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THE ENOL ETHER SYNTHESIS OF POLYENES

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Abstract—Convenient methods for the preparation of 1-alkoxydienes are reviewed. It is shown that 1-alkoxydienes are very reactive and can be successfully used for the synthesis of polyene compounds. These include some important natural products, such as polyene aldehydes, vitamin A aldehyde, the ethers and esters of vitamin A, β-ionolidenacetaldehyde, β-C_{19}-aldehyde and other related compounds.

A convenient method of synthesis of polyene dialdehydes, dicarboxylic acids and their derivatives is described. These compounds can be used for the synthesis of carotenoids.

1. INTRODUCTION

The possibility of condensing vinyl alkyl ethers with aldehyde acetals was first established in 1936.[1] In 1949 Hoaglin and Hirch carried out the condensation of some aldehyde acetals with vinyl alkyl ethers and proposed a mechanism for this reaction.[2] Isler *et al.* (Switzerland) were the first to apply this reaction to the synthesis of polyene compounds and in particular to the synthesis of carotenoids.

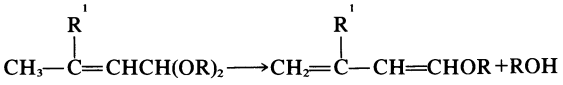
The brilliant achievements of Isler and his colleagues in this field are well known[3,4] and I shall not discuss them. I should like in my report to describe the work which has been carried out in Moscow, and in particular, the work connected with the use of 1-alkoxy-1,3-dienes.

2. SYNTHESIS OF 1-ALKOXY-1,3-DIENES

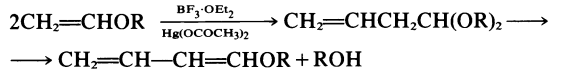
Only a few 1-alkoxy-1,3-dienes were known before our investigations. For example, 1-methoxy- and 1-ethoxybutadiene were obtained by Flaig[5] in 1950 by passing the vapours of α,β-unsaturated aldehyde acetals or 1,1,3-trialkoxyalkanes over acidic catalysts.

In our laboratory we have worked out three convenient methods of preparation for 1-alkoxydienes.

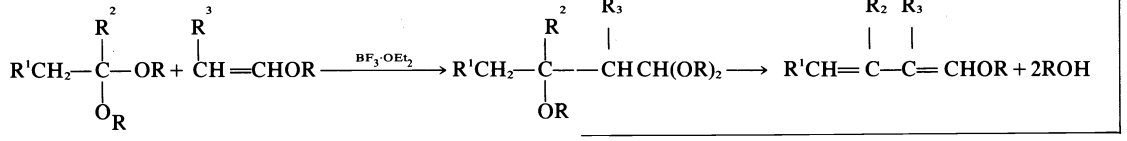
(a) The pyrolysis of α,β-unsaturated aldehyde acetals.[6–8]



(b) The pyrolysis of vinylacetaldehyde acetals. The latter are conveniently obtained from vinyl alkyl ethers.[9]



(c) The pyrolysis of 1,1,3-trialkoxyalkanes, which can easily be obtained by the condensation of acetals or ketals with vinyl alkyl ethers.[6–8]

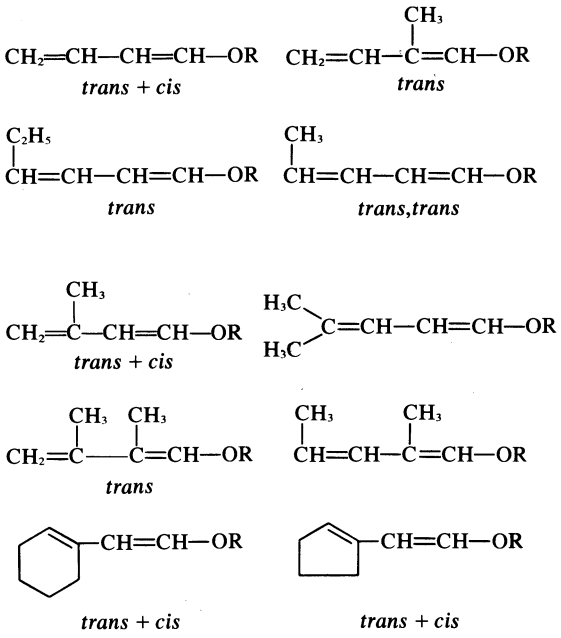


The pyrolysis of these acetals can be carried out either in the vapour phase or in the liquid phase.

The vapour phase pyrolysis is carried out by passing the vapours of acetals or alkoxyacetals over acid type catalysts *in vacuo* at 300–350°C. The most useful of these catalysts are NaH_2PO_4, $MgHPO_4$ and $NH_4H_2PO_4$.

The liquid phase pyrolysis is carried out at 165–220°C in the presence of acid type catalysts. To avoid the polymerisation of 1-alkoxydienes, it is necessary to remove low boiling alcohols and the 1-alkoxydienes from the reaction medium via a fractional distillation column.

The yields vary with the starting materials and are about 50–80% by either route. In this way we have prepared the 1-alkoxydienes in Scheme 2.



Scheme 2. 1-Alkoxydienes.

In recent years much attention has been paid to the investigation of geometrical isomerism in 1-alkoxy-1,3-dienes. By means of preparative gas–liquid chromatography and u.v., i.r., and NMR spectroscopy it has been established that the isomeric composition of the 1-alkoxy-1,3-dienes varies with structure, but as a rule the pyrolysis reactions lead either to pure *trans*-isomers or to mixtures

of *cis–trans* isomers in which the *trans* forms predominate (see Scheme 2).[10–14]

1-Alkoxydienes are of great synthetic interest. They are very reactive because of the two conjugated double bonds and the labile alkoxy group. They have been successfully applied to the syntheses of different types of unsaturated and polyenic compounds including some important natural products for example vitamin A, β-carotene and other related compounds.

3. *Synthesis of vitamin A and carotenoids*

Many important syntheses are based on bromoalkoxylation of 1-alkoxydienes.[15] This reaction leads to many unsaturated bifunctional compounds of use in the syntheses of vitamin A and carotenoids (Scheme 3).

The bromoalkoxylation of 1-alkoxydienes is carried out by interaction of 1-alkoxydienes with N-bromosuccinimide and alcohols, the acetals of α,β-unsaturated γ-bromoaldehydes (I) being obtained.

The γ-bromoacetals (I) react with sodium alkoxydes or with potassium acetate to give γ-alkoxy- (II) or γ-acetoxy- (III) acetals of α,β-unsaturated aldehydes respectively in good yield.

The hydrolysis of compounds (II) and (III) with dilute phosphoric acid leads to γ-alkoxy- (IV) and γ-acetoxy- (V) substituted α,β-unsaturated aldehydes respectively.

The γ-bromoacetals (I) easily react with triphenylphosphine to give phosphonium salts (VI). When γ-bromoacetals (I) and sodium diethylphosphite react, the phosphonates (VII) are obtained.

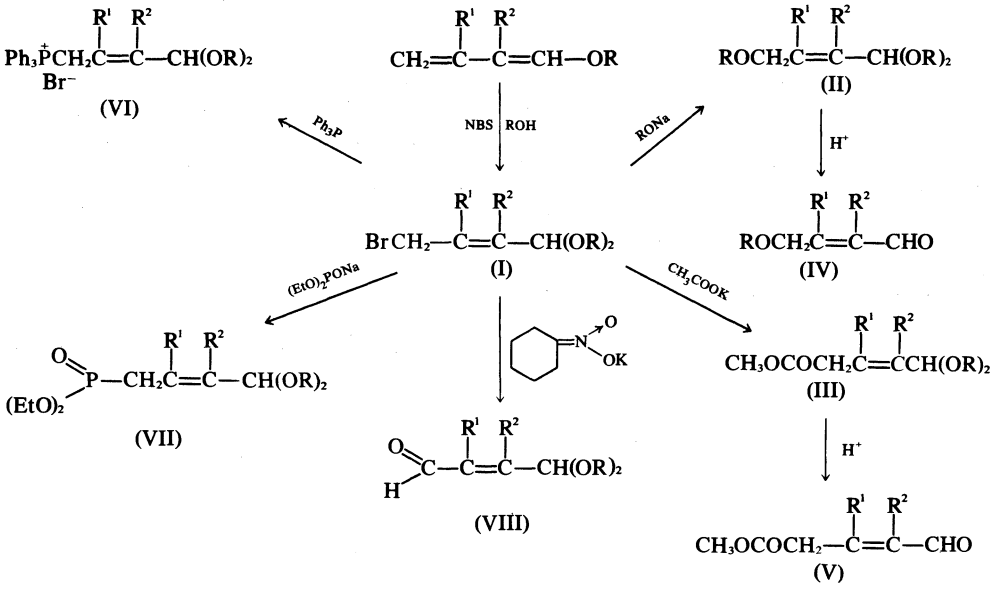
The bromomethyl group can be successfully oxidized to the aldehyde group with the help of nitrocyclohexane in alkaline solution. By means of this reaction previously inaccessible fumaric aldehyde monoacetals (VIII) and their alkylderivatives have become readily available.

The bifunctional unsaturated compounds described above were then used in the synthesis of different polyene compounds including vitamin A and carotenoids.

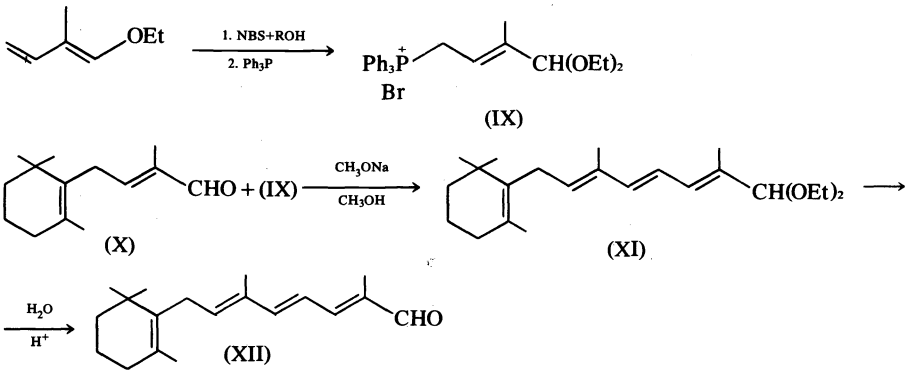
Thus, 1-ethoxy-2-methylbuta-1,3-diene was used for the synthesis of β-C_{19}-aldehyde, which is an important intermediate in the synthesis of β-carotene[16] (Scheme 4).

The condensation of the phosphonium salt (IX) with the β-C_{14}-aldehyde (X) in sodium methoxide solution gave β-C_{19}-aldehyde acetal (XI) which by means of acid hydrolysis was easily converted into the β-C_{19}-aldehyde (XII) as a mixture of *cis* and *trans* isomers.

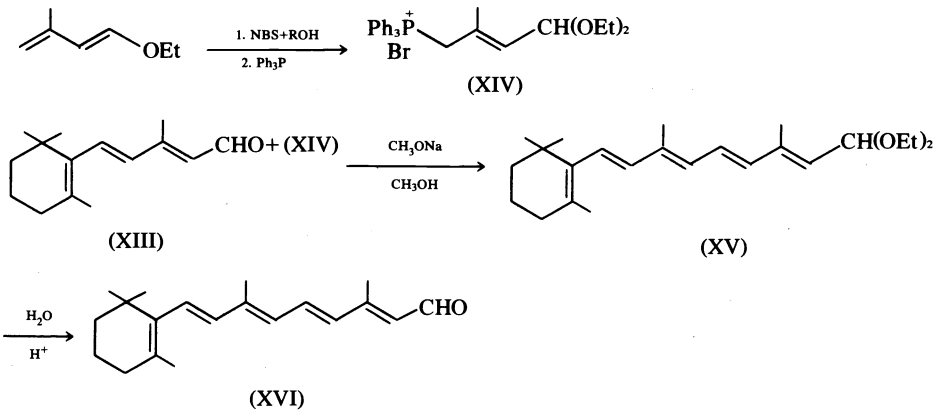
Similarly the reaction between β-ionylidene-acetaldehyde (XIII) and the phosphonium salt (XIV), obtained from 1-ethoxy-3-methyl-butadiene, gave vitamin A aldehyde acetal (XV) which after mild acid hydrolysis yielded vitamin A aldehyde (XVI)[17] (Scheme 5).



Scheme 3. Synthesis of bifunctional compounds.



Scheme 4. Synthesis of β-C_{19}-aldehyde.



Scheme 5. Synthesis of vitamin A aldehyde.

4. SYNTHESIS OF ETHERS AND ESTERS OF VITAMIN A

Several methods for the synthesis of vitamin A ethers and esters have been devised using 1-alkoxydienes.

(a) *Wittig reaction synthesis*

γ-Methoxy- (XVII, R=CH_3) and γ-acetoxy- (XVII, R=$OCOCH_3$) tiglaldehyde acetals (obtained from 1-ethoxy-2-methylbutadiene) were condensed with vinyl ethyl ether to give 1,1,3-trialkoxy-compounds (XIX) which on heating with 90% acetic acid were converted into γ-substituted hexa-2,4-dienals (XX), λ_{max}. EtOH 271–273 nm.[18]

Two methods for the synthesis of vitamin A ethers and esters were then studied.[18] (Scheme 6.)

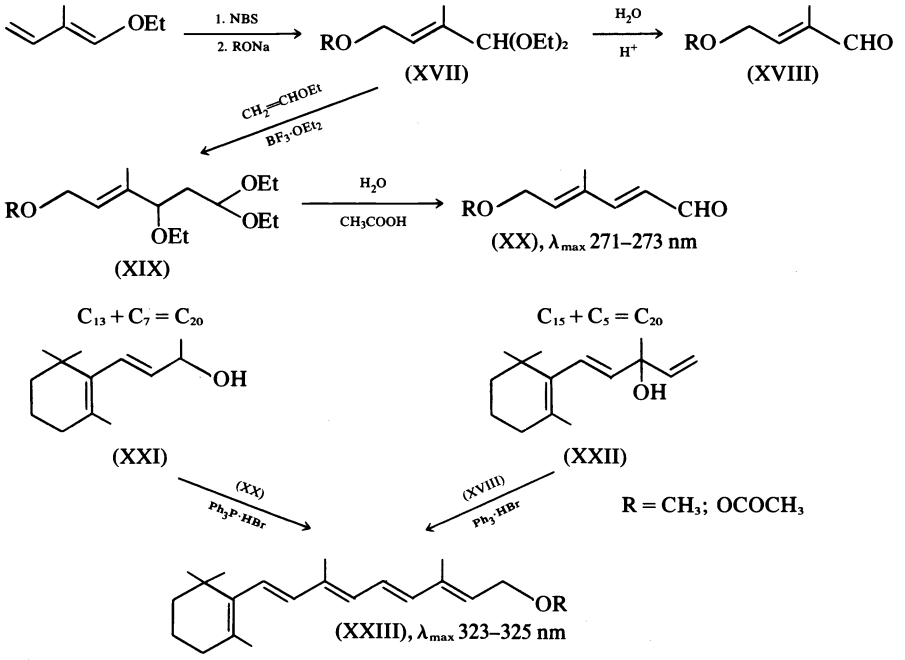
The $C_{13}+C_7=C_{20}$ *approach.* β-Ionol (XXI) reacted with triphenylphosphine hydrobromide to give phosphonium salt, which was then condensed with the C_7-component (XX) in the presence of sodium methoxide, to give ethers and esters of vitamin A (XXIII). This procedure was carried out very simply in one step without isolating the intermediate products. Vitamin A methyl ether (XXIII, R=CH_3) was obtained by this method in 63.5% yield. This method was also applied to the preparation of vitamin A acetate (XXIII, R=$OCOCH_3$).

The $C_{15}+C_5=C_{20}$ *approach.* Vitamin A methyl ether was obtained according to this scheme in one step by heating the mixture of vinyl- β-ionol (XXII) triphenylphosphine hydrobromide, γ-methoxy-tiglaldehyde (XVIII, R=CH_3) and sodium methoxide in dimethylformamide solution. The yield was about 22%. Most of the vinyl- β-ionol was recovered.

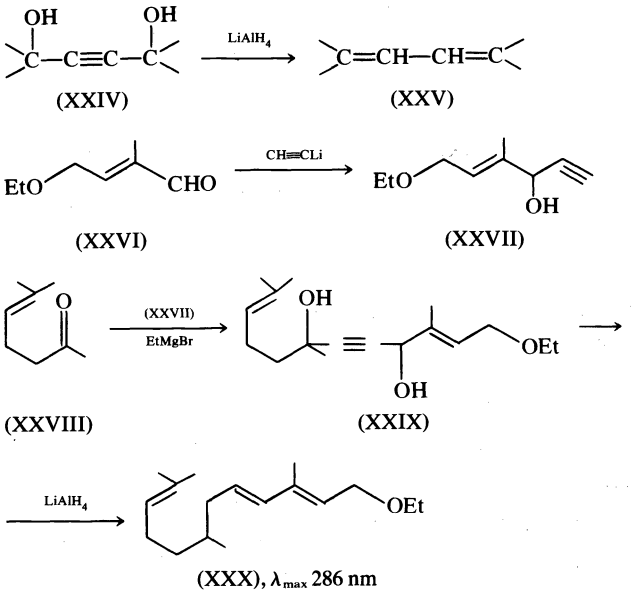
(b) *From acetylenic glycols*

This method is based on a reaction published in 1954 by Whiting.[19] Acetylenic glycols (XXIV) on treatment with lithium aluminium hydride are easily converted into polyenes (XXV) (Scheme 7).

We carried out the condensation of γ-ethoxytiglaldehyde (XXVI) with acetylene in liquid ammonia to give the C_7-acetylenic alcohol (XXVII) in 71% yield.[20] As a model, the synthesis of dehydrofarnesol ethyl ether (XXX) was carried out. The acetylenic alcohol (XXVII) was treated with ethylmagnesium bromide and the



Scheme 6. Synthesis of ethers and esters of vitamin A.



Scheme 7. Synthesis of dehydrofarnesol ethyl ether.

product condensed with the methylheptenone (XXVIII) to give the acetylenic glycol (XXIX).

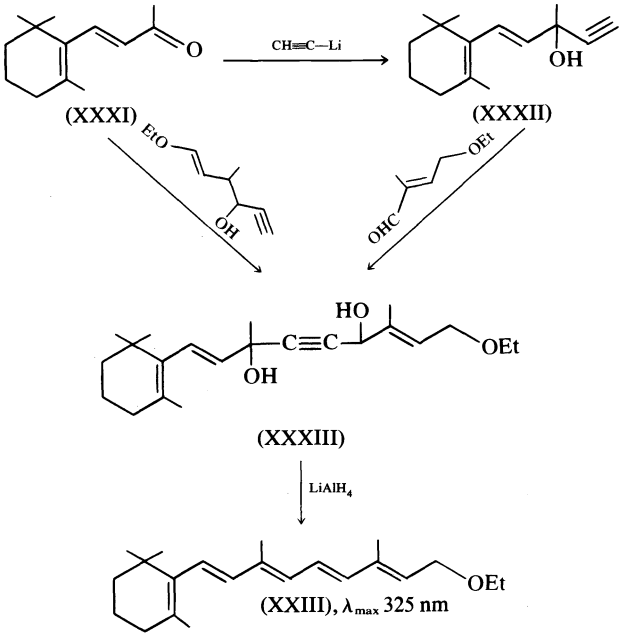
This glycol (XXIX) was then converted by the action of lithium aluminium hydride into dehydrofarnesol ethyl ether (XXX) in 43% yield, $\lambda_{max.}$ 232 nm (ϵ 286), 286 nm (ϵ 18000).[20]

The method described above was then applied to the synthesis of vitamin A ethyl ether (XXIII) (Scheme 8).

5. CONDENSATION OF 1-ALKOXYDIENES WITH α,β-UNSATURATED ALDEHYDE ACETALS

1-Alkoxydienes, like vinyl alkyl ethers, are easily condensed with α,β-unsaturated aldehyde acetals in the presence of aprotic acids (e.g. $ZnCl_2$, BF_3) to give 1,1,3-trialkoxyalkanes. The condensation of crotonaldehyde acetal and of β-methylcrotonaldehyde acetal with 1-ethoxybuta-1,3-diene,[22,23] 1-ethoxy-2-methylbuta-1,3-diene,[24] 1-ethoxy-3-methylbuta-1,3-diene,[22,24] 1-ethoxypenta-1,3-diene[25] and 1-ethoxy 2,3-dimethylbuta-1,3-diene[24] has been studied in detail.

The reactions of acetals with 1-alkoxy-dienes proceed by 1,4-addition to the diene system. The α,β-unsaturated alkoxyacetal formed reacts with another molecule of 1-alkoxydiene to produce a mixture of unsaturated alkoxyacetals (XXXIV). The composition of the mixture depends upon the initial molar ratio of reagents. A twofold excess of the acetal favours the conversion to



Scheme 8. Synthesis of vitamin A ethyl ether.

the required product (XXXIV, $n = 1$). The mixtures of alkoxy-acetals are easily separated by fractional distillation. The mechanism of this reaction has been discussed[24] and is probably that shown in the Scheme 9.

It is interesting to note that the condensation between β-methylcrotonaldehyde acetal (XXXV) and 1-ethoxy-3-methylbutadiene (XXXVI) leads to isoprenoid compounds (XXXVIII).

The hydrolysis of the resulting alkoxy-acetals (XXXVII) under mild conditions with dilute phosphoric acid leads to alkoxyaldehydes (XXXVIII) which on heating in the presence of a small amount of toluene-*p*-sulphonic acid in toluene solution, are easily converted into polyenals (XXXIX). The same polyenals (XXXIX) can be obtained by heating the alkoxy-acetals (XXXVII) with 90% acetic acid. Polyenes with different substitution patterns in the polyene chain were obtained by this method.[22–25] This method also has been applied to the synthesis of vitamin A and its relatives (Scheme 10).

The condensation of β-cyclocitral acetal (XL) with 1-ethoxy-3-methylbutadiene in the presence of zinc chloride catalyst affords a mixture of the C_{15}-aldehyde ethoxy-acetal (XLI) and the $C_{22}0$-aldehyde diethoxyacetal (XLII) in yields of 44.6 and 25%, respectively.[26]

The C_{15}-alkoxyacetal (XLI), on heating with aqueous phosphoric acid, is readily converted into β-ionolidenacetaldehyde (XLIII) in good yield. The acetalisation of β-ionolidenacetaldehyde (XLIII) followed by condensation of the acetal (XLIV) with 1-ethoxy-3-methyl-butadiene gives the C_{20}-ethoxyacetal (XLV) (yield 62%), the hydrolysis of which affords dihydrovitamin-A ethoxyaldehyde (XLVI) quantitatively. This ethoxy-aldehyde (XLVI) is converted by passing through in alumina into vitamin A aldehyde (XLVII), which can be reduced with sodium borohydride to give vitamin A alcohol.

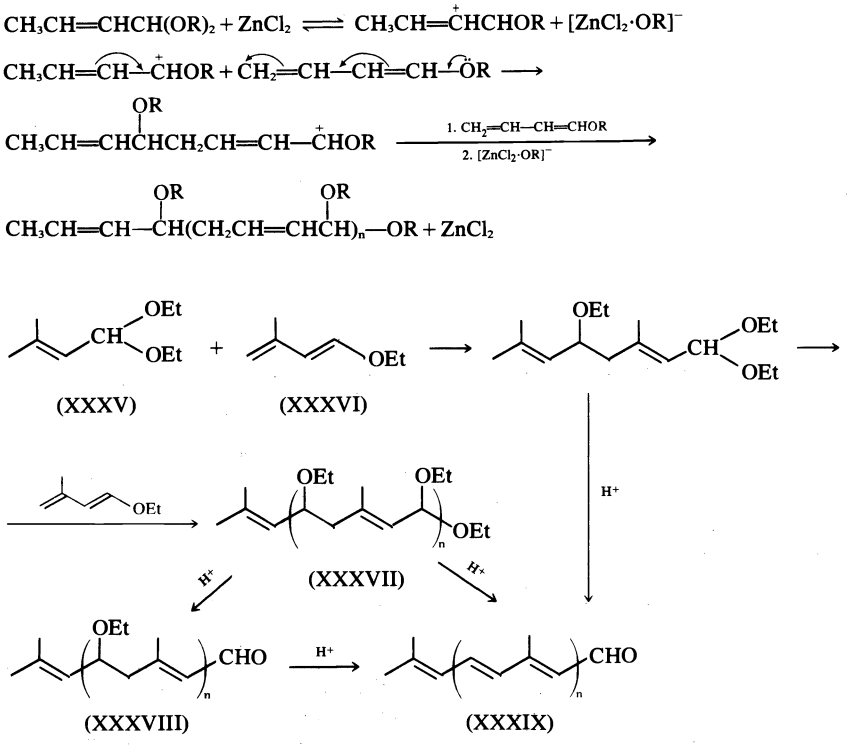
As it is shown in Scheme 10, the hydrolysis of the β-C_{20}-diethoxyacetal (XLII) leads to diethoxydihydro-vitamin A aldehyde (XLVIII) and reduction of the latter with sodium borohydride affords diethoxy-tetrahydro-vitamin A alcohol (XLIX).[27,28]

Recently an investigation has been carried out of the possibility of using ethoxydihydrovitamin-A aldehyde (XLVI) in poultry feeds.[29,30] It has been found that the biological activity of this substance (XLVI) is very high (1,100,000 i.u. in grams) and thus ethoxydihydrovitamin-A aldehyde (XLVI) can be successfully used as an equivalent of vitamin A.

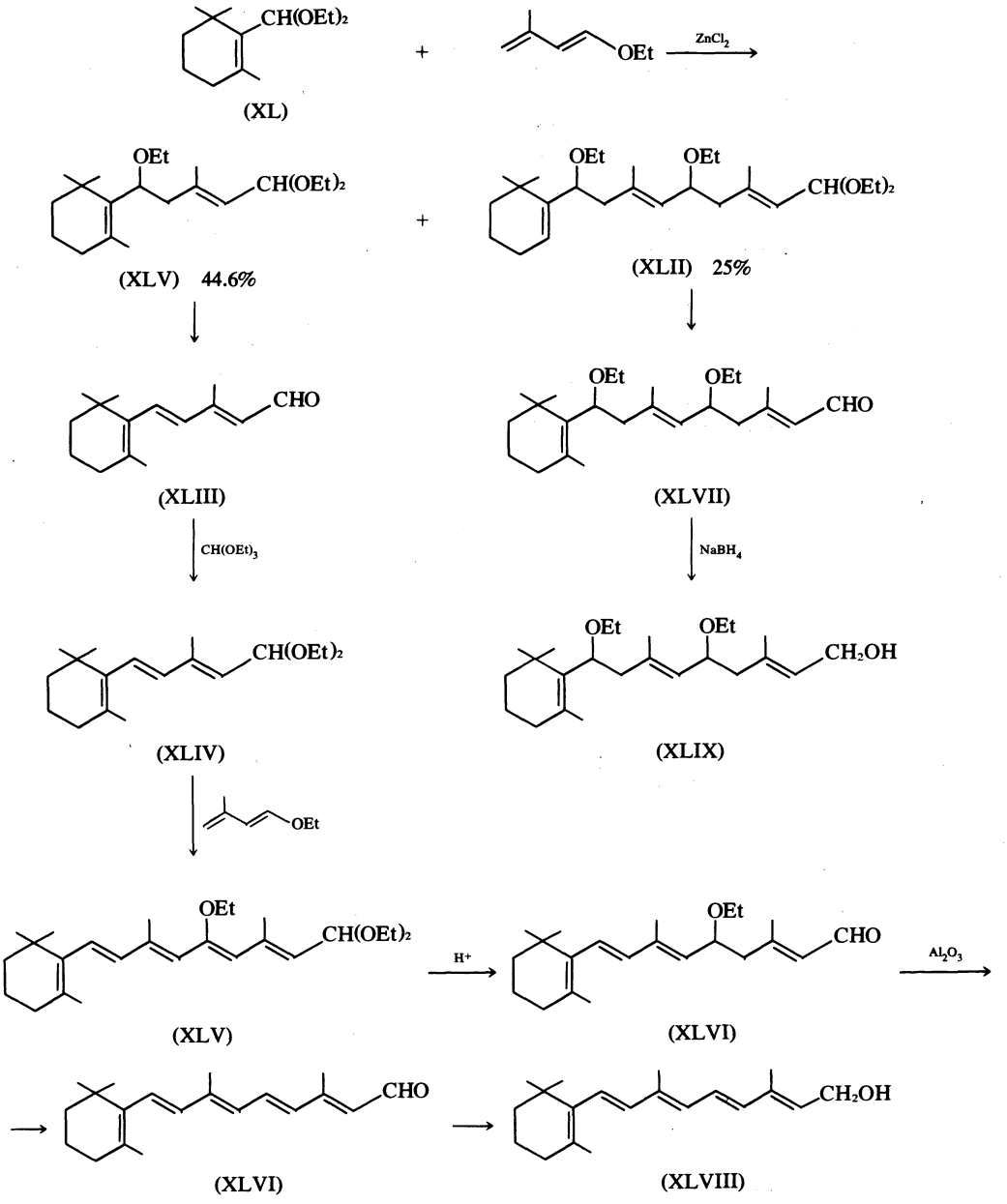
It is interesting to note that as a rule any change in the structure of vitamin A leads to the full loss of the biological activity. Apparently the high biological activity of ethoxydihydrovitamin-A aldehyd (XLVI) can be explained by the easy elimination of alcohol from the molecule of (XLVI) in the living organism and the conversion of this substance into vitamin A aldehyde. The condensation described above has been then applied to the synthesis of the β-C_{19}-aldehyde (Xii).[31] (Scheme 11).

The reaction between the β-C_{19}-aldehydeacetal (L) and 1-ethoxy-2-methylbutadiene gave the β-C_{19}-ethoxy-acetal (LI) (42%) and the β-C_{24} diethoxyacetal (16%) as a mixture. These ethoxyacetals were quantitatively converted into the β-C_{19}-ethoxyaldehyde (LIII) and the β-C_{24}-diethoxyaldehyde (LIV) respectively by heating with dilute phosphoric acid. The β-C_{19}-ethoxyaldehyde (LIII) on being heated in the presence of toluene-*p*-sulphonic acid in toluene solution yielded the *crystalline* all-*trans* β-C_{19}-aldehyde, m.p. 64–65°, λ_{max} 331 nm (ε 43,700), 337 nm (ε 43,000).

The condensation described above has been successfully applied to the synthesis of other polyene systems, for example, phenylpolyenes and furylpolyenes.[32,33]



Scheme 9. Condensation of 1-alkoxydienes with α,β-unsaturated aldehyde acetals.



Scheme 10. Synthesis of vitamin A and its relatives.

6. CONDENSATION OF 1-ALKOXYDIENES WITH α,β-UNSATURATED ALDEHYDES

1-Alkoxydienes in the presence of acids such as BF_3, $ZnCl_2$, $H_3BO_3 + (COOH)_2$ react with α,β-unsaturated aldehydes to give the mixture of unsaturated alkoxyaldehydes, which can be easily converted into polyenals by the heating with dilute acids. Thus the condensation of crotonaldehyde with 1-alkoxybutadiene or 1-alkoxy-3-methylbutadiene in the presence of $BF_3 \cdot OEt_2$ as a catalyst leads to the mixture of alkoxyaldehydes (LV) and (LVI) with the yields 42–45 and 18–22% respectively[34] (Scheme 12).

The heating of the resulting alkoxyaldehydes (LV) and (LVI) with dilute phosphoric acid affords polyenals with good yields. 2,4,6-Octatrienal (LVII, R=H), 3-methyl-2,4,6-octatrienal (LVII, R=CH_3) and 2,4,6,8,10-dodecapentaenal (LVIII) were obtained by this method.

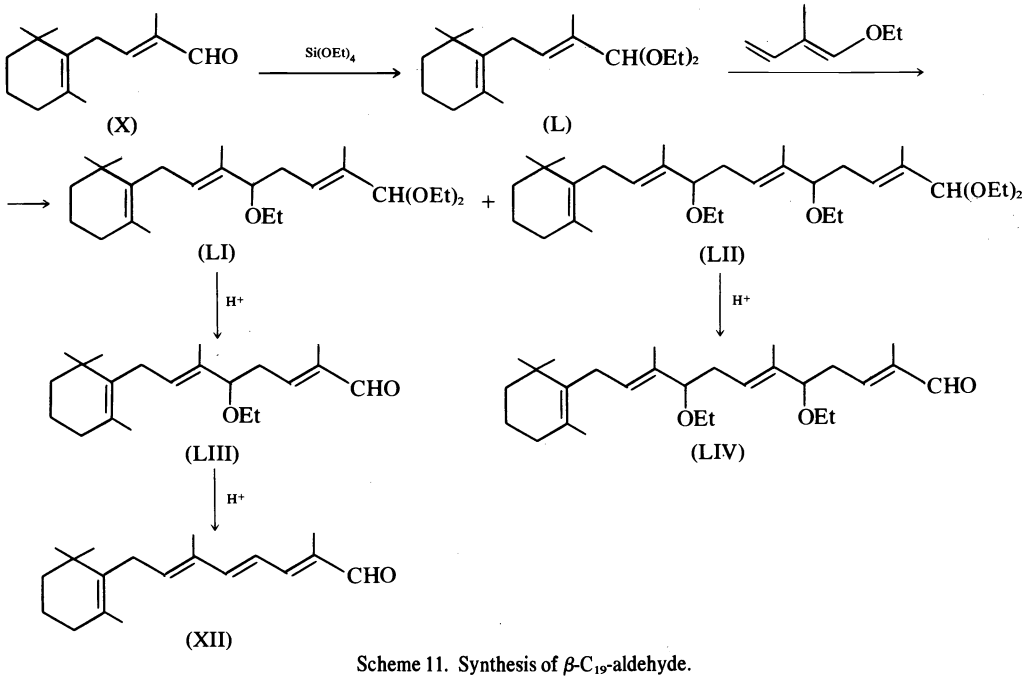
This method has also been applied to the synthesis of isoprenoid compounds.[34]

β-Methylcrotonaldehyde is easily condensed with 1-ethoxy-3-methylbutadiene in the presence of acid catalyst to give 5-ethoxycitral (LIX) (the yield 45%) and 5,9-diethoxyfarnesal (LX) (the yield 17%). These compounds are easily separated by distillation *in vacuo*.

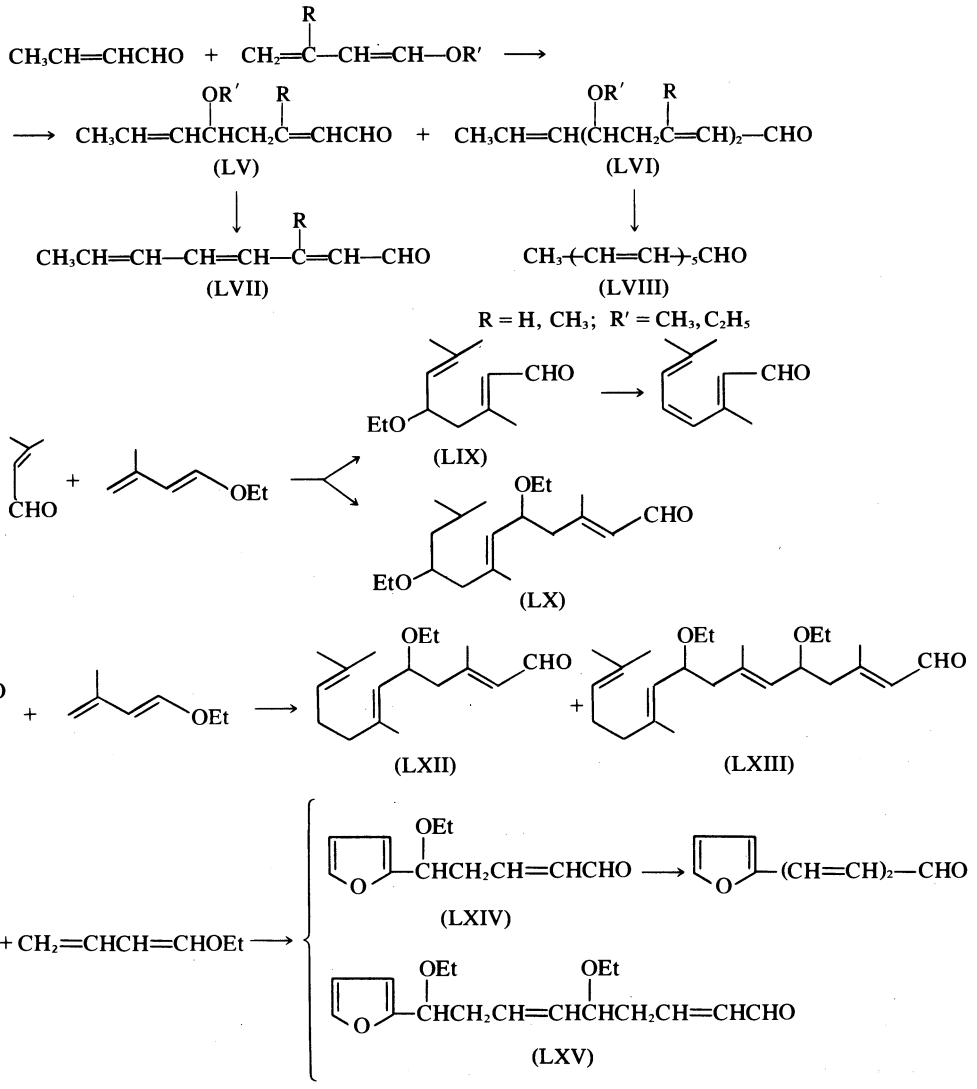
Similarly the condensation of citral (LXI) with 1-ethoxy-3-methyl-1,3-butadiene leads to a mixture of 5-ethoxyfarnesal (LXII) and diethoxyaldehyde (LXIII). It is interesting to note that β-cyclocitral does not condense with 1-alkoxydienes under these conditions.

Furfural reacts easily with 1-ethoxybutadiene in the presence of $BF_3 \cdot OEt_2$ to give 5-furyl-5-ethoxy-3-pentenal (LXIV) and 9-furyl-5,9-diethoxynona-2,6-dienal (LXV).

We suppose that the condensation of α,β-unsaturated aldehydes with 1-alkoxy-1,3-dienes proceeds via the



Scheme 11. Synthesis of β-C_{19}-aldehyde.



Scheme 12. Condensation of 1-alkoxydienes with α,β-unsaturated aldehydes.

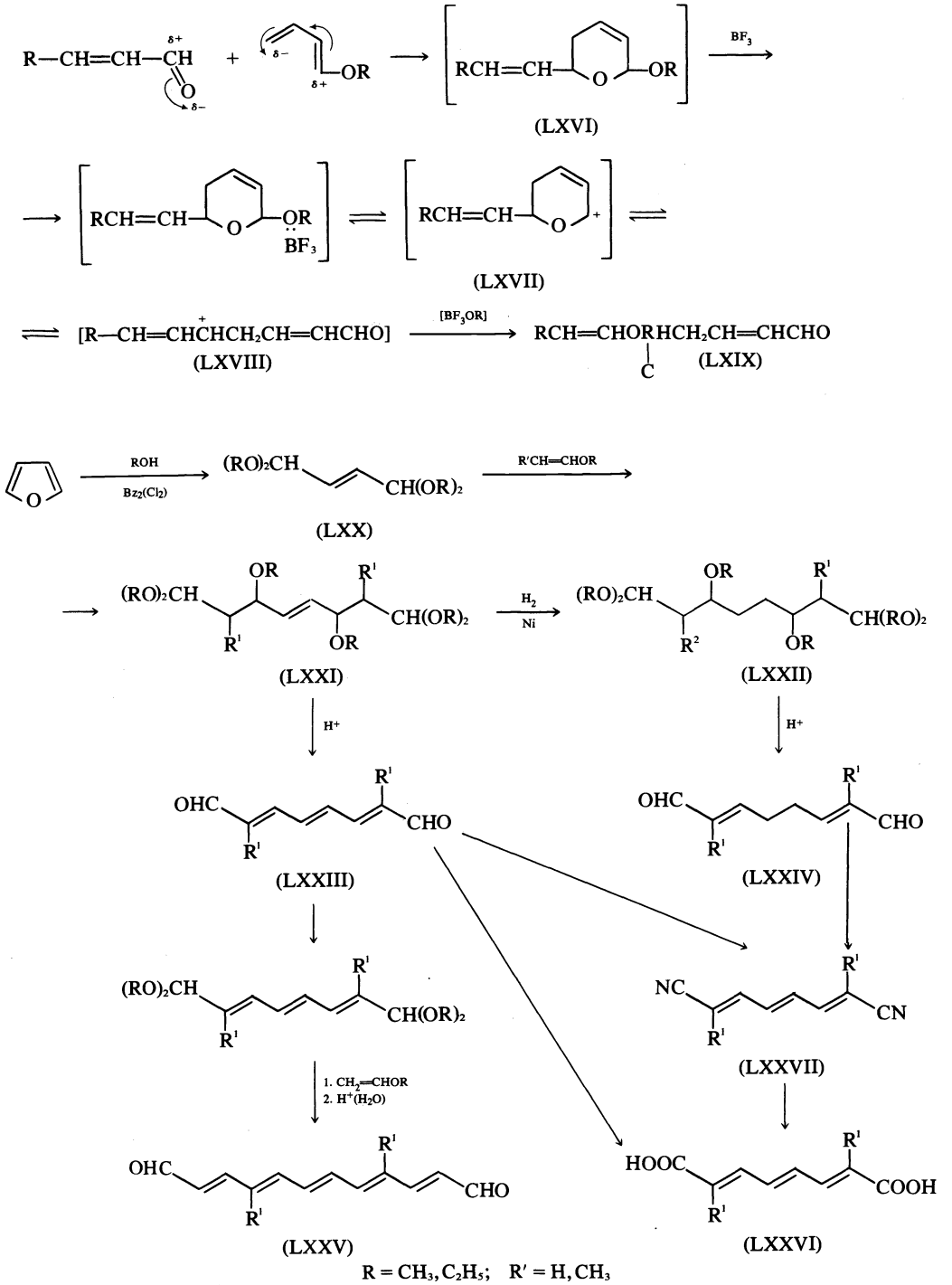
formation of intermediate dihydropyran (LXVI). By the action of an acid catalyst ($BF_3 \cdot OEt_2$, for example) on (LXVI), the unstable carbonium ion (LXVII) is formed, which then is rearranged into the more stable α,β-unsaturated carbonium ion (LXVIII). The reaction of (LXVIII) with the anion $BF_3O\bar{R}$ leads to δ-alkoxyaldehydes (LXIX).[12]

The analogous rearrangement has recently been found with 2,6-dialkoxy-Δ^3-dihydropyranes which are easily converted into glutaconic aldehyde monoacetals under the influence of $BF_3 \cdot OEt_2$.

7. SYNTHESIS OF POLYENE DIALDEHYDES

The value of conjugated polyene dialdehydes as intermediates for the synthesis of carotenoids is well known. The carbon skeleton of many symmetrical carotenoids can be built up quite simply by using polyene dialdehydes.

We worked out a very convenient method for the synthesis of fumaric aldehyde acetals (LXX) from furan using the alkoxylation reaction[36] (Scheme 13). The cleavage of the furan ring depends on the temperature and on the concentration of the hydrogen halide acid formed. We



Scheme 13. Synthesis of polyene dialdehydes.

found conditions under which the yield of fumaric aldehyde acetals was 83%.

By condensation of fumaric aldehyde acetals (LXX) with vinyl alkyl ethers, and by hydrolysis of the resulting alkoxy compounds (LXXI, LXXII), we have prepared the polyene dialdehydes (LXXIII–LXXV) and the dicarboxylic acid (LXXVI) and its derivative (LXXVII),[37–40] as shown in Scheme 13.

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