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U. D. C. 547.316.61

SYNTHESIS AND SOME PROPERTIES OF αω-DISUBSTITUTED (DIFUNCTIONAL) POLYENES

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I. INTRODUCTION

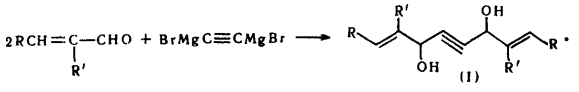
αω-Disubstituted (difunctional) polyenes are fairly widely distributed in nature. They include, for example, various branched and unbranched dicarboxylic acids (crocetin, bixin, corticrocin, descrocetin), which are the normal metabolites of certain plants and micro-organisms, polyene diketones (capsorubin — one of the pigments of cayenne, etc.). Many disubstituted difunctional polyenes are the degradation products of polyene antibiotics, such as, for example, fumagillin, lagosin, tetrin, etc. Finally, difunctional polyenes serve as the starting materials in the synthesis of other important natural compounds, for example, carotenoids (β-carotene, lycopene, etc.). In this connection synthetic methods have been investigated and developed for individual representatives of substances of this type, in the first place those with the isoprenoid structure; some of these have been described in reviews devoted to advances in the synthesis of carotenoids and vitamin A [1-3]. However, a complete description of the synthetic methods for αω-disubstituted (difunctional) polyenes has not been given so far. And yet in recent years considerable new advances have been achieved in this field, as a result of which the principal types of difunctional polyenes have become fully available. The advances in the synthetic field led to a number of theoretical findings based on the study of many properties of these compounds, particularly studies concerning the effect of the terminal substituents in the polyene chain on one another.

The present review is devoted to the advances in the synthesis of αω-disubstituted (difunctional) polyenes and certain properties of polyenes.

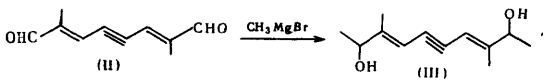
II. SYNTHESIS OF POLYENES WITH THE SAME SUBSTITUENTS AT THE ENDS OF THE CHAIN

Glycols

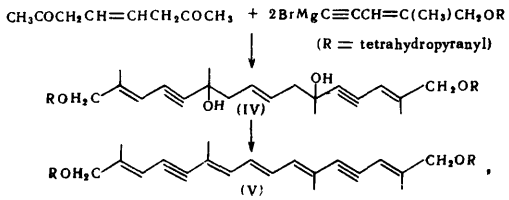
Primary and secondary glycols of the polyene and polyenyne series might serve as convenient starting compounds for the synthesis of other disubstituted (difunctional) polyenes, and therefore much attention has been devoted to their synthesis. The first and oldest method of preparing glycols consists in organometallic synthesis. This procedure leads mainly to secondary glycols. Best results have been obtained in the reaction of the simplest αβ-unsaturated monoaldehydes with the Iotsich complex. Thus when acrolein[4], methacrolein[5-11] or tiglic aldehydes[12] are allowed to act on bis(bromomagnesium)acetylene in ether, octa-1,7-dien-4-yne-3,6-diol (I, R = R′ = H), 2,7-dimethylocta-1,7-dien-4-yne-3,6-diol (I, R = H, R′ = CH_3), and 3,8-dimethyldeca-2,8-dien-5-yne-4,7-diol (I, R = R′ = CH_3) were obtained in yields of the order of 70%:



Dialdehydes and Grignard reagents can also be used in this reaction[12,13]. For example, the reaction of methylmagnesium bromide with 2,7-dimethylocta-2,6-dien-4-yne-1,8-dial (II) gave 3,8-dimethyldeca-3,7-dien-5-yne-1,9-diol (III):



However, attempts to synthesise primary glycols using the reaction between a Grignard reagent with the appropriate functional group and a diketone[14],



were not very successful because dehydration of compound (IV) gave the bistetrahydropyranyl ether (V) in a yield of only 8%.

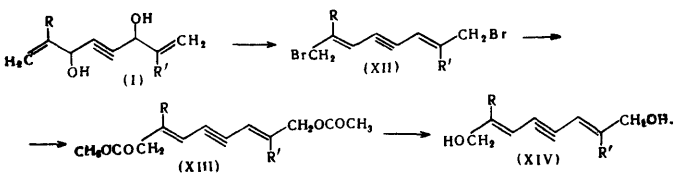
The attempt to use for the synthesis of glycols the Grignard reaction between hex-4-en-1-yn-3-ol (VI) or hex-3-en-1-yn-5-ol (VII) and acetaldehyde was also unsuccessful. Although the corresponding reaction products, oct-6-en-3-yne-2,5-diol (VIII) and oct-5-en-3-yne-2,7-diol (IX) are formed in high yields[15], selective hydrogenation of the glycol (IX) by chemical or catalytic methods gave octa-3,5-diene-2,7-diol (X) in a very low yield. The hydrogenation

of the glycol (VIII) took place smoothly, but the anionotropic rearrangement of the glycol (XI) gave mainly octa--4,6-diene-2,3-diol instead of the desired glycol (X):

$$\begin{array}{lll} CH_3CH{=}CHCH(OH)C{\equiv}CH & \rightarrow & CH_3CH(OH)CH{=}CHC{\equiv}CH \\ (VI) \quad \downarrow & & (VII) \quad \downarrow \\ CH_3CH{=}CHCH(OH)C{\equiv}CCH(OH)CH_3 & \rightarrow & CH_3CH(OH)CH{=}CHC{\equiv}CCH(OH)CH_3 \\ (VIII) \quad \downarrow & & (IX) \quad \downarrow \\ CH_3CH{=}CHCH(OH)CH{=}CHCH(OH)CH_3 & & CH_3CH(OH)(CH{=}CH)_2CH(OH)CH_3. \\ (XI) & & (X) \end{array}$$

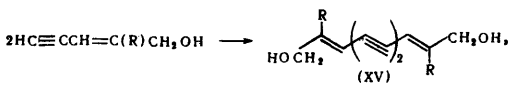
Thus organometallic synthesis can be used conveniently only for the synthesis of the simplest secondary glycols, based on monoaldehydes and the Iotsich reagent.

Anionotropic rearrangement is used for the preparation of primary glycols[5,7-9], but this frequently does not take place smoothly. Comparatively recently a new method has been proposed for the conversion of secondary glycols into primary glycols[11], in which the secondary glycol (I) is converted into the primary dibromide (XII) by the action of phosphorus tribromide[10] or hydrobromic acid[6,11]; the dibromide (XII) is then converted into the diacetate (XIII) by treatment with sodium acetate and the product (XIII) is hydrolysed with alkali to give the primary glycol (XIV). All the conversions take place readily and the yield of the glycol (XIV) is fairly high:



It should be noted incidentally that this promising method for the conversion of secondary glycols into primary glycols has so far been developed only for a few isolated cases.

A second synthetic method, which is suitable for the preparation of both primary and secondary glycols, is based on the oxidative coupling of primary or secondary enyne alcohols. Thus the corresponding primary enyne glycols (XV) were obtained in a high yield from pent-2-en--4-yn-1-ol or 2-methylpent-2-en-4-yn-1-ol[14]:



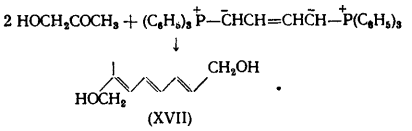
where R = H or CH_3.

The oxidative coupling reaction is used particularly extensively for the synthesis of secondary glycols[15-18]. For example, the oxidative coupling of the readily available but-3-yn-2-ol[17,18] gave the diacetylene glycol (XVI), the reduction of which led to the glycol (X):

$$HC{\equiv}CCH(OH)CH_3 \rightarrow HOCH(CH_3)(C{\equiv}C)_2CH(CH_3)OH \rightarrow (X).$$
(XVI)

Despite the ready availability of the initial enyne alcohols and the high yields of the glycols, this method has one important disadvantage: the selective reduction of the diacetylene system often constitutes a very difficult problem. Therefore, despite the obvious advantages of this method for the synthesis of glycols, preference is given at the present time to organometallic synthesis.

Quite recently yet another synthetic procedure for primary polyglycols has been described[19] — the Wittig reaction between 2-butene-1,4-diylidenebis(triphenylphosphorane) and hydroxyacetone, but the yield of the product (XVII) was only 10%:

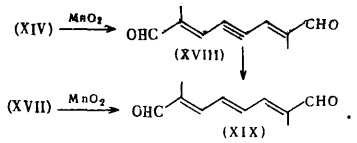


Dialdehydes

Dialdehydes are the most important starting compounds for reactions whereby substances of other classes can be obtained. Only the successful discovery of readily accessible and simple methods for the synthesis of dialdehydes of the polyene and polyenyne series could lead to the ready availability of the principal types of difunctional polyenes. In this connection, the interest shown by many investigators in this problem is fully justified.

The first synthetic procedure for dialdehydes was based on the oxidation of primary polyene glycols or polyenyne glycols with subsequent selective hydrogenation of the triple bonds. Each of the modifications proposed differed from the others by the method of synthesising the initial glycols (see above).

The oxidation of glycols of type (XIV) or (XVII) by the Oppenauer method or with t-butyl chromate is unsuccessful. Excellent results are, however, obtained in the presence of activated manganese dioxide[6-10], the yields of dialdehydes of type (XVIII) or (XIX) reaching 85–95%:

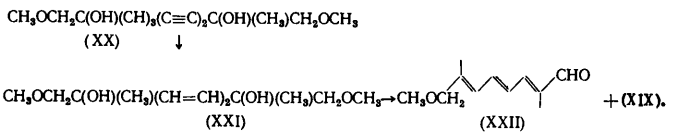


However, this universal method is not very suitable for the preparation of large amounts of dialdehydes because of the necessity to use extremely large amounts of manganese dioxide and solvent. Furthermore, the scope of this method is also restricted by the low availability of the starting compounds, because, as pointed out above, only the simplest glycols can be regarded as readily available.

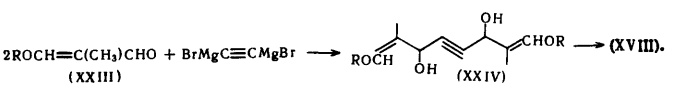
The hydrogenation of enyne dialdehydes to polyene dialdehydes takes place best in the presence of Lindlar's catalyst[7,20]. The *cis*-isomers produced in this process are isomerised to the *trans*-form on standing, on boiling in benzene solution, or under the action of traces of iodine or ultraviolet light.

The second method which was developed to prepare polyene dialdehydes consists in the synthesis of divinyl ethers, which are then hydrolysed to the dialdehydes. For example, oxidative dimerisation of 1-methoxy-2-methylbut-3-yn-2--ol[21,22] gives 1,8-dimethoxy-2,7-dimethylocta-3,5-diyne--2,7-diol (XX), the reduction of which with lithium aluminium hydride leads to the *trans-trans*-dienediol (*trans*-XXI), while hydrogenation in the presence of palladium poisoned with quinoline leads to the *cis-cis*-dienediol (*cis*-XXI).

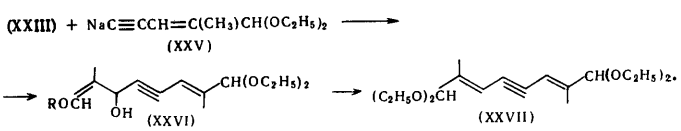
However, dehydration and hydrolysis of both dienediols resulted in a mixture of the dialdehyde (XIX) and the monoaldehyde (XXII):



It has also been suggested that the aldovinyl ether (XXIII) be condensed with the Iositch complex[23,24] and that the resulting divinyl ether (XXIV) be hydrolysed to the dialdehyde (XVIII):

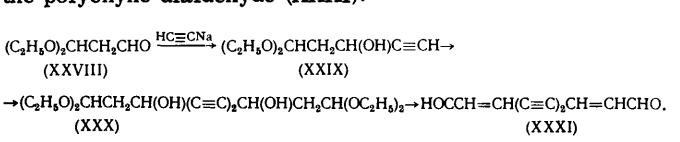


In another modification of this method[23,24] the aldovinyl ether (XXIII) is condensed with the sodio-derivative of the diethyl acetal of 2-methylpent-2-en-4-ynal (XXV) to give the hydroxy-acetal (XXVI), the latter being hydrolysed with the formation of the bisacetal (XXVII) without isolating in a pure form the intermediate dialdehyde (XVIII):

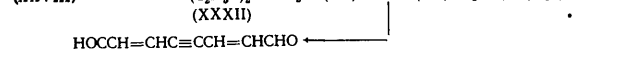


The method described above gives satisfactory yields of the final products, but it is not general.

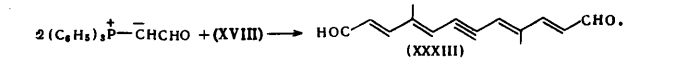
The third method for the synthesis of dialdehydes is also non-general. In this procedure ββ-diethoxypropionaldehyde (XXVIII) is condensed with sodium acetylide or the Iositch reagent[25]. The hydroxy-acetal (XXIX) obtained in the first case is subjected to oxidative dimerisation to the dihydroxy-bisacetal (XXX) and the latter is hydrolysed with simultaneous dehydration, which leads to the formation of the polyenyne dialdehyde (XXXI):



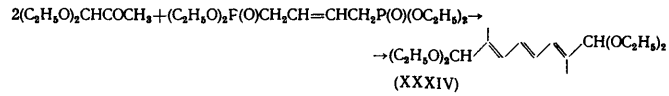
In the second case the resulting dihydroxy-bisacetal (XXXII) is also hydrolysed with simultaneous dehydration:



The fourth method for the synthesis of dialdehydes is based on the Wittig reaction. It was found[26] that formylmethylenetriphenylphosphorane reacts with the dialdehyde (XVIII), the product being 4,9-dimethyldodeca-2,4,8,10-tetraen-6-yne-1,12-dial (XXXIII):

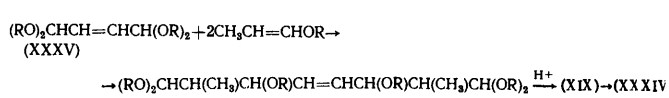


However, despite the fact that according to spectroscopic data the yield of compounds (XXXIII) was 50%, the amount of the dialdehyde isolated from the reaction mixture was only 15%, this being due, according to the authors, to the difficulty of separating compound (XXXIII) from triphenylphosphine oxide. Incidentally, the attempt[27] to increase the yield of compound (XXXIII) by using in the reaction with the dialdehyde (XVIII) formylmethylene(*p*-diethylaminophenyl)diphenylphosphorane, the oxide formed from which is readily soluble in dilute hydrochloric acid, was unsuccessful: the yield of the dialdehyde (XXXIII) was only 12%. A patent[19] describes the synthesis of the bis(diethyl acetal) of 2,7-dimethylocta-2,4,6-triene-1,8-dial (XXXIV) in the reaction between the diphosphonate (obtained from 1,4-dichlorobutene and triethyl phosphite) and the acetal of methylglyoxal:



However, these data have not been confirmed so far. Furthermore, the method described is to some extent non-general.

Until recently, despite the many attempts made, there was no simple general and reliable method for the synthesis of polyene dialdehydes, based on readily available starting materials. Such a method was developed on the basis of the reaction of divinyl ethers with acetals of aldehydes. It involves three stages: (1) the conversion of the dialdehyde into the bisacetal, (2) the condensation of the bisacetal with two moles of vinyl ether [catalysts $BF_3(C_2H_5)_2O$, $ZnCl_2$, etc.], and finally (3) hydrolysis of the resulting dialkoxy-bisacetal with simultaneous removal of the alkoxy-groups by heating with a solution of sodium acetate in acetic acid, or with phosphoric acid, etc. Usually all three stages are carried out in succession without isolating and purifying the products and thus they are in fact combined into a single stage. This method was first used for the synthesis of isoprenoid dialdehydes[28-36] from the bisacetal of but-2-ene-1,4-dial (XXXV):



The dialdehyde (XIX), which is a key product of fundamental importance, was obtained in this way. The repetition of this procedure with the bisacetal (XXXIV) using ethyl vinyl ether gave 4,9-dimethyldodeca-2,4,6,8,10-pentaenedial and subsequently crocetin dialdehyde. This synthetic procedure was proposed[37-39] for the preparation of unbranched dialdehydes of the type $OHC(CH{=}CH)_nCHO$. It is noteworthy that all the stages of the synthesis often take place with very high yields and lead to the formation of pure products.

Since bisacetals of but-2-ene-1,4-dial are nowadays readily available[37-38], the above method may be regarded as ideal for the synthesis of polyene dialdehydes. Here we have a harmonious combination of ready availability of the starting materials and the ease of the synthetic procedure and the isolation and purification of the product, which makes this method superior to all others. The method is also flexible and universal. Thus polyene dialdehydes have now become fully available.

It is noteworthy that both maleic and fumaric bisacetals react with ethyl vinyl ether equally readily[37-39], the condensation of maleic bisacetal (increase in size) being

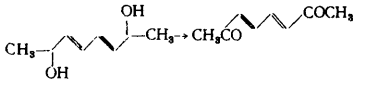
accompanied by a complete conversion of the *cis*-configuration into the *trans*-configuration[37]. In contrast to this, the condensation of the bisacetal of *cis-cis*-muconic dialdehyde[25] is not accompanied by complete isomerisation and leads to a mixture of isomeric dialkoxy-bisacetals. However, hydrolysis of the dialkoxy-bisacetals results, as a rule, in the formation of only the pure *trans*-isomers.

Asymmetric condensation (increase in the chain length) of the bis(dimethyl acetal) of fumaric dialdehyde using ethyl vinyl ether and butyl vinyl ether was achieved by Makin[39], but the yields of products were only 16–20%:

$$(CH_3O)_2CHCH{=}CHCH(OCH_3)_2+CH_2{=}CHOCH_3\rightarrow$$
$$\rightarrow(CH_3O)_2CHCH{=}CHCH(OCH_3)CH_2CH(OCH_3)_2.$$

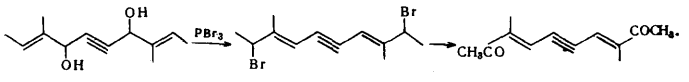
Diketones

Three procedures have been proposed for the synthesis of polyene diketones. The first is based on the oxidation of secondary glycols, using activated manganese dioxide[15]. For example, the oxidation of the secondary glycol (XXXVI) gives the diketone (XXXVII) in 91% yield (when aluminium t-butoxide was used, the yield fell to 5%):



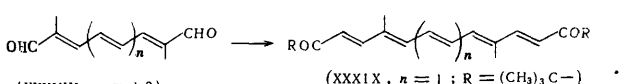
(XXXVI) (XXXVII)

Secondary glycols are also converted into diketones by a reaction involving the initial conversion into bromides (with isomerisation), this being followed by oxidation with 2-nitropropane in an alkaline medium[11]:



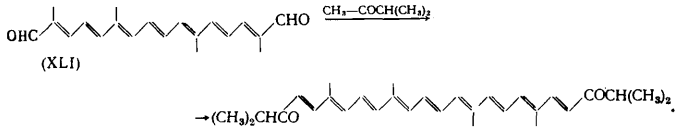
The oxidative method for the synthesis of diketones suffers from the same disadvantages as the oxidative method for the synthesis of dialdehydes (see above) and its scope is also restricted by the availability of the initial glycols.

The second method for the synthesis of polyene diketones is based on the Claisen condensation[40-43] in the presence of aluminium t-butoxide[14,41,42], an alcoholic solution of potassium hydroxide[43], and piperidine or piperidinium acetate[44-47]. In most cases this procedure leads to fairly high yields of diketones. Thus the condensation of 2,7-dimethylocta-2,4,6-triene-1,8-dial (XXXVIII, n = 1) with pinacoline in the presence of aluminium t-butoxide gives the diketone (XXXIV, n = 1) in 35% yield. Under the same conditions hexaene diketones (XI, n = 2) were obtained in yields of 40–50% from the dialdehyde (XXXVIII, n = 2) and acetone or pinacoline[41,42]:



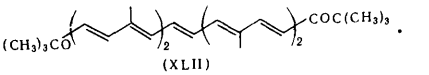
(XXXVIII, n = 1,2) (XXXIX, n = 1; R = $(CH_3)_3C-$)
(XL, n = 2; R = CH_3, $(CH_3)_3C-$)

The condensation of isopropyl methyl ketone with crocetin dialdehyde (XLI) in the presence of alcoholic potassium hydroxide at room temperature also takes place with high yields (70–80%)[43]:



(XLI)

However, the condensation of the dialdehyde (XXXVIII, n = 1) with tiglylidenepinacolone gave the diketone (XLII) in a yield of only 1–2%:[42]



(XLII)

The Claisen condensation was also used in the synthesis of the natural polyene diketone canthaxanthin[42], the results also being satisfactory.

Since at the present time polyene dialdehydes are readily available, the above method for the synthesis of polyene diketones is undoubtedly convenient and simple.

Finally the third method for the synthesis of polyene diketones consists in the Wittig reaction between acylmethylenetriphenylphosphoranes and polyene dialdehydes[48]:

$$OHC(CH{=}CH)_nCHO+2(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCOR\rightarrow RCO(CH{=}CH)_{n+2}COR$$

(XLIII) n=2, 3, 4; R=CH_3, C_6H_5
n=2, 3, 4

The reaction takes place readily on heating acetylmethylenetriphenylphosphorane or benzoylmethylenetriphenylphosphorane with dialdehydes (XLIII) in benzene or toluene. The yields of polyene diketones reach 60–68%. The polyenes thus obtained are entirely in the *trans*-configuration. When the initial aldehydes are available, both the Wittig reaction and the Claisen condensation can be successfully used for the synthesis of polyene diketones.

We may conclude that at the present time polyene diketones are also fully accessible.

Dicarboxylic Acids and Their Esters

A number of synthetic procedures have been proposed for polyenedicarboxylic acids. The first, oldest method is based on the condensation of monocarboxylic acid esters with diethyl oxalate in the presence of alkaline reagents[49-51]:

$$C_2H_5OOCCOOC_2H_5+CH_3(CH{=}CH)_mCOOC_2H_5\rightarrow C_2H_5OOCCOCH_2(CH{=}CH)_mCOOC_2H_5\rightarrow$$
(XLIV) (XLV)
$$\rightarrow C_2H_5OOCC(OCOCH_3){=}CH(CH{=}CH)_mCOOC_2H_5\rightarrow$$
(XLVI)
$$\rightarrow C_2H_5OOCCH(OCOCH_3)(CH{=}CH)_mCH_2COOC_2H_5\rightarrow HOOC(CH{=}CH)_nCOOH$$
(XLVII) (XLVIII)

The condensation of the polyene ester (XLIV) with diethyl oxalate into the keto-diester (XLV) takes place in yields of 65–70% with the lower members of the series (XLIV, n = 1, 2), but with higher members (n = 4–6) the yields fall to 10–27%. The acetylation of the keto-diester (XLV) with acetic anhydride to give the compound (XLVI) takes place smoothly as a rule, but the reduction of the compound (XLVI) with aluminium amalgam or zinc dust in a mixture of pyridine and acetic acid is sometimes not smooth, for example in the case of compound (XLVI, n = 6), and is accompanied by hydrogenolysis with formation of the diester of dihydrodescrocetin[51]. Finally treatment of the compound (XLVII) with a solution of alkali gives the polyenedicarboxylic acid (XLVIII) containing one double bond more than the initial monocarboxylic acid ester (XLIV). The dicarboxylic acids (XLVIII, n = 3, 4, 5, 7) were obtained by this method. The main disadvantage of the method is the large number of stages. Furthermore, the method is not general — the attempts to extend it to the synthesis of branched higher polyene acids (crocetin, bixin) were unsuccessful.

The second method for the synthesis of polyenedicarboxylic acids consists in the oxidative dimerisation of acetylenemonocarboxylic acids with subsequent alkaline isomerisation of the resulting diacetylenedicarboxylic acids into polyenedicarboxylic acids[52,53]. The first complete synthesis of corticrocin (XLVIII, $n = 6$) was achieved by this method. For this purpose, the diacetylenedicarboxylic acid (L) was obtained by the oxidative coupling of hept-2-en-6-ynoic acid (XLIX), the salt of corticrocin being obtained by boiling the acid (L) with an aqueous solution of potassium hydroxide:

$$\underset{\text{(XLIX)}}{HC{\equiv}CCH_2CH_2CH{=}CHCOOH} \rightarrow \underset{\text{(L)}}{HOOCCH{=}CHCH_2CH_2(C{\equiv}C)_2CH_2CH_2CH{=}CHCOOH} \rightarrow \underset{\text{(XLVIII, } n = 6)}{\rightarrow}$$

This comparatively simple procedure gives, however, very low yields of the final product, mainly due to the stage involving the isomerisation of diacetylene. Furthermore, the initial polyenynoic acids are also usually not readily accessible.

A more convenient modification is the direct dimerisation of the enynoic acids or their esters with subsequent selective hydrogenation of the resulting acetylenedicarboxylic acids or their esters[14,25]. For example:

$$HC{\equiv}C(CH{=}CH)_nCOOC_2H_5 \rightarrow C_2H_5OOC(CH{=}CH)_n(C{\equiv}C)_2(CH{=}CH)_nCOOC_2H_5 \rightarrow$$
$$\underset{\text{(LI)}}{\rightarrow} C_2H_5OOC(CH{=}CH)_n\underset{\text{(LII)}}{(CH{=}CH)_2}(CH{=}CH)_nCOOC_2H_5 \rightarrow \underset{\text{(LIII)}}{C_2H_5OOC(CH{=}CH_2)_{n+2}COOC_2H_5}.$$

Polyenedicarboxylic acids with central *cis*-bonds can be obtained by this procedure. The diethyl esters of 4,6-*cis*-*cis*-deca-2,4,6,8-tetraene-1,10-dioic acid (LIII, $n = 1$) and 6,8-*cis*-*cis*-corticrocin (LIII, $n = 2$) were obtained in this way.

It is noteworthy that on hydrogenation of compound (LI, $n = 2$) in the dark at a weight ratio substance : catalyst = 0.5, the *cis*-*cis*-isomer (LII, $n = 2$) forms, while at a weight ratio substance : catalyst = 1.5 the product is the diethyl ester of *cis*-*cis*-corticrocin, which is also produced by the isomerisation of (LII, $n = 2$).[25] The use of this modification leads to high yields of the final products, but its application is restricted by the availability of the initial enyne esters.

Yet another modification of the synthetic procedure has been proposed for the preparation of polyenedicarboxylic acids[54]. Thus dimersiation of pent-2-en-4-ynol yields the primary glycol (LIV), which is converted into the dibromide (LV) under the action of phosphorus tribromide. On treatment under copper cyanide, the latter yields the dinitrile (LVI). Hydrolysis of compound (LVI) with a solution of hydrogen chloride in methanol yields the dimethyl ester (LVII), which is converted by alkaline isomerisation into the dimethyl ester of dodeca-2,4,8,10-tetraen-6-yne-1,2-dionic acid (LVIII). When the compound (LVIII) is hydrogenated in the presence of Lindlar's catalyst and isomerised, the dimethyl ester of dodeca-2,4,6,8,10-pentaenedioic acid (LIX), fully in the *trans*-configuration, is obtained:

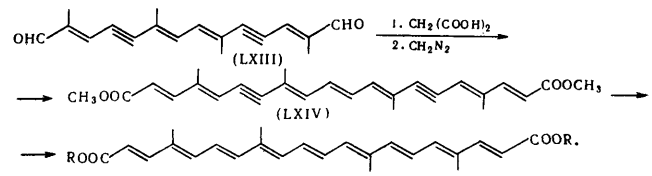
$$\rightarrow \underset{\text{(LVI)}}{\overset{\text{(LIV)}}{NCCH_2CH{=}CH(C{\equiv}C)_2CH{=}CHCH_2CN}} \rightarrow \underset{\text{(LVII)}}{\overset{\text{(LV)}}{CH_3OOCCH_2CH{=}CH(C{\equiv}C)_2CH{=}CHCH_2COOCH_3}} \rightarrow$$
$$\rightarrow \underset{\text{(LVIII)}}{CH_3OOC(CH{=}CH)_2C{\equiv}C(CH{=}CH)_2COOCH_3} \rightarrow \underset{\text{(LIX)}}{CH_3OOC(CH{=}CH)_3CO}.$$

All the stages of the synthesis take place with fairly high yields, but, as a whole, the synthesis is inconvenient in view of the large number of stages and the limited availability of the initial compound.

In a procedure similar to that described above[54] the ester of the tetracarboxylic acid (LX), obtained by the reaction of the dibromide (LV) with the potassiomalonic ester, is hydrolysed and decarboxylated to the dicarboxylic acid (LXI) and the latter is isomerised to give corticrocin (XLVIII, $n = 6$). This modification suffers from the disadvantage characteristic of the synthesis involving the dinitrile formation stage (see above) and in addition it is inconvenient because in the last two stages the yields of products are low:

$$\text{(LV)} + KHC(COOC_4H_9\text{-}t)_2 \rightarrow$$
$$\rightarrow \underset{\text{(LX)}}{(t\text{-}C_4H_9OOC)_2CHCH_2CH{=}CH(C{\equiv}C)_2CH{=}CHCH_2CH(COOC_4H_9\text{-}t)_2} \rightarrow$$
$$\rightarrow \underset{\text{(LXI)}}{HOOCCH_2CH_2CH{=}CH(C{\equiv}C)_2CH{=}CHCH_2CH_2COOH} \rightarrow \text{(XLVIII, } n = 6).$$

The third method of synthesising polyenecarboxylic acids is based on the Doebner reaction applied to polyene and polyenyne dialdehydes[14,41,42,54]. The first complete synthesis of bixin (LXII) was achieved in this way[14]:

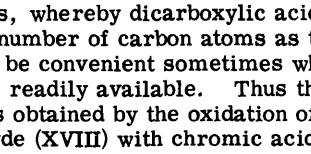


For this purpose, the enyne dialdehyde (LXIII) is condensed with malonic acid by heating in pyridine in the presence of piperidine, the resulting acid is esterified with diazomethane, the dimethyl ester of 6,7,14,15-bisdehydrobixin (LXIV) being obtained in 20% yield (in two stages); its hydrogenation in the presence of Lindlar's catalyst gave the dimethyl ester of *trans*-bixin (LXII), probably via the intermediate *cis*-forms.

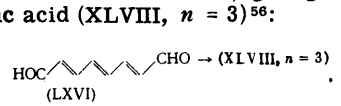
2,2′-bisnorcrocetin was obtained similarly by the condensation of 2,7-dimethylocta-2,4,6-triene-1,8-dial with ethylidenemalonic acid in the presence of trimethylbenzylamine oxide at room temperature[41]. However, attempts to condense 2,9-dimethyldeca-2,8-diene-4,6-diyne-1,10-dial with malonic acid were unsuccessful[54].

The Doebner reaction can probably be sometimes successfully employed in the synthesis of polyenedicarboxylic acids, because at the present time the corresponding dialdehydes are readily available.

The fourth synthetic procedure for polyenedicarboxylic acids consists in the oxidation of the corresponding glycols and dialdehydes, whereby dicarboxylic acids are obtained with the same number of carbon atoms as the initial compound. It can be convenient sometimes when the initial compounds are readily available. Thus the dicarboxylic acid (LXV) was obtained by the oxidation of the glycol (XIV) or the dialdehyde (XVIII) with chromic acid mixture in yields of 30% and 95% respectively[10]. It is interesting that the dialdehyde (XVIII) is not oxidised by silver oxide:

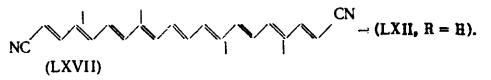


On the other hand, octa-2,4,6-triene-1,8-dial (LXVI) is smoothly oxidised with silver oxide, giving an 88% yield of the dicarboxylic acid (XLVIII, $n = 3$)[56]:



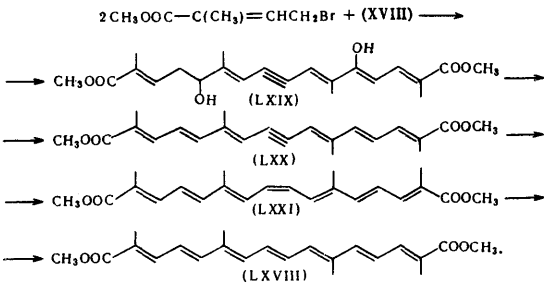
→ (XLVIII, $n = 3$)

The fifth method of synthesis of polyenedicarboxylic acids consists in the hydrolysis of dinitriles. It also yields polyenedicarboxylic acids with the same number of carbon atoms and can find limited application when the dinitriles are available. Thus norbixin (LXII, R = H), with a fully *trans*-configuration, was obtained on cautious hydrolysis of the dinitrile (LXVII)[55]:



→ (LXII, R = H).

The sixth method is based on the Reformatsky reaction between polyene and polyenyne dialdehydes and bromo--acid esters. The syntheses of the dimethyl ester of crocetin (LXVIII) and methyl bixin (LXII) were achieved in this way[7,8,13]. For example, the acetylenic dialdehyde (XVIII) is made to undergo the Reformatsky reaction with methyl γ-bromotiglate in tetrahydrofuran under carefully selected conditions, the glycol (LXIX) being obtained in high yield. Dehydration of the glycol (LXIX) with *p*-toluenesulphonic acid gives the dimethyl ester of 8,8′-dehydrocrocetin (LXX). On hydrogenating the compound (LXX) and then isomerising the dimethyl ester of 8,8′-*cis*--crocetin (LXXI) by irradiation with ultraviolet light in the presence of iodine, the dimethyl crocetin ester (LXVIII), fully in the *trans*-configuration, is obtained:

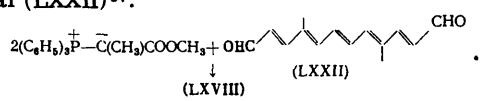


A bottleneck in the application of the Reformatsky reaction to the synthesis of polyenedicarboxylic acids is the stage involving the dehydration of the resulting hydroxy--esters, in which the yields are frequently very low [for example, the dehydration of compound (LXIX) gave compound (LXX) in a yield of only 1%].

The seventh method of synthesis of polyene dicarboxylic acids is based on the Wittig reaction between polyene or polyenyne dialdehydes and alkoxycarbonylmethylenediphenylphosphoranes or the diethyl esters of alkoxycarbonylmethylphosphonic acids, or their derivatives. Isler[57] was the first to apply the Wittig reaction in the synthesis of isoprenoidpolyenedicarboxylic acids. Thus a number of norbixin esters (LXII) were obtained in high yields (75–85%) on boiling a benzene solution of crocetin dialdehyde (XLI) with alkoxycarbonylmethylenetriphenylphosphoranes:

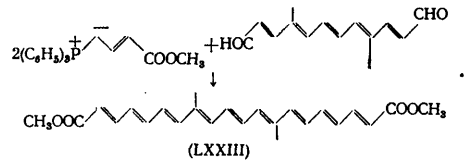


The use of α-alkoxycarbonylethylidenetriphenylphosphoranes permits the introduction not only of the alkoxycarbonylmethylene group but also of a methyl side-group. The dimethyl ester of crocetin (LXVIII) was thus obtained in 80–95% yield from α-methoxycarbonylethylidenetriphenylphosphorane and 4,9-dimethyldodeca-2,4,6,8,10-pentaene--1,12-dial (LXXII)[57]:



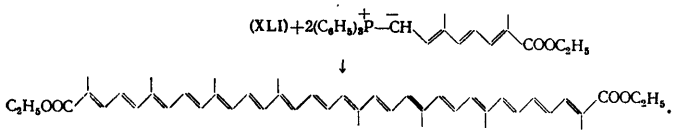
The esters of 8,8′-dehydrocrocetin and 10,10′-dehydronorbixin were obtained similarly[58].

Phosphoranes obtained from unsaturated ω-halogeno--acids can also be used in the synthesis of polyenedicarboxylic acids. For example, it has been proposed that the dimethyl ester of crocetin (LXVIII), the dimethyl ester of norbixin (LXII, R = CH_3), and dimethyl ester of 4,4′-desmethylnorbixin (LXXIII) be synthesised by the condensation of the corresponding dialdehydes with phosphoranes obtained from the methyl esters of γ-bromodimethylacrylic, γ-bromocrotonic, and γ-bromotiglic acids[59–62]:

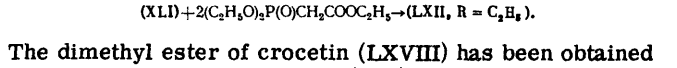


The yields of the final products reach 75–80%.

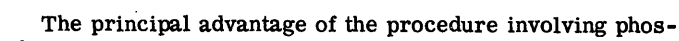
However, the use of the phosphoranes derived from the methyl ester of 4-methyl-6-bromosorbic acid and the ethyl ester of 2,6-dimethyl-8-bromo-octa-2,4,6-trienoic acid[63] results in much lower yields of the final product (of the order of 15%). For example,



A convenient modification of the Wittig reaction has been described in patents[19,64], where it is suggested that phosphonates be used instead of phosphoranes. Thus a solution of the diethyl ester of an ethoxycarbonylmethylphosphonic acid in dimethylformamide is treated with sodium alkoxide and then crocetin dialdehyde (XLI) is introduced into the reaction mixture, which leads to a high yield of the diethyl ester of norbixin (LXII, R = C_2H_5):

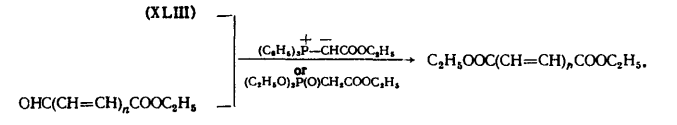


The dimethyl ester of crocetin (LXVIII) has been obtained similarly from the dialdehyde (XIX) and diethyl (3-methoxycarbonylbut-2-en-1-yl)phosphonate:



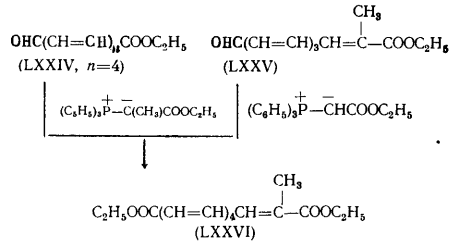
The principal advantage of the procedure involving phosphonate esters consists in the exceptional ease with which the final products are isolated, frequently by simple dilution of the reaction mixture with water, while the compounds formed in the presence of phosphoranes are often difficult to purify from triphenylphosphine oxide.

Both modifications of the Wittig reaction have been used for the synthesis of unbranched polyene acids[25,37,65,66]:



For example the diethyl esters of descrocetin and corticrocin have been synthesised in this way.

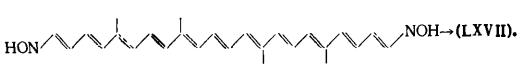
In the reaction of ethoxycarbonylvinylmethylenetriphenylphosphorane with unbranched dialdehydes the yields of the final products are only 9–13%, which is much lower than in the reaction where unbranched isoprenoid dialdehydes or ethoxycarbonylmethylenetriphenylphosphorane are used. However, this is frequently compensated by the fact that more readily available lower polyene dialdehydes serve as the starting materials in the reaction. The use of esters of aldehydo-acids (LXXIV) permits the synthesis of esters of asymmetric dicarboxylic acids[65]. The diethyl ester of 2-methyldodeca-2,4,6,8,10-pentaene-1,12-dioic acid (LXXVI), a degradation product of natural fungichromin, was obtained by the reaction of the aldehyde (LXXIV, n = 4) with α-ethoxycarbonylethylidenetriphenylphosphorane or the aldehyde (LXXV) with ethoxycarbonylmethylenetriphenylphosphorane:



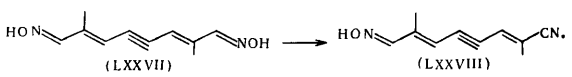
The study of the stereochemistry of the Wittig reaction with unbranched aldehydes and esters of aldehydo-acids[38,65,66] showed that in all cases the reaction is stereospecific, the *trans*-isomers of the polyenedicarboxylic acid esters being formed exclusively. On the basis of the analysis of the above data, one may conclude that the synthesis based on the use of phosphonates is the most convenient because of the ease with which it can be carried out, the ease of isolating the final products, and because of the high yields of the diesters. The application of this synthesis in practice made a wide variety of polyenedicarboxylic acid esters of different structures readily available.

Dinitriles

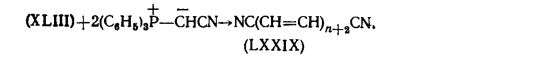
Comparatively recently the dinitriles of polyenedicarboxylic acids were almost unknown. Only the dinitrile of bixin (LXVII), obtained by the dehydration of bixin dialdehyde dioxime with acetic anhydride, was described in the literature[55]:



Recently the same procedure was used to prepare octa-2,4,6-triene-1,8-dinitrile[56] from the dioxime of octa-2,4,6-trienedial. However, this procedure cannot be regarded as sufficiently satisfactory, because the preparation and isolation of the dioximes of unsaturated aldehydes often constitute a very complex problem. Furthermore, the conversion of dioximes into dinitriles is not always possible. Thus dehydration of the dioxime (LXXVII) leads only to the hydroxyimino-nitrile (LXXVIII)[10]:



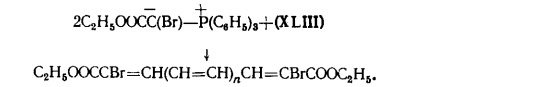
The second method of synthesising dinitriles, based on the Wittig reaction between cyanomethylenetriphenylphosphorane or diethyl cyanomethylphosphonate with polyene dialdehydes, is much more promising[25]. This procedure has been successfully applied in the preparation of a number of polyene-dinitriles (LXXIX):



As in the synthesis of the esters of polyenedicarboxylic acids, the employment of phosphonates greatly facilitates the isolation of the dinitriles from the reaction mixture and their purification. The yields of the dinitriles are quite satisfactory, reaching 50–70%. Thus polyene dinitriles too can now be regarded as fully accessible compounds.

Esters of $\alpha\alpha'$-Dibromopolyene Acids

Earlier these compounds were unknown. The possibility of their synthesis arose when the readily accessible synthetic procedure for dialdehydes had been developed and ethoxycarbonylbromomethylenetriphenylphosphorane began to be used in the Wittig reaction[25]:



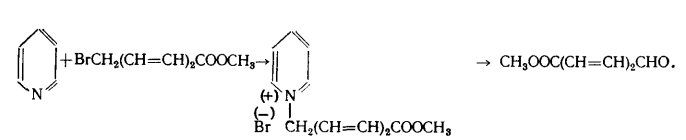
The yields of the final products range from 63 to 90%.

III. SYNTHESIS OF POLYENES WITH DIFFERENT SUBSTITUENTS AT THE ENDS OF THE CHAIN

Until recently polyenes with different substituents at the ends of the chain were relatively unknown and virtually no methods for their synthesis were developed. General methods for the synthesis of acetals of the type $(R'O)_2CH-R-Y$, where Y is a functional group and R a polyene chain, were found only in very recent years, which made it possible to develop general synthetic procedures for polyenes substituted in a wide variety of ways, based on the increase in the length of the polyene chain by condensation with vinyl ethers, with subsequent conversion of the aldehyde group into any other functional group by the Wittig reaction or other reactions. Thus polyene series with various substituents at the ends of the chain, which were formerly difficult to obtain or altogether unknown, became available.

Esters of Aldo-Acids and Their Acetals

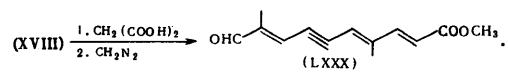
The synthesis of the lowest member of the series of polyene aldo-acids was achieved as follows[67]:



However, this method of synthesis was not extended to higher members of the series.

The ester of the aldo-acid (LXXX) was obtained in 10% yield by the Doebner condensation of the dialdehyde (XVIII)

with malonic acid and subsequent esterification with diazomethane:



New synthetic procedures for aldo-acid esters (LXXXI) became available when the reaction involving an increase in the chain length of the acetals of aldo-acids by condensation with vinyl ethers was proposed[65,68,69]:

$$(RO)_2CH(CH{=}CH)_nCOOC_2H_5+CH_2{=}CHOC_2H_5\rightarrow$$
$$\rightarrow(RO)_2CHCH_2CH(OC_2H_5)(CH{=}CH)_nCOOC_2H_5\rightarrow OHC(CH{=}CH)_{n+1}COOC_2H_5.$$
(LXXXI; n=1–4)

A similar reaction was used to prepare the ethyl ester of 5-formyl-2-methylhexa-2,6-dienoic acid[68,69] and for the synthesis of asymmetrically substituted polyene aldo-acids[65]:

$$(RO)_2CH(CH{=}CH)_nCH{=}C(CH_3)COOC_2H_5+CH_2{=}CHOC_2H_5\rightarrow$$
$$\rightarrow(RO)_2CHCH_2CH(OR)(CH{=}CH)_nCH{=}C(CH_3)COOC_2H_5\rightarrow OHC(CH{=}CH)_{n+1}CH{=}C(CH_3)-.$$
$$-COOC_2H_5 \quad (n=1-3)$$

These modifications of the synthesis were quite realistic and easy to carry out, because a simple method had been developed for the preparation of the initial acetals of aldo-acids by the Wittig reaction between readily available monoacetals of glyoxal and but-2-ene-1,4-dial (fumaric dialdehyde) and ethoxycarbonylmethylenetriphenylphosphorane (or better the diethyl ester of ethoxycarbonylmethylphosphonic acid)[65,70,71]:

$$(C_2H_5O)_2CH(CH{=}CH)_nCHO\rightarrow(C_2H_5O)_2CH(CH{=}CH)_nCH{=}C(R)COOC_2H_5.$$
(n=0, 1, 2) (n=0, 1, 2; R=H, CH_3)

Acetals of symmetrical and asymmetric aldo-acids were thus obtained in high (up to 70%) yields; these acids could also be hydrolysed to the corresponding aldehydes in the presence of phosphoric acid.

An unusual method for the synthesis of the ethyl ester of 10-formyldeca-2,4,6,8-tetraenoic acid (LXXXI, n = 3), based on the reaction of octa-2,4,6-triene-1,8-dial (XLIII, n = 3) with an equimolar amount of ethoxycarbonylmethylenetriphenylphosphorane in benzene solution, which involves preferentially one of the aldehyde groups, was proposed quite recently by Kovalev et al.[72] This method is particularly promising for the synthesis of higher asymmetrically substituted polyenes, because the dialdehyde (XLIII, n = 3) is very readily available, and the acetal can be smoothly obtained from the ester of the aldo-acid (XXXI, n = 3).

The development of a general method of synthesis of monoacetals of dialdehydes and esters of aldo-acids has opened up wide possibilities for the synthesis of other polyenes substituted with various functional groups.

Aldo-Nitriles and Their Acetals

The starting material for the synthesis of a number of polyene aldo-nitriles and their acetals has been the monoacetal of fumaric dialdehyde, the reaction of which with the diethyl ester of cyanomethylphosphonic acid gave a 70% yield (with cyanomethylenetriphenylphosphorane the yield was much lower) of the acetal of 5-cyanopenta-2,4-dien-1-al (LXXXII) as a mixture of *cis-trans*-isomers (in this case the Wittig reaction is not stereospecific)[25,73]. The increase in the chain length of the compound (LXXXII) in the usual way using ethyl vinyl ether with subsequent hydrolysis of the ether-acetal (LXXXIII) and the simultaneous removal of the methoxy-group led, however, to 7-cyanohepta-2,4,6-trien-1-al (LXXXIV, n = 3), which was fully in the *trans*-configuration as a result of isomerisation during the chain growth process and hydrolysis. It is noteworthy that the hydrolysis of the mixture of the *cis-trans*-isomers of compound (LXXXII) also gave a product which was fully in the *trans*-configuration:

$$(CH_3O)_2CHCH{=}CHCHO\rightarrow NC(CH{=}CH)_2CH(OCH_3)_2\rightarrow$$
(LXXXII)
$$\rightarrow NC(CH{=}CH)_2CH(OCH_3)CH_2CH(OCH_3)(OC_2H_5)\rightarrow NC(CH{=}CH)_nCHO.$$
(LXXXIII) (LXXXIV, n=3)

Compound (LXXXIV, n = 4) was obtained by the reaction of the octatrienedial (XLIII, n = 3) with an equimolar amount of cyanomethylenetriphenylphosphorane[72]. A general method was thus developed and aldo-nitriles and their acetals have become readily accessible.

Aldo-Ketones and Their Acetals

The method of synthesis of the acetals of aldo-ketones was outlined using as an example the reaction of the monoacetal of fumaric dialdehyde with acetylmethylenetriphenylphosphorane, where the dimethyl acetal of 6-formylhexa-3,5-dien-2-one (LXXXV) was obtained in high yield[25]:

$$(CH_3O)_2CHCH{=}CHCHO+(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCOCH_3\rightarrow(CH_3O)_2CH(CH{=}CH)_2COCH_3.$$
(LXXXV)

The reaction of equimolar amounts of the octatrienedial (XLIII, n = 3) with acetylmethylenetriphenylphosphorane was used for the preparation of 10-formyldeca-3,5,7,9-tetraen-2-one[72]:

$$(XLIII,\ n=3)+(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCOCH_3\rightarrow OHC(CH{=}CH)_4COCH_3.$$

Esters of Keto-Acids

The hydration of hepta-2,4-dien-6-ynoic acid by heating with dilute sulphuric acid in the presence of mercury sulphate[52] leads to 6-oxohepta-2,4-dienoic acid:

$$HC{\equiv}CCH{=}CHCH{=}CHCOOH\rightarrow CH_3CO(CH{=}CH)_2COOH.$$

When the starting compounds are available, this method can be used in principle for the synthesis of keto-acids. When aldo-esters are available, the synthesis of esters of polyene keto-acids by the reaction between acetylmethylenetriphenylphosphorane and aldo-esters becomes of general importance. The ethyl esters of the keto-acids (LXXXVI) were obtained in this way[25,72]:

$$C_2H_5OOC(CH{=}CH)_nCHO+(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCOCH_3\rightarrow C_2H_5OOC(CH{=}CH)_3COCH_3.$$
(LXXXVI)

Esters of Cyano-Acids

The general method for the synthesis of esters of cyano-acids (LXXXVII) is based on the reaction of cyanomethylenetriphenylphosphorane or diethyl cyanomethylphosphonate with esters of aldo-acids (LXXXI)[25,72,73]:

$$(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCN+(LXXXI)\rightarrow NC(CH{=}CH)_nCOOC_2H_5.$$
(LXXXVII)

In addition, esters of cyano-acids have been obtained in high yields by the reaction of aldo-nitriles (LXXXIV) with diethyl esters of ethoxycarbonylmethylphosphonic acid (or the corresponding phosphorane)[72,73]:

$$(\text{LXXXIV}) + (C_2H_5O)_2P(O)CH_2COOC_2H_5 \rightarrow (\text{LXXXVII}).$$

The compounds formed are fully in the *trans*-configuration.

Esters of Nitro-Acids

The general method for the synthesis of these esters[74] is based on the condensation of aldo-acid esters with nitromethane followed by the dehydration of the hydroxynitro-compounds (LXXXVIII) formed:

$$\underset{(n=0-3)}{C_2H_5OOC(CH{=}CH)_nCHO} + CH_3NO_2 \rightarrow \underset{(\text{LXXXVIII})}{C_2H_5OOC(CH{=}CH)_nCH(OH)CH_2NO_2} \rightarrow C_2H_5OOC(CH{=}CH)_{n+1}NO_2.$$
$$(\text{LXXXIX})$$

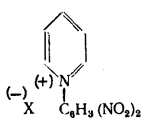
To achieve the dehydration, the hydroxynitro-compounds (LXXXVIII, n = 0–2) are converted into halogenonitro-derivatives, which can be dehydrohalogenated by treatment with sodium acetate, without isolation. In the synthesis of the ethyl ester of ω-nitronona-2,4,6,8-tetraenoic acid (LXXXIX, n = 3) it is best to carry out the dehydration directly by passing the compound down an alumina column. The yields of the nitro-acid esters are satisfactory. The nitro-esters (LXXXIX, n = 1–3) of the *trans*-series, which were formerly unknown, were obtained in this way.

Amino-Aldehydes

A general method for the synthesis of ω-dimethylamino-polyenals (XC) and ω-*N*-methyl-*N*-phenylpolyenals (XCI) with fairly high yields (50–70%) has been described[75-77]:

$$\underset{(\text{XCII})}{[RR'N(CH{=}CH)_nCH{=}NRR']X} \xrightarrow{OH^-} \underset{\substack{(\text{XC}, R=R'=CH_3)\\(\text{XCI}, R=CH_3;\ R'=C_6H_5)}}{RR'N(CH{=}CH)_nCHO}.$$

However, a general procedure for the synthesis of compounds (XCII) has not been developed. Thus compound (XCII, n = 2) is most conveniently obtained by the reaction of secondary amines with an alcoholic solution of 1-(2′,4′-dinitrophenyl)pyridinium halide at 60–70°:[76,77]



$$\xrightarrow{RR'NH} (\text{XCII}, n = 2).$$

Compound (XCII, n = 3) can be obtained by the reaction[75]:

$$\underset{(n=2)}{(\text{XC}) \text{ or } (\text{XCI})} \xrightarrow[H^+]{HC{\equiv}CMgBr} HC{\equiv}C(CH{=}CH)_2CHO \xrightarrow[RR'NH\cdot HClO_4]{RR'NH} (\text{XCII}, n = 3, X = HClO_4).$$

For this purpose, the amino-aldehyde (XC, n = 2) or (XCI, n = 2) is allowed to react with ethynylmagnesium bromide, after which the product is hydrolysed with sulphuric acid. The resulting hepta-2,4-dien-6-ynal is treated with a mixture of dimethylamine and dimethylammonium perchlorate or of *N*-methylaniline and *N*-methylanilinium perchlorate, compounds (XCII, R = R′ = CH, n = 3) (yield 38%) or (XCII, R = CH_3, R′ = C_6H_5, n = 3) (yield 93%) being obtained.

Finally the following synthetic procedure has been developed for compounds of the series (XCII, n = 4–6, X = $HClO_4$)[75]:

$$\underset{(n=2-4)}{(\text{XCI})} \xrightarrow[2.\ H^+]{1.\ CH_3OCH{=}CHC{\equiv}CMgBr} \underset{(\text{XCIII})}{CH_3OCH{=}CHC{\equiv}C(CH{=}CH)_nCHO} \xrightarrow{H_2} \underset{(\text{XCIV})}{CH_3O(CH{=}CH)_{n+2}CHO} \xrightarrow[RR'NH\cdot HClO_4]{RR'NH} (\text{XCII}, n = 4-6, X = HClO_4).$$

The amino-aldehydes (XCI, n = 2–4) are condensed with 1-methoxybut-2-en-4-ynylmagnesium bromide, the product is hydrolysed with a solution of tartaric acid, and the resulting enyne methoxy-aldehydes (XCIII) are hydrogenated in the presence of Lindlar's catalyst. Treatment of the unstable polyene methoxy-aldehydes (XCIV) with secondary amines and the corresponding perchlorates yields the required compound (XCII). The above reaction constitutes at the present time the only way of synthesising compounds of this type. Despite the satisfactory yields at all stages, this procedure is inconvenient because of the large number of stages involved.

Amino-Acid Esters

The Wittig reaction between amino-aldehydes and diethyl ethoxycarbonylmethylphosphonates has been proposed for the synthesis of amino-acid esters[73]. For example:

$$(\text{XCI}, n = 2) + (C_2H_5O)_2P(O)CH_2COOC_2H_5 \rightarrow RR'N(CH{=}CH)_3COOC_2H_5,$$

where the yield is 40% for R = R′ = CH_3 and 70% for R = CH_3 and R′ = C_6H_5. Isomers which are fully in the *trans*-configuration are formed.

Hydroxy-Aldehydes

The hydroxy-aldehydes of the polyene series are the enol forms of dialdehydes of the type of glutaconic aldehyde and are known in the form of salts and benzoates (XCV). The sodium salts of hydroxy-aldehydes (XCVI, n = 1–3) are formed on heating dimethylaminopolyenals (XC) with aqueous methanolic sodium hydroxide solution[75]:

$$(\text{XC}) \rightarrow \underset{(\text{XCVI})}{NaO(CH{=}CH)_nCHO}.$$

The salts (XCVI, n = 1, 2) are formed in 90–95% yields, while the yield of the salt (XCVI, n = 3) is low. The dimethylaminopolyenal (XC, n = 4) does not hydrolyse under these conditions at all. Although the compounds (XC, n = 3, 4) are capable of undergoing hydrolysis on heating with a solution of potassium hydroxide in a mixture of water and 1-methylpyrrolidone, the compounds (XC, n = 5, 6) are no longer hydrolysed under these conditions. The change in the reactivity of dimethylaminopolyenals (XC) with increase in the number of double bonds can be explained by the weakening of the electronic effect (+M-effect) of the dimethylamino-group of the aldehyde group with increasing chain length:

$$\underset{(\text{XC})}{(CH_3)_2\ddot{N}{-}(CH{=}CH)_n{-}CH{=}O}.$$

The benzoates (XCV) are formed when benzoyl chloride is allowed to react with pyridine solutions of potassium salts of hydroxy-aldehydes[75]:

$$\underset{(n=2,3,4)}{KO(CH{=}CH)_nCHO} + C_6H_5COCl \rightarrow \underset{(\text{XCV})}{C_6H_5COO(CH{=}CH)_nCHO}.$$

ωω-Dichloro-Aldehydes

A number of unbranched ωω-dichloropolyenals (XCVII) have been described[78,79]. In their synthesis the readily available ωω-dichloroacrolein is converted into an acetal which is then allowed to react with ethyl vinyl ether, according to the general procedure for the synthesis of polyenals:

$$Cl_2C{=}CHCH(OC_2H_5)_2 \xrightarrow{CH_2{=}CHOC_2H_5} Cl_2C{=}CHCH(OC_2H_5)CH_2CH(OC_2H_5)_2 \xrightarrow{H^+} \rightarrow Cl_2C{=}CHCH{=}CHCHO \xrightarrow{HC(OC_2H_5)_3} Cl_2C{=}CHCH{=}CHCH(OC_2H_5)_2 \rightarrow \rightarrow Cl_2C{=}CH(CH{=}CH)_nCHO.$$

(XCVII)

The chain growth reaction is performed in the presence of zinc chloride and boron trifluoride-ether and the hydrolysis is carried out by heating with a 15% solution of sodium acetate in 85% acetic acid: ωω-dichloropolyenals (XCVII, n = 1–4) are obtained in a yield of 70–90%.

ωω-Dichloro-Alcohols

A series of ωω-dichloropolyene alcohols (XCVIII) have been obtained[79] by the reduction of ωω-dichloropolyenals (XCVII) with lithium aluminium hydride (yield 40–50%):

$$(XCVII) \rightarrow Cl_2C{=}CH(CH{=}CH)_nCH_2OH.$$
$$(XCVII),\ n = 1{-}4)$$

ωω-Dichloro-Acids

ωω-Dichloropolyene acids (XCIX) have been obtained by the oxidation of ωω-dichloropolyenals (XCVII) with silver oxide[78], the yield being 30–37%:

$$(XCVII) \rightarrow Cl_2C{=}CH(CH{=}CH)_nCOOH.$$
$$(XCIX)$$

In addition, another method has been proposed for the synthesis of these acids[73]. In this procedure ωω-dichloropolyenals (XCVII) are converted into esters of ωω-dichloro--acids (C) by reaction with the diethyl ester of ethoxycarbonylmethylphosphonic acid and then compound (C) is subjected to alkaline hydrolysis, which results in a high yield of ωω-dichloro-acids (XCIX) containing one double bond more than the initial ωω-dichloropolyenals (XCVII):

$$(XCVII) + (C_2H_5O)_2P(O)CH_2COOC_2H_5 \rightarrow \underset{(C)}{Cl_2C{=}CH(CH{=}CH)_{n+1}COOC_2H_5} \rightarrow (XCIX).$$

It is quite evident from the data presented above that a wide variety of polyenes with different substituents at the ends of the chain have now become accessible.

IV. SOME PROPERTIES OF POLYENES

Those properties of substituted polyenes with different functional groups which have been investigated to elucidate the effect on them of the length of the polyene chain or the effect on the properties of the functional group due to the substituents in the ω-position will be considered in this section. It is noteworthy that in the literature there still persists a quite definite view on this subject, which arose as a result of a comparison of the reactivities of saturated compounds, on the one hand, and of mono-olefins and dienes, on the other. In the first place this view is in conflict with the well known and long established analogy between the behaviour of certain saturated and unsaturated compounds in reactions, which gave rise to the concept of vinylogy — the transfer of the mutual influence of atoms along a system of conjugated double bonds, the concept having now become firmly established in organic chemistry. The principle of vinylogy proved very fruitful and made it possible to explain many facts. However, within the framework of synthetic chemistry the limits of the application of this principle to the series of aliphatic conjugated polyenes have not been investigated and it has been assumed *a priori* that the principle of vinylogy is applicable to all $X(CH{=}CH)_nY$ systems, regardless of the chain length and the structure of the end groups. This hypothesis is still to be found in monographs and text books on theoretical organic chemistry.

Wide acceptance of this view has been favoured both by studies of the properties of $X(CH{=}CH)_nY$ systems, where n = 1 or 2 or X and Y are the conjugated groups (as in cyanine and polymethine dyes), and the results of the first quantum-mechanical calculations, which showed that, when the length of the polyene chain increases, an equalisation of bond orders and hence of the lengths of double and single bonds apparently takes place. However, the use of various methods (the molecular orbital–linear combination of atomic orbitals method, the valence bond method, and the free electron method) in subsequent quantum-mechanical calculations demonstrated unambiguously that in the ground electronic state polyenes are systems with an alternating charge density, the density maxima corresponding to the double bonds in the classical formula.

We shall examine further the results of studies on the transfer of the mutual influence of atoms along the chain.

Polarographic Reduction of Polyenes

The polarographic reduction of the polyenals $CH_3(CH{=}CH)_nCHO$ (n = 1–5)[80–82] in aqueous dioxan buffer solutions has been investigated in the pH range 1–11. The dependence of the half-wave potential and the ratio $id/Cm^{2/3}t^{1/6}$ on the pH of the medium and the number of double bonds has also been studied. The investigators adopted the following mechanism for the reduction at a dropping mercury electrode:

$$CH_3(CH{=}CH)_nCHO + H^+ + e \rightleftarrows CH_3(CH{=}CH)_n\dot{C}HOH \rightarrow \rightarrow CH_3(CH{=}CH)_nCH(OH)CH(OH)(CH{=}CH)_nCH_3.$$

In the range pH 1–11 one distinct polarographic wave was observed and, over a narrower pH range, a second wave of the same height as the first occurred at pH values which were lower the greater was the number of double bonds. The ratio $id/Cm^{2/3}t^{1/6}$ for the first and second waves is approximately the same and independent of the pH and the number of double bonds. The half-wave potentials of both waves are displaced towards less negative potentials with increase in the number of double bonds, the increment per double bond becoming smaller as the chain length increases. Thus the difference between the half--wave potentials of crotonic and sorbic aldehydes is 0.23 V, while that between the values for deca-2,4,6,8-tetraenal and dodeca-2,4,6,8,10-pentaenal is only 0.07 eV. The same has also been found for the half-wave potential of the second wave.

Thus accumulation of double bonds facilitates the polarographic reduction of polyenals, but the introduction of each new double bond makes an increasingly smaller contribution to the polarographic behaviour of the molecule. The diffusion coefficient D of polyenals, calculated from the Ilkovič equation, also tends to decrease to a definite limit:

n	1	2	3	4	5
D, 10^6 cm^2 s^{-1}	6.1	5.3	5.1	4.3	4.2.

Dipole Moments of Polyenes

The dipole moments of the dimethylaminopolyenals $(CH_3)_2N(CH{=}CH)_nCHO$ (n = 0–4) in benzene solution have been determined at 25° [83] and the following values (dipole moments μ in Debye units) have been found:

n	0	1	2	3	4
μ	3.86	6.24	7.62	8.24	8.50.

It is evident that the dipole moments increase with chain length, but the difference between the values of μ for adjacent members decreases, i.e. the dipole moment tends to a limit.

On the basis of the data obtained and the calculation of the charge transfer from end to end along the system of conjugated double bonds using various stereochemical models, it was concluded [83] that each end-group has a restricted sphere of action, extending approximately over three double bonds.

Infrared Spectra

Infrared spectroscopy is widely used to characterise substituted polyenes with different functional groups (see, for example, Lapitskii et al. [56]), but few papers dealing with the effect of the number of double bonds or the relative positions of the functional groups on the infrared spectra of polyenes have been published. In 1948 the infrared spectra of the dimethylpolyenes $CH_3(CH{=}CH)_nCH_3$ (n = 2–6), the polyenals $R(CH{=}CH)_nCHO$ (R = CH_3, α-furyl, n = 1–4), and the corresponding azines were investigated in the range 1440–1900 cm^{-1} to elucidate the effect of the accumulation of conjugated double bonds on absorption in the region corresponding to double bond vibrations. On the basis of their data, the investigators concluded that the vibration bands associated with the double bonds are displaced towards lower frequencies with increase in the number of double bonds, the charge per double bond decreasing with the number of such bonds [84].

The infrared spectra of compounds of the type $X(CH{=}CH)_nCOOC_2H_5$ with all the double bonds in the *trans*-configuration, where X = CH_3 (n = 1–4), $COOC_2H_5$ (n = 1–7), CHO (n = 1–4), NO_2 (n = 1–4), and OC_2H_5 (n = 1, 2), were investigated recently [85], special attention being devoted to the problem of the mutual influence of the end-groups via the system of conjugated double bonds. The CO stretching frequencies in the spectra of these compounds are presented in Table 1 as a function of the number of double bonds. Table 1 shows that in the spectra of the compounds investigated the CO stretching frequencies due to the ethoxycarbonyl group approach one another as the length of the polyene chain increases: the maximum differences between the frequencies amount to 24 cm^{-1} for n = 1, 16 cm^{-1} for n = 2, 7 cm^{-1} for n = 3, and only 3 cm^{-1} for n = 4. Hence the authors concluded that the mutual influence of atomic groups in the ground electronic state of the molecule decays rapidly with increase in the length of the intervening chain of conjugated bonds.

TABLE 1. CO vibration frequencies in the compounds $X(CH{=}CH)_nCOOC_2H_5$ (in carbon tetrachloride, values of ν in cm^{-1}).

n	R					
	CH_3	NO_2	CHO		$COOC_2H_5$	OC_2H_5
1	1724	1735	1733	1704	1730	1711
2	1718	1727	1725	1695	1721	1711
3	1714	1721	1718	1688	1715	
4	1715	1717	1716	1688	1714	
5					1713	
6					1713	
7					1714	

It has also been established that the intensity of the infrared absorption bands in the region of 1600 cm^{-1} (vibrations of the polyene chain) is determined mainly by the number of double bonds (increasing with the latter) involved in the vibrations, the relation between the absolute integral intensity of the absorption bands in the region of 1600 cm^{-1} and the number of double bonds being linear. On the basis of the experimental data and a comparison of the experimental and calculated relative intensities of the absorption bands in the region of 1600 cm^{-1}, it was concluded [85] that there is an alternation of charges at carbon atoms along the polyene chain.

Yukhnovski [86], who compared the frequencies and the integral intensities associated with the nitrile group in β-phenyl-substituted trans-α-cyanostilbenes and the corresponding benzonitriles, also concluded that the effect of substituents on the frequency and integral intensity of the band due to the nitrile group in compounds of the type *trans*-$RC_6H_4CH{=}CH(C_6H_5)CN$ weakens with increase in the length of the conjugation chain.

Raman Spectra

The Raman spectra of the diethyl esters of the polyene-$\alpha\omega$-dicarboxylic acids $C_2H_5OOC(CH{=}CH)_nCOOC_2H_5$ (n = 1–8) have been analysed [87]. The frequencies ω of the most intense lines of the Raman spectra of acetone solutions of these compounds are presented in Table 2 (exciting light–the Hg*e* mercury blue line, frequency μ = 22 938 cm^{-1}). The lines with the frequencies ω_1 and ω_2 characterise the vibrations of the polyene chain and the line with the frequency ω_3 characterises the behaviour of the carbonyl group. The spectra of the diesters with n = 6–8 contain overtones, because these absorption bands and the exciting lines occur in the resonance region.

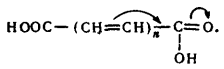
TABLE 2. Principal frequencies (in cm^{-1}) of the Raman spectra of $C_2H_5OOC(CH{=}CH)_nCOOC_2H_5$.

n	ω_1	ω_2	ω_3	n	ω_1	ω_2
1	1210	1664	1733	5	—	1570
2	1135	1644	1726	6	1142	1562
3	1139	1621	1721	7	1140	1550
4	1139	1596	1717	8	1137	1540

Analysis of the vibration frequencies of the polyene diesters led to the conclusion[87] that, in the first place, there is a comparatively small change in the vibration frequencies of the polyene chain as its length increases and examination of compounds in the range from $n = 3$ to $n = 8$ shows that in long chains of conjugated double bonds there is no appreciable "equalisation" of the multiple bonds. In the second place, since with increase in chain length the addition of each new unit has a smaller effect on the frequencies, the mutual influence of the atomic groups becomes weaker as the length of the intervening chain of conjugated double bonds becomes greater.

pK_a Values of Polyenoic Acids

To elucidate the effect of electron-acceptor substituents on the pK_a values of polyenoic acids, the latter were determined for $CH_3(CH=CH)_nCOOH$ and $HOOC(CH=CH)_nCOOH$ ($n = 1-4$).[88] The data obtained are presented in Table 3. The lower pK_a values of dicarboxylic acids compared with the monocarboxylic acids when $n = 1$ and 2 can be explained by the enhanced acidity of the dicarboxylic acid due to the $-M$-effect of the second carbonyl group:



The appreciable increase of the pK_a on going from muconic acid to octa-2,4,6-triene-1,8-dioic acid indicates a weakening of the $-M$-effect, i.e. a rapid decay of the effect of the electron-acceptor carboxy-group on the pK_a.

Ultraviolet Spectra

The relation between the length of the polyene chain and the positions and intensities of the bands in the electronic absorption spectra has attracted the attention of investigators for a long time. The studies in this field were made in 1935 by Hausser and Kuhn[89-92], who investigated the ultraviolet spectra of the polyenals $CH_3(CH=CH)_nCHO$ ($n = 1-3$), the polyenemonocarboxylic acids $CH_3(CH=CH)_nCOOH$ ($n = 1-4$), α-furylpolyenals and α-furylpolyenoic acids ($n = 1-3$), and also the diphenylpolyenes $C_6H_5(CH=CH)_nC_6H_5$ ($n = 1-7$). It was established that (1) the introduction of each new double bond causes a shift of the band towards the visible part of the spectrum and (2) the magnitude of the shift decreases with the number of double bonds.

Subsequently the ultraviolet spectra of polyenes were investigated by a number of workers. Thus one may refer to the work of Blout and Fields[93], who investigated the polyenals $CH_3(CH=CH)_nCHO$ ($n = 1-7$), the dimethylpolyenes $CH(CH=CH)_nCH_3$ ($n = 1-7$), the ω-furylpolyenals ($n = 0-6$), and certain azines. In other investigations dimethylpolyenes[94-96], *NN*-dimethylaminopolyenals[75], ferrocenylpolyenes[97], etc. were studied. All these investigations confirmed the principal conclusions of Hausser and Kuhn. Furthermore, a comparative study of the spectra of ω-dimethylaminopolyenals, the sodium salts of ω-hydroxypolyenals, and $[(CH_3)_2N(CH=CH)_nCH=N(CH_3)_2].HClO_4$ led to the conclusion[75] that the spectra of the linear polyenes $X(CH=CH)_nY$ differ in principle from the spectra of polyene cyanine dyes and from the spectra of polyene molecules with charges at the end of the chain, of the type $\bar{O}(CH=CH)_nCHO$.

TABLE 3. pK_a values for certain polyenoic acids (in 50% aqueous alcohol).

n	$CH_3(CH=CH)_nCOOH$ pK_a	$HOOC(CH=CH)_nCOOH$ pK_{a_1}
1	4.66	2.98
2	4.62	2.70
3	5.37	5.01
4	5.42	5.11

There exist very numerous data on the ultraviolet spectra of isoprenoids with different functional groups, such as vitamin A and carotenoids, because the spectra are widely used to characterise compounds of this kind. However, the presence of methyl side-groups and in many cases the complexity of the end-groups make the interpretation of the optical properties difficult, but several empirical equations relating the position of the absorption bands to the structure of polyenes of this kind have been postulated[98-100]. In this connection we shall examine the studies dealing with unbranched polyenes with different functional groups. Table 4 lists the principal absorption maxima of the unbranched polyenes.

Analysis of the ultraviolet spectra of linear polyenes led to the following conclusions[101].

1. The replacement of the methyl group in a dimethylpolyene by an electron-donor or an electron-acceptor substituent causes a bathochromic shift, which increases in the following sequence of substituents:

$$OC_2H_5 < COOC_2H_5 < CHO \leqslant COCH_3 < NO_2.$$

TABLE 4. Principal absorption maxima of polyenes (solvent – alcohol, other solvents indicated in brackets, literature references indicated in footnotes).

X	Y	n = 1	2	3	4	5	6
		$X(CH=CH)_nX$					
CH_3		—	227[a]	263[b]	307[a]	343[c]	374[a]
CN[a]		—	259[d]	297	330	379	—
$COOC_2H_5$[a]		210	264	303	335	365	391
CHO[a]		225[e] (iso-octane)	269[c]	347	352	388	—
$COOH_3$[a]		226[g]	276[g]	—	351	380.5	406
COC_6H_5[a]		—	—	—	385	415	
		$X(CH=CH)_nY$					
CH_3	$CCOC_2H_5$[a]	206	258	301	334	365	
CH_3	CHO[a]	218	272	315	351	380	
CH_3	$COCH_3$	220[h]	273.5[a]	316[i]	351[i]	—	
CH_3	NO_2[j]	229	309				
CHO	$COOC_2H_5$[a]	208	268	309	341	—	
CHO	CN[a]	—	263	305	—	—	
CHO	$N(CH_3)_2$[k]	287[a]	361.5	421.5	462.5	491.5	
			(methylene chloride)				
$COOC_2H_5$	CN[a]	—	—	299	332	—	
$COOC_2H_5$	$COCH_3$[a]	—	—	310	—	—	
$COOC_2H_5$	NO_2[a]	222	281	327	363	—	
$COOC_2H_5$	OC_2H_5[a]	231	289	—	—	—	
$COOC_2H_5$	$N(CH_3)_2$[l]	—	—	394	—	—	
$COOC_2H_5$	$Cl_2C=CH$[l]	270	302	332	—	—	

[a]Ref. 101; [b]Ref. 93; [c]Ref. 102; [d]Ref. 103; [e]Refs. 104 and 105; [f]Ref. 106; [g]Ref. 107; [h]Ref. 108; [i]Ref. 109; [j]Ref. 110; [k]Ref. 74; [l]Ref. 73.

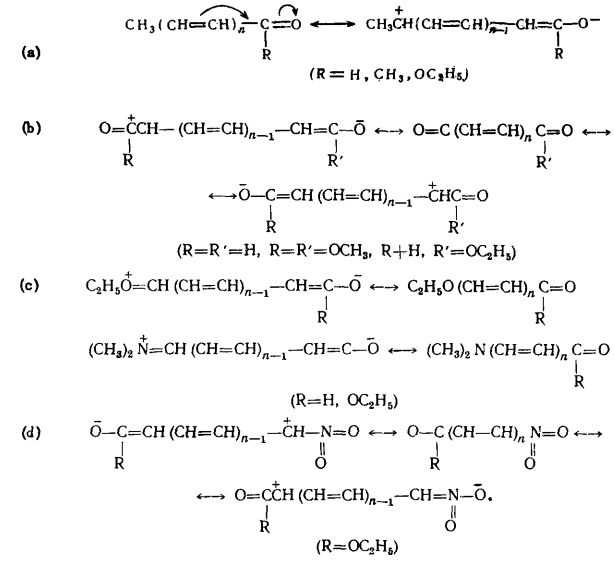
2. The replacement of the methyl group in the series $CH_3(CH=CH)_nR$, where R = CHO or $COOC_2H_5$, by electron-acceptor groups in which one carbon atom is linked by a multiple bond to the atom of another element (CHO, $OCCH_3$, $COOC_2H_5$, CN) gives rise to very slight hypsochromic or bathochromic shifts, whose absolute magnitude does not exceed 10 nm (see also Refs. 111 and 112).

3. The replacement of the methyl group in CH_3. $.(CH=CH)_nCOOC_2H_5$ by the nitro-group results in an appreciable bathochromic shift (30–59 nm).

4. The replacement of the methyl group in the series $CH_3(CH=CH)_nR$, where R = CHO or $COOC_2H_5$, by an electron donor group causes an appreciable bathochromic shift (29–75 nm).

In the last two cases the bathochromic shift increases as the double bonds accumulate.

The observed features were explained by the nature of the polarisation of the molecules in the excited state[101]:



In case (a) the electrons in the molecule in the excited state are displaced in the direction indicated by the arrow and therefore the introduction of the CO group is equivalent to the introduction of yet another double bond. When a second chromophore of the type of CO is introduced into the ω-position in the molecule, simultaneous polarisation of both CO groups is unlikely and therefore the observed displacement of the band is similar to that which occurs on introduction of a single substituent [case (b)]. In case (c) the free electron pair of nitrogen or oxygen participates in conjugation, which makes a considerable contribution to the excited state of the molecule, the mobility of the electrons of the auxochromes and the decrease of the polarisation energy becoming more pronounced as the chain length increases. Finally, as a result of the considerable difference in the polarisation energies of the ethoxycarbonyl and nitro-groups, in case (d) polarisation probably occurs preferentially at the group for which the polarisation energy is smaller, which can alter the principal absorption maximum, compared with the corresponding monosubstituted polyenes.

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UBIQUINONES (COENZYME Q)

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