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REACTIONS OF ACETALS WITH UNSATURATED ETHERS

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I. INTRODUCTION

Acetals are a broad and readily available class of organic compounds, but for a long time they found no significant application in organic synthesis. The only synthetic reaction in which the acetal group was used was that between acetals and organomagnesium compounds discovered by Chichibabin[1]. But this reaction, occurring under severe conditions, at temperatures above 100°, did not find wide use. The main use of acetals was connected with the need to protect carbonyl groups, for example, in the synthesis of steroids[2]. Characteristically, acetals formed as intermediates in the industrial syntheses of alcohols from carbon monoxide and hydrogen are considered to be undesirable products and find only limited application[3].

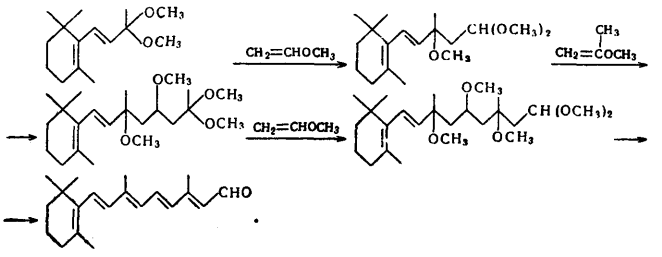
The position changed only after Müller-Cunradi and Pieroh's discovery[4], in 1939, of the reaction of acetals

with alkyl vinyl ethers under the influence of boron trifluoride. Ten years later Hoaglin and Hirsh[5], by defining the mechanism of the reaction, showed that it could be used for obtaining unsaturated aldehydes. After this, the reaction was intensively developed by the chemists of many countries and several patents and research works devoted to this reaction have appeared.

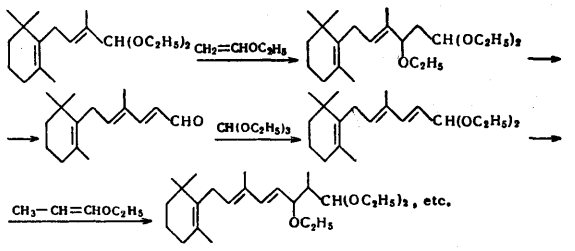
The preparation of unsaturated aldehydes by the reaction of acetals with alkyl vinyl ethers is brought about thus:

$$R{-}CH(OR')_2 + CH_2{=}CHOR' \longrightarrow R{-}(CH{-}CH_2)_n{-}CH(OR')_2 \longrightarrow R{-}(CH{=}CH)_n{-}CHO.$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OR'$$

This method of synthesising polyene compounds was considered extremely promising and even one of the first patents, taken out by Copenhaver[6], contained the idea of using it to obtain Vitamin A. The essence of the proposed method was the successive condensation of β-ionone dimethyl acetal with methyl vinyl ether and isopropenyl methyl ether:



However, it is now clear that this scheme for obtaining vitamin A, which is masterly in its simplicity, is impracticable in that form and is evidently purely theoretical. Although there are others, the most unreal aspect of this scheme was the preparation of the initial acetal of β-ionone by the method described in the patent. It was only recently (1963) that Mikhailov and Povarov[7] obtained β-ionone acetal and described its properties and reaction with ethyl vinyl ether. In 1956 Isler[8] used a similar scheme to construct the β-carotene polyene chain, the starting point being not β-ionone acetal, but the acetal of the so-called C_{14} aldehyde obtained from β-ionone; the route was rather complex:



Isler and coworkers[9-13], and also Inhoffen and Erdmann[14] used the same route to synthesise lycopene, zeaxanthin, cryptoxanthin, and several other carotenoids and intermediates. Mikhailov and Povarov used the reaction of acetals with alkyl vinyl ethers to synthesise difficultly accessible arylated polyene hydrocarbons[15-17].

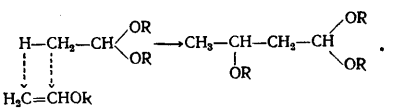
The success in the synthesis of polyene compounds encouraged the rapid increase in investigations in this direction and a further widening of the field of application of the new reaction. It was found that an extremely wide range of acetals and unsaturated ethers could be used in the reaction, and also some other unsaturated compounds with an activated double bond. For example, aliphatic or alicyclic saturated or unsaturated acetals, aromatic or heterocyclic acetals, cyclic acetals, ketals, ortho esters, etc. can be used as the acetal component. Alkyl vinyl ethers, unsaturated ethers which are substituted in the 1- or 2-positions, $\alpha\beta$-unsaturated sulphides, $\alpha\beta$-unsaturated cyclic ethers, alkoxydienes, ketens, ethoxyacetylenes, etc. can be used as the ether component. Zinc chloride, iron(III) chloride, aluminium chloride, etc. can be used instead of boron trifluoride as the catalyst.

All these facts show that the reaction of acetals with unsaturated compounds has great prospects for future development.

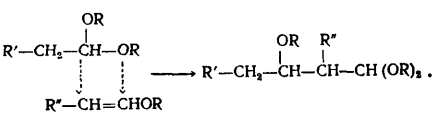
The progress achieved in investigating the reaction has already been partly surveyed in several reviews[18-20]; but there have been many new papers since then, some of which are of great interest. Furthermore it is now necessary to consider in greater detail the special features of the reaction mechanism in the light of the latest results and to generalise the information on the reactivity of acetals and ethers in this reaction. The present article is devoted to these questions.

II. MECHANISM OF THE REACTION

Müller-Cunradi and Pieroh[4], on discovering the reaction of acetals with alkyl vinyl ethers, considered that the condensation proceeds through the mobile hydrogen of the acetal by the scheme:



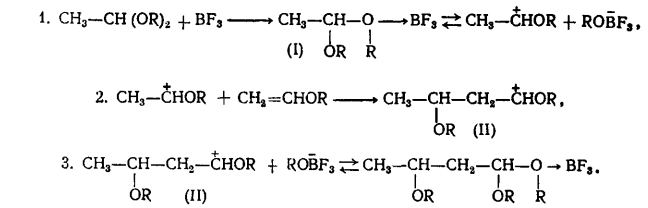
This seemed natural by analogy to some extent with the aldol condensation. However, in later work Hoaglin and Hirsh[5] found the error in this explanation without much difficulty, by performing the reaction with substituted acetals and substituted alkyl vinyl ethers. It transpired that the products are formed in accordance with another reaction scheme:



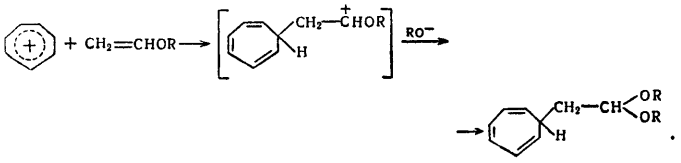
This mechanism was completely new to organic chemistry and there was no known analogy to it. Before long it received confirmation from the results of an investigation of the reactions of benzaldehyde dialkyl acetals with alkyl vinyl ethers[21,22]. In these reactions there were high yields of addition products whose formation under these circumstances was possible only by the second scheme.

Hoaglin and Hirsh[5] proposed the following scheme for the reaction mechanism with participation of the boron

trifluoride catalyst, and this was accepted subsequently by other investigators:



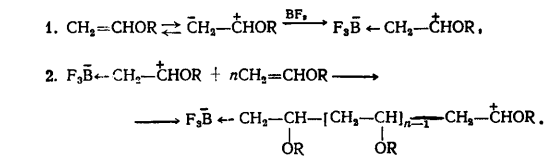
Vol'pin and coworkers[23] specially investigated the problem of the probability of a carbonium ion arising in a side reaction. For this purpose they studied the reaction of the stable tropylium ion with ethyl vinyl ether. It appeared that tropylium salts readily react with various vinyl ethers, and that the tropylium cation always attacks only the CH_2 group of the vinyl ether, to form a cycloheptatrienylacetaldehyde acetal:



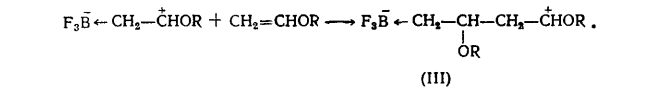
These results confirm the course of the reaction through the formation of a carbonium ion.

In simple vinyl ethers, when there is an alkoxy-group at the double bond not only is there an inherent negative induction effect but there is also a positive mesomeric effect due to the conjugation of the lone pair of electrons of the oxygen atom with the π electrons of the double bond. The actions of these effects on the π electrons are opposite but the mesomeric effect predominates in this instance, and as a result the electron density at the β carbon atom is increased and consequently this atom acquires enhanced nucleophilic properties. Such a picture also holds with the analogues of simple vinyl ethers, such as cyclic unsaturated ethers of the dihydrofuran and dihydropyran type, alkoxydienes, $\alpha\beta$-unsaturated sulphides, and ketens. This can explain the high reactivity of these compounds towards electrophilic reagents, and particularly the carbonium ion produced by the action of boron trifluoride on acetals in accordance with the scheme given above, and the absence of this behaviour with unsaturated compounds having an electron-acceptor substituent at the double bond.

It is noteworthy that Hoaglin and Hirsh's ionic mechanism[5] for the reaction of acetals with vinyl ethers is reminiscent of the mechanism of cationic polymerisation, characteristic for the simple vinyl ethers[24]:

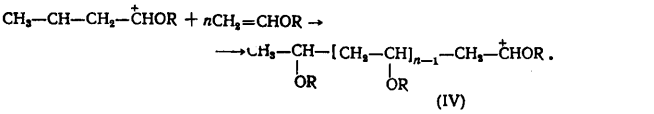


Evidently during the polymerisation a cation (III) analogous to cation (II) is produced:



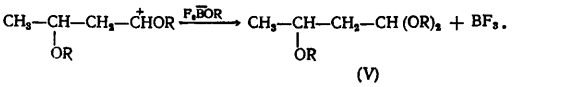
(III)

However, unlike cation (III), to which there is further addition of the vinyl ether during the polymerisation, the fate of cation (II) in the reaction of acetals with vinyl ethers can be different: in the presence of an excess of a vinyl ether it can serve as the initial link in a cationic polymerisation (first boundary case):



(IV)

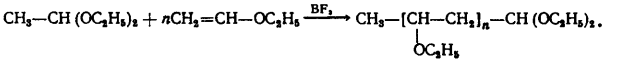
In the presence of a large excess of acetal, cation (II) is stabilised by addition of an alkoxy-group (another boundary case):



(V)

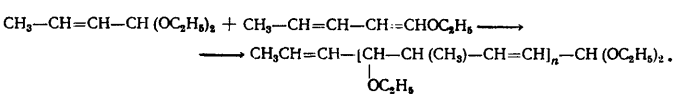
In real intermediate cases, a mixture of reaction products is formed, containing both (V) and (IV) with various values of n. For example, Hoaglin and Hirsh[5] obtained a curve (see Figure) for the dependence of the yield of the primary condensation product (a 1,1,3-trialkoxybutane) on the ratio of the initial acetal and vinyl ether.

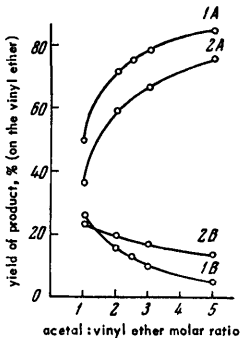
Makin and Sudakova[25] investigated the distribution of the addition products at different ratios of the initial reagents in the reaction:



Their results are in Table 1.

There are similar results for the reactions of unsaturated acetals with alkoxydienes, for example, for the reaction of crotonaldehyde diethyl acetal with 1-ethoxypenta-1,3-diene[26] (see Table 2):





Dependence of the yields of condensation products on the acetal : vinyl ether ratio: 1A) 1,1,3-trimethoxybutane; 2A) 1,1,3-triethoxybutane; 1B) 1,1,3,5-tetramethoxyhexane; 2B) 1,1,3,5-tetraethoxyhexane.

TABLE 1. Distribution of the addition products as a function of the reagent ratio.

$CH_3-[CH(OC_2H_5)-CH_2]_n-CH(OC_2H_5)_2$

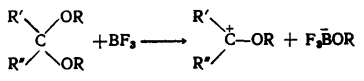
Acetal : ether molar ratio	Yield of addition products, %					
	$n=1$	$n=2$	$n=3$	$n=4$	higher	total yield
2	63	14.9	3.6	1.6	—	83.2
0.75	26.5	38.6	11.3	5.5	4.5	86.0
0.5	16.5	19.0	31.0	12.8	6.5	85.8
0.2	3.9	8	11.1	22.0	17.8	62.7

TABLE 2. Distribution of the addition products as a function of the ratio of initial reagents.

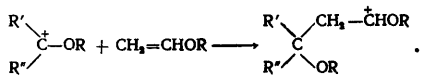
$CH_3CH=CH-[CH(OC_2H_5)-CH(CH_3)-CH=CH]_n-CH(OC_2H_5)_2$

Ethoxydiene : : acetal molar ratio	Yield of addition products, %				
	$n=1$	$n=2$	$n=3$	$n=4$	total yield
1:2	48	30	12	3	93
2:3	28	41	16.5	5	90.5
1:1	27	12	37	8.5	84.5
2:1	9.5	6	26.5	26.5	68

Hence the reaction of acetals with unsaturated ethers behaves as a reaction which is regulated by ionic telomerisation[27], in which the proportions of the products depend on the ratio of the initial reagents: the acetal (telogen) and the unsaturated ether (taxogen). However, the analogy with telomerisation reactions is not always observed. In the instances considered above, the addition of a molecule of the unsaturated compound to the type (I) cation led to the formation of a type (II) cation, differing little in reactivity from the initial cation (I). Moreover, it is obvious that the nature of the products formed will depend on the relation between the reactivities of cations (I) and (II) as well as on the ratio of the reagents. When the reactivity of cation (I) is extremely low in comparison with cation (II) then the reaction product will be a polymer. This occurs, for example, with certain acetals of ketones, the reaction being:

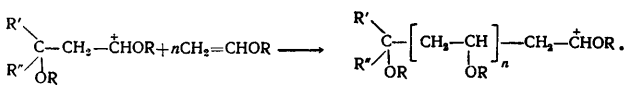


(VI)



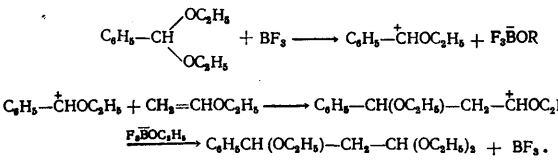
(VII)

The cation (VII) formed is much more reactive than cation (VI) and hence the further addition of the unsaturated ether is to (VII) (the first boundary case):

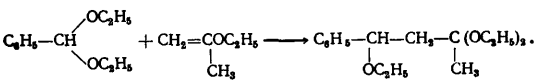


Thus, Mikhailov and Povarov[28] observed that in the reaction of the acetal of 4-ethoxy-6-methylhept-5-en-2--one with ethyl vinyl ether the primary reaction product — an acetal of 3,5-diethoxy-3,7-dimethyloct-6-enal (an acetal of diethoxycitronellal) — was formed in only insignificant quantities even when there was a large excess of the original acetal. Obviously the moderate yield of the product obtained on condensing an acetal of 6-methylhept-5--en-2-one with ethyl vinyl ether[29] was for the same reason.

When the reactivity of the initial type (I) cation is much higher than that of the newly formed type (II) cation (the opposite case to the previous one), a primary addition product of type (V) will be formed almost exclusively. An example of this is the condensation of benzaldehyde diethyl acetal with ethyl vinyl ether[22]. Even at a 1 : 1 ratio of the original reagents the primary condensation product (1,1,3-triethoxy-3-phenylpropane) is obtained in $>70\%$ yield, that is, the reaction proceeds mainly according to the scheme:



Another example is the condensation of a benzaldehyde acetal with ethyl isopropenyl ether[17]. Here the yield is still greater (81%) since the primary product formed — 1,3,3-triethoxy-1-phenylbutane — is even less reactive in subsequent condensations.



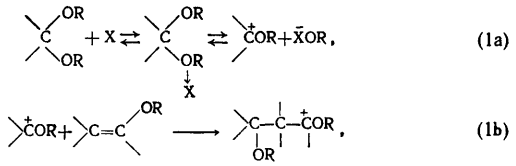
The reaction of acetals with β-bromovinyl ethers[30] and ketens[31] is also of this type, the products formed being incapable of further condensation. These reactions are considered in detail below.

Hence in these instances there is no analogy with telomerisations. In addition to the above factors the nature of the catalyst employed greatly affects the course of the reaction.

III. EFFECT OF CATALYSTS

Lewis acids and metal chlorides are used as catalysts of the reaction; they include boron trifluoride[5], zinc chloride[8], iron(III) chloride[32-34], and also aluminium chloride, titanium(IV) chloride, and tin(IV) chloride[35], etc. The ether addition compounds of boron trifluoride and zinc chloride are most frequently employed, the latter in the form of solutions in ether, ethyl acetate, or acetic acid. Of the catalysts mentioned, boron trifluoride is the most effective, but its use is limited by its vigorous reaction with the initial acetals. For example, the acetals of the $\alpha\beta$-unsaturated series (in particular terpenes) undergo resinification in the presence of boron trifluoride. A milder catalyst in this sense is zinc chloride, particularly its solutions in ether and ethyl acetate. But it is not just a matter of the reactive nature of the catalyst with respect to the acetals.

As already mentioned, the reaction of the acetals with unsaturated ethers is connected with the dissociation of the acetals:

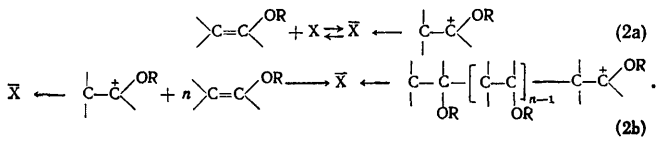


(1a)

(1b)

where X is the catalyst.

On the other hand the catalyst can cause direct cationic polymerisation of the unsaturated ether:



(2a)

(2b)

Usually the two reactions occur simultaneously but it is obvious that for the preferential occurrence of condensation by reaction (1b) it is necessary for dissociation by scheme (1a) to proceed more rapidly than the formation of the cation by scheme (2a), leading to polymerisation by Eqn. (2b). It is also evident that the ratio between the rates of reactions (1a) and (2a) will depend on the catalyst X. This can explain the fact that when ethyl isopropenyl ether reacts with an acetal of benzaldehyde in the presence of boron trifluoride the ether is polymerised according to Eqn. (2b) but in the presence of zinc chloride an addition product is formed according to Eqn. (1b) in high yield[17]. Consequently, with boron trifluoride ionisation according to scheme (2a) predominates, but with zinc chloride dissocation proceeds according to scheme (1a).

Other examples can be mentioned where the correct choice of catalyst was the deciding factor for successfully effecting the condensation. For example, 1-alkoxydienes condense with acetals almost exclusively in the presence of zinc chloride[28,36,37]. However, some acetals have not been condensed with unsaturated ethers, despite the use of a variety of catalysts. This demonstrates the low reactivity of acetals, for which their structure is responsible.

IV. EFFECT OF ACETAL STRUCTURE

The reactivity of acetals has not been determined directly but it can be judged from how they participate in reactions with various types of unsaturated ethers. In polymerisations by scheme (2b) 1-substituted alkyl vinyl ethers are more reactive than the unsubstituted ethers[38,39]. 1-Alkoxydienes are still more reactive[40]. Hence from their tendency to polymerise, unsaturated ethers can be arranged in a series: vinyl ethers unsubstituted in the 1-position < 1-substituted vinyl ethers < 1-alkoxydienes. The tendency to ionisation by scheme (2a) will increase in the same sequence. Saturated acetals readily react with alkyl vinyl ethers unsubstituted in the 1-position according to scheme (1), but in their reaction with ethyl isopropenyl ether (ethyl 1-methylvinyl ether) and 1-alkoxydienes the polymerisation of the unsaturated ethers by scheme (2) predominate. Aromatic acetals react by scheme (1) with alkyl vinyl ethers, whether substituted or unsubstituted in the 1-position, but do not give addition products with 1-alkoxydienes. Finally, $\alpha\beta$-unsaturated acetals readily give addition products with all three types of unsaturated ethers. Consequently, here dissociation by scheme (1a) takes place most readily and predominates over ionisation by scheme (2a) with any of the unsaturated ethers mentioned. On this basis these types of acetals can be arranged in the following sequence of reactivity: saturated acetals < < aromatic acetals < $\alpha\beta$-unsaturated acetals. Moreover, this order agrees with the tendency of these acetals to hydrolyse. Table 3 shows the equilibrium constants determined by Hartung and Adkins[41] for the formation of acetals (the back reaction to hydrolysis). The decrease in K corresponds to an increase in the tendency to hydrolysis. For acetals such as that of bromoacetaldehyde K is high and this corresponds to the complete inability of this acetal to react even with ethyl vinyl ether by scheme (1). As a result of this reaction only a polymer by scheme (2) is formed. On the $\alpha\beta$-unsaturated acetals only acrolein acetal has an equilibrium constant higher than the aromatic benzaldehyde acetal. This suggests that acrolein acetel will be less able to condense with unsubstituted ethers, but there are no experimental results on this.

TABLE 3. Equilibrium constants for the reaction:

$$RCHO + 2\,ROH \rightleftarrows RCH(OR')_2 + H_2O$$

R	K	$-RT \ln K$	R	K	$-RT \ln K$
$HClH_2N-CH_2-$	0.1340	119±200	iso-C_3H_7-	0.0355	1980±30
$BrCH_2-$	0.1121	1130±200	$ClCH_2-CH_2-$	0.0294	2090±200
$N\equiv C-CH_2-$	0.1070	1320±200	$HOCH_2-$	0.0202	2300±200
$C_6H_{13}-$	0.0970	1380±30	$CH_2=CH-$	0.00455	3270±30
C_4H_9-	0.0782	1510±30	C_6H_5-	0.00163	3810±30
$HClNH=CH-$	0.0770	1520±200	$C_6H_5-CH=CH-$	0.00089	4160±30
CH_3-	0.0744	1540±30	$CH_3-CH=CH-$	0.00063	4360±30
C_3H_7-	0.0691	1580±30			

TABLE 4. Rate of hydrolysis of the acetals $R_1R_2C(OC_2H_5)_2$ in 49.6% dioxan + 50.4% water mixture at 25°.

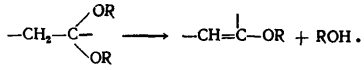
R_1	R_2	k_2	R_1	R_2	k_2
CH_3	H	0.248	$ClCH_2$	CH_3	8.60×10^{-3}
$HOCH_2$	H	8.47×10^{-4}	$C_2H_5OCH_2$	H	8.62×10^{-4}
C_6H_5	H	0.267	$C_6H_5CH_2$	CH_3	8.45×10
$C_6H_5CH_2$	H	8.70×10^{-3}	$C_6H_5OCH_2$	CH_3	0.350
$ClCH_2$	H	1.03×10^{-5}	$HOCH_2$	CH_3	1.16×10
H	H	4.13×10^{-5}	CH_3COOCH_2	CH_3	0.228
CH_3	CH_3	7.52×10^{2}	$BrCH_2$	CH_3	0.138
neo-C_5H_{11}	CH_3	9.20×10^{2}	C_6H_5	H	7.07
C_2H_5	CH_3	7.20×10^{2}	$CH_3CH=CH$	H	2.98×10^{2}
$C_6H_5CH=CH$	H	1.52×10^{2}			

The rate constants for the hydrolysis of various acetals[42] also confirm that there is a correlation between the tendency of acetals to hydrolyse and the reactivity in relation to unsaturated ethers (see Table 4).

V. EFFECT OF TEMPERATURE

The possibility of influencing the course of the reaction with unsaturated ethers by changing the temperature is very restricted. Usually the reactions are performed within the limits 5–50°. On raising the temperature the reaction rate increases, but there is also a decrease in the stability of acetals sensitive to acids, both the initial acetals and those formed in the reaction. On heating, even in the

presence of insignificant amounts of acidic reagents, acetals readily decompose into unsaturated ethers and alcohols[28]:



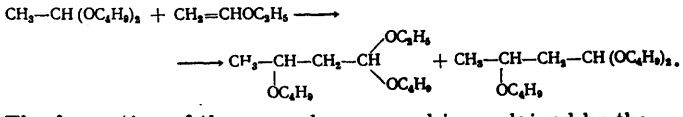
This determines the upper temperature limit of the reaction.

In many instances the reaction proceeds with evolution of heat and the reaction mixture must be cooled to avoid overheating. Occasionally, when the acetals are stable the reactants can be heated to 130–140°.[43] With highly reactive and acid-sensitive unsaturated compounds, such as 1-alkoxydienes and keten, the reaction takes place at reduced temperatures, in the last instance at -80°.[31]

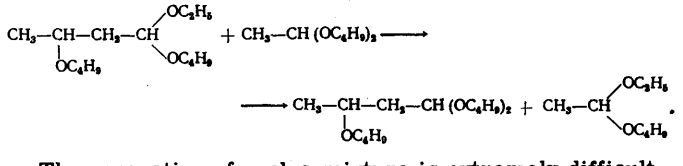
VI. MIGRATION OF ALKOXY-RADICALS

Alkoxy-radicals in acetals exhibit great mobility and are able to migrate in the presence of acid catalysts[44,45]. This phenomenon also occurs in the reaction of acetals with unsaturated ethers under the influence of Lewis acids.

Hoaglin and Hirsh[5] showed that when an acetal and a vinyl ether have different alkoxy-groups the reaction results in the formation of a mixture containing products of the exchange of alkoxy-groups. For example, 1,3-dibutoxy-1-ethoxybutane and 1,1,3-tributoxybutane were isolated from the products of the reaction of 1,1-dibutoxyethane and ethyl vinyl ether:

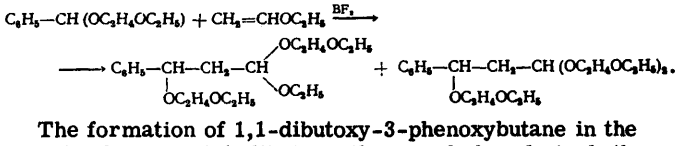


The formation of the second compound is explained by the reaction:

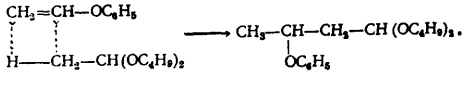


The separation of such a mixture is extremely difficult, therefore to obtain an addition product of known structure it is necessary to start with an acetal and an unsaturated ether with the same alkoxy-groups.

Povarov and Mikhailov[46] observed the migration of alkoxy-groups in studying the reaction of benzaldehyde bis-ethoxyethyl acetal with ethyl vinyl ether. They also obtained a mixture of products:

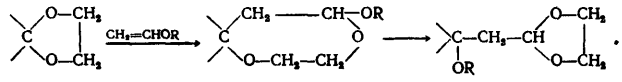


The formation of 1,1-dibutoxy-3-phenoxybutane in the reaction between 1,1-dibutoxyethane and phenyl vinyl ether, studied by Shostakovskii and Bogdanov[43], was evidently due to the migration of the phenoxy-group. The presence of this product in the reaction mixture led to authors to conclude that there was another mechanism for the reaction of acetals with phenyl vinyl ether:

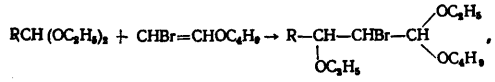


However, the formation of this product is undoubtedly due to the redistribution of the butoxy- and phenoxy-groups, particularly as the reaction is carried out at 120°.

Mikhailov and Povarov[47] showed that in the reaction of cyclic acetals with alkyl vinyl ethers the primary condensation product undergoes rearrangement, which can be explained by the intramolecular migration of alkoxy-groups:



The reaction of acetals with alkyl 2-bromovinyl ethers is another matter[30]. The course of this reaction is quite analogous to that for the alkyl vinyl ethers but there are several peculiarities. The condensation products are 2-bromoacetals in which the alkoxy-groups are only slightly mobile. The result is the absence of migration of alkoxy-groups, which was established by the example of the condensation of benzaldehyde diethyl acetal and 1,1-diethoxyethane with 2-bromovinyl butyl ether. Only the normal addition products were isolated; products of the migration of alkoxy-groups were not observed:

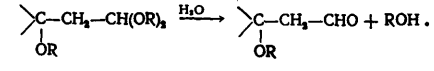


where R = CH_3 or C_6H_5.

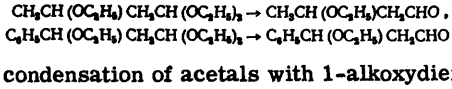
Another peculiarity of the reaction was the absence of products of secondary condensation with the unsaturated ether, also the result of the deactivating action of bromine in the 1-position on the mobility of alkoxy-groups.

VII. HYDROLYSIS AND ELIMINATION OF ALCOHOL FROM ALKOXYACETALS

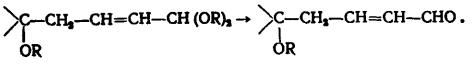
Usually the condensation products of acetals and unsaturated ethers — alkoxyacetals — are not used directly, but are hydrolysed to liberate aldehydes or ketones:



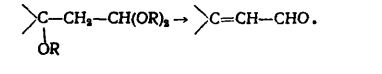
3-Alkoxyacetals are similar to saturated acetals as regards hydrolysis; they are hydrolysed by heating with aqueous acid. For example, 3-ethoxybutanal[5] and 3-ethoxy-3-phenylpropanal[22] were thus obtained:



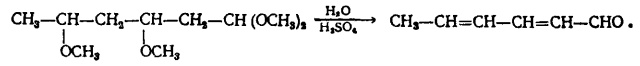
In the condensation of acetals with 1-alkoxydienes, $\alpha\beta$-unsaturated acetals are formed, which are readily hydrolysed in the presence of mineral acids in the cold[37]:



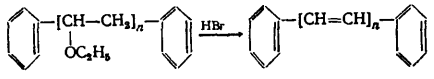
Often the hydrolysis of acetals is accompanied by the elimination of an alcohol with the aim of making unsaturated carbonyl compounds:



This is done in various ways. For example, hexa-2,4-dienal was obtained from 1,1,3,5-tetramethoxyhexane by boiling with 5% sulphuric acid[5]:

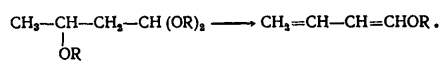


Usually under such conditions the reaction is accompanied by marked resinification, and therefore milder reagents and conditions are used, for example, heating with acetic acid in the presence of sodium acetate[8], heating with a dilute solution of phosphoric acid in dioxan[8], heating with a dilute solution of *p*-toluenesulphonic acid in toluene[37]. As Mikhailov and Povarov found[15-17], the best method of eliminating an alcohol from the diphenylpolyalkoxyalkanes, obtained as the products of the condensation of benzaldehyde acetals with vinyl ethers, consists of boiling with alcoholic hydrogen bromide:



where n = 2, 3, 4, or 5.

Sometimes an alcohol is eliminated from alkoxyacetals in an anhydrous medium without hydrolysis. For example, 1-alkoxydienes are obtained from 1,1,3-trialkoxyalkanes in this way:



Mikhailov and Povarov[28] developed a liquid-phase method of carrying out this reaction under the action of *p*-toluenesulphonic acid in quinoline. Others have also employed this method[48].

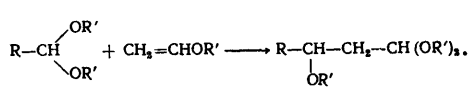
The earlier known method of vapour-phase splitting of 1,1,3-alkoxybutanes[40,49,50] were perfected by Nazarov and his coworkers[51] and used for the synthesis of several 1-alkoxydienes. Makin and Sudakova[52] employed it to make 1-ethoxyhexatriene and 1-ethoxyoctatetraene. The possibility of eliminating an alcohol from alkoxyaldehydes with aluminium oxide has also been demonstrated[53].

The above general rules for the reaction of acetals with unsaturated ethers do not exhaust the special features inherent in the reactions of various classes, which will be considered in the following Sections.

VIII. REACTIONS OF ACETALS OF VARIOUS CLASSES

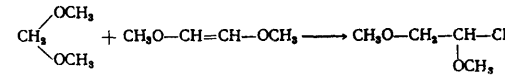
1. Reactions of Aliphatic Saturated Acetals

Aliphatic saturated acetals, in reacting with unsaturated ethers, form primary addition products in rather high yields (60–70%) when the reaction is carried out with a large (three- to five-fold) excess of the acetal[5]:

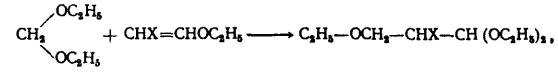


The 3-ethoxyacetals thus formed are also rather highly reactive in comparison with the initial acetals and, as they accumulate, compete with them for the molecules of vinyl ether, giving secondary addition products. When there is an excess of the vinyl ether, high-molecular-weight telomers are formed[33].

The simplest acetal, formaldehyde dimethyl acetal (methylal), was shown by Shostakovskii and coworkers[54] to react with 1,2-dimethoxyethylene, giving 1,1,2,3-tetramethoxypropane in 50% yield:

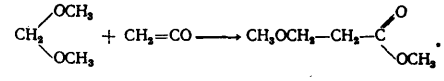


Formaldehyde diethyl acetal (ethylal) condensed with ethyl 2-chloro- and ethyl 2-bromo-vinyl ethers[55], addition products being obtained in high yields in each instance:



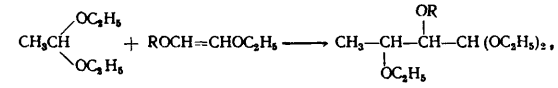
where X = Cl or Br.

Formaldehyde dimethyl acetal gives an addition product with keten[56], the yield being high:



The reaction is done in the presence of boron trifluoride between -60° and -80°.

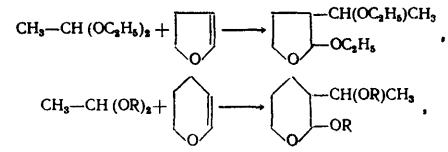
The reactions of acetaldehyde dialkyl acetals have been the most widely investigated. The dimethyl[5,57], diethyl[5,58], and dibutyl[32-34] acetals of acetaldehyde react smoothly with alkyl vinyl ethers. 2-Alkyl-substituted vinyl ethers react with an acetaldehyde acetal similarly to the unsubstituted vinyl ether — the substituent in the 2-position has no significant effect on the condensation[5,58]. However, addition products are not obtained with an alkyl 1-methylvinyl ether; the ether polymerises even in the presence of zinc chloride. Acetaldehyde acetal condenses with 1,2-diethoxyethylene and 2-ethoxy-1-phenoxyethylene at an initial component ratio of 1 : 1, giving a high yield of addition products according to the scheme[59]:



where R = C_2H_5 or C_6H_5.

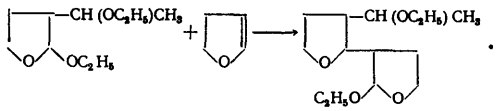
Obviously the ethoxy- or phenoxy-group in the 2-position to the acetal group deactivates the latter, preventing the formation of telomers.

Cyclic $\alpha\beta$-unsaturated ethers, such as dihydrofuran and dihydropyran, react with acetaldehyde dialkyl acetals to form derivatives of tetrahydrofuran and tetrahydropyran, respectively[60]:



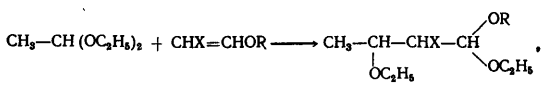
where R = CH_3, C_2H_5, or iso-C_4H_9.

Secondary condensation products are also formed:



However, the reactivity of the primary condensation products is less than for the initial acetaldehyde acetal, so that with a 1 : 1 ratio of the reagents there is a high yield of primary products (60–80%).

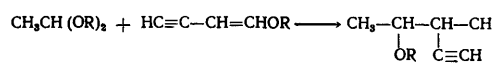
2-Chlorovinyl ethyl ether[55,61], 2-bromovinyl ethyl ether[30,55,61], and 2-bromovinyl butyl ether[30] react analogously to alkyl vinyl ethers with acetaldehyde diethyl acetal:



where X = Cl or Br and R = C_2H_5, or C_4H_9.

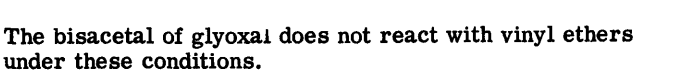
This reaction is interesting because the halogen in the vinyl ether neither reverses the order of addition of the acetal nor inhibits the reaction, although the presence of halogen atoms might be expected to change considerably the nature of the polarisation of the double bond.

Addition products of acetaldehyde acetals with 1-alkoxydienes have not been obtained. Under rigorous conditions (125–140°) alkyl 2-ethylvinyl ethers react according to the scheme[62]:



In the reaction of 1,1-dimethoxyethane with keten, methyl 3-methoxybutyrate is obtained as an addition product[63]. With diketen there is a complex reaction giving a mixture of three products[64].

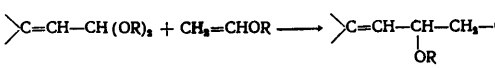
The acetals of propionaldehyde[58,56] and butyraldehyde[58] react with alkyl vinyl ethers analogously to acetaldehyde acetals. Vinyl ethers can also be condensed with saturated acetals of dialdehydes[66,67], for example, malonaldehyde bisacetal. To obtain the optimum yield of primary condensation product, a large excess of the initial bisacetal is required:



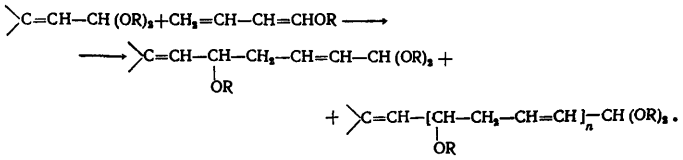
The bisacetal of glyoxal does not react with vinyl ethers under these conditions.

2. Reactions of Unsaturated Aliphatic and Alicyclic Acetals

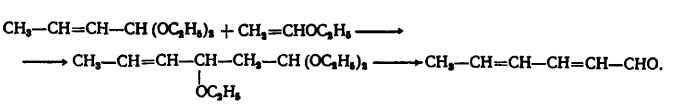
$\alpha\beta$-Unsaturated acetals readily add on to alkyl vinyl ethers[8–12], including also 1-substituted ethers[28,68], and give high yields of the addition products (sometimes over 90%). The reaction products here are 3-alkoxyacetals, whose reactivity is much less than that of the initial acetals, which helps to reduce the secondary reactions:



In addition, $\alpha\beta$-unsaturated acetals are able to add on to 1-alkoxydienes[28,37,69–72]. Addition at the 1,4-positions occurs and as a result of the reaction $\alpha\beta$-unsaturated acetals are regenerated, with reactivities similar to the original acetals. As a result, telomers are formed as well as the primary addition products:

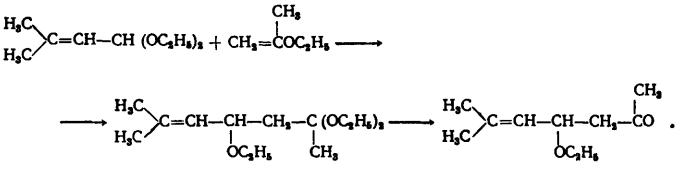


The reaction of $\alpha\beta$-unsaturated aldehydes is very widely used to make polyene compounds. Crotonaldehyde acetal reacts with ethyl vinyl ether in the presence of zinc chloride to form 1,1,3-triethoxyhex-4-ene, which on hydrolysis and elimination of ethanol gives sorbaldehyde[68]:

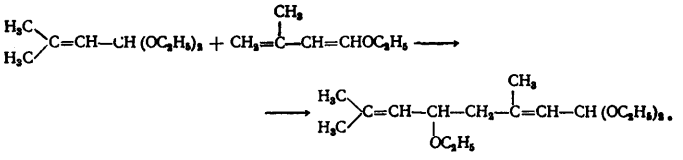


The reaction with ethyl isopropenyl ether also proceeds readily. The reactions of crotonaldehyde acetal with various 1-alkoxydienes, such as 1-ethoxybutadiene[70], 1-ethoxy-2-methylbutadiene and 1-ethoxy-3-methylbutadiene[73], and 1-ethoxypenta-1,3-diene[26], have also been studied.

3-Methylcrotonaldehyde acetal and ethyl isopropenyl ether form 2,2,4-triethoxy-6-methylhept-5-ene, in 60% yield, which on hydrolysis gives 4-ethoxy-6-methylhept-5--en-2-one[28]:

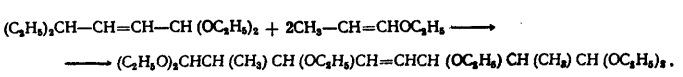


The latter was used in the synthesis of monoarylated polyene hydrocarbons[74]. The reaction of the ethyl acetal of 3-methylcrotonaldehyde with 1-ethoxybutadiene and 1-ethoxy-3-methylbuta-1,3-diene proceeds smoothly. The second combination gives an acetal of ethoxycitral[28,37]:

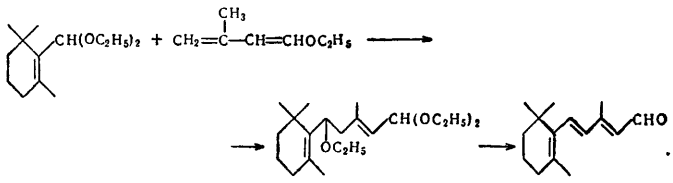


High yields of additions products are given by sorbaldehyde acetal with ethyl vinyl and ethyl isopropenyl ethers[68]. Products of the condensation of citral acetal with one and two molecules of 1-ethoxy-3-methylbuta-1,3-diene have been obtained[28].

The acetals of unsaturated dialdehydes react with unsaturated ethers to form addition products at both acetal groups[75–78], for example:

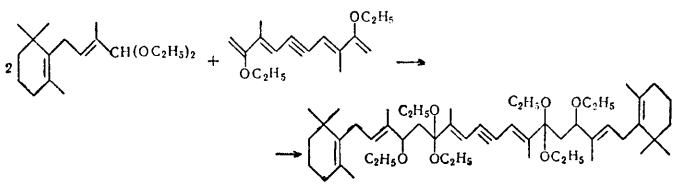


The $\alpha\beta$-unsaturated acetals of the alicyclic series react with unsaturated ethers quite analogously. For example, condensation products of cyclocitral acetal with 1-ethoxybutadiene and with 1-ethoxy-3-methylbuta-1,3-diene have been obtained[37]. From the latter reaction β-ionylideneformaldehyde [3-methyl-5-(2,5,5-trimethylcyclohex-1-enyl)penta-2,4-dienal (Ed. of Translation)], which is an intermediate in the production of Vitamin A, was isolated after hydrolysis and elimination of alcohol:



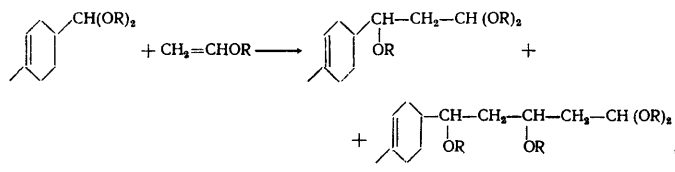
This synthesis path for β-ionylideneformaldehyde appears rather simple, but cyclocitral acetal itself is not readily available. Furthermore the reaction is complicated by the formation of telomers.

The reaction of $\alpha\beta$-unsaturated ethers with the acetal of 2-methyl-4-(2,6,6-trimethylcyclohex-1-enyl)but-2-enal — the so-called C_{14} aldehyde — has been used for a series of syntheses of carotenoids. With ethyl vinyl ether the condensation product is formed in yields of up to 92%.[8] The bis-addition product of an acetal of the C_{14} aldehyde with an unsaturated ether of such a complicated structure as 2,9-diethoxy-3,8-dimethyldeca-1,3,7,9-tetraen-5-yne has been obtained[79]:



The bis-addition product obtained was used to synthesise β-carotene. Apart from the C_{14} aldehyde acetal, other analogous $\alpha\beta$-unsaturated alicyclic acetals have also been used for the synthesis of carotenoids[80,81]. The reaction of β-ionylideneformaldehyde acetal with 1-ethoxy-3-methylbuta-1,3-diene has been described[53].

Unsaturated cycloaliphatic acetals with the double bond distant from the acetal group react like saturated acetals. Thus, in the reaction of acetals of 4-methylcyclohex-3-enal with alkyl vinyl ethers a mixture of primary and secondary condensation products was obtained[82]:



where R = C_2H_5 or C_4H_9.

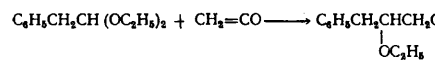
The yield of the primary condensation product is not high (~12%). Hence the double bond in the $\beta\gamma$-position does not activate the acetal group.

Acetals containing a triple bond in the $\alpha\beta$ position, such as propiolaldehyde acetal, do not react with unsaturated ethers.

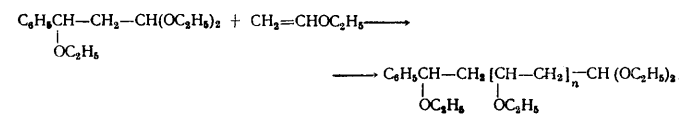
3. Reactions of Aliphatic-Aromatic and Aromatic Acetals

The reactions of acetals of the aliphatic-aromatic series with $\alpha\beta$ unsaturated ethers have been little studied. However, the available literature suggests that a phenyl ring in the 3-position in the acetal group no longer has any significant effect on the reactivity of the acetal and the reaction proceeds as for unsaturated aliphatic acetals.

Only condensation with keten has been described[63] for phenylacetaldehyde acetal. This reaction yields ethyl 3-ethoxy-4-phenylbutyrate:



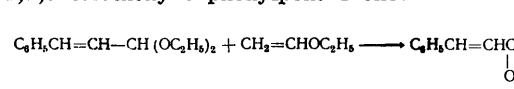
Mikhailov and Povarov[22] studied the reaction of 3-ethoxy-3-phenylpropanal acetal (obtained in the condensation of benzaldehyde acetal with ethyl vinyl ether) with ethyl vinyl ether. As a result they obtained a primary addition product 1,1,3,5-tetraethoxy-5-phenylpentane, in only 10% yield at a 1:1 ratio of the initial reagents and in 50% yield when the acetal was in threefold excess. In addition there was a telomerisation product:



where n = 1, 2, or 3.

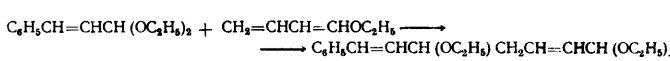
Analogously, in the condensation of 3-ethoxy-3-phenylpropanal acetal with ethyl propenyl ether 1,1,3,5-tetraethoxy-2-methyl-3-phenylpentane was obtained in 50% yield[17]. The reaction of 3-ethoxy-3-phenylbutanal acetal with ethyl vinyl ether has also been studied[72].

Aliphatic-aromatic acetals with a double bond in the $\alpha\beta$ position to the acetal group behave analogously to $\alpha\beta$ unsaturated aliphatic acetals in their reaction with unsaturated ethers. An example is the reaction of cinnamaldehyde acetal, which with ethyl vinyl ether and either boron trifluoride[47] or zinc chloride[69] readily forms 1,1,3-triethoxy-5-phenylpent-4-ene:



Methylcinnamaldehyde acetal also reacts smoothly with ethyl vinyl ether[72].

Like the aliphatic $\alpha\beta$-unsaturated acetals, cinnamaldehyde acetal reacts with 1-ethoxybutadiene, forming 1,1,5-triethoxy-7-phenylhepta-2,6-diene in good yield[69]:



Higher condensation products are also formed.

Of the aromatic acetals, the benzaldehyde dialkyl acetals have been best studied as regards reaction with unsaturated ethers. In the presence of boron trifluoride, the dimethyl acetal[21] and diethyl acetal[22] form with alkyl vinyl ethers 3-alkoxy-3-phenylpropanal acetals, and even at a 1:1 molar ratio of the reagents the yield of primary addition product reaches 70%:



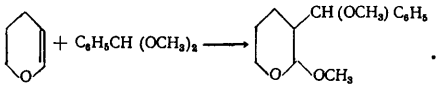
where R = CH_3 or C_2H_5.

Products of further condensation are also formed in small quantities, but their yield is insignificant, as the reactivity of 3-alkoxy-3-phenylpropanal acetals is much less than that of the original benzaldehyde acetal. Condensation with ethyl isopropenyl ether in the presence of zinc chloride[17] is even better and as a result a 4-ethoxy-4--phenylbutan-2-one acetal is formed in 81% yield. However, benzaldehyde acetals do not give addition products with 1-alkoxydienes under these conditions, which shows that although the aromatic acetals surpass the saturated acetals in reactivity they are less reactive than the $\alpha\beta$-unsaturated acetals. However, benzaldehyde acetal evidently reacts with alkoxydienes such as 3-ethoxy-1-phenylbuta-1,3--diene. This was explained[83] by the formation of 3,3,5-triethoxy-1,5-diphenylpent-1-ene:

$$C_6H_5CH(OC_2H_5)_2 + C_6H_5CH{=}CHC(OC_2H_5){=}CH_2 \longrightarrow C_6H_5CH{=}CHC(OC_2H_5)_2CH_2CH(OC_2H_5)C_6H_5.$$

As this equation shows, the addition to the alkoxydiene here takes place at the 1,2 positions of the conjugated diene system. Benzaldehyde bisethoxyethyl acetal — readily obtainable from benzaldehyde and Ethyl Cellosolve — gives an addition product with ethyl vinyl ether[46].

The reaction of benzaldehyde dimethyl acetal with the cyclic unsaturated ether dihydropyran, leads to the 2-methoxy-3-(methoxyphenylmethyl)tetrahydropyran[60]:



Benzaldehyde acetal reacts with alkyl 2-halogenovinyl ethers in the presence of boron trifluoride to form 3-alkoxy-2-halogeno-3-phenylpropanal acetals in high yields. The reactions are carried out either at 50°[30] or at higher temperatures (100–200°).[84] The halogen atom evidently makes the 3-alkoxy-2-halogeno-3-phenylpropanal acetal stable not only as regards further condensation but also to decomposition at high temperatures.

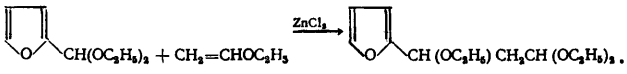
Esters of 3-ethoxy-3-phenylpropionic acid were obtained by reaction of keten with benzaldehyde acetal[63].

A mixed acylal benzaldehyde acetal also reacts with keten, esters of 3-ethoxy-3-phenylpropionic acid again being formed[85].

The reaction of terephthalaldehyde bisacetal with ethyl vinyl ether simultaneously at both acetal groups has also been described[86].

4. Reaction of Heterocyclic Acetals

Only a few representatives of the heterocyclic aldehydes have been studied in reactions with unsaturated ethers. Mikhailov and Ter-Sarkisyan[69] showed that furfural acetal reacts with ethyl vinyl ether to give (similar to benzaldehyde acetal) 3-ethoxy-3-furylpropanal acetal in high yield even at a 1:1 ratio of the initial reagents:



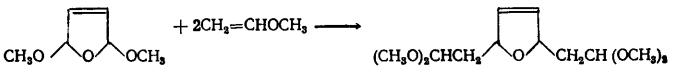
5-Nitrofurfural acetal reacts analogously[87].

Unlike benzaldehyde acetal, furfural acetal gives an addition product with 1-ethoxybutadiene, although the yield of the primary addition product is very moderate (23.7% on the converted acetal and ~5% on that taken).[69] Secondary condensation products are also formed. This is evidence of the somewhat higher reactivity of furfural acetal.

3-(Fur-2-yl)acrolein acetal reacts smoothly with ethyl vinyl ether, like an $\alpha\beta$-unsaturated acetal, and with 1-ethoxybutadiene, forming 1,1,3-triethoxy-5-(fur-2-yl)-pentene in 74.6% yield with the former and 1,1,5-triethoxy--7-(fur-2-yl)hepta-2,6-diene in 40.4% yield with the latter[69].

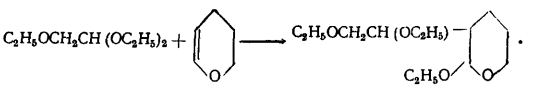
We must also remember the reaction of tetrahydro-4--keto-2,2-dimethylpyran diethyl acetal with ethyl vinyl ether, leading to 4-(2,2-diethoxyethyl)-4-ethoxytetrahydro--2,2-dimethylpyran[88].

The unusual heterocyclic bisacetal 2,5-dihydro-2,5-dimethoxyfuran has been shown to react with methyl vinyl ether, forming addition products at both acetal groups[89]:



5. Reactions of Substituted Acetals

Functional substituents have most effect only when they are situated at the 2-carbon atom with respect to the acetal group. More distant substituents do not affect the reactivity significantly. For example, 2-ethoxyacetaldehyde acetal does not condense with ethyl vinyl ether under ordinary conditions, while the vinyl ether polymerises[60]. 2-Ethoxyacetaldehyde acetal gives an addition product with dihydropyran but the yield (37%) is only half that for acetaldehyde acetal:



2-Bromoacetaldehyde acetal also does not form an addition product with ethyl vinyl ether[90].

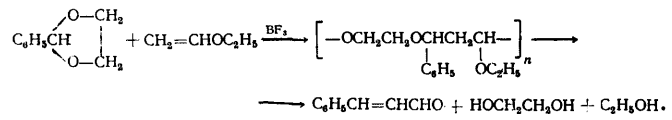
Mikhailov and Povarov[30] noted that acetals such as 1,1,3-trialkoxy-2-bromo-3-phenylpropane and 1,1,3-trialkoxy-2-bromobutane do not react with unsaturated ethers.

As already mentioned, the presence of an alkoxy-substituent in the 3-position to the acetal does not affect its reactivity. The presence of an ethoxycarbonyl group in the 3-position also does not affect the reactivity of crotonaldehyde acetal, which reacts with ethyl vinyl ether to form the ethyl ester of 1,1-diethoxy-2-methylbut-2-en-4-oic acid[91]. An addition product is formed similarly by 6,6-diethoxyhexanoic ester with ethyl vinyl ether[92]. 3,3-Dichloroacrolein, 5,5-dichloropenta-2,4-dienal, and 7,7-dichlorohepta-2,4,6-trienal acetals react smoothly with vinyl ethers[93,94]. Their behaviour does not differ from that of the corresponding unsubstituted, unsaturated acetals.

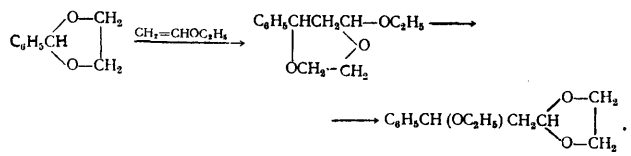
6. Reactions of Cyclic Acetals

Because of the special structure of the acetal group, cyclic acetals react uniquely with unsaturated ethers. It has been shown[47] that the reaction of benzaldehyde ethylene acetal [2-phenyl-1,3-dioxolan (Ed. of Translation)] in the

absence of a solvent leads to a polymer which in the presence of mineral acids is readily hydrolysed and splits off an alkoxy-group, giving cinnamaldehyde:

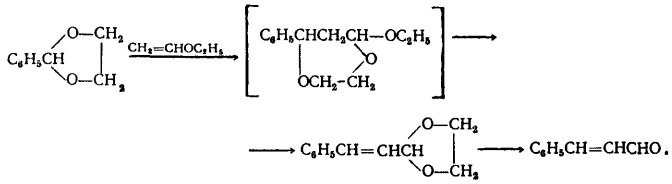


When the reaction is carried out in dilute solution an unstable primary condensation product can be isolated as a mixture with the stable isomer formed by rearrangement:



Aliphatic cyclic acetals and ketals† react analogously [95].

Reactions of cyclic acetals with alkyl vinyl ethers are used for the synthesis of several unsaturated aldehydes and ketones. The ethylene acetals of benzaldehyde, cinnamaldehyde, and 3-ethoxycarbonyl-2-methylacrolein have been condensed with ethyl vinyl and ethyl propenyl ethers, as also has been β-ionone ethylene ketal [96]. Different conditions were used to treat the reaction mixture and ethylene acetals were isolated from the reaction products hydrolysed further to the corresponding unsaturated aldehydes and ketones, for example:

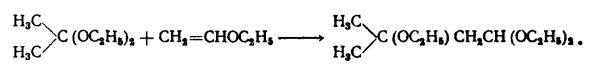


The mechanism of formation of cinnamaldehyde ethylene ketal (2-styryl-1,3-dioxolane) is not completely clear.

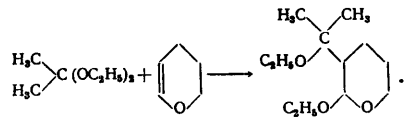
7. Reactions of Ketals†

The reactions of ketals with αβ-unsaturated ethers proceed mainly by analogy with the reactions of acetals, but at the same time are distinguished by special features.

2,2-Diethoxypropane with ethyl vinyl ether forms 1,1,3-triethoxy-3-methylbutane:

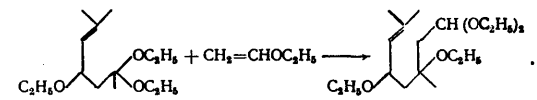


The reaction was performed in the presence of boron trifluoride both at 50° [89] and under milder conditions (at 5°) [51]. Reaction with methyl vinyl ether [21] and ethyl propenyl ether [88] have also been described. 2,2-Diethoxybutane reacts with ethyl vinyl ether analogously to 2,2-diethoxypropane [88]. 2,2-Diethoxypropane forms an addition product with dihydropyran [60]:



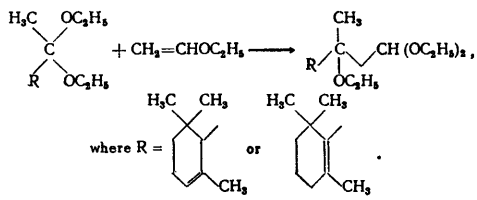
The ketals of cyclic ketones (cyclopentanone, cyclohexanone, pyranone) react with alkyl vinyl ethers by the usual scheme [88].

Ketals have frequently been used to synthesise terpene derivatives. Thus diethoxycitronellal acetal was obtained by condensing 2,2,4-triethoxy-6-methylhept-5-ene with ethyl vinyl ether [28]:



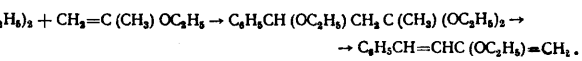
By condensing 2,2,4-triethoxy-6-methyl-hept-5-ene with ethyl vinyl ether, 1,1,3-triethoxy-3,7-dimethyloct-6-ene was obtained similarly, and was converted into citral by hydrolysis and the elimination of ethanol [29].

Mikhailov and Povarov [7] obtained ketals of α- and β-ionones and condensed them with ethyl vinyl ether:



The acetals obtained were converted into α- and β-ionylideneacetaldehydes.

In several instances the reactions of ketals are accompanied by elimination of alcohol, as ketals are more sensitive to the action of acid agents. For example, it has been reported that 1,3,3-triethoxy-1-phenylbutane formed by the reaction of benzaldehyde acetal, is partly converted into 3-ethoxy-1-phenylbutadiene by the elimination of the elements of the alcohol [83]:



This work also showed that 1,3,3-triethoxy-1-phenylbutane does not condense very well with ethyl vinyl ether.

Mikhailov and Ter-Sarkisyan [72] observed the formation of acetaldehyde acetal in the reaction of 1,1-diethoxy-1-phenylethane with ethyl vinyl ether, which was explained by the reaction of ethyl vinyl ether with the alcohol eliminated from the reaction product.

As already noted, cyclic ethylene ketals of acetone and ionone react with ethyl vinyl ether in a similar manner to cyclic acetals [96].

8. Reactions of Ortho-Esters

Ortho-esters — of which esters of orthoformic acid and, to a lesser extent, orthoacetic acid have been studied

† This name has been abandoned by IUPAC (Ed. of Translation).

— form addition products (bisacetals) with various $\alpha\beta$-unsaturated ethers, including 1-substituted ethers:

$$CR(OR')_3 + CH_2{=}CHOR' \rightarrow RC(OR')_2CH_2CH(OR')_2,$$

where R = H or CH_3.

At the same time they are evidently incapable of forming addition products with alkoxydienes. This is evidence that ortho-esters are more reactive than saturated acetals but less reactive than $\alpha\beta$-unsaturated acetals. That is, just the same as aromatic acetals. As with aromatic acetals, even at a 1 : 1 ratio of the initial reagents (ortho--ester and vinyl ether) the yield of the primary addition product is high (~ 75%) despite the fact that the addition product formed is a bisacetal capable of further addition. However, its reactivity is evidently less than that of the original ortho-ester.

Hultquist[97] brought about the first reactions using an orthoformic ester and ethyl vinyl ether. In later years many patents were taken out for the use of this reaction to synthesise bisacetals[98-113].

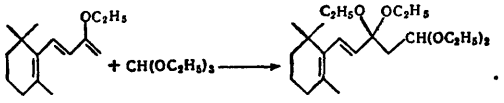
Protopova and Skoldinov[66] made a detailed study of the reaction between ethyl orthoformate and methyl vinyl, ethyl vinyl, propyl vinyl, and butyl vinyl ethers. They found that in addition to the primary addition product the products of further condensation are formed, for example, the bisacetal of ethoxyglutaraldehyde [1,1,3,5,5-pentaethoxypentane (Ed. of Translation)]:

$$CH(OC_2H_5)_3 + CH_2{=}CHOC_2H_5 \rightarrow (C_2H_5O)_2CH[CH_2CH]_n CH_2CH(OC_2H_5)_2,$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OC_2H_5$$

where n = 0, 1, 2, or over.

Yanovskaya and coworkers[114] brought about the reaction of triethyl orthoformate with ethyl propenyl, ethyl isopropenyl, ethyl 1,2-dimethylvinyl, cyclohexenyl ethyl, and 2-bromovinyl ethyl ethers. Whereas with vinyl ethers unsubstituted in the 1-position the reaction proceeds with 75% yields, the yield with methyl-substituted ether was appreciably less (35%). In the same work the reaction between orthoacetic ester and ethyl isopropenyl and 1,2-dimethylvinyl ethyl ethers was studied.

Orthoformic ester is capable of adding on to 1-substituted vinyl ethers of complex structure. Thus, it has been shown[115] that ethers of the enolic forms of α- and β-ionones react with orthoformic ester. For example, the reaction for the ether of the β-ionone enol proceeds thus:



It was also found[116] that orthoformic ester reacts with keten to form an ester of 3,3-diethoxypropionic acid:

$$CH(OC_2H_5)_3 + CH_2{=}CO \rightarrow (C_2H_5O)_2CHCH_2C(=O)OC_2H_5.$$

The reaction of orthoformic ester with diketen is more complex[114].

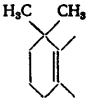
The addition of an ortho-ester to 1-chloro-1,2-diethoxyethylene has been described[117].

9. Reactions of Thioacetals

Mikhailov and Ter-Sarkisyan[118,119] investigated the reaction of thioacetals with ethyl vinyl ether. It appeared that thioacetals of aldehydes such as benzaldehyde, cinnamaldehyde, cyclocitral in the presence of boron trifluoride or zinc chloride react with ethyl vinyl ether by the same scheme as acetals:

$$RCH(SC_2H_5)_2 + CH_2{=}CHOC_2H_5 \longrightarrow RCH(SC_2H_5)CH_2CH\begin{matrix}OC_2H_5\\SC_2H_5\end{matrix},$$

where R = C_6H_5, $C_6H_5CH{=}CH-$, or



The yields of the primary addition products are considerably less than for the corresponding acetals. The formation of secondary condensation products is also noted. The example of 1-ethoxy-1,3-bisethylthio-3-phenylpropane showed that monothioacetals react with ethyl vinyl ether with loss of an alkylthio-group and not of an alkoxy-group:

$$C_6H_5CH(SC_2H_5)CH_2CH\begin{matrix}OC_2H_5\\SC_2H_5\end{matrix} + CH_2{=}CHOC_2H_5 \longrightarrow$$
$$\longrightarrow C_6H_5CH(SC_2H_5)CH_2CH(OC_2H_5)CH_2CH\begin{matrix}OC_2H_5\\SC_2H_5\end{matrix}.$$

Even earlier, the reaction of trithioorthoformic ester with ethyl vinyl ether was investigated, also in the presence of boron trifluoride. This reaction leads to 1-ethoxy--1,3,3-trisethylthiopropane[120]:

$$CH(SC_2H_5)_3 + CH_2{=}CHOC_2H_5 \longrightarrow (C_2H_5S)_2CHCH_2CH\begin{matrix}OC_2H_5\\SC_2H_5\end{matrix}.$$

Later the trithioorthoformic esters were condensed with ethyl vinyl and butyl vinyl esters and also with ethyl vinyl and phenyl vinyl sulphides[121]. The last gave bisthioacetals of malonaldehyde:

$$CH(SC_2H_5)_3 \xrightarrow{CH_2{=}CHSC_2H_5} (C_2H_5S)_2CHCH_2CH(SC_2H_5)_2$$
$$CH(SC_2H_5)_3 \xrightarrow{CH_2{=}CHSC_6H_5} (C_2H_5S)_2CHCH_2CH\begin{matrix}SC_2H_5\\SC_6H_5\end{matrix}.$$

IX. RELATED REACTIONS

The progress in the investigation and application of the reactions of acetals with unsaturated ethers has entailed the realisation of a whole series of conversions of analogous nature, involving acetals, aldehydes, unsaturated ethers, and alkenes.

1. Reactions of Acetals with Alkenes

Several studies have shown that under the influence of boron trifluoride, acetals are capable of addition to alkenes just as they do to unsaturated ethers. With unsaturated

ethers the reaction proceeds in such a way that the alkoxy--group adds on to the 1-carbon atom of the ether.

The α carbon atom in unsymmetrical alkenes has a lower electron density than the 1-carbon atom of unsaturated ethers, therefore the order of the addition is the reverse. This corresponds to the orientation observable in the reaction of formaldehyde with alkenes[122]. For example, in the reaction of methylal with propene the main reaction product is 1,3-dimethoxybutane[123]:

$$CH_3OCH_2OCH_3 + CH_3CH{=}CH_2 \xrightarrow{BF_3} CH_3CH(OCH_3)CH_2CH_2OCH_3\ (39\ \%).$$

The reaction of methylal with 2-methylprop-2-ene, styrene, and α-pinene is similar. With styrene, 1,3-dimethoxy-1--phenylpropane is formed in 72% yield. With ethylal these alkenes react more slowly. The reaction of acetals of acetaldehyde and higher aldehydes with 2-methylprop-1--ene is still more difficult. For example, in the reaction of acetaldehyde acetal the "normal" product of the addition — 2,4-diethoxy-2-methylpentane — was obtained in a yield of only 15.5%. Several other products were also obtained[124]:

$$CH_3CH(OC_2H_5)_2 + (CH_3)_2C{=}CH_2 \xrightarrow{BF_3} CH_2{=}C(CH_3)CH_2CH(OC_2H_5)CH_3 +$$

$$+ CH_3C(CH_3)(OC_2H_5)CH_2CHCH_3 + CH_3CH(OC_2H_5)C(C_2H_5O)=CH_2 + CH_3CH(OC_2H_5)CHCH_3 + (CH_3)_3COC_2H_5.$$

The reaction of ortho-esters with alkenes is of considerable interest. Copenhaver[125] took out a patent on the addition of ortho-esters to 2-methylprop-1-ene, indene, and cyclopentadiene. Another patent[126] described the reaction of trithioorthoformic ester with styrene in the presence of boron trifluoride at 50°.

The condensation of triethyl orthoformate with styrene[114] proceeds thus:

$$C_6H_5CH{=}CH_2 + CH(OC_2H_5)_3 \rightarrow C_6H_5CH(OC_2H_5)CH_2CH(OC_2H_5)_2.$$

but the yield of 1,1,3-triethoxy-3-phenylpropane does not exceed 5%, most of the styrene remaining unchanged.

2. Reaction of Aldehydes with $\alpha\beta$-Unsaturated Ethers

A considerable number of investigations[127-137] concern the reaction of aldehydes with $\alpha\beta$-unsaturated ethers. The mechanism of this reaction is somewhat similar to that of the reaction of cyclic acetals with vinyl ethers. As a result, a polymer is formed, the acid hydrolysis and destruction of which leads to unsaturated aldehydes:

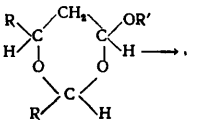
$$R{-}CH{=}O + CH_2{=}CHOR' \xrightarrow{BF_3} R{-}CH(O{-}\ddot{B}F_3){-}CH_2{-}CH(OR'){-}\rightarrow$$

$$\rightarrow [-OCH(R){-}CH_2{-}CH(OR'){-}]_n \xrightarrow{H^+} R{-}CH{=}CH{-}CHO.$$

In this way, cinnamaldehyde was obtained in 60% yield from benzaldehyde and ethyl vinyl ether[127].

Saikachi and Ogawa[87] and Hoaglin and Hirsh[128] have shown that 1,3-dioxan derivatives may be intermediates in the reaction:

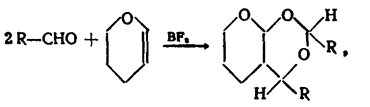
$$R{-}CHO + CH_2{=}CHOR' \xrightarrow{BF_3} [R{-}CH(O^-){-}CH_2{-}\overset{+}{C}HOR'] \xrightarrow{RCHO}$$



$$\rightarrow R{-}CH{=}CH{-}CHO + R{-}CHO + ROH.$$

Such an intermediate was isolated in the reaction with *p*-nitrobenzaldehyde[87]. An intermediate could not be isolated when furfural was used.

The reaction was also extended to cyclic unsaturated ethers. As it transpired[133], butyraldehyde and isobutyraldehyde react with dihydropyran to form 2,4-dipropyl- and 2,4-diisopropyl-hexahydropyrano[2,3-*d*]-*m*-dioxin respectively, with ~59% yields, according to the scheme:



where R = n-C_3H_7 or iso-C_3H_7.

It was also shown[130-132] that, depending on the aldehyde and catalyst, the reaction can go in another direction, with formation of alkoxyaldehydes. For example, in the condensation of crotonaldehyde with ethyl vinyl ether 3-ethoxyhex-4-enal was obtained in 46% yield:

$$CH_3{-}CH{=}CH{-}CHO + CH_2{=}CHOC_2H_5 \longrightarrow CH_3{-}CH{=}CH{-}CH(OC_2H_5){-}CH_2{-}CHO.$$

There are several patents on the use of this reaction[127-129], from which it appears that it can be employed with both aliphatic saturated and unsaturated aldehydes and also aromatic and heterocyclic aldehydes.

Krasnaya and Kucherov[134] showed that aldehydes also react with 1-alkoxydienes:

$$RCH{=}CHCHO + CH_2{=}C(R')CH{=}CHOR'' \xrightarrow{BF_3}$$

$$\rightarrow RCH{=}CHCH(OR'')CH_2C(R'){=}CHCHO + RCH{=}CH[CH(OR'')CH_2C(R'){=}CH_2]CHO.$$

The reactions were carried out with crotonaldehyde, dimethylacrolein, citral, benzaldehyde, and furfural. The yields sometimes exceeded 40%.

Arens and his coworkers[135,136] found that aldehydes, and also ketones, are able, in the presence of boron trifluoride, to react with ethoxyacetylene and form esters of unsaturated acids:

$$R_2C{=}O \ldots BF_3 + HC{\equiv}COC_2H_5 \longrightarrow \left[R_2C(O{-}\ddot{B}F_3){-}CH{=}C{-}OC_2H_5\right] \longrightarrow$$

$$\rightarrow R_2C{=}CHCOOC_2H_5.$$

Krasnaya and Kucherov[137] also used in this reaction such unsaturated aldehydes and ketones as crotonaldehyde, heptadienone, cyclocitral, etc., the yields of addition products reaching 67%.

3. Autocondensation of Acetals

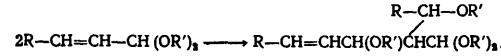
Under the influence of boron trifluoride or zinc chloride acetals of saturated aldehydes dimerise with loss of a molecule of alcohol[138]:

$$R{-}CH(OC_2H_5)_2 + R{-}CH_2CH(OC_2H_5)_2 \xrightarrow{BF_3 \text{ or } ZnCl_2}$$

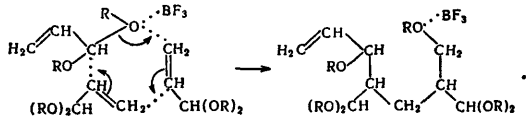
$$\rightarrow R{-}CH(OC_2H_5)CH(R)CH(OC_2H_5)_2 + C_2H_5OH.$$

1,1,3-triethoxybutane can be obtained by this reaction with yields of up to 50%.

The dimerisation of the acetals of $\alpha\beta$-unsaturated aldehydes takes place by addition at the double bond:



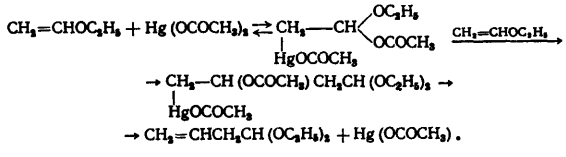
For example, crotonaldehyde diethyl acetal gives a dimer of the above structure with a yield of up to 80%. Yufit and Kucherov[139] made a detailed study of the autocondensation of acrolein acetal and found that the dimer is obtained in 5–10% yield, the main product of the reaction being a trimer, whose formation they explained by the following mechanism of cyclic electron transfer in a six-membered ring:



The formation of a trimer here seems to be a self-contained reaction taking place in parallel with the formation of the dimer.

4. Autocondensation of Vinyl Ethers

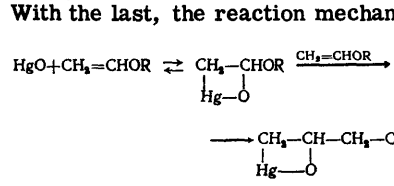
Vinyl ethers are known to polymerise extremely readily in the presence of Friedel-Crafts catalysts[44], but low-molecular-weight polymerisation products have not been obtained. Hoaglin and coworkers[140] found that the use of boron trifluoride in conjunction with mercury(II) acetate enables polymerisation to be avoided and dimers, trimers, and tetramers of alkyl vinyl ethers obtained. Polymers are also formed but in reduced amounts. The products of the dimerisation are unsaturated acetals and ketals. The authors suggested that the mercury(II) acetate participated in the formation of the dimers thus:



The formation of trimers and tetramers evidently takes place as a result of the reaction of the acetals thus obtained with the alkyl vinyl ether by the usual mechanism. The dimer of ethyl vinyl ether — a vinylacetaldehyde acetal — was obtained in 72% yield, ethyl but-1-enyl ether gave a dimer in 30% yield, and ethyl isopropenyl ether gave only 11% yield.

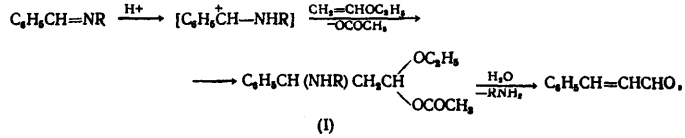
The autocondensation of vinyl ethers has also been described in a Japanese patent[141]. In this work the autocondensation of methyl vinyl and ethyl vinyl ethers with catalysts such as boron trifluoride/mercury(II) acetate and boron trifluoride/mercury(II) oxide was studied.

Makin and Kruptsov[142] studied several complex catalysts, such as boron trifluoride/mercury(II) sulphate, iron(III) chloride/mercury(II) oxide, iron(III) chloride/mercury(II) acetate, and zinc chloride/mercury(II) oxide. The best results were obtained with boron trifluoride/mercury(II) acetate and boron trifluoride/mercury(II) oxide. With the last, the reaction mechanism is thought to be:



The authors investigated the autocondensation of ethyl vinyl, butyl vinyl, and pentyl vinyl ethers.

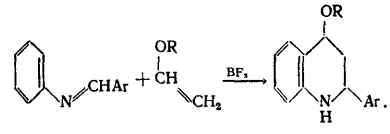
Apart from acetals and their sulphur analogues (thioacetals), nitrogen derivatives of carbonyl compounds, such as imines, have been used in the reaction with $\alpha\beta$-unsaturated ethers. Povarov and Mikhailov[143] showed that imines react with ethyl vinyl ether in an acetic acid medium; the reaction has many similarities to that with acetals and leads to 3-*N*-alkyl- or 3-*N*-aryl-aminoacylals (I). When the latter are split they give, like the 3-alkoxyacetals, an unsaturated aldehyde:



(I)

where R = $-CH_2CH=CH_2$, iso-C_4H_9, or C_6H_5.

The same authors[144] found that in the presence of boron trifluoride, aromatic imines (Schiff bases) also react with $\alpha\beta$-unsaturated ethers, but here the reaction not only occurs at the carbonyl group, but also by addition of the $\alpha\beta$-unsaturated ethers in the 1,4 position to the diene system formed by the aromatic ring and the iminomethine group:

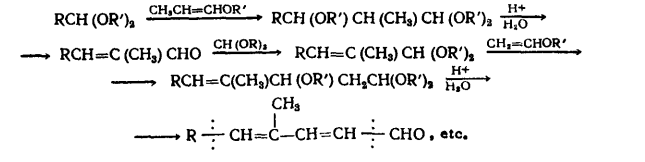


This reaction will not be discussed in this review.

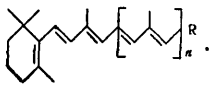
X. SYNTHESES BASED ON THE REACTION OF ACETALS WITH $\alpha\beta$-UNSATURATED ETHERS

1. Synthesis of Isoprenoid Systems

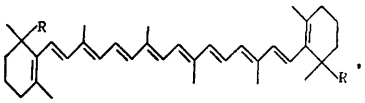
The use of the reaction of acetals with unsaturated ethers in the synthesis of isoprenoid systems seemed especially fruitful. Here above all mention must be made of the many papers and patents of Isler and his coworkers[8-13,145-160] and certain other patents[161-164]. With this reaction the authors obtained a series of yellow and red carotenoid pigments. The isoprenoid chain was built up by successive condensations of the initial acetals with ethyl propenyl and ethyl vinyl ethers:



By combining the reaction of acetals and unsaturated ethers with the Reformatski and Wittig reactions and with the acetylene synthesis, Isler and his coworkers obtained, in high yields, β-carotene, lycopene, zeaxanthin, cryptoxanthin, and other carotenoids of the type:

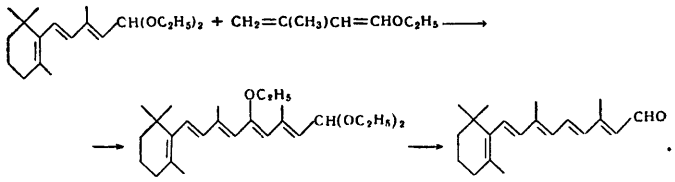


This method was also used to synthesise homologues of carotene[165]:



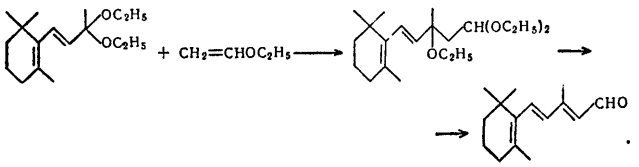
where R = C_2H_5 or iso-C_4H_9.

Krasnaya and Kucherov[53] arrived at the aldehyde of Vitamin A, by using the reaction of 1-ethoxy-3-methylbuta-1,3-diene with the acetal of β-ionylideneacetaldehyde:



Vitamin A itself was also obtained by reduction of the aldehyde.

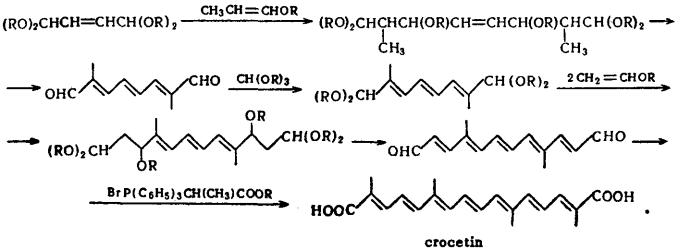
Mikhailov and Povarov[7] obtained an intermediate product in the synthesis of Vitamin A — β-ionylideneacetaldehyde — by condensation of β-ionone ketal with ethyl vinyl ether:



The condensation of acetals and ketals with unsaturated ethers has been used in the synthesis of bicyclodehydrofarnesenic acid[166], pseudoirone[67], citral[29], dihydrocitral[37], etc.

2. Synthesis of Unsaturated Dicarboxylic Acids

Isler and his coworkers[75,168] developed methods of synthesising polyene dicarboxylic acids, such as crocetin, and bixin. For this they used the reaction of bisacetals with ethyl propenyl and ethyl vinyl ethers in conjunction with subsequent Wittig reactions with a carbethoxyethylenephosphorane:

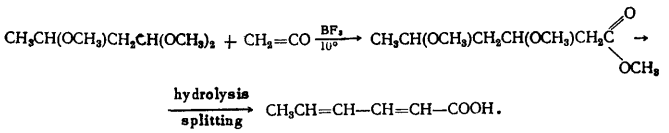


crocetin

Bixin was obtained by an analogous path.

Kucherov, Yanovskaya, and their coworkers[78,169-171] developed a path for synthesising polyenedicarboxylic acids of the corticrocin type containing either an even or an odd number of bonds in the chain, also providing a combination of the bisacetal condensation and the Wittig reaction.

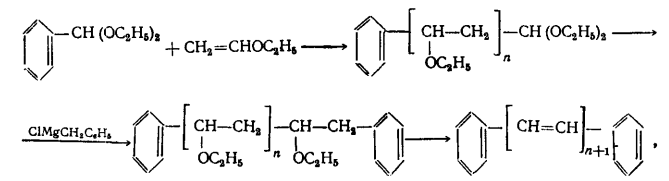
A convenient method of obtaining monobasic polyene acids is the reaction of 3-alkoxyacetals with keten[172]:



The yield of sorbic acid reaches 85%.

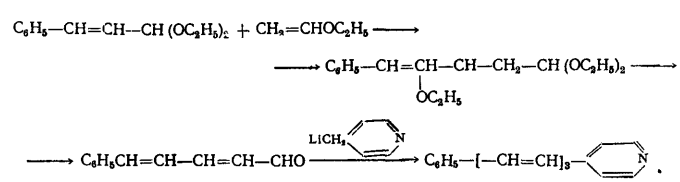
3. Synthesis of Arylated Polyene Hydrocarbons

Mikhailov and coworkers[15-17,36,74,173] developed new methods of synthesising arylated polyene hydrocarbons on the basis of the condensation of acetals with alkyl vinyl ethers and alkoxydienes. After Kuhn's well-known work, diphenylpolyenes from 1,4-diphenylbutadiene to 1,10-diphenyldecapentaene were obtained for the first time[15]:



where n = 1, 2, 3, or 4.

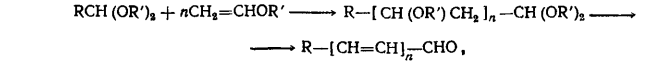
In addition, unsymmetrical diarylpolyenes[16], diphenylpolyenes methylated in various positions[17], and monoarylated polyenes[74] have been obtained. Mikhailov and Ter-Sarkisyan[173] obtained polyenes with heterocyclic substituents, by using phenylpolyenals obtained by the condensation of cinnamaldehyde acetal with ethyl vinyl ether or 1-ethoxybutadiene:



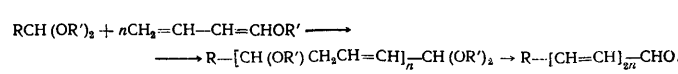
Arylated polyenes are of interest as organic luminophores.

4. Synthesis of Polyenals and 1-Alkoxypolyenes

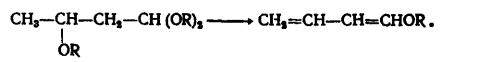
An extremely large number of syntheses of polyene aldehydes and ketones which previously were inaccessible or obtained with difficulty have been effected by the scheme:



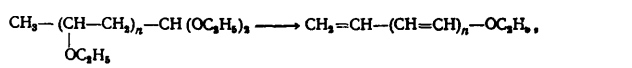
or by use of 1-alkoxydienes by the scheme:



Alkoxyacetals are now widely used to make 1-alkoxydienes, which are valuable intermediates in several syntheses:



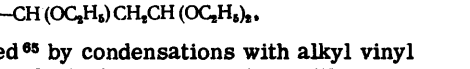
Polyenes and other higher 1-alkoxypolyenes have been obtained by using the corresponding polyalkoxyacetals[25]:



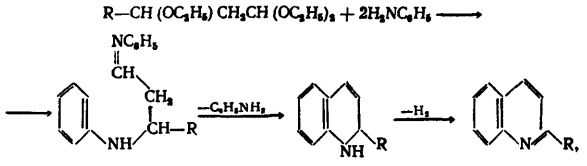
where n = 2, 3, or 4.

5. Synthesis of Quinolines

γ-Ethoxyacetals of the type:

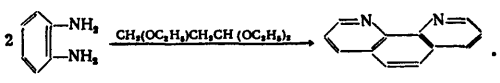


which can be obtained[65] by condensations with alkyl vinyl ethers, give quinoline derivatives on reacting with aromatic amines. By analogy with the suggested mechanism of the quinaldine synthesis, the reaction mechanism can be represented as follows:



where R = H, CH_3, C_2H_5, or C_6H_5.

With diamines, phenanthrolines are formed similarly:



The examples given do not exhaust all the fields of use of the reactions of acetals with unsaturated ethers.

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