plays the role of a catalyst and reactant, there is a possibility of the occurrence of a series of competing reactions: non-ionic interaction between the orthoester and the initial compound (XV); the reaction of the amino-component with the acid; the interaction of the orthoester with the acid; the attack by dialkoxycarbonium ions on the active groups in the initial and intermediate compounds; acid-catalysed cyclisation reactions.

Presumably the products of the substitution in the amino-group of type (XVIII) and (XIX) are not formed in versions (*C*) and (*D*) as a consequence of the protonation of the amino-group of the initial compound (XV).

In the presence of an excess of acid in the reaction mixture, compounds (XX) and (XXI) were not detected apparently because in the presence of acid their conversion into the bicyclic product (XVI) is facilitated.

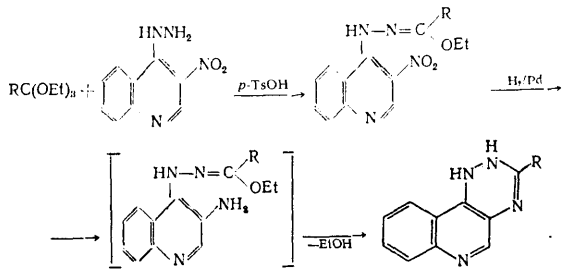
The anomalous behaviour of orthoformate can apparently be accounted for by the fact that the cations $HC^{\oplus}(OR)_2$ formed as a result of its interaction with the acid are least stable in the series of dialkoxycarbonium ions. For this reason, non-ionic processes leading to the formation of compounds

(XVI) and (XVII), which are also formed without the addition of acid, can predominate in the reactions of orthoformate. Compounds of type (XX) and (XXI), where R = H, could be formed as intermediates, but they cyclise to compound (XVI) more readily than others, which follows from the examination of the transition state (XXII).

The study of Lovelette and Geagan[18] clearly demonstrated how significant is the alteration of conditions in the reaction between orthoesters and polyfunctional amino-components.

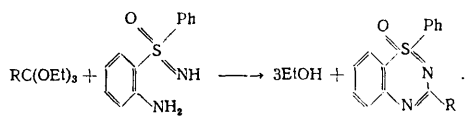
Compounds (XXIII), possessing anti-inflammatory activity greatly exceeding that of acetylsalicylic acid, have been obtained from alkyl orthoesters and 4-hydrazino-3-nitroquinoline.[19]

The first stage represents a typical interaction of an alkyl orthoester with the hydrazino-group of the initial quinoline catalysed by toluene-p-sulphonic acid. On hydrogenation in the presence of palladium, the nitro-group is reduced to the amino-group, as a consequence of which intermolecular cyclisation becomes possible:

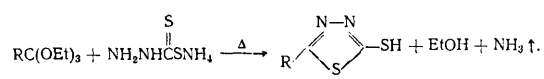


(XXIII)

New cyclic sulphoximides have been obtained by the reaction of orthoacetates (and orthoformates) with *S*-(*o*-aminophenyl)-*S*-phenylsulphoximide:[20]



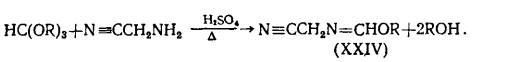
Five-membered thiadiazole rings, containing the mercapto-group in the side chain, can be conveniently obtained by refluxing orthoesters with salts of *N*-aminodithiocarbamic acid:[21]



Because of the wide variety of the products obtained, the reaction between orthoesters and aminonitriles are of undoubted interest.

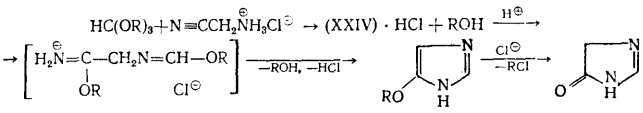
A fundamentally new approach to the methods of synthesis of 5-imidazolones has been described.[22] It is based on the interaction of orthoesters with aminoacetonitrile.

The reaction between orthoformate and aminoacetonitrile has its characteristic features. If the interaction is carried out in the presence of catalytic amounts of sulphuric acid with simultaneous removal of the alcohol, then alkyl *N*-cyanomethylacetimidate (XXIV) is obtained in a high yield:



(XXIV)

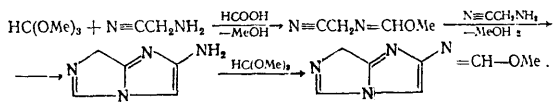
When the orthoester is made to react with the hydrochloride of aminoacetonitrile, the only product is 5-imidazolinone (XXV) (yield in excess of 90%). According to the authors' hypothesis,[22] the product (XXIV) is formed initially, its nitrile group undergoing acid-catalysed (HCl) alcoholysis. This is followed by cyclisation to 5-alkoxy-1*H*-imidazole and the latter is converted, after being attacked by the halide ion, into the 5-imidazolinone (XXV) with elimination of the corresponding alkyl halide:



(XXV)

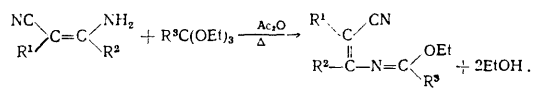
This method ensures a high yield of compound (XXV) and is simpler and more convenient in practice than the earlier procedures.[23,24]

Trimethyl orthoformate taken in excess reacts differently with aminoacetonitrile in the presence of catalytic amounts of formic acid. The reaction proceeds in several stages and the final product is methyl *N*-{7*H*-imidazo[1,5-*a*]-imidazol-2-yl acetimidate (XXVI), isolated in 24% yield:



(XXVI)

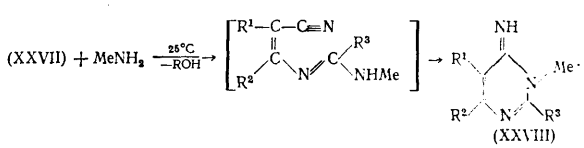
Orthoesters combined with enaminonitriles proved to be the best reagents for the synthesis of *C*-alkylated 1,6-dihydro-6-imino-1-methylpyrimidines (XXVIII).[25] The reaction of the orthoester with an enaminonitrile gives rise to the corresponding ethoxyalkylidene derivative (XXVII):



(XXVII)

The reaction proceeds, as with aminoacetonitrile, in the absence of acids[22] with the sole difference that here there is a possibility of the formation of the *cis*- and *trans*-isomers, depending on the structure of the initial enaminonitrile.

By treating compound (XXVII) with an alcoholic solution of methylamine, it is easy to achieve the substitution of ethoxy-groups. This reaction is accompanied by spontaneous cyclisation to the pyrimidine (XXVIII):



(XXVIII)

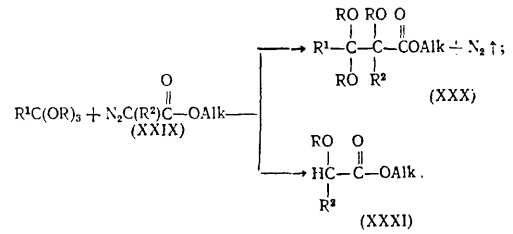
Derivatives of this type were previously difficult to obtain.[26] They are of interest as convenient objects for the study of the mechanism of the Dimroth rearrangement.[25]

A number of reactions involving orthoesters and amino-components of different types (amines, amides, and carboxylic acid amidrazones) have been examined in a book.[27]

4. Reactions with Diazo-compounds

Alkyl orthoesters, particularly orthoformate, orthoacetate, and orthopropionate, readily react with diazo-compounds (XXIX).[28] The reaction is catalysed by Lewis acids:

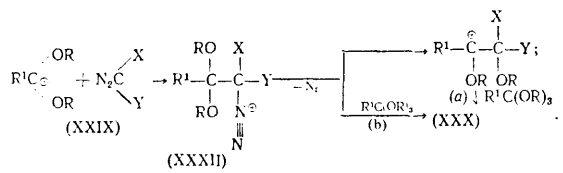
copper(II) trifluoromethanesulphonate, rhodium tetra-acetate, and boron trifluoride etherate:



(XXIX) (XXX) (XXXI)

The reactions led to the isolation of the main product (XXX) and the side product (XXXI). Neither the reaction time nor the amount of catalyst affected the yield of the main product (XXX) and only the nature of the catalyst employed was found to be important. When copper(II) trifluoromethanesulphonate or boron trifluoride etherate are used, the amount of side product (XXXI) is small.

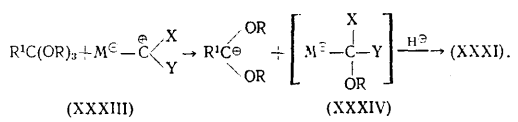
It has been suggested[28] that the catalysts enumerated, bound in a complex with the diazo-component, promote the formation of a dialkoxycarbonium ion, which is itself an active reagent. It adds to the diazo-derivative, after which nitrogen is eliminated and the product (XXX) is formed:



(XXIX) (XXXII) (XXX)

When nitrogen is split off from the intermediate (XXXII), a new electrophilic centre to which the alkoxy-group can migrate (*a*) or the usual substitution of the diazonium group takes place (*b*), is probably formed.

The product (XXXI) becomes the main one if transition metal compounds are used as catalysts. The transition metal and the diazo-component apparently form a dipolar carbene complex (XXXIII), to the electrophilic centre of which the alkoxy-group of the orthoester can be transferred, as a result of which one obtains the dialkoxycarbonium ion and the active complex (XXXIV). When a proton is captured by the complex (XXXIV), the product (XXXI) is formed with dissociation of the carbon–metal bond:



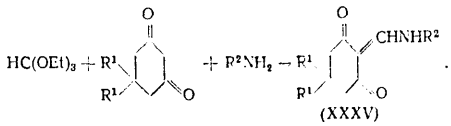
(XXXIII) (XXXIV) (XXXI).

III. THREE-COMPONENT CONDENSATIONS

One of the most promising applications involves the use of orthoesters in three-component condensation reactions. The high reactivity of orthoesters and the numerous varieties of reagents employed in these reactions create a unique possibility for the synthesis of new structures. The mechanism of the three-component condensation has been described in a general form and discussed in detail in a review.[4]

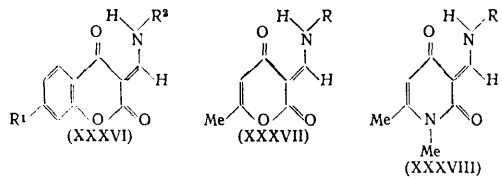
A number of studies[29–32] have been devoted to reactions in which alkyl orthoesters interact simultaneously with a carrier of an active methylene group and a carrier of an amino-group. A convenient method of synthesis of an extensive class of compounds, namely acyl- and diacyl-enamines, is based on this reaction.

For example, orthoformates readily react with cyclohexane-1,3-diones and aromatic amines to form the corresponding enaminodiketones (XXXV), which can in their turn be converted into hexahydroquinolinediones:[29]



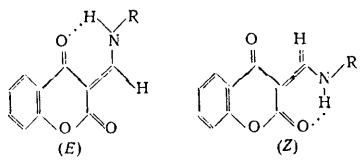
(XXXV)

Thus 3-anilinomethylenechroman-2,4-diones (XXXVI), 3-anilinomethylene-6-methyl-2,3-dihydropyran-2,4-diones (XXXVII), and 3-anilinomethylene-1,6-dimethyl-2,3-dihydropyridine-2,4-diones (XXXVIII) have been obtained from orthoformates, anilines, and cyclic six-membered 1,3-diketones of more complex structure:[30]



(XXXVI) (XXXVII) (XXXVIII)

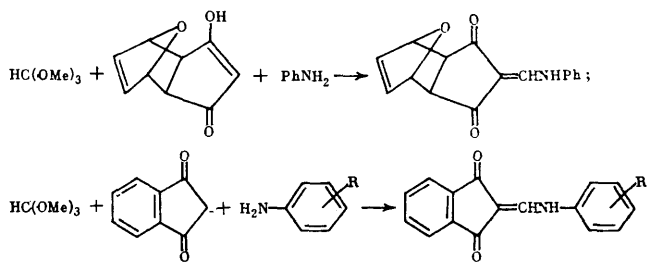
Probably by virtue of steric factors, only orthoformate can react with six-membered diketones and aromatic amines. It has been shown[30] that the reaction products consist of a mixture of stereoisomers:



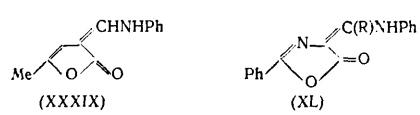
(*E*) (*Z*)

The use of five-membered cyclic 1,3-diketones in the three-component condensation also proved to be successful.[31] In this version it is possible to employ aliphatic primary amines as well as aromatic amines.

Condensed systems can also serve as the methylene components. The only important factor is that the active methylene group should belong to a five-membered ring. The following reactions proceed smoothly:[31]



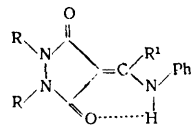
Compounds (XXXIX) and (XL), each of which can be resolved into geometrical isomers with the aid of fractional crystallisation, have also been obtained:[31]

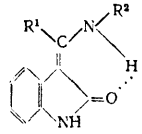


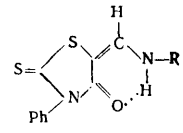
(XXXIX) (XL)

The derivatives (XLI) and (XLII) have been synthesised with participation of orthoacetate and orthopropionate. It has

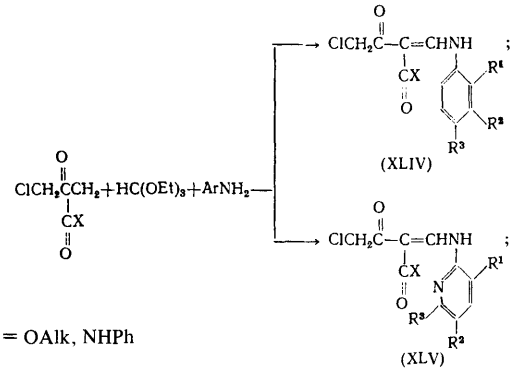
been noted that compound (XLII) has cytotoxic properties:[31]


(XLI)


(XLII)


(XLIII)

Compounds (XLIII) are obtained by the interaction of orthoformates with aliphatic amines and *N*-phenylrhodanine at an elevated temperature (150 °C).[31] Alkyl γ-halogenoacetoacetates can be used successfully in three-component condensation subject to the condition that their reaction partners are orthoformate and aromatic amines.[32] The derivatives (XLIV) are then obtained from anilines and compounds (XLV) are obtained from 2-aminopyridines, both in the form of mixtures of *E*- and *Z*-isomers:

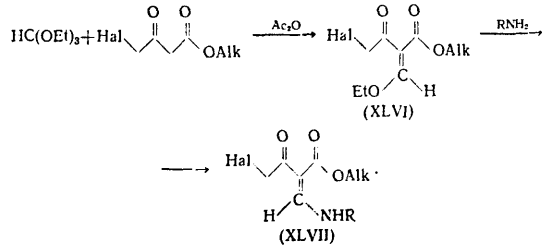

(XLIV)

(XLV)

X = OAlk, NHPh

Compounds (XLIV) and (XLV) are used as intermediates in the synthesis of derivatives of 3-hydroxypyrroles, pyrido-1,2-pyrimidones, and quinolines.[32]

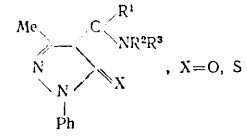
The three-component condensation of orthoesters, halogenoacetoacetates, and aliphatic amines is complicated by side reactions.[32] For this reason, the corresponding derivatives of *N*-alkylaminomethylene-γ-halogenoacetoacetic acid (XLVII) can be more conveniently obtained in two stages. The orthoformate is initially made to react with the methylene component in the presence of acetic anhydride, which leads to the formation of the ethoxymethylene derivatives (XLVI). The latter are treated with aliphatic amines and the required product (XLVII) is isolated:


(XLVI)

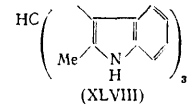
(XLVII)

Thus it has been demonstrated clearly by means of a number of examples that the method of synthesis of ββ-diacylenamines and their analogues via a type of three-component condensation has advantages over previous procedures.[33–35] In the vast majority of cases it consists of a single stage, is carried out under mild conditions, and there is only one side product, an alcohol, which can be readily removed from the reaction mixture.

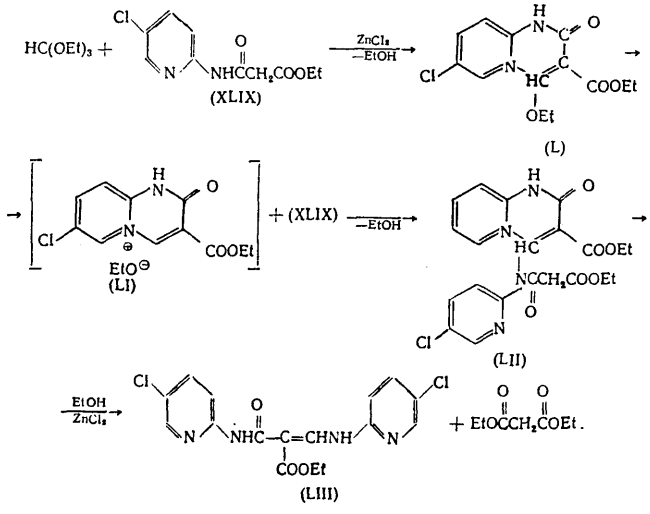
The choice of methylene components is not limited to carbonyl derivatives. Together with alkylaminomethylene-5-pyrazolinones, their thio-analogues have been obtained by the method of three-component condensation:[31]



Some of the methylene components tested under the conditions of three-component condensation behaved anomalously. For example, 1-indanone and 2-methylindole reacted with orthoformate without the participation of the amino-component, to form products of type (XLVIII):[31]


(XLVIII)

The interaction of orthoesters with polyfunctional compounds can proceed via a mechanism of the type of three-component condensation. For example, in the reaction with orthoformic ester, one molecule of 2-ethoxycarbonylacetamidopyridine (XLIX) behaves as the methylene component, while the other behaves as the amino-component.[36] The authors suggest that this reaction mechanism can be represented schematically as follows:


(XLIX)

(L)

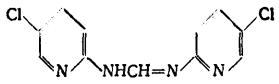
(LI)

(LII)

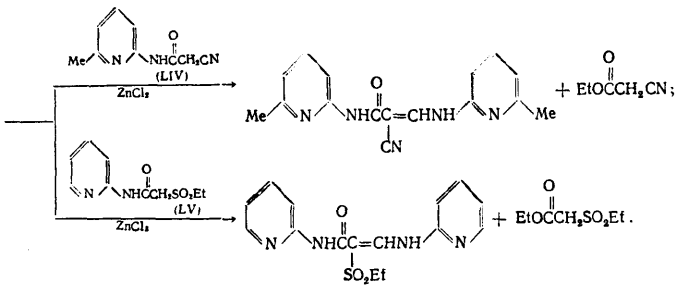
(LIII)

The configuration of compound (L) is such that, under the influence of the electronegative nitrogen atom of the pyridine ring on the nearest ethoxy-group, the elimination of the latter in the form of the corresponding anion is facilitated. An active ionic compound (LI), which can react with the amide nitrogen atom of the initial compound (XLIX), is formed under these conditions. The product (LII) obtained undergoes alcoholysis under the influence of the alcohol, formed as a side product under the conditions of catalysis by zinc chloride, malonic ester being split off. Compound (LIII) is obtained in this way. In order to increase the yield of compound (LIII) from 24% to 41%, it was found to be sufficient to replace the acetic anhydride, normally employed as the solvent in such reactions, by ethyl alcohol.[36]

The reaction of 2-amino-5-chloropyridine with orthoformate is of the same type, the product being a formamidine:[36]



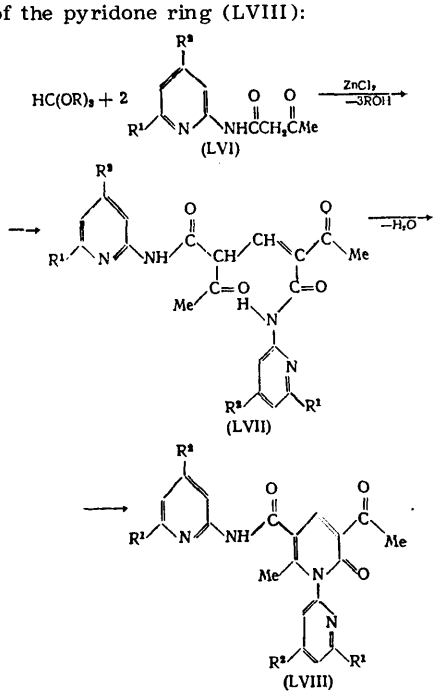
When the corresponding cyanoacetyl derivative (LIV) and the ethanesulphonylacetyl derivative (LV) were introduced into the reaction with the orthoester instead of the ethoxycarbonyl derivative, analogous products were obtained, although the yield of the main product in these cases was low (18–29%):



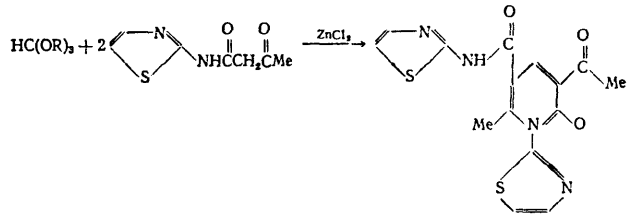
IV. REACTIONS OF ORTHOESTERS WITH COMPOUNDS CONTAINING AN ACTIVE HYDROGEN ATOM

1. Interaction of Orthoesters with CH Acids

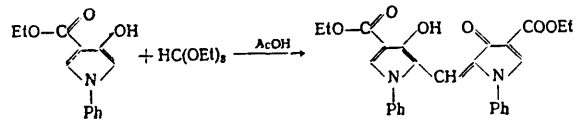
Certain reactions of this type lead to unexpected results. For example, when orthoformates interact with substituted 2-acetoacetylaminopyridines (LVI) in the presence of zinc chloride, complex tricyclic products (LVIII) are obtained.[37] Two molecules of the initial compound (LVI), which functions as the methylene component, react with a molecule of the orthoformic ester. The carbonyl and amide group approach one another so much in compound (LVII) that, under the catalytic influence of zinc chloride, intramolecular condensation takes place with elimination of a water molecule and formation of the pyridone ring (LVIII):



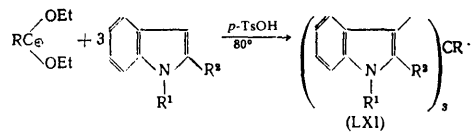
The interaction of orthoformate with 2-acetoacetylaminothiazole takes place analogously:[37]



The reaction of triethyl orthoformate with 3-hydroxy-4-ethoxycarbonyl-1-phenylpyrrole [32] leads to a compound containing the hydroxypyrrole and pyrrolinone groups:



Derivatives of indole are typical representatives of CH acids. The behaviour and reactivity of orthoesters in reactions with disubstituted indoles in the presence of organic acids have been investigated[38] and it has been shown that alkyl orthoesters participate in this reaction in the form of the corresponding dialkoxycarbonium ions, which attack the 3-position, where the electron density is highest, to form tri-indolylmethanes:



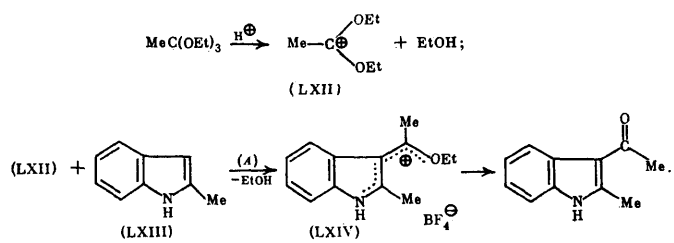
(LIX): R=H;
(LX): R=Me

Kinetic data have shown that the behaviour of the carbonium ions (LIX) and (LX) in reactions of this type is approximately the same, trimethoxycarbonium ions proving to be the least reactive.

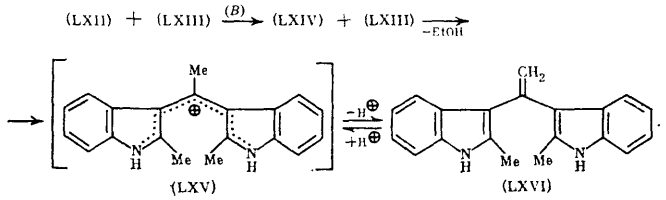
Reactions in which analogous products (XLVIII) were obtained by the interaction of 2-methylindole with orthoesters in the presence of organic bases were considered above; unfortunately the reaction mechanism was not discussed by Wolfbeis.[31]

By altering the reaction conditions, it is possible to obtain different products of the reaction of orthoesters with 2-substituted alkylindoles. A convenient method of synthesis of the pharmacologically active indolylcarbazole (LXVII) from ethyl orthoacetate and 2-methylindole has been proposed.

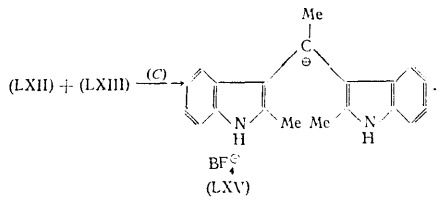
If the reaction between triethyl orthoacetate and 2-methylindole (LXIII) is carried out in methylene chloride in the presence of HBF_4 at 0 °C [version (*A*)], then the main product is 1-ethoxy-1-(2-methylindol-3-yl)ethyl tetrafluoroborate (LXIV). This relatively stable salt has been isolated in 46% yield. In aqueous organic media, it is gradually converted into 3-acetyl-2-methylindole.



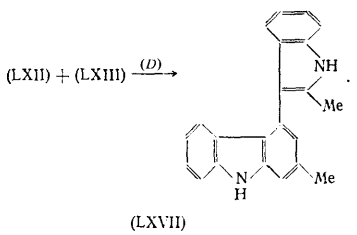
When the starting materials are refluxed in methanol in the presence of catalytic amounts of concentrated sulphuric acid [version (*B*)], the bisindolyl derivative (LXVI) is formed. The product (LXIV) formed initially apparently reacts under these conditions with yet another molecule of the initial indole (LXIII) and the intermediate bisindolylcarbonium ion (LXV) is converted on deprotonation into 1,1-bis(2-methylindol-3-yl)ethylene (LXVI) (yield 37%):



The cation (LXV) was isolated directly in the form of the tetrafluoroborate salt. For this purpose, the initial indole (LXIII) was activated with a Grignard reagent, namely ethylmagnesium bromide, and was then made to react with the orthoester in the presence of boron trifluoride [version (*C*)], the yield being 19%:



Under more severe conditions, after prolonged refluxing of the reactants in acetic acid or methanol in the presence of concentrated sulphuric acid [version (*D*)], 2-methyl-4-(2-methylindol-3-yl)-9*H*-carbazole (LXVII) is formed:

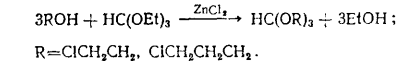


2. Reactions with Alcohols and Mercaptans

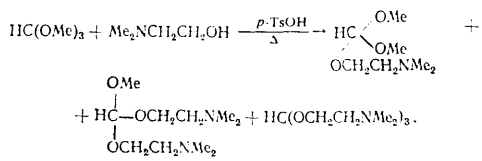
The reactions of alkyl orthoesters with alcohols have been investigated in fair detail.[1,2,4-6] They consist in the exchange of the alkoxy-group of the orthoesters with the corresponding alcohol residue. Using certain polyfunctional alkanols, it is possible to introduce additional active groups into the orthoester molecule. For this purpose, alkyl orthoesters are made to react with chloroalcohols, aminoalcohols, alkylaminoalcohols, and ethylenecyanohydrin.[40]

One, two, and three alkoxy-groups of the orthoester can exchange for the *O*-alkyl group of the alcohol depending on the structure of the latter and the reaction conditions (molar reactant ratio and the character of the catalyst employed). The reaction usually results in the formation of a mixture of products of similar structure, which makes it difficult to separate them.

Individual products have been obtained from ethyl orthoformate and ethylenechlorohydrin and also 3-chloropropanol in the presence of zinc chloride as the catalyst:



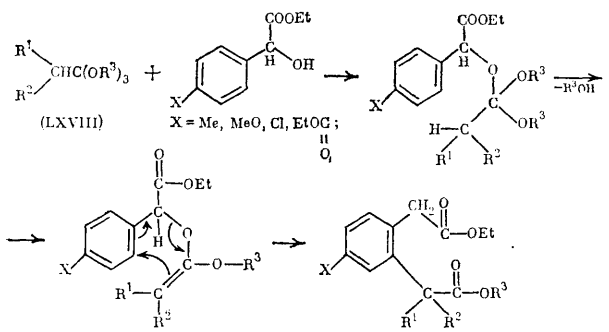
When orthoesters react with aliphatic aminoalcohols in the presence of acid catalysts (toluene-*p*-sulphonic acid, zinc chloride, or tin chloride), mixtures of mono-, di-, and trisubstituted aminoalkyl orthoesters are obtained and are separated by fractional distillation,[40-43] for example:



The mechanism of the interaction of orthoesters with unsaturated alcohols is much more complex, since reactions of this kind are usually accompanied by intramolecular rearrangements of the type of the Claisen rearrangement.[1,44-49,51,52]

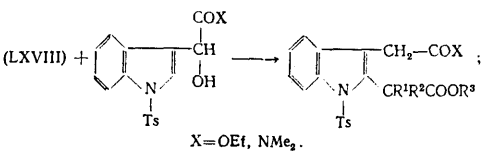
A series of studies[44-46] have been devoted to the mechanism of the interaction of orthoesters with aromatic derivatives containing a hydroxy-group in the α-position in the side chain.

A convenient method has been proposed[44] for the synthesis of substituted arenes, which is distinguished by a high regio- and stereo-specificity. It is based on the application of the reaction of orthoesters with the ethyl esters of mandelic acid and its analogues:

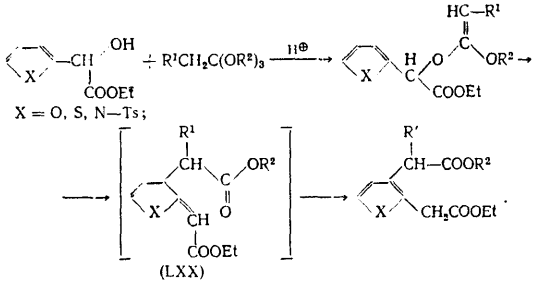


In the first stage of the synthesis, one alkoxy-group of the orthoester is substituted by the alkoxy-residue of the initial alcohol; the alcohol R^3OH is split off from the product (LXIX) and this is followed by the Claisen rearrangement proper, which leads to the formation of a new carbon–carbon bond. The influence of neighbours of the hydroxy- and ethoxycarbonyl groups facilitates the intramolecular rearrangement.

The same chain of transformations is observed in the reactions of alkyl orthoesters with the esters and amides of 3-indolylglycolic acid:[44]



The interaction of orthoesters with other heterocyclic hydroxyesters proceeds analogously to the reaction described above,[45,46] but in this instance it is necessary to introduce an acid catalyst. 2,3-Disubstituted derivatives of furan, thiophen, and pyrrole are obtained in this way using hexanoic acid as the catalyst:[45]

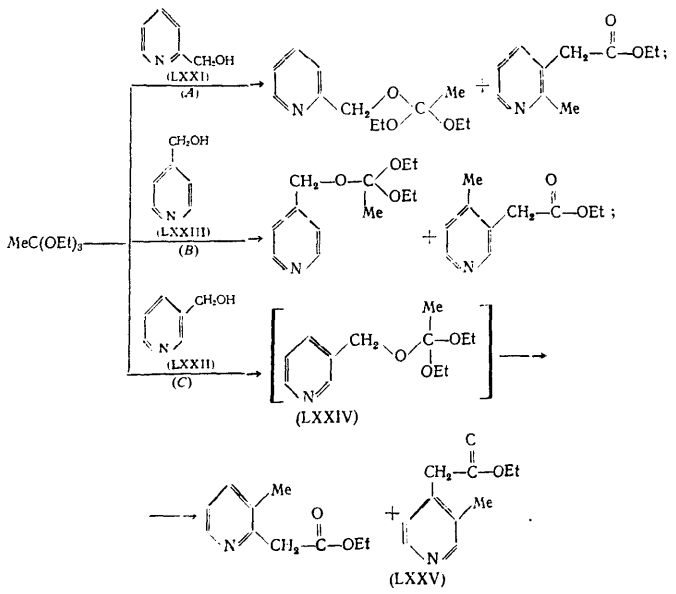


(LXX)

The ethoxycarbonyl group stabilises the intermediate (LXX). When 3-substituted furans, thiophens, and pyrroles are used as the initial derivatives, mixtures of 2,3- and 3,4-disubstituted heterocyclic products are formed.[45]

The Claisen rearrangement can also be studied for a series of hydroxymethylpyridines and hydroxymethylpyridones;[46] the authors noted that the rearrangement involving the latter proceeds in an unusual manner.

An essential condition for the smooth rearrangement in the reaction of orthoesters with the pyridine derivatives (LXXI) to (LXXIII) is an increase of temperature to 195 °C. The results of the reactions (*A*) and (*B*) of triethyl orthoacetate with 2- and 4-hydroxymethylpyridines differ from the results obtained for 3-hydroxymethylpyridine [reaction (*C*)] in which the rearranged product (LXXIV) was not isolated at all:

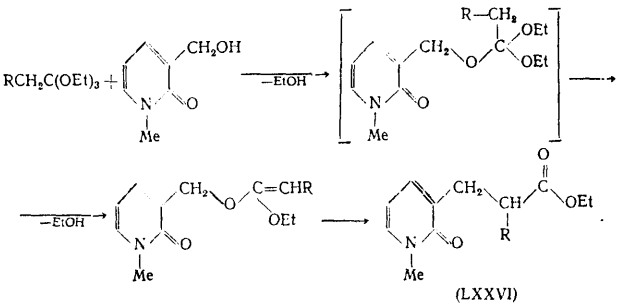


(LXXIV)

(LXXV)

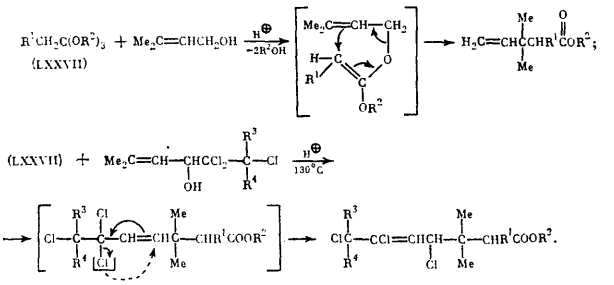
Calculation of the relative electron densities in different positions in the pyridine ring has shown that the density is a maximum in the 3-position. These data explain why the carbon–oxygen bond in compound (LXXIV) is dissociated much more readily than in the other two cases. This is why the product (LXXIV) has not been detected.

The reaction of orthoesters with 3-hydroxylmethyl-1-methyl-2-pyridine does not lead to the formation of products of type (LXXV), compounds (LXXVI) being formed instead:



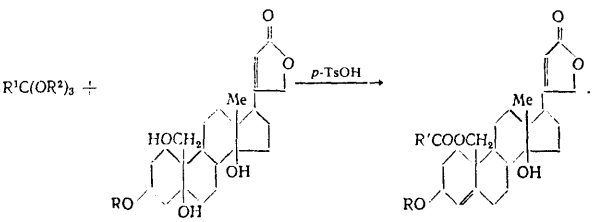
(LXXVI)

The interaction with unsaturated acyclic alcohols is used for different purposes. New methods of synthesis of unsaturated carboxylic acid esters are based on the reactions of orthoesters with allyl alcohols,[47,48] including halogenoalkyl-substituted derivatives.[49] The reaction is carried out in the presence of acid catalysts with the simultaneous removal of the lower alcohol formed as a side product, while in the case of halogeno-derivatives it is performed at elevated temperatures in a stream of nitrogen:

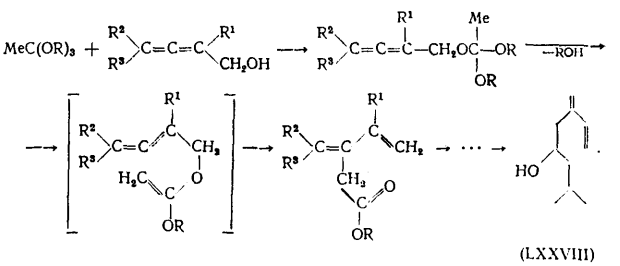


In the latter case the Claisen rearrangement is accompanied by the transfer of the chloride anion and the migration of the double bond.[49]

The synthesis of analogues of cardiotonic glycosides (by the conversion of cardenolides into cardadienolides) has been achieved with the aid of alkyl orthoesters:[50]

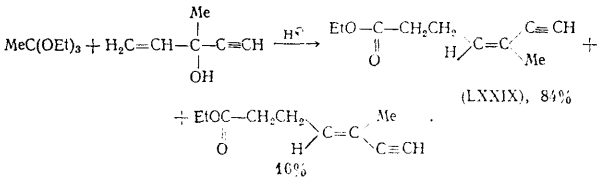


The reactions of orthoesters with alcohols of the type of allenylmethanol have been used in one of the stages of the synthesis of the terpenoids ipsenol (LXXVIII) and ipsdienol:[51]



(LXXVIII)

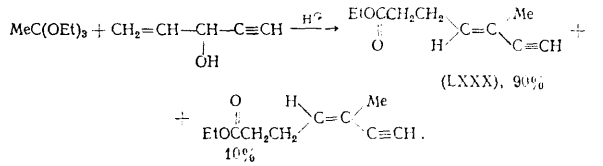
The reactions of orthoesters with vinylalkynylmethanols have been studied in detail.[52] Attention has been concentrated on the study of the structure of the product. It has been shown that the reactions of triethyl orthoacetate and tertiary allylalkynyl alcohols followed by the Claisen rearrangement yields mainly the esters (LXXIX), in which the acetylenic group occupies the *cis*-position relative to the ester side chain. The *trans*-products are formed in very small amounts, for example:



(LXXIX), 84%

10%

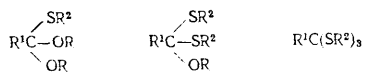
The reactions of orthoesters with secondary allylalkynyl alcohols also proceed stereospecifically, although in this instance the products are mainly the *trans*-substituted compounds (LXXX):



(LXXX), 90%

10%

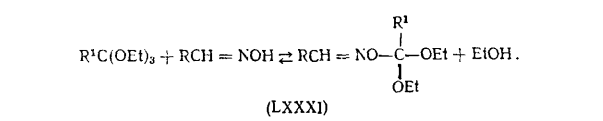
The reactions involving the exchange of the alkoxy-group of the orthoester for the alkylthio-group of a mercapto-compound are analogous to the reactions with alcohols[1,4-6] but proceed more vigorously. Thio-analogues of orthoesters the same three types as the products of the reactions with alcohols can be obtained:



By varying the conditions (by altering the temperature and the reactant ratio and by selecting the appropriate catalyst), it is possible to increase the yield of derivatives of all these types. For example, the use of aluminium chloride as the catalyst promotes the formation of mainly trithio-orthoesters.[53]

3. Reactions with Oximes

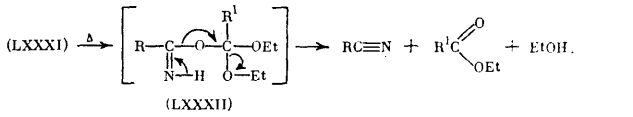
Orthoesters readily react with oximes, whereupon one alkoxy-group of the orthoester is substituted by the oxime residue formed after the abstraction of a proton:[54]



(LXXXI)

When the reactivities of the stereoisomers of oximes were compared, it was found that the *Z*-isomer reacts with the orthoester more slowly than the *E*-isomer and NMR data showed that the oxime does not isomerise under the given conditions.

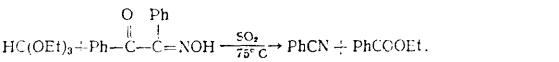
It is important to note that only in the absence of acids are the derivatives (LXXXI) relatively stable; under the conditions of acid catalysis, they undergo the "Beckmann fragmentation", which yields the corresponding nitrile, ester, and alcohol. Judging from the structure of the product (LXXXI) and the substances obtained after its fragmentation, one can postulate that the Beckmann rearrangement takes place initially and is followed by the decomposition of the product (LXXXII):



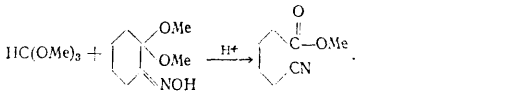
(LXXXII)

The reactions between orthoesters and oximes in liquid sulphur dioxide take place over a period of several minutes, because the solvent plays the role of the catalyst.

Thus the interaction of orthoesters with oximes constitutes an effective method of synthesis of the corresponding nitriles.[54] For example, when benzil monoxime is heated with a 10% excess of triethyl orthoformate in liquid sulphur dioxide at 75 °C, benzonitrile and ethyl benzoate can be obtained in quantitative yields:

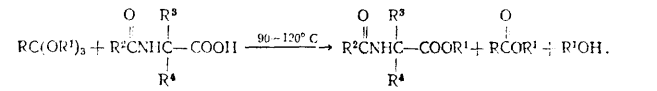


Trimethyl orthoformate and the dimethyl ketal of 2-hydroxyiminocyclohexanone react analogously in the presence of methane sulphonic acid at −10 °C to form methyl 5-cyanopentanoate:



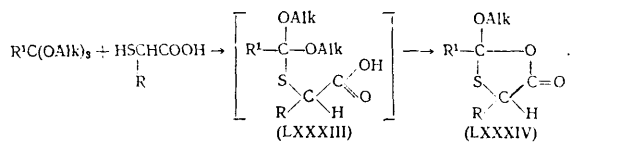
4. Reactions with Carboxylic Acids

The high reactivity of orthoesters makes it possible to use them for the esterification of carboxylic acids.[55] The esters of orthocarbonic and orthoacetic acids give rise to the corresponding *N*-acylaminoacid esters in quantitative yield in the absence of catalysts:[56]



The reaction is not accompanied by side processes and racemisation and proceeds smoothly even in the case of sterically hindered aminoacids.

Orthoesters react very readily with carboxylic α-mercaptoacids.[57,58] The products are 2-alkoxy-1,3-oxathiolan-5-ones (LXXXIV). It is assumed that the orthoester initially reacts with the mercapto-group and that the heterocycle (LXXXIV) is formed from the intermediate (LXXXIII) as a result of the elimination of the corresponding alcohol AlkOH:



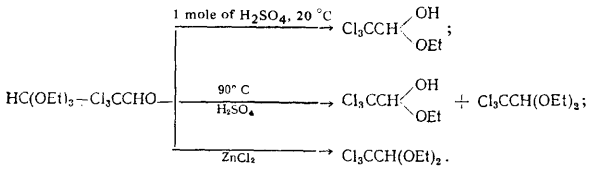
(LXXXIII) (LXXXIV)

The oxathiolanones (LXXXIV) obtained are effective reagents for the synthesis of the amides of carboxylic α-mercaptoacids.[59,60]

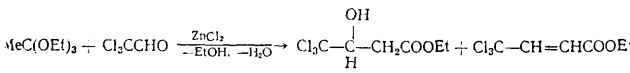
V. INTERACTION OF ORTHOESTERS WITH CARBONYL COMPOUNDS

1. Reactions with Aldehydes and Ketones

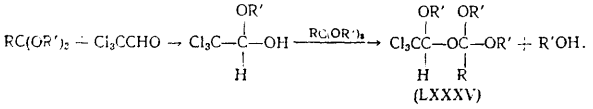
The application of orthoesters in the synthesis of acetals and ketals has been studied in fair detail. However, there is little information in the literature about the interaction of orthoesters with perhalogeno-derivatives of aldehydes and ketones.[61,62] The reaction of orthoesters with chloral is of interest.[61] In the presence of acid catalysts chloral gives rise to hemiacetals and acetals, like all other aldehydes:



In the presence of zinc chloride, ethyl orthoformate and ethyl orthocarbonate react with chloral to form only the corresponding diethyl acetal, while ethyl orthoacetate behaves differently in this reaction. Its interaction with chloral yielded a mixture of the ethyl esters of 4,4,4-trichloro-3-hydroxybutanoic and trichlorobutanoic acids:



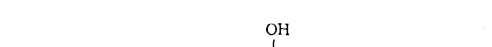
The reaction of orthoesters with chloral takes place in an unusual manner in the absence of catalysts:



(LXXXV)

It has been found that, when weak bases (whose pK does not exceed the limits 7.4–9.2) are used as the catalyst and the reaction temperature is raised to 100 °C, the yield of the product (LXXXV) rises considerably (from 18 to 60%). The mechanism of the reaction involving bases has not unfortunately been discussed by Petrov et al.[61] A product of type (LXXXV) is formed in the reaction of orthoformate with fluoral (with a higher yield).[62]

Even in the absence of catalysts, orthoformates and orthoacetates react vigorously with the hydrates of fluoral, hexafluoroacetone, and dichlorotetrafluoroacetone, forming hemiacetals and hemiketals.[62] On raising the reaction temperature to 60 °C, ethyl orthoacetate undergoes a reaction with fluoral of the type of aldol condensation, which demonstrates the relative mobility of the α-protons in the orthoacetate molecule:

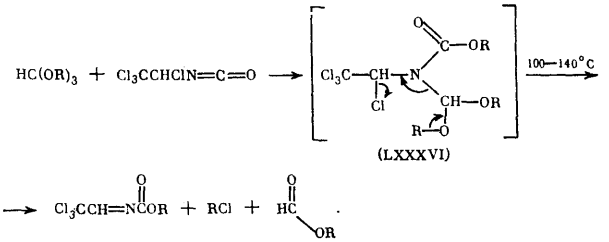


Similar products are obtained also in the reactions of alkyl orthoacetates with hexafluoroacetone and dichlorotetrafluoroacetone.

2. Reactions with Isocyanates

The products of the reactions of orthoesters with isocyanates vary as a function of the reactivity and structure of the isocyanate.

Being more reactive, α- and β-chloro-substituted alkyl isocyanates react with orthoesters in the absence of catalytic additives, which leads to the formation of chloro-substituted N-alkoxycarbonylaldimines.[63] The reaction has been followed with the aid of IR spectroscopy. The IR spectroscopic data led to the hypothesis that the intermediate (LXXXVI) is formed. The final products are an azomethine, an alkyl halide, and a formate:

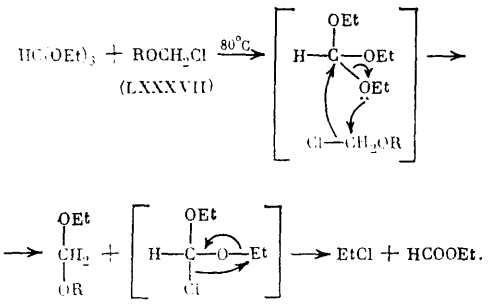


(LXXXVI)

VI. REACTIONS OF ORTHOESTERS WITH COMPOUNDS CONTAINING AN ACTIVE HALOGEN ATOM

1. Reactions with Halogenoethers

One of the non-traditional methods of synthesis of mixed formals and acetals is based on the reaction of alkyl orthoesters with α-chloroethers.[64] The active halogen atom in the initial reactant (LXXXVII) is substituted by the alkoxy-group of the orthoester. The most reactive halogenoethers, for example α-chloromethyl ether, react with orthoesters at room temperature. The tentative reaction mechanism is



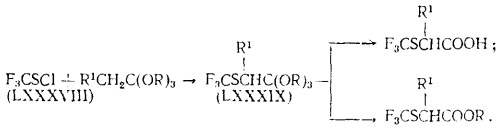
The method is simple and convenient and ensures a high yield of the required product.[64]

2. Reactions with Sulphenyl Chlorides

A new method for the sulphenation of orthoesters with the aid of trihalogenomethanesulphenyl chlorides has been proposed.[65] The mono- and bis-(trihalogenomethylthio)-orthoesters obtained in satisfactory yields are intermediates in the synthesis of halogenoalkylthio-derivatives of carboxylic acids.

Trifluoromethanesulphenyl chloride (LXXXVIII) is the most reactive among the proposed sulphenating agents. Its interaction with the orthoester is completed after several seconds by the formation of the monothio-derivatives (LXXXIX); the orthoester is taken in excess and the reaction is carried out

with cooling (between −10° and +10 °C):

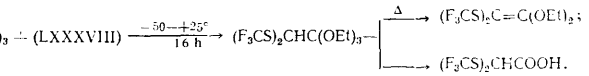


Even "inert" orthoesters such as, for example, ethyl orthoisobutyrate, react with compound (LXXXVIII), because steric factors are not decisive in this reaction:

$$(\text{LXXXVIII}) + Me_2CHC(OEt)_3 \rightarrow F_3CSCMe_2C(OEt)_3 .$$

The yield of the monosulphenated products (LXXXIX) is 75–80%. The behaviour of dichlorofluoromethanesulphenyl chloride in the reactions with orthoesters is similar to that of compound (LXXXVIII).

If the sulphenating agent is taken in excess and at the same time the reaction time and temperature are increased, only bis(trihalogenomethylthio)orthoesters are formed. They are less stable than the monothio-derivatives, so that they are converted into 2,2-dialkoxy-1,1-dialkylthioethylenes even during distillation with elimination of an alcohol molecule:



According to Mendelson et al.[65], trichloromethanesulphenyl chloride interacts with orthoesters via a radical mechanism. Orthoesters react with this compound only in the presence of a free radical initiator—azobisisobutyronitrile (XC):

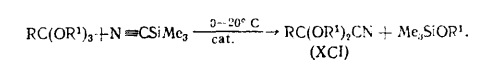
$$MeC(OR)_3 + Cl_3CSCl \xrightarrow{(XC),\ 80^\circ C} Cl_3CSCH_2C(OR)_3 .$$

The proposed reaction mechanism is

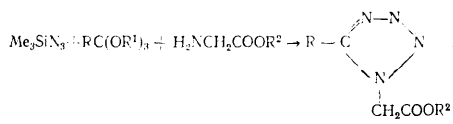
$$Cl_3CSCl \xrightarrow{(XC)} Cl_3C\dot{S} + \dot{C}l ;$$
$$\dot{C}l + CH_3C(OR)_3 \rightarrow \dot{C}H_2C(OR)_3 + HCl ;$$
$$Cl_3CSCl + \dot{C}H_2C(OR)_3 \rightarrow \dot{C}l + Cl_3CSCH_2C(OR)_3 ;$$
$$Cl_3C\dot{S} + \dot{C}H_2C(OR)_3 \rightarrow Cl_3CSCH_2C(OR)_3 .$$

VII. INTERACTION OF ORTHOESTERS WITH ORGANOSILICON COMPOUNDS

Alkyl orthoesters and cyanotrimethylsilane are convenient reagents for the synthesis of nitriles of type (XCI).[66,67] The reaction proceeds in the presence of Lewis acids as catalysts: tin dichloride and boron trifluoride etherate:

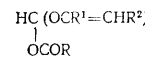


The reaction is not complicated by side processes and leads to the formation of dialkoxynitriles (XCI) in high yields. Previously acyl cyanides were used to introduce the cyano-group into the reaction with the orthoester; the reaction was as a rule accompanied by the formation of a number of side products.[68] It has been shown[69] that trimethylsilyl azide is an effective and at the same time a non-explosive reagent for the synthesis of 1-substituted tetrazole derivatives from orthoesters and aminoacid esters. The method ensures a high yield (90%) and a purity of the product not less than 95%:

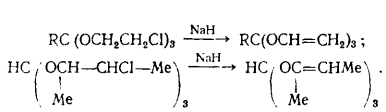


VIII. DEHYDROHALOGENATION OF HALOGENOALKYL ORTHOESTERS

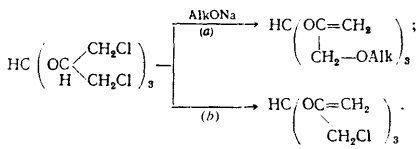
Alkenyl orthoesters,[70] compounds which are known to be highly reactive, are obtained by the dehydrohalogenation of β-chloroalkyl orthoesters. Their application in the synthesis of di(alkenyloxy)alkyl carboxylates has been described:[70]



The dehydrohalogenation of β-chloro-derivatives of orthoesters is carried out by treatment with sodium hydride or sodium butoxide:



When halogenoalkyl orthoesters are treated with solutions of alkoxides, the exchange reaction (*a*) takes place together with the elimination reaction. This side reaction can be excluded by using potassium hydroxide in an aqueous organic medium as the dehydrohalogenating agent [reaction (*b*)]:



IX. INTERACTION OF ALKYL ORTHOESTERS WITH SULPHUR DIOXIDE

In a number of instances liquefied sulphur dioxide is used as the solvent for reactions with orthoesters. It is noteworthy that this compound is not inert with respect to orthoesters. Depending on the conditions, the products of the interaction of alkyl orthoesters with sulphur dioxide can be various.

It has been established that,[71] at low temperatures after prolonged irradiation with UV light, orthoformates and orthocarbonates give rise to the corresponding trialkoxycarbonium ions in liquid sulphur dioxide:

$$HC(OMe)_3 \rightarrow \overset{\oplus}{C}(OMe)_3 ;$$
$$HC(OEt)_3 \rightarrow \overset{\oplus}{C}(OEt)_3 ;$$
$$C(OMe)_4 \rightarrow \overset{\oplus}{C}(OMe)_3 .$$

When the temperature is raised to −20 °C, the above carbonium ions begin to decompose and are converted into dialkyl carbonates. It has been suggested that[71] the carbonium

ions are formed with direct participation of sulphur dioxide:

$$(RO)_3C{-}H \xrightarrow[h\nu]{SO_2} (RO)_3C{-}SO_2H \rightarrow \overset{\oplus}{C}(OR)_3.$$

This reaction takes place under extensive cooling conditions (−75 °C) as a consequence of the activation of the molecules by UV irradiation.

Apart from the main product, the side product (XCII) was isolated. It is formed as a result of the addition of the nucleophile (SO_2) to the electropositive carbon atom of the alkoxy-group of the orthoester:

$$(MeO)_2CHOMe \xrightarrow{SO_2} \underset{(XCII)}{(MeO)_2CHOCH_2SO_2H}.$$

If the mixture of liquefied sulphur dioxide with the alkyl orthoester is maintained in a sealed tube at room temperature, the reaction products are dialkyl sulphites and esters:[72]

$$RC(OR^1)_3 + SO_2 \xrightarrow[24\ h]{20^\circ C} O{=}S\begin{matrix}OR^1\\OR^1\end{matrix} + RCOOR^1.$$

Orthoformate, which is relatively passive in sulphur dioxide in the absence of irradiation, is an exception. Only on heating with a large excess of SO_2 does it react slowly, forming diethyl carbonate in addition to ethyl formate and diethyl sulphite.

It has been shown with the aid of ^1H NMR [72] that the addition of even catalytic amounts of SO_2 to mixtures of orthoesters entails the immediate exchange of the alkoxy-groups as a consequence of the appearance of dialkoxyalkylcarbonium ions. The proposed mechanism of the reaction with SO_2 is as follows:

$$RC(OEt)_3 + SO_2 \underset{}{\overset{(A)}{\rightleftharpoons}} \underset{(XCIII)}{R{-}\overset{OEt}{\overset{|}{C}}(\overset{\oplus}{O}SO_2^{\ominus})(OEt)(Et)};$$

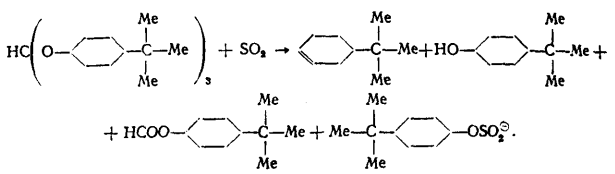
$$(XCIII) \overset{(B)}{\rightleftharpoons} RC(OEt)_2^{\oplus} + EtOSO_2^{\ominus};$$

$$R{-}C(OEt)(\overset{\oplus}{O}Et) + EtOSO_2^{\ominus} \xrightarrow{(C)} RCOOEt + (EtO)_2S{=}O;$$

$$(XCIII) + EtOSO_2^{\ominus} \xrightarrow{(D)} RCOOEt + EtOSO_2^{\ominus} + (EtO)_2S{=}O.$$

The intermediate (XCIII) is apparently formed via the coordinate bond between the sulphur atom in sulphur dioxide and the free electron pair of the oxygen atom in the alkoxy-group of the orthoester (*A*). It decomposes subsequently at the C–O bond (*B*). Both these reactions are reversible. It has been suggested that the main reaction products are obtained as a result of the attack by the alkyl sulphite anion on the dialkoxycarbonium ion (*C*) or on the intermediate (XCIII) (*D*).

The validity of the proposed mechanism has been confirmed by the behaviour of secondary trialkoxymethanes in reactions with SO_2 under the same conditions. The substitution by the resulting secondary alkyl sulphite anion at a secondary carbon atom of the carbonium ion (XCIV) is sterically hindered and for this reason the corresponding olefin, alkanol, secondary alkyl formate, and alkylsulphurous acid are formed. For example:[72]



Thus, in contrast to the photochemical reaction, the interaction of orthoester molecules with SO_2 in the absence of a supply of energy from outside leads to the formation of dialkoxycarbonium ions which are less stable than trialkoxycarbonium ions.

X. BROMINATION OF ORTHOESTERS

The behaviour of dimethoxycarbenium bromides in liquid sulphur dioxide has been investigated.[73] The orthoesters were brominated at temperatures between −60° and −80 °C. Orthoesters react with bromine via an ionic mechanism and the reaction was followed with the aid of NMR. It is a typical nucleophilic substitution reaction. The $Br^{\oplus}$ ion abstracts the alkoxide anion from the orthoester molecule and $Br^{\ominus}$ promotes the stabilisation of the dialkoxyalkylcarbonium ion formed:

$$RC(OR^1)_3 + Br_2 \rightarrow RC(\overset{\oplus}{O}R^1)(OR^1) \; Br^{\ominus} + BrOR^1.$$

It has been shown that, when the orthoesters are brominated in the presence of orthocarbonate, the more stable trialkoxycarbonium ions are formed. This takes place via the irreversible migration of the methoxy-group from the orthocarbonate to the dialkoxycarbonium ion:

$$RC(\overset{\ominus}{O}Me)(OMe)\,Br^{\ominus} + Br_2 + C(OMe)_4 \xrightarrow[SO_2]{-80^\circ C} RC(OMe)_3 + MeO{-}\overset{\oplus}{C}(OMe)_2Br^{\ominus}.$$

The role of the solvent was not discussed in the above communication.

Dimethoxycarbenium bromides are stable only at temperatures below −50 °C, decomposing at higher temperatures in accordance with the following scheme:

$$RC(\overset{\oplus}{O}Me)(OMe) + :\ddot{B}r:^{\ominus} \rightarrow RC(=O)(OMe) + MeBr.$$

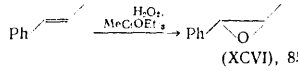
XI. ORTHOESTERS IN TRANSFER OXIDATION REACTIONS

It has been found[74,75] that, in the presence of orthoesters, hydrogen peroxide can be conveneintly used for the mild oxidation of olefins to the corresponding epoxy-derivative. It has been suggested that orthoesters interact with hydrogen peroxide to form the intermediate (XCV) (these are relatively stable as a result of hydrogen bonding), which serve as agents which transfer and generate atomic oxygen:

$$C(OEt)_4 + H_2O_2 \xrightarrow{-EtOH} \underset{(XCV)}{\left[EtO{-}C(OEt)(O{-}H\cdots O)\right]} \xrightarrow{-EtOH} [O] + (EtO)_2CO.$$

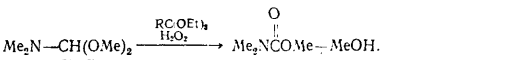
The ethyl esters of formic, acetic, orthobenzoic, and carbonic acids have been tried together with hydrogen peroxide as transfer oxidising agents. Regardless of the structure of the olefin oxidised, the best results were obtained in the first place using ethyl orthocarbonate and then ethyl orthoacetate. This method makes it possible to obtain epoxy-derivatives which are otherwise difficult to

synthesise, for example, compound (XCVI), in a higher yield:



(XCVI), 85%

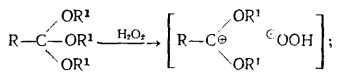
Peroxides such as 9,10-endoperoxy-9,10-diphenylanthracene, can be obtained by the same procedure. Oxidation of the amidoacetals (XCVII) by this method leads to the isolation of the corresponding carbamates:



(XCVII)

The reaction mechanism has not been specially investigated. The hypothetical structure of the intermediate (XCV) has not been confirmed by physicochemical research techniques. We believe the hypothesis that the active oxidising agent may be an ionic complex of type (XCVIII) to be acceptable.

Like other weak acids, hydrogen peroxide added to orthoesters is capable of producing dialkoxycarbonium ions, which are stabilised by combining with the anion $HOO^{\ominus}$:



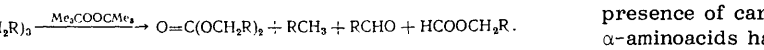
(XCVIII)

R=Me (a), OR^1 (b), Ph (c);
R^1=Et.

Since the complexes (XCVIIIb) are more stable than the complexes (XCVIIIa) while complexes of type (XCVIIIc) are relatively stable but sterically hindered compared with (XCVIIIa), the reason why orthocarbonate is preferable to other orthoesters becomes understandable.

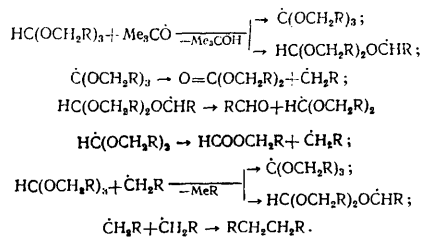
XII. FREE-RADICAL REACTIONS OF ORTHOESTERS

Two investigations have been made of the behaviour of trialkoxymethanes in reactions with free radicals at elevated temperatures (120–150 °C).[76,77] It has been shown by EPR that alkyl orthoformates react with free radicals to form tri- and mono-alkoxyalkyl radicals, whose fragmentation leads to the formation of the corresponding carbonates and formates. The radical reactions were initiated by t-butoxy-radicals:



Conclusions concerning the reactivity of orthoformates in reactions of the above type compared with linear and cyclic acetals were reached on the basis of kinetic data.

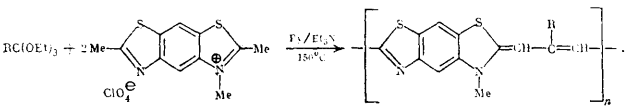
The mechanism of the homolytic liquid-phase reactions of alkyl orthoformates can be demonstrated in relation to triethoxymethane:



It was found that radical chain reactions involving orthoesters can be observed also at much lower temperatures (60 °C) when dicyclohexyl peroxycarbonate is used as the free radical initiator.[78] The chain of radical reactions is analogous to that described above and the main products are the same as under high-temperature conditions.

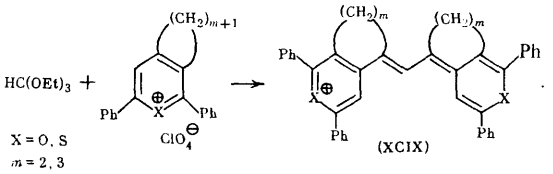
XIII. SOME APPLICATIONS OF ORTHOESTERS

Orthoesters have been known for a long time as irreplaceable reagents in the synthesis of dyes.[4] Progress in the field of cyanine dyes has continued successfully.[79] A new method of synthesis of polymeric cyanines based on orthoesters and 2,3,6-trimethylthiazolo[4,5-*f*]benzothiazolium perchlorate in the presence of weak organic bases has been proposed:[80]



The reaction conditions make it possible to achieve a high degree of condensation, which is favourably reflected in the quality of the dyes obtained.

Pyrylocarbocyanines (XCIX),[81] which are geometrical isomers of the pyrylo-2-cyanines described previously,[82] have been obtained[81] by the reaction of diethyl orthoformate salts of the diphenyl-substituted derivatives of cyclopenta-[c]pyrylium and also its thio-analogue and 5,6,7,8-tetrahydrobenzo-3,4-pyrylium:



(XCIX)

It has been shown[81,82] that the introduction of bridging ethylene and trimethylethylene groups not only stabilises the dyes obtained but also deepens their colour.

Derivatives of isoxazolopyrimidine, which exhibit a high selective herbicidal activity before and after germination, have been obtained by a series of reactions from aliphatic alkyl orthoesters and malononitrile.[83] Propyl orthocarbonate and propyl orthobenzoate proved to be highly effective additives leading to the manifestation of synergism by certain insecticides.[84]

The possibility of using orthoesters, apart from aldehydes and epoxides, in the catalytic carbonylation reactions in the presence of carboxylic acid amides in order to obtain N-acyl-α-aminoacids has been discovered.[85]

Orthoesters have found the widest applications as components of active and stereospecific catalysts in the polymerisation of propene[86–89] and ethylene,[90] while aminoalkyl orthoesters are most widely used in the synthesis of polyurethanes[41–43] and polyisocyanates.[43]

It has been found[91] that orthoesters are essential components in the synthesis of special elastic cementing materials.

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