A T H E S I S

entitled

INVESTIGATIONS ON THE SYNTHESIS OF NATURAL ALLENIC AND ACETYLENIC SYSTEMS

submitted by

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in part fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in the

UNIVERSITY OF OXFORD

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July, 1960.

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A C K N O W L E D G M E N T S

I would like to express my deep and sincere gratitude to Professor E.R.H.Jones, F.R.S., for giving me the opportunity to carry out this work in his laboratories under his guidance, and for his leadership and encouragement.

I wish to thank Dr.M.C.Whiting for his many helpful suggestions, constructive criticism, and above all, for his friendliness.

My thanks are also due to my colleagues for their assistance, so freely given, and for many helpful discussions.

I am grateful to Mrs.I.Croxon and Miss D. Trafford, of the Spectrographic Department, and to all the technicians of the Dyson Perrins Laboratory, for their patience and co-operation.

Finally I wish to acknowledge the award of an I.C.I. Fellowship by the University of Oxford.

J.B. JONES.

A B S T R A C T

(i) Odyssic acid and odyssin were isolated in 1955 by Jones and his collaborators[1] from cultures of the Basidiomycete "B841", and were assigned the structures (IV; R=H) and (V) respectively on the basis of degradative studies.[2] Although work on the synthesis of the two compounds could be justified on the grounds of confirmation of structure alone, other factors were also of importance, e.g. investigation of the antibiotic activity was desired. Owing to the sensitivity of the allene-acetylene system present in odyssin, the following synthetic scheme was devised in which the allene was to be introduced in the final step.

Condensation of ethynylmagnesium bromide with β-carbethoxypropionaldehyde gave a 50% yield of the hydroxy-ester (I; R=H, R′ =Et), which was then hydrolysed quantitatively to the free acid (I; R=R′=H). Attempted coupling of both the free acid (I; R=R′=H) and the protected acid (I; R=2′-tetrahydropyranyl; R′=H), as the bromo-magnesium derivatives, with the bromide (II; X=Br) in the presence of cuprous chloride gave none of the required product (III) even though model work on

hydrocarbons had been successful.

$$HC{\equiv}C.MgBr + OHC.CH_2.CH_2.CO_2Et$$

$$\downarrow$$

$$HC{\equiv}C.CH(OR).CH_2.CH_2.CO_2R'$$

(I)

$$\downarrow \quad \begin{matrix}(1)\ EtMgBr \\ (2)\ CH_3.(C{\equiv}C)_2.CH_2X/\ Cu_2Cl_2\end{matrix}$$

(II)

$$\downarrow$$

$$CH_3.(C{\equiv}C)_2.CH_2.C{\equiv}C.CH(OR).CH_2.CH_2.CO_2H$$

(III)

$$\downarrow B^-$$

$$CH_3.(C{\equiv}C)_2CH{=}C{=}CH.CH(OR).CH_2.CH_2.CO_2H$$

(IV)

$$\downarrow$$

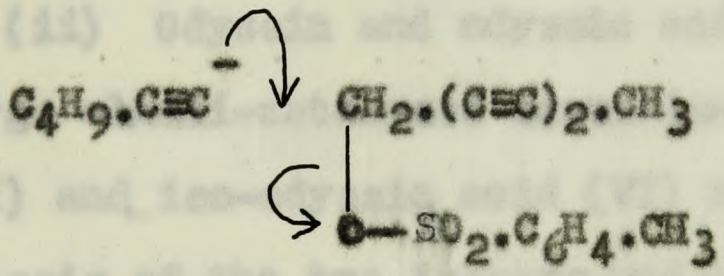
$$CH_3.(C{\equiv}C)_2.CH{=}C{=}CH.CH.CH_2.CH_2.CO$$

$$O$$

(V)

Attention was then focussed on an alternative

preparative route to the $\equiv C.CH_2.C\equiv$ system which incorporated the reaction of an acetylenic Grignard reagent with a βγ-acetylenic sulphonate. As preferential reaction with the halogen anion of the bromo-magnesium destroyed half the sulphonate, model experiments were carried out with halogen free dialkynylmagnesium solutions. Dihex-1-ynylmagnesium and the tosylate (II; X=p-$SO_3.C_6H_4.CH_3$) reacted to the extent of 65%, but the product when isolated had rearranged to a mixture of all the possible isomers, the composition of which is given below.



$C_4H_9.C\equiv C.CH_2.(C\equiv C)_2.CH_3$ (6%)

+

$C_4H_9.CH=C=CH.(C\equiv C)_2.CH_3$ (42%)

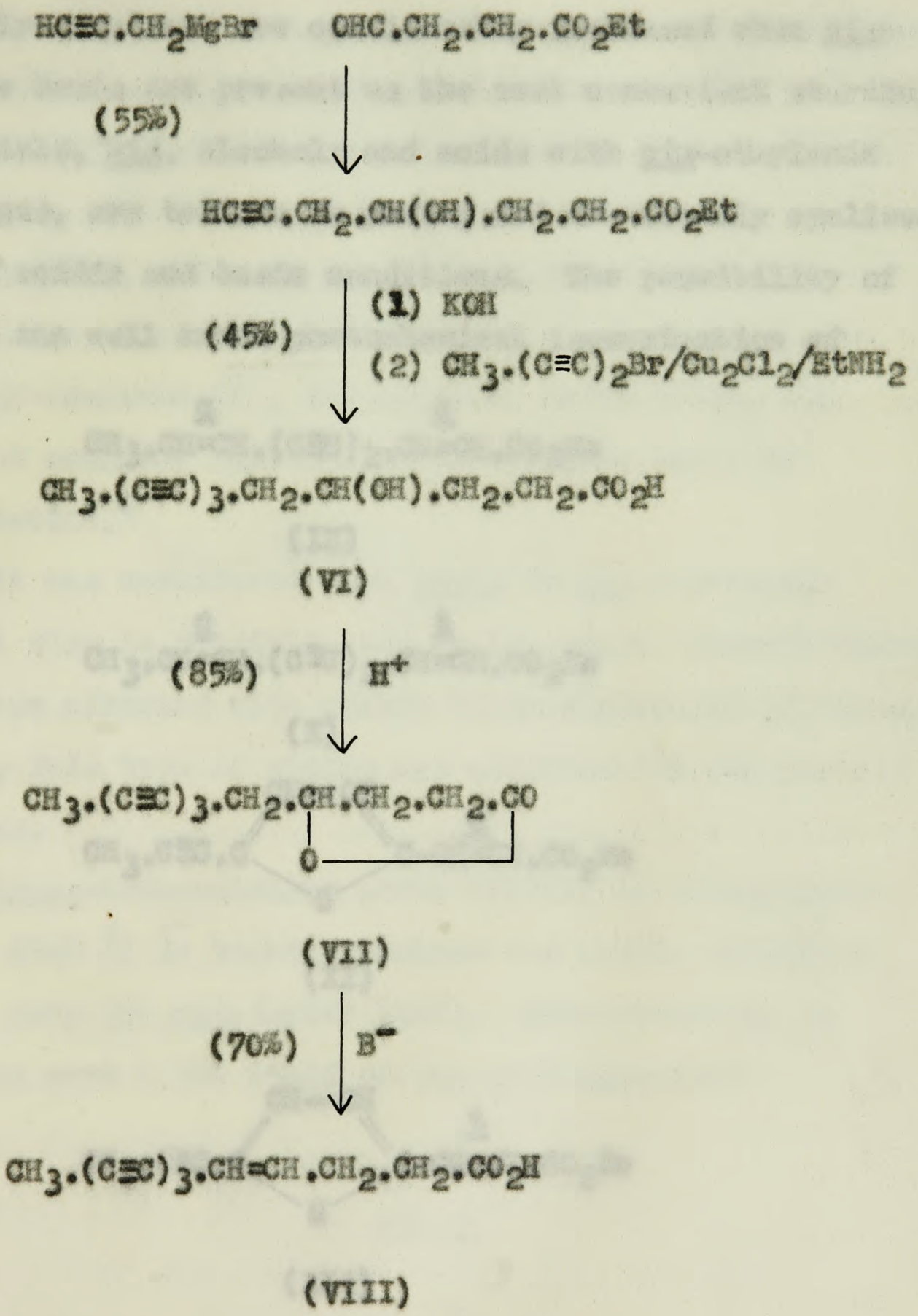
+

$C_4H_9.CH_2.C\equiv C.(C\equiv C)_2.CH_3$ (17%)

Application of the model conditions to the magnesium

derivative of the protected acid (I; R=2′-tetrahydropyranyl; R′=H) and the above tosylate in ether gave a heterogeneous reaction mixture which, after isomerisation, afforded only a 0.0006% yield of 2′-tetrahydropyranyl odyssic acid (IV; R=2′-tetrahydropyranyl). In tetrahydrofuran, a homogeneous solution was obtained, but the conditions required to replace the ethynyl proton of the protected acid (with diethylmagnesium) resulted in the conversion of the carboxyl group to an ethyl ketone.

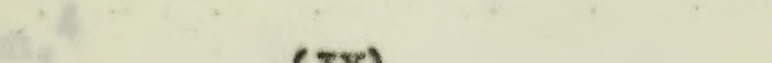
(ii) Odyssin and odyssic acid were known to undergo alkali-catalysed isomerisation to odyssin A (VIII) and iso-odyssic acid (VI) respectively[2]. The synthesis of the two isomers and also of iso-odyssic lactone (VII) was accomplished by the scheme outlined overleaf.


HC≡C.CH2MgBr
OHC.CH2.CH2.CO2Et
(55%)
HC≡C.CH2.CH(OH).CH2.CH2.CO2Et
(45%)
(1) KOH
(2) CH3.(C≡C)2Br/Cu2Cl2/EtNH2
CH3.(C≡C)3.CH2.CH(OH).CH2.CH2.CO2H
(VI)
(85%)
H+
CH3.(C≡C)3.CH2.CH.CH2.CH2.CO
O
(VII)
(70%)
B−
CH3.(C≡C)3.CH=CH.CH2.CH2.CO2H
(VIII)

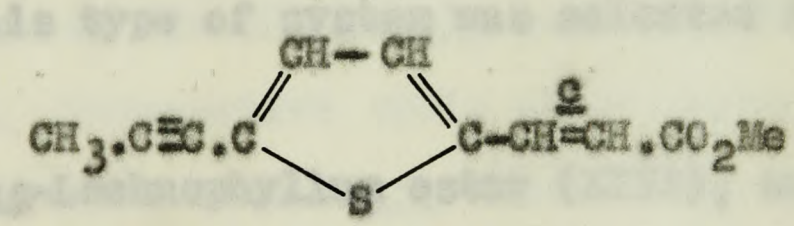
(iii) The difficulties associated with the synthesis of polyacetylenes are considerably increased when cis-double bonds are present as the most convenient starting materials, viz. alcohols and acids with cis-ethylenic linkages, are tedious to purify and are readily cyclised under acidic and basic conditions. The possibility of using the well known photochemical isomerisation of



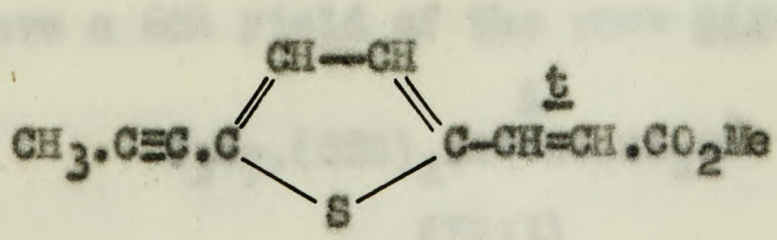
(IX)



(X)



(XI)



(XII)

double bonds as a preparative method for converting the more readily available trans-polyacetylenes into the cis-forms was therefore investigated. Two examples only of photoequilibration in the polyacetylene field had been reported, both being cis to trans conversions.

In 1941, Sørensen et al.[3] discovered that cis-matricaria ester (IX) could be photoisomerised to the "trans"-compound (X), and eighteen years later, the sulphur compound (XI) was converted into (XII) by irradiation.[4]

It was considered that trans to cis conversion should also be possible, and as the above isomerisations had been effected with double bonds conjugated to an ester group, this type of system was selected for the initial studies.

trans-Lachnophyllum ester (XIII), on irradiation ($\lambda > 2900$ Å) in light petroleum was mainly converted (80%) into the cis-isomer (XIV). Chromatography on alumina gave a 60% yield of the pure cis-ester.

$$C_3H_7.(C{\equiv}C)_2.\overset{t}{CH}{=}CH.CO_2Me$$

(XIII)

$$C_3H_7.(C{\equiv}C)_2.\overset{c}{CH}{=}CH.CO_2Me$$

(XIV)

It was of interest to discover whether or not the ester activation could be relayed by an acetylenic chain. For this purpose the trans-ester (XV) was used. It was readily photoisomerised (under the above conditions) to

$$CH_3.CH\overset{t}{=}CH.(C\equiv C)_2.CO_2Me$$

(XV)

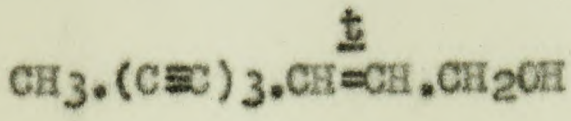
$$CH_3.CH\overset{c}{=}CH.(C\equiv C)_2.CO_2Me$$

(XVI)

a mixture which was shown by vapour phase chromatography to consist of 45% of the cis- and 55% of the trans-compound. Preparative scale experiments were not attempted as decomposition of the cis-ester (XVI) occurred during chromatographic purification.

An ethylenic system with acetylenic activation only was considered next. trans-Dehydromatricarianol (XVII) was irradiated ($\lambda > 2200$ Å) in ethanol and was partly converted (27%) into the cis-isomer. (XVIII). A portion of the latter had cyclised during the experiment to give the dihydrofuran.(XIX) (10% overall) which on careful

chromatography was resolved into its 4,5-double bond isomers. The structure of (XIX) was authenticated by comparison of its ultraviolet spectrum with that of a synthetic specimen of the new chromophore.



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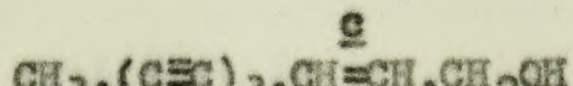
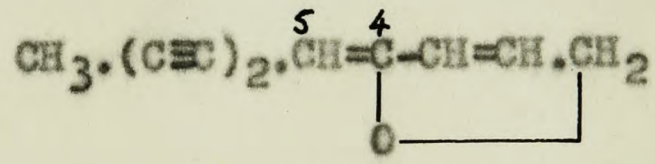


(XVIII)



(XIX)

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1 Bu'Lock, Jones and Leeming, J., 1955, 4270

2 idem., J., 1957, 1097.

3 Sørensen and Stene, Annalen, 1941, 549, 80.

4 Guddal and Sørensen, Acta Chem.Scand., 1959, 13, 1185.

PART I

PART I, SECTION I

Synthetic Routes to Odyssic Acid and Odyssin

INTRODUCTION

In 1950, Anchel, Kavanagh, and co-workers[1,2] isolated, from the extracts of an unidentified Basidiomycete and also from Poria corticola and Poria tenuis, two dextro-rotatory, highly unsaturated, alkali sensitive, antibiotics to which the names nemotin and nemotinic acid were given. Observations of the properties, in particular the light absorption spectra, indicated that nemotin and nemotinic acid might contain conjugated triple bonds, and that the optical activity might be due to asymmetrically substituted allenic groups.

Jones and his collaborators, as a result of their interest in synthetic polyacetylenes, investigated the problem further in order to determine the structures of the compounds. Jones, Bu'Lock, and Leeming[3] studied the extract of cultures of the Basidiomycete "B841", and by careful countercurrent distribution succeeded in separating, in addition to nemotin and nemotinic acid, small amounts of two new compounds for which the names odyssin and odyssic acid were proposed.

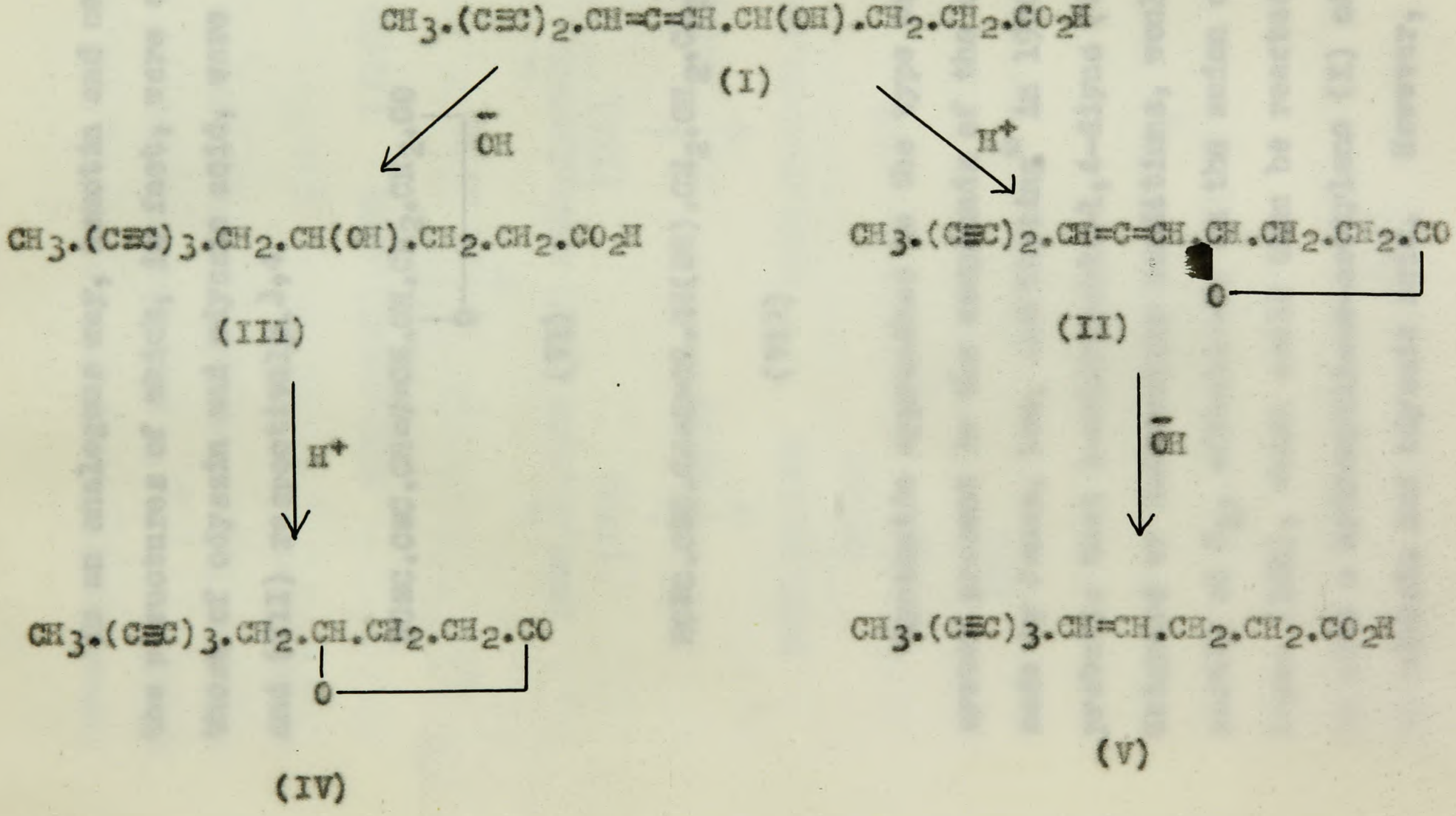
The structures of the four compounds were elucidated by the methods applicable to natural polyacetylenes in general, which are described below in their application to

the structural determinations of odyssin and odyssic acid.[4,5]

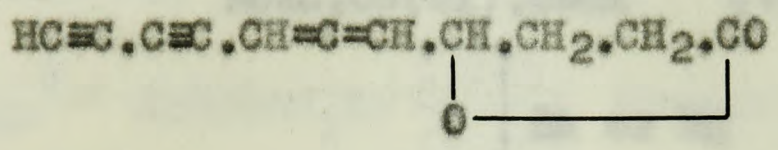
Odyssin and odyssic acid were found to be strongly dextro-rotatory, and their ultraviolet absorption spectra were typical of the ene-diyne chromophore. The infrared absorption spectrum of odyssin contained bands at 1960 (CH=C=CH) and 1785 cm.$^{-1}$ (γ-lactone CO). Treatment of odyssic acid with dioxan-sulphuric acid afforded odyssin, thereby establishing the relationship between the two compounds, and showing odyssic acid to be a 4-hydroxy acid.[5] On treatment with mild alkali, odyssin rearranged to an optically inactive acid, odyssin A, the ultraviolet absorption of which showed the presence of the ene-triyne system. The infrared spectrum showed no absorption due to hydroxyl, allenic, or lactone groups. Perhydrogenation of odyssin A gave n-dodecanoic acid, identified by mixed m.p. comparison of the p-toluidide with an authentic specimen, thus showing the skeleton of odyssin and odyssic acid to be a 12 C-atom, unbranched chain. Odyssic acid was also isomerised on treatment with mild alkali giving a weakly optically active acid, iso-odyssic acid, which on treatment with dioxan-sulphuric acid gave an optically active γ-lactone, iso-odyssic lactone. The ultraviolet spectra showed typical triyne absorption maxima and no bands due

to allenic groups were present in the infrared spectra. Hence the optical activity must be due to the asymmetric centre at C_4, which carries the oxygen function.

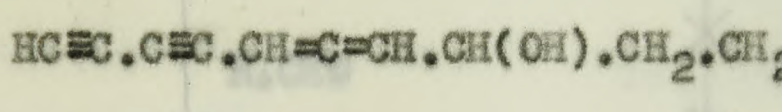
On the basis of the above data, the only structures possible for odyssic acid and odyssin which are in accord with all the experimental and spectroscopic evidence are (I) and (II) respectively. The relationships between (I), (II), and their isomerisation products iso-odyssic acid (III), iso-odyssic lactone (IV), and odyssin A (V), are given below.


CH3.(C≡C)2.CH=C=CH.CH(OH).CH2.CH2.CO2H
(I)
⁻OH
H+
CH3.(C≡C)3.CH2.CH(OH).CH2.CH2.CO2H
(III)
CH3.(C≡C)2.CH=C=CH.CH.CH2.CH2.CO
O
(II)
H+
⁻OH
CH3.(C≡C)3.CH2.CH.CH2.CH2.CO
O
(IV)
CH3.(C≡C)3.CH=CH.CH2.CH2.CO2H
(V)

In an analogous way, nemotin and nemotinic acid, the structures of which, in fact, were elucidated before those of odyssin and odyssic acid, were shown to be (VI) and (VII) respectively.[3,4]



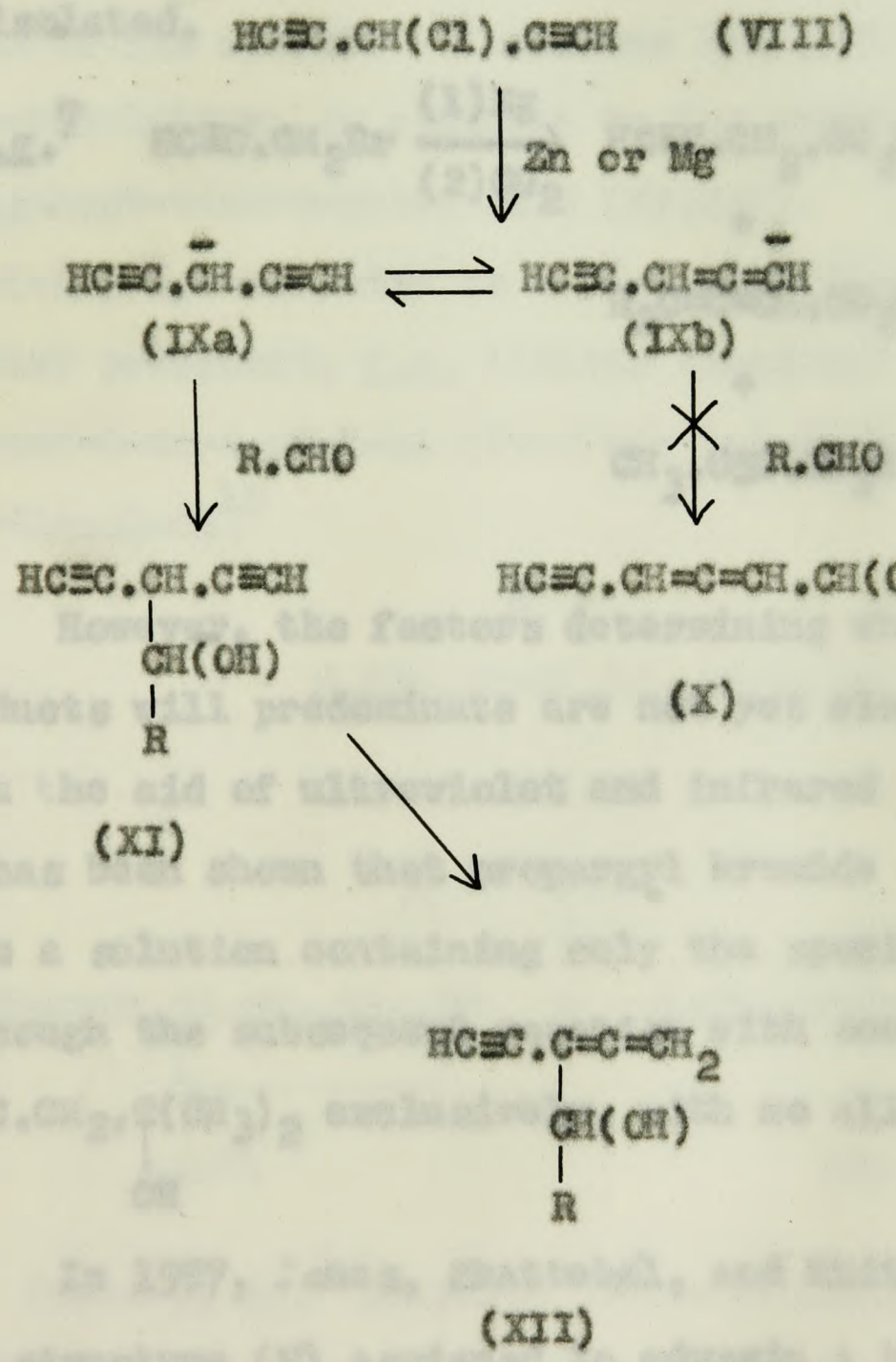
(VI)



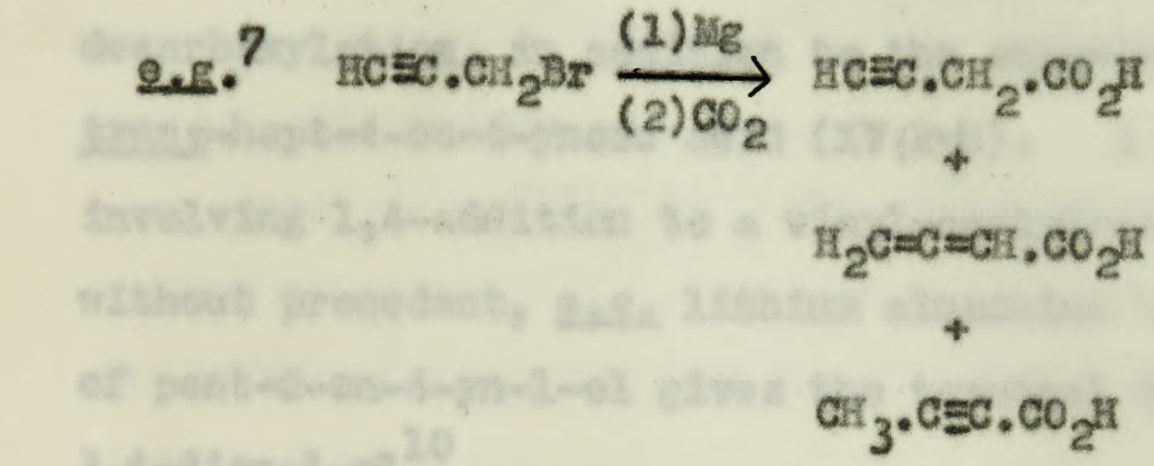
(VII)

Synthetic approaches to the type of allene-acetylene system present in the compounds of the odyssin series were made by Jones, Lee, and Whiting[6] in 1956. They considered it probable that 3-chloropenta-1,4-diyne (VIII), under Grignard or Reformatsky conditions, would react at least partly at C_1, effectively as the anion of penta-3,4-dien-1-yne (IXb), which could then be reacted with an aldehyde to give a hydroxyallene-acetylene (X) of the type present in odyssin and odyssic acid. However, the anion (IXa)

formed initially proved to be the more stable, and underwent reaction at C_3 to give the unconjugated product (XI), followed by prototropic rearrangement to the terminal allene-acetylene (XII).



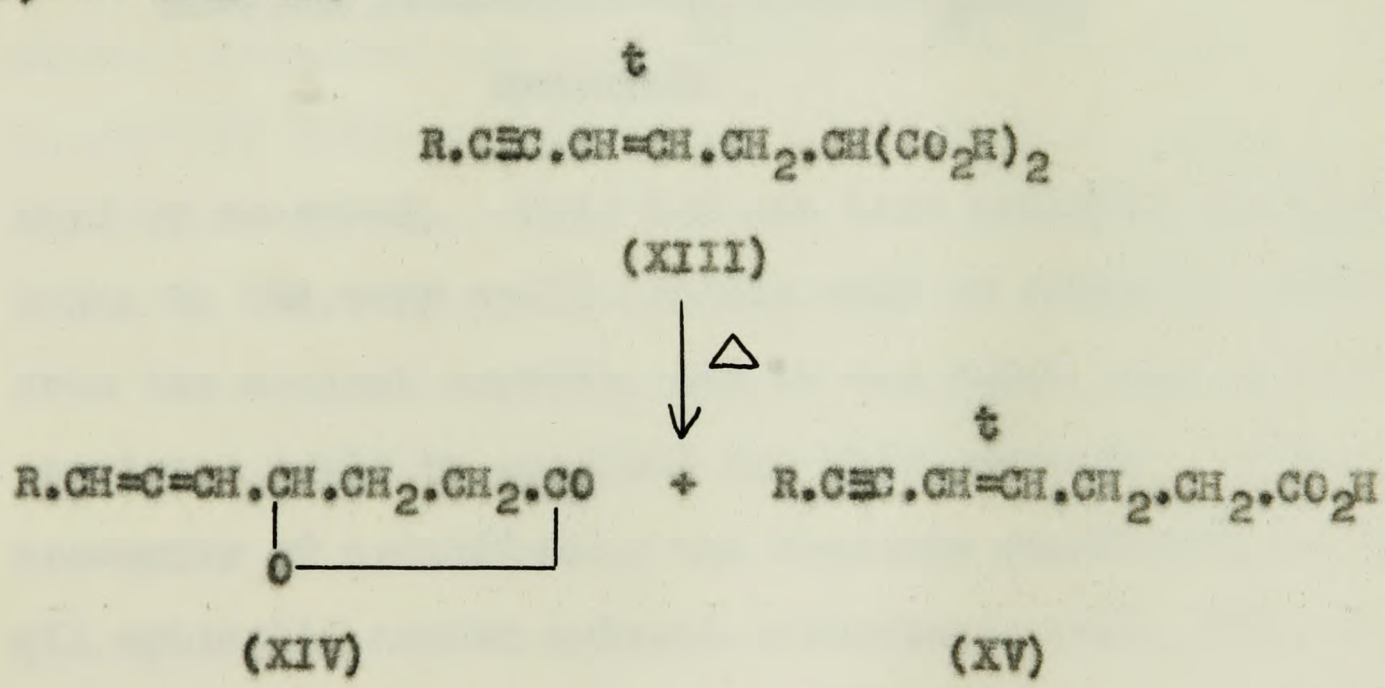
Analogies for the type of rearrangement hoped for above are to be found in the reactions of organometallic derivatives of βγ-acetylenic halides, from which the products of reaction at all possible reactive centres may be isolated.



However, the factors determining which of the possible products will predominate are not yet clear, and recently, with the aid of ultraviolet and infrared spectroscopy, it has been shown that propargyl bromide and zinc react to give a solution containing only the species $H_2C{=}C{=}CH.ZnBr$ although the subsequent reaction with acetone gives $HC{\equiv}C.CH_2.C(CH_3)_2$ (OH) exclusively, with no allenic product.[8]

In 1957, Jones, Skattebøl, and Whiting[9] confirmed the structure (V) assigned to odyssin A by synthesis of

trans-dodec-4-ene-6,8,10-triynoic acid (see p.30).
In the course of the synthesis, the above workers discovered that one of their intermediates, trans-hex-3-en-5-yne-1,1-dicarboxylic acid (XIII; R=H), gave a small yield of the allenic γ-lactone (XIV;R=H) on thermal decarboxylation, in addition to the expected product trans-hept-4-en-6-ynoic acid (XV;R=H). A reaction involving 1,4-addition to a vinyl-acetylene system is not without precedent, e.g. lithium aluminium hydride reduction of pent-2-en-4-yn-1-ol gives the terminal allene penta-3,4-dien-1-ol.[10]



Jones et al.[6] prepared the acid (XIII; R=$CH_3.(C{\equiv}C)_2$) in the hope that a similar rearrangement would take place on

heating to give a mixture of odyssin (II), (XIV; R=$CH_3.C{\equiv}C)_2$) and odyssin A (V), (XV; R=$CH_3.(C{\equiv}C)_2$). However, not unexpectedly, (XIII; R=$CH_3.(C{\equiv}C)_2$) underwent extensive decomposition during attempted decarboxylation.

PRESENT WORK

The present work was concerned with the development of synthetic routes to odyssin and odyssic acid. The synthesis of these compounds was considered necessary for several reasons. Obviously, synthetic confirmation for the structures assigned to the compounds by degradative methods was the primary aim[11], but other factors were also of importance.

The antibiotic properties reported for the allene-acetylenes mycomycin[12] and nemotin (VI)[1,2] made it desirable that the activities of odyssin and odyssic

$$HC{\equiv}C.C{\equiv}C.CH{=}C{=}CH.CH{=}CH.CH{=}CH.CH_2.CO_2H$$

mycomycin

acid be measured. This had not been possible previously owing to the very small amounts only of material isolated from the natural sources, and it was hoped that synthetic specimens could be provided for this purpose. Also, the necessity of establishing the absolute configuration of all optically active natural products is being more and more widely realised, as correlations involving this feature are vital to the eventual understanding of all biosynthetic processes.[13] The very recent work by Jones,

Loder, and Whiting[14] in which the absolute configuration of an optically active allene has been ascertained, has opened up possibilities of establishing those of naturally occurring allenes, thereby contributing towards the vast store of knowledge which must be accumulated before all the observed facts of biosynthesis can be fitted together into the ordered, logical pattern which must exist in nature.

Until fairly recently, the synthetic methods available for the synthesis of acetylenic-allenes were insufficiently developed to further the above aims. However, over the past few years general interest in allene chemistry has increased[15], and new synthetic routes to allenic compounds have been devised, thus enabling approaches to be made to very labile compounds with an optimism which would not previously have been justified.

With these considerations in mind, a survey of available routes to odyssin was carried out. Owing to the extreme instability of the allene-acetylene system in odyssin, it was considered imperative that this grouping should be introduced at a late stage in the synthesis. The general allene syntheses did not readily lend themselves to a problem of this type, but the recent advances

in the synthesis of compounds containing the $C{\equiv}C.CH_2.C{\equiv}C$ group 16-21, which may be easily isomerised with alkali to $C{\equiv}C.CH{=}C{=}CH.$,[20] provided the basis for an approach which it was thought might prove fruitful. Accordingly, the following scheme was drawn up in which the allenic group was introduced in the final step.

$HC{\equiv}C.MgBr$ + $OHC.CH_2.CH_2.CO_2Et$

$\downarrow$

$HC{\equiv}C.CH(OH).CH_2.CH_2.CO_2R$

(XVI)

$\downarrow$ (1) 3 EtMgBr

(2) $CH_3.(C{\equiv}C)_2.CH_2Br/Cu_2Cl_2$

$CH_3.(C{\equiv}C)_2.CH_2.C{\equiv}C.CH(OH).CH_2.CH_2.CO_2H$

$\downarrow$ $\bar{O}H$

$CH_3(C{\equiv}C)_2.CH{=}C{=}CH.CH(OH).CH_2.CH_2.CO_2H$

(I)

$\downarrow$ H^+

$CH_3.(C{\equiv}C)_2.CH{=}C{=}CH.CH.CH_2.CH_2.CO$ (O bridging the CH and CO)

(II)

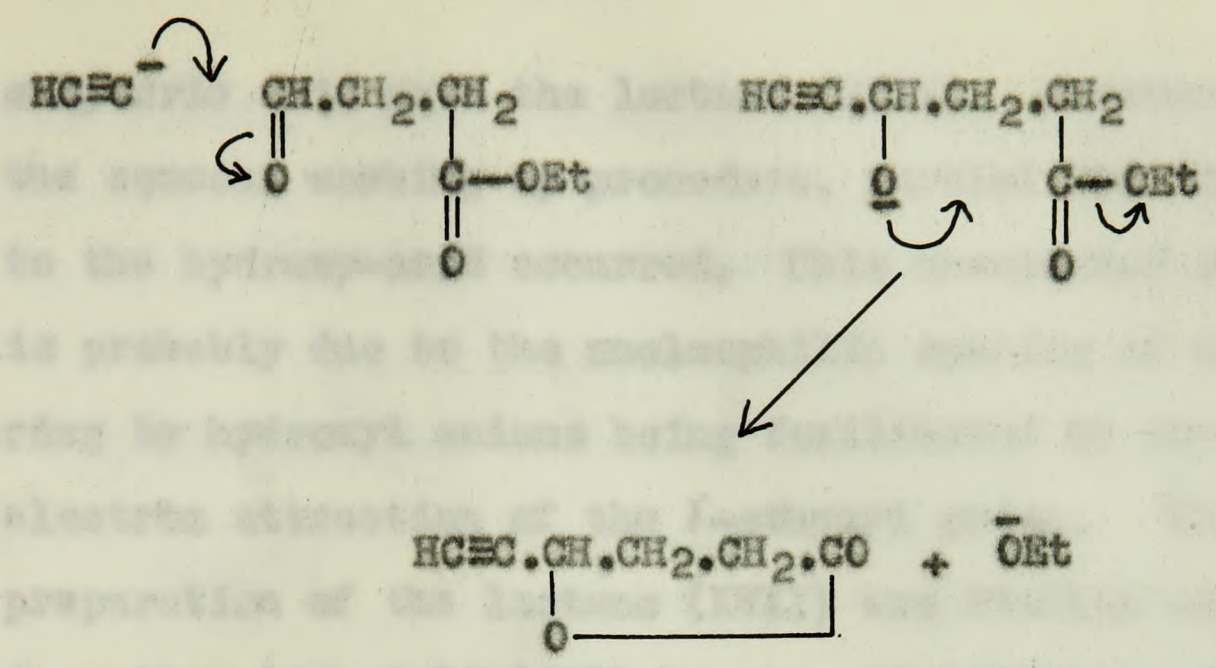
The discussion of some model experiments for the last two stages of the above route, which were of course carried out before the commencement of the main investigation, has been deferred until Part I, Section IIIc.

β-Carbethoxypropionaldehyde was chosen as a convenient starting material for the preparation of the γ-hydroxy-acid (XVI; R=H). A survey of the literature showed that selective Grignard condensation with the aldehyde group to give a γ-hydroxy-ester, and hence γ-lactones, was possible[22], but that very little use of this reaction as a general route to γ-lactones had been made. An investigation of the laboratory and high pressure[23] methods (the latter by I.C.I. (Billingham) Research Department, to whom I would like to express my gratitude) showed that the preparation was accompanied by many difficulties, which may perhaps have retarded its development as a chemical intermediate. The laboratory preparative problems have now been surmounted and the difficulties which had to be overcome are summarised below.

The condensation of diethyl succinate and ethyl formate in the presence of sodium proceeded smoothly to give ethyl α-formylsuccinate in 65% yield[24]. However, the subsequent partial hydrolysis and decarboxylation to β-carbethoxypropionaldehyde by heating with water either

at 100°[25] or at 120°[24] could not be easily controlled, and further hydrolysis to β-formylpropionic acid occurred.[26] The problem was overcome by using a phosphate buffer solution of pH7 as the hydrolysing agent, which gave reproducible yields of 60-65% of the aldehydo-ester, with very little further hydrolysis to the free acid. It was found to trimerise very readily, but a 10% solution in ether could be stored indefinitely at -40°. All subsequent reactions were carried out with freshly distilled material.

Preferential attack on the aldehyde group[22] was achieved when ethynylmagnesium bromide[27] was added to the aldehydo-ester in tetrahydrofuran at -70° to give ethyl 4-hydroxyhex-5-ynoate (XVI; R=Et). The unwanted side reaction with the ester group, which consumed two molecular proportions of Grignard reagent, was found to proceed to a small extent, thereby greatly reducing the amount of the bromomagnesium available for condensation with the aldehyde, and optimum yields (50%) were obtained by using an excess of ethynylmagnesium bromide. Small amounts (5-10%) of the lactone (XVII), estimated from the intensity of the band at 1802 cm.$^{-1}$ in the infrared spectrum, were also formed in the reaction, presumably by internal trans-esterification as shown overleaf.



(XVII)

The ester (XVI; R=Et) and the lactone (XVII), surprisingly, were of very similar polarity and could not be readily separated by distillation or by chromatography on alumina. Accordingly, purification was not attempted at this stage, and the mixture was hydrolysed by treatment with aqueous ethanolic potassium hydroxide solution at 20°, the acid (XVI; R=H) being obtained in quantitative yield. Attempts to crystallise the acid were unsuccessful, and on heating above 50°, partial lactonisation was observed. The acid (XVI; R=H) was eventually characterised as the methyl ester (XVI; R=Me), which was obtained only in 40% yield however, by the action of ethereal diazomethane.

Treatment of the hydroxy-acid (XVI; R=H) with dioxan-

sulphuric acid gave the lactone (XVII). However, during the aqueous working up procedure, partial hydrolysis back to the hydroxy-acid occurred. This unexpected complication is probably due to the nucleophilic opening of the lactone ring by hydroxyl anions being facilitated by the powerful electron attraction of the γ-ethynyl group. The preparation of the lactone (XVII) was finally accomplished in rather low yield (30%) by slow distillation of the hydroxy-acid in the presence of toluene-p-sulphonic acid. The carbonyl absorption at 1802 cm.$^{-1}$ in the infrared spectrum is outside the range (1780-1760 cm.$^{-1}$) quoted[28] for saturated γ-lactones, but is in agreement with the values given for saturated γ-lactones having strongly electronegative substituents in the γ-position.[29]

As all attempts to purify 4-hydroxyhex-5-ynoic acid had been unsuccessful, the crude acid, the infrared spectrum of which showed no substantial impurity, was used in the attempted coupling reaction described below.

1-Bromohexa-2,4-diyne (XIX), the other component required for coupling, was prepared in two steps from propargyl alcohol.

Chodkiewicz coupling[30] of 1-bromoprop-1-yne with propargyl alcohol gave hexa-2,4-diyn-1-ol (XVIII; R=H)

(90% yield), which on treatment with phosphorus tribromide

$$CH_3.C{\equiv}C.Br \;+\; HC{\equiv}C.CH_2OH$$

$$CH_3.(C{\equiv}C)_2.CH_2OR \longrightarrow CH_3.(C{\equiv}C)_2.CH_2Br$$

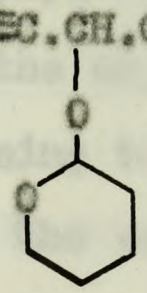
(XVIII) (XIX)

and pyridine[31] afforded the bromide (XIX) (45% yield) as a sweet smelling, fairly unstable, liquid.

An attempt was made to couple the hydroxy acid (XVI; R=H), as its tribromomagnesium derivative, with 1-bromohexa-2,4-diyne (XIX) in tetrahydrofuran in the presence of cuprous chloride. (For model reactions, see Part I, Section III c). Unfortunately, as had been feared, the Grignard derivative proved insoluble in tetrahydrofuran, and an ultraviolet spectroscopic examination after the mixture had been stirred for 24 hours at 20°, and then treated with alkali, showed that no coupling had taken place. The negative result was considered to be due to the heterogenous nature of the reaction mixture, and in order to increase the solubility of the Grignard component it was decided to protect the hydroxyl group of (XVI; R=H) as the 2′-tetrahydropyranyl

ether. This group, being stable to Grignard reagents and easily removed under mild acidic conditions, seemed ideal for use with a potentially alkali sensitive molecule.

The ester (XVI; R=Et) was mixed with one equivalent of 2,3-dihydropyran and a trace of phosphorus oxychloride;[32] and purification by chromatography on alumina and by distillation gave the tetrahydropyranyloxy-ester (XX; R=Et) in 70% yield. Hydrolysis of the ester was effected



(XX)

by keeping overnight at 20° with aqueous ethanolic potassium hydroxide solution (quantitative yield), and the potassium salt was converted to the free acid (XX; R=H) at pH5 to avoid cleavage of the protecting group. An attempt to prepare the tetrahydropyranyl ester of the protected acid (XX; R=2′-tetrahydropyranyl) from the hydroxy-acid (XVI; R=H) was unsuccessful, as the phosphorus oxychloride catalyst caused lactonisation before protection of the hydroxyl groups could take place.

Again, the protected acid (XX; R=H) could not be

crystallised, and the crude preparation, judged to be of reasonable purity from an examination of its infrared absorption, was used for further coupling reactions.

Treatment of the tetrahydropyranyloxy acid in tetrahydrofuran at 20° with two equivalents of ethylmagnesium bromide gave a clear solution, which refused to couple with the bromide (XIX) in the presence of cuprous chloride. A possible reason for the lack of reaction was that the ethynyl hydrogen atom had not been replaced by -MgBr under the experimental conditions, but even so it was surprising that the 1-bromohexa-2,4-diyne had not coupled with the second equivalent of ethylmagnesium bromide.

Zerewitinoff active hydrogen determinations were carried out[33] with ethylmagnesium bromide in tetrahydrofuran on a number of compounds containing free ethynyl groups in order to ascertain the ease of replacement of the active hydrogen atom. The results, summarised in the table given below, showed that in general ethynyl hydrogen atoms may be expected to be readily replaced at 20°, but that for the acid (XX; R=H), although the carboxylic proton reacted with the Grignard reagent at 20°, the acetylenic proton required a reaction temperature of 50°

for a period of two hours before replacement was complete.

Compound	EtMgBr at 20°	EtMgBr at 50°	CH_3Li at 20°
$HC\equiv C.CH_2.CO_2H$	2 mol.C_2H_6		
(XX; R=H)	1 mol.C_2H_6	1 further mol.	2 mol.CH_4
(XX; R=Et)	1 mol.C_2H_6		

The difficulty of replacement applied to the acid (XX; R=H) only in its reaction with the Grignard reagent, as with ethereal methyl-lithium[34] two molecular proportions of methane were evolved at 20°. (N.B. The use of the lithium derivatives for coupling[35] was precluded by the knowledge that the carboxyl group of (XX; R=H) would be converted into a ketone when treated with alkyl- or aryl-lithium compounds[36]). The possibility of steric hindrance of the ethynyl proton by the tetrahydropyranyl group as a valid reason for non-replacement was excluded by the ready reaction observed when the ester (XX; R=Et) was mixed with ethylmagnesium bromide at 20°.

Before repeating the coupling of the tetrahydropyranyloxyacid (XX; R=H) with the bromide (XIX) under conditions which ensured replacement of the acetylenic hydrogen atom, it was considered desirable to carry out further model experiments, as the failure of the bromide to couple with the excess ethylmagnesium bromide in the previous attempt was somewhat disturbing.

Attempts were therefore made to couple hex-1-ynylmagnesium bromide[37] and the bromo-compound (XIX) under a variety of conditions, in ether and tetrahydrofuran using both cuprous and cobaltous chloride[38] catalysis. In no case was any coupled product detected and the reactants were recovered unchanged. The failure of the $(C{\equiv}C)_2.CH_2Br$ system to react under the conditions found to be effective with $\beta\gamma$-acetylenic bromides (see Part I, Section IIIc), may be due to abnormal interaction with the catalyst, as vivid green solutions were formed immediately on addition of cuprous chloride to the reaction mixtures. The possibility of employing the alternative coupling approach, using penta-1,3-diynylmagnesium bromide and propargyl bromide, is being considered in an attempt to circumvent this difficulty (see p. 29).

The reaction of acetylenic Grignard reagents with

methane sulphonates and toluene-p-sulphonates, without catalysis, is known to proceed smoothly[39] and the condensation of an acetylenic bromo-magnesium compound with a $\beta\gamma$-acetylenic mesylate has been applied by Raphael and Sondheimer[16] to the preparation of the $\equiv C.CH_2.C\equiv$ grouping (designated for convenience as the "skipped diyne" groups by Gensler et al.[40]). The possible application of this alternative method of skipped diyne preparation to the synthesis of odyssin was therefore considered.

Hexa-2,4-diyn-1-ol (XVIII; R=H) reacted with methanesulphonyl chloride under basic conditions[16] to give the mesylate (XVIII; $R=SO_2.CH_3$) (50%) but complete separation of the product from unchanged carbinol could not be achieved either by fractional recrystallisation or by chromatography on alumina. The corresponding tosylate (XVIII; $R=p\text{-}SO_2.C_6H_4.CH_3$)was readily obtained in 60% yield by reaction of (XVIII; R=H) with toluene-p-sulphonyl chloride in aqueous acetonitrile, using potassium hydroxide as the base.[41] In condensations with Grignard reagents, two molecular proportions of the mesylate or tosylate are usually employed, one proportion being destroyed by the preferential displacement of $R.SO_3^-$ by

halogen anion. In order to determine the relative ease with which nucleophilic displacement occurred with respect to Grignard or to halogen anion, hex-1-ynylmagnesium bromide was mixed with one molecular proportion of the diyne tosylate in tetrahydrofuran at 20°. The bromide (XIX) was formed exclusively with none of the skipped diyne, thus showing that the use of one extra proportion of tosylate could not be avoided in this route. As the tosylate (XVIII; R=p-$SO_2.C_6H_4.CH_3$) was relatively valuable, attention was focussed on the elimination of all reactive nucleophiles other than the acetylenic anion from the solution, thereby obviating the loss of 50% of the tosylate in each reaction.

A reagent which appeared to fit the above requirements was the pseudo-Grignard reagent, methylmagnesium methyl sulphate[42], which when mixed with an alk-1-yne should give rise to the acetylenic anion and the only very weakly nucleophilic anion SO_4^{--}. However, a model experiment with methylmagnesium methyl sulphate, hex-1-yne, and the tosylate gave no skipped diyne, the starting materials being recovered unchanged. Further qualitative experiments showed that the reaction of methylmagnesium methyl sulphate with water, and with acetone, was sluggish and that its

properties in general were those of a rather unreactive Grignard reagent, and therefore unsuited to the present work.

The alternative approach considered incorporated the use of dialkynylmagnesium compounds. As a model for study, dihex-1-ynylmagnesium was prepared by the method of Wotiz and co-workers[43] in which the magnesium bromide from the ethereal ethylmagnesium bromide starting solution had been precipitated with dioxan[44]. Dioxan failed to precipitate magnesium bromide from a solution of ethylmagnesium bromide in tetrahydrofuran. The dioxan-magnesium bromide complex was not completely inactive (cf. Wotiz et al. [43]) as when a coupling of ethereal di-hex-1-ynylmagnesium and the tosylate was attempted in the presence of the precipitated complex, some displacement of the tosyl group by bromide occurred. Using filtered ethereal dihex-1-ynyl magnesium however, the skipped diyne (XXI) was formed initially (65%), but when isolated was found to have been mainly rearranged, presumably by traces of magnesium hydroxide, to dodeca-6,7-diene-2,4-diyne (XXII) and dodeca-2,4,6-triyne (XXIII). The percentage of each isomer present was estimated by quantitative ultra-violet spectroscopy, the amount of the skipped diyne (XXI)

remaining being determined by isomerisation with alkali to the allene (XXII). The results obtained are summarised below.

$$CH_3.(C{\equiv}C)_2.CH_2OTs \quad + \quad Mg(C{\equiv}C.C_4H_9)_2$$

(XVIII, R= p-$SO_2.C_6H_4.CH_3$)

$$\downarrow$$

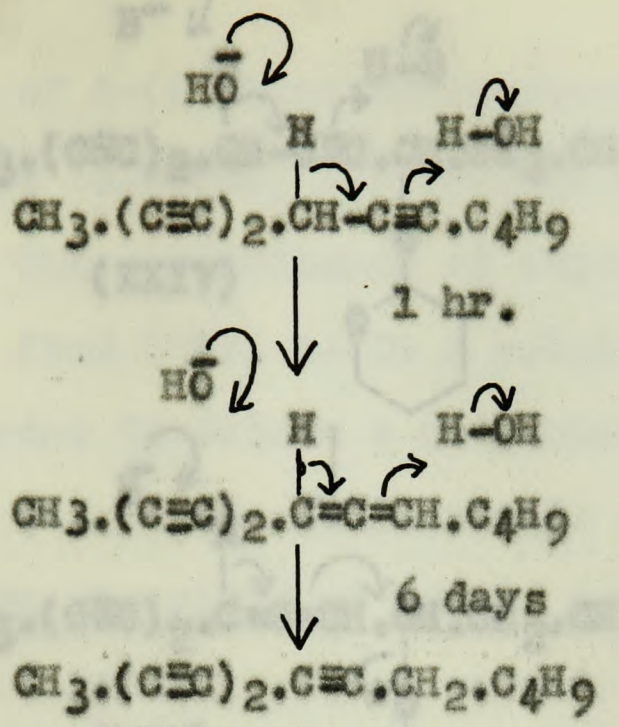
$CH_3.(C{\equiv}C)_2.CH_2.C{\equiv}C.C_4H_9$ (XXI) (6%)

\+ $CH_3.(C{\equiv}C)_2.CH{=}C{=}CH.C_4H_9$ (XXII) (42%)

\+ $CH_3.(C{\equiv}C)_3.CH_2.C_4H_9$ (XXIII) (17%)

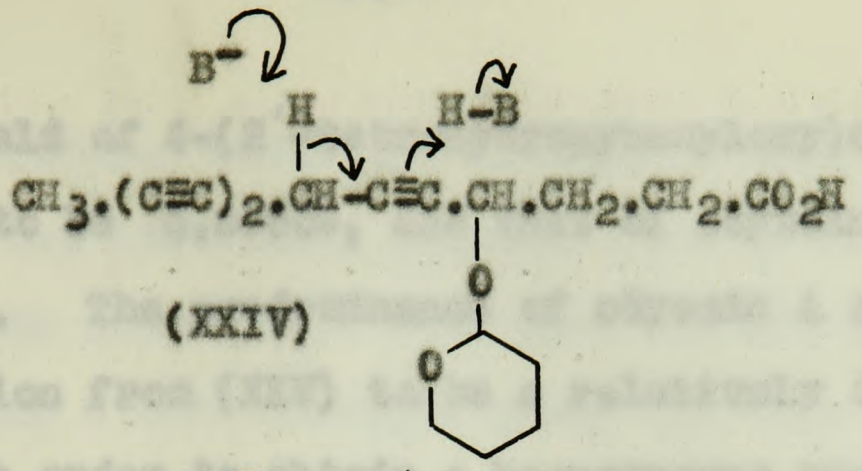
The rates of isomerisation of (XXI) to (XXII) and (XXIII) with 0.1N-potassium hydroxide solution at 20° were determined quantitatively. (see p.25).

Having at last accomplished the preparation of the $(C{\equiv}C)_2.CH_2.C{\equiv}C$. system, the successful model conditions were applied to the coupling of the protected acid (XX; R=H) with the tosylate (XVIII; R=p-$SO_2.C_6H_4.CH_3$). The acid was mixed with an excess of ethereal diethylmagnesium, and the mixture refluxed to ensure replacement of the acetylenic proton. The resulting derivative was

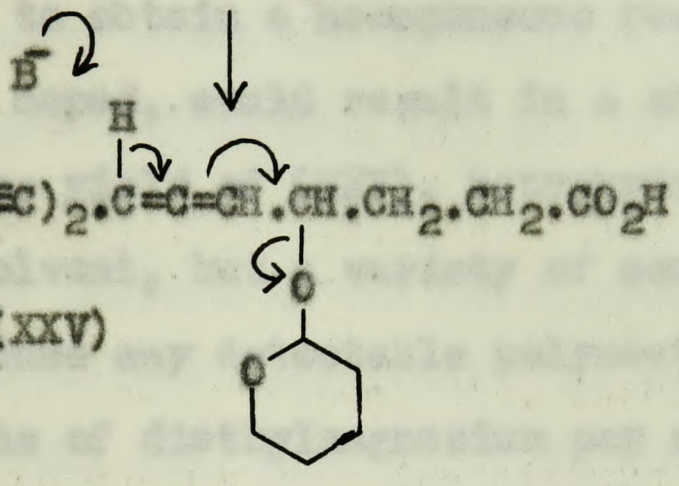


unfortunately, but not unexpectedly, insoluble in ether, and gave a heterogeneous reaction mixture when treated with an ethereal solution of the tosylate. Nevertheless, work on the attempted coupling was continued, and after a five hour reflux period spectroscopic examination showed the presence of a minute amount of the ene-triyne chromophore (λ max., 2420, 2570, 2730, 2890, 3080, and 3290 Å) of odyssin A, presumably formed by magnesium hydroxide-catalysed rearrangement of the required product (XXIV) to (XXV), followed by further rearrangement and elimination of the tetrahydropyranyloxy group.

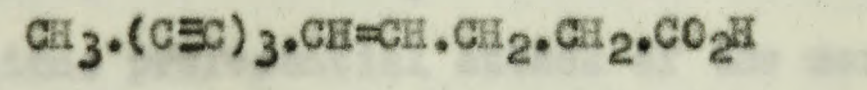
Purification of the acidic fraction <u>via</u> sodium carbonate solution, thus isomerising any remaining (XXIV)



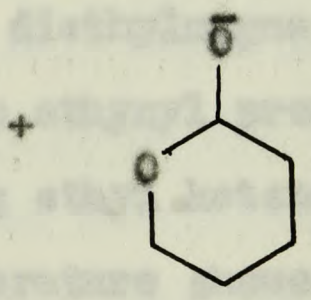
(XXIV)



(XXV)



(V)



to (XXV), followed by ultraviolet spectroscopic examination, showed the presence of a trace of a compound with the ene-diyne chromophore (λ max., 2510, 2630, and 2800 Å), presumably of (XXV), together with the ene-triyne (V).

A quantitative spectroscopic determination showed

the yield of 4-(2'-tetrahydropyranyloxy)odyssic acid (XXV) to be 0.0006%, and that of odyssin A (V) to be 0.002%. The predominance of odyssin A suggests its formation from (XXV) to be a relatively facile reaction.

In order to obtain a homogeneous reaction mixture, which, it was hoped, would result in a significant increase in the yield of (XXV), tetrahydrofuran was employed as solvent, but a variety of coupling conditions failed to produce any detectable polyacetylene. When two equivalents of diethylmagnesium per molecular proportion of the acid (XX; R=H) were used, 50% only of the acid was recovered. It was suspected that under the homogeneous conditions preferential attack of the carboxyl group by the second equivalent of diethylmagnesium might occur before replacement of the ethynyl proton thereby giving rise to the corresponding ethyl ketone.

Recourse to the literature showed that the reaction of carboxylic acids with organomagnesium compounds has been but little investigated but that further attack of CO_2MgX is by no means uncommon[45]. Confirmation of the suspicion of further attack was provided by the conversion (75%) of β-phenylpropionic acid to 1-phenyl-pent-3-one by treatment with diethylmagnesium in

tetrahydrofuran under the same conditions employed to replace the acetylenic hydrogen atom of (XX; R=H).

This observation precludes the use of any intermediate containing a free carboxyl group for this route to odyssin, unless a protecting group can be found which is stable to organo-magnesium compounds, and can be removed under conditions which will not affect the very sensitive allene-acetylene system present in the final product. Protection as the trioxoadamantane derivative[46] by treatment of the ortho-ester of (XX; R=H) with cis-1,3,5-trihydroxy-cyclohexane, which would be stable to all organo-metallic compounds, might provide a solution to the problem, but the regeneration of the carboxyl group in the final step by treatment with mineral acid might destroy the allene-acetylene system. However, plans for the immediate future are concerned with an investigation of the following synthetic scheme, which holds considerable promise of success.

$$CH_3.(C{\equiv}C)_2.MgBr + BrCH_2.C{\equiv}CH$$

$\downarrow Cu_2Cl_2$

$$CH_3.(C{\equiv}C)_2.CH_2.C{\equiv}CH$$

$\downarrow$ (1) $EtMgBr$
(2) $OHC.CH_2.CH_2.CO_2MgBr$

$$CH_3.(C{\equiv}C)_2.CH_2.C{\equiv}C.CH(OH).CH_2.CH_2.CO_2H$$

$\downarrow \bar{O}H$

$$CH_3.(C{\equiv}C)_2.CH{=}C{=}CH.CH(OH).CH_2.CH_2.CO_2H$$

PART I, SECTION II

The Synthesis of Iso-odyssic Acid, Iso-odyssic Lactone, and Odyssin A.

I N T R O D U C T I O N

As described previously (p.2), odyssin (II), on treatment with mild alkali, rearranged to odyssin A (V)[5]. Iso-odyssic lactone (IV) was also found to isomerise to odyssin A under the same conditions[5], albeit in low yield. The evidence for the formulation of odyssin A as (V) has been summarised on pp. 2-3.

Synthetic confirmation of the structure of odyssin A was provided in 1956 by Jones, Skattebøl, and Whiting[9], who synthesised the compound (V) by the following route.

$$CH_3.(C{\equiv}C)_2H \;+\; HC{\equiv}C.CH{=}CH.CH_2.CH_2.CO_2H$$

$$\downarrow \; Cu_2Cl_2/H_2O_2$$

$$CH_3.(C{\equiv}C)_3.CH{=}CH.CH_2.CH_2.CO_2H$$

(V)

Unfortunately, the yield was depressingly low owing to the predominance of the symmetrical coupling reactions, and only sufficient material for mixed m.p. and spectral comparisons with the naturally derived material could be

obtained.

The discovery by Chodkiewicz[30] in 1957 of a satisfactory method of mixed coupling of acetylenes overcame one of the major problems of synthetic polyacetylene chemistry, and made possible the synthetic scheme shown below, which in addition to providing an alternative route to odyssin A (V), also gave iso-odyssic acid (III), and iso-odyssic lactone (IV), the other two compounds derived from odyssin and odyssic acid by alkaline isomerisation.

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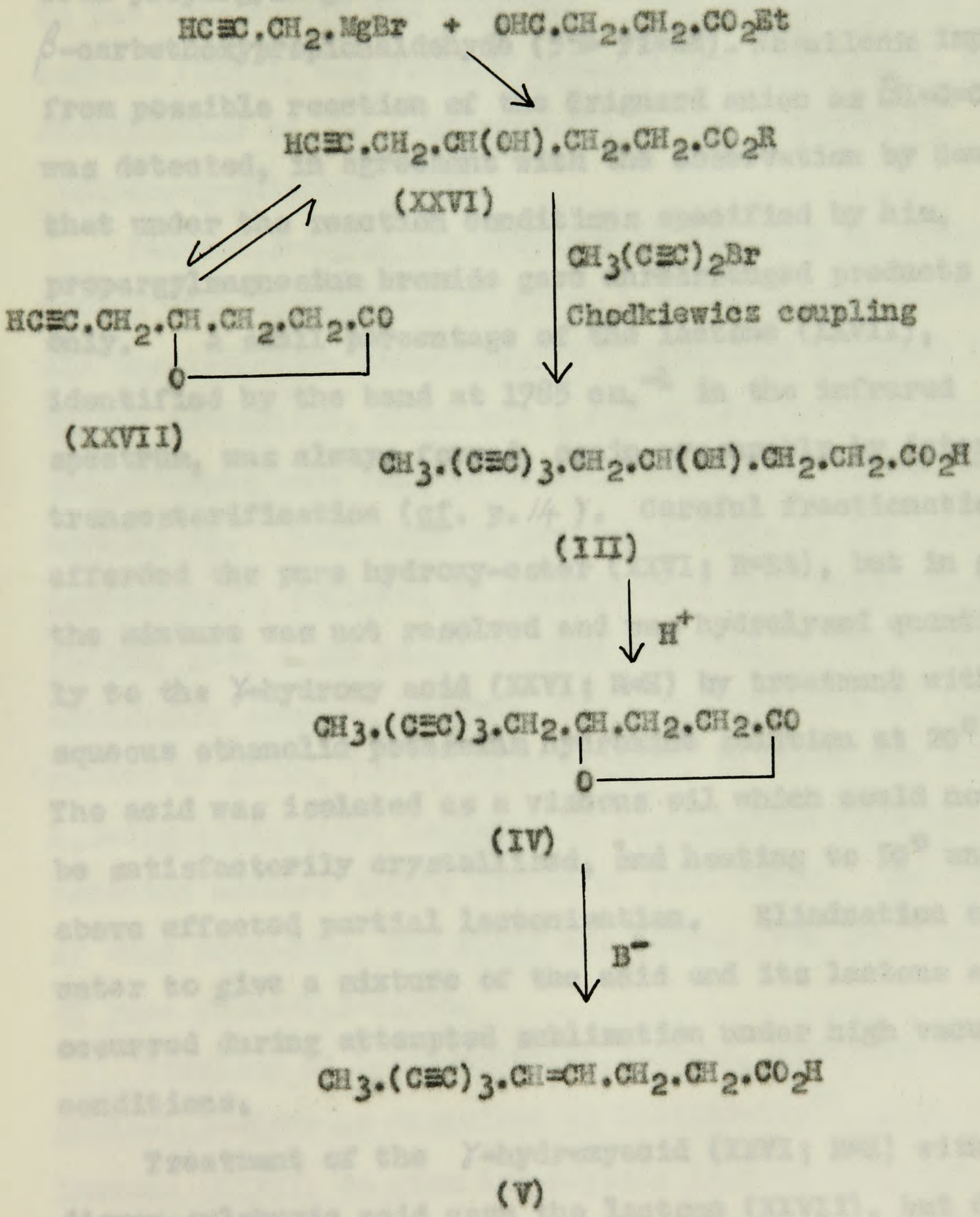


Ethyl 4-hydroxyhept-6-ynoate (XXVI; R=Et) was prepared from propargylmagnesium bromide and freshly distilled β-carbethoxypropionaldehyde (55% yield). No allenic impurity, from possible reaction of the Grignard anion as $\bar{C}H=C=CH_2$[7], was detected, in agreement with the observation by Gaudemar[47] that under the reaction conditions specified by him, propargylmagnesium bromide gave unrearranged products only. A small percentage of the lactone (XXVII), identified by the band at 1785 $cm.^{-1}$ in the infrared spectrum, was always formed, again presumably by internal transesterification (cf. p. 14). Careful fractionation afforded the pure hydroxy-ester (XXVI; R=Et), but in general the mixture was not resolved and was hydrolysed quantitatively to the γ-hydroxy acid (XXVI; R=H) by treatment with aqueous ethanolic potassium hydroxide solution at 20°. The acid was isolated as a viscous oil which could not be satisfactorily crystallised, and heating to 50° and above effected partial lactonisation. Elimination of water to give a mixture of the acid and its lactone also occurred during attempted sublimation under high vacuum conditions.

Treatment of the γ-hydroxyacid (XXVI; R=H) with dioxan-sulphuric acid gave the lactone (XXVII), but during

the aqueous working up procedure partial hydrolysis back to the hydroxyacid was observed. The preparation of the lactone (XXVII) was finally accomplished (82% yield) by distillation of the γ-hydroxyacid in the presence of toluene-p-sulphonic acid.

Penta-1,3-diyne was prepared by reaction of methyl iodide with diacetylene [48] (from 1,4-dichlorobut-2-yne[49]). All the isolation techniques[48,50] described involved liquid butane extraction, which was a rather tedious operation, and attempts were made to obviate the use of butane in working up. Isolation of penta-1,3-diyne as the mercury derivative[51], followed by regeneration with acid-potassium iodide, gave a 30% yield of pure material. The method eventually adopted, however, was a modification of the method of Allan, Jones, and Whiting[50], in which the penta-1,3-diyne was first isolated by distillation from the reaction mixture into a series of cold traps. By application of this procedure, the yield was raised from 36%[50] to 49% of pure penta-1,3-diyne.

Coupling of 1-bromopenta-1,3-diyne, obtained from penta-1,3-diyne as described by Chodkiewicz[30], with the lactone (XXVII) to give iso-odyssic lactone (IV) directly could not be achieved although a variety of conditions

was studied. The mixed coupling reaction of acetylenes was very fully investigated by Chodkiewicz[30] who found that the yields were very dependent on the temperature and on the base employed. The optimum temperature ranges for various systems were worked out by him on an empirical basis, and his survey of basic conditions showed that primary amines gave the best results. However, in the present work the use of primary amines resulted in the immediate conversion of the lactone (XXVII) into amides, which then coupled normally to give the corresponding amides (XXVIII) of iso-odyssic acid. Iso-odyssic ethylamide (XXVIII; R=Et) was prepared (20% yield) by this method. No reaction occurred when pyridine[30], which precludes amide formation, was employed.

$CH_3.(C{\equiv}C)_3.CH_2.CH(OH).CH_2.CH_2.CO.NH.R$ (XXVIII)

The preparation of iso-odyssic acid (III) was finally accomplished (45% yield) by coupling 1-bromopenta-1,3-diyne with the potassium salt (XXVI; R=K), the latter being obtained from the lactone (XXVII) with one equivalent of potassium hydroxide. The ultraviolet absorption

confirmed the presence of the triyne chromophore and the frequencies of the bands in the infrared spectrum agreed with those quoted for the naturally derived material.

In the same way, the lower homologue, 4-hydroxyundeca-5,7,9-triynoic acid (XXIX) was prepared in 35% yield from 1-bromopenta-1,3-diyne and the potassium salt (XVI; R=K).

$$CH_3.(C{\equiv}C)_3.CH(OH).CH_2.CH_2.CO_2H$$

(XXIX)

As the iso-odyssic acid derived from the natural product was too unstable to be readily handled[5], the synthetic specimen was not fully purified, but was converted directly (85%) into iso-odyssic lactone (IV) by treatment with dioxan-sulphuric acid at 20°.[5] The m.p. of the racemic, synthetic, iso-odyssic lactone agreed with the highest value quoted[5] for the naturally derived, optically active, polymorphous compound, and the infrared and ultra-violet absorption spectra were found to be identical.

The isomerisation of naturally derived iso-odyssic lactone to odyssin A with 10% aqueous potassium carbonate

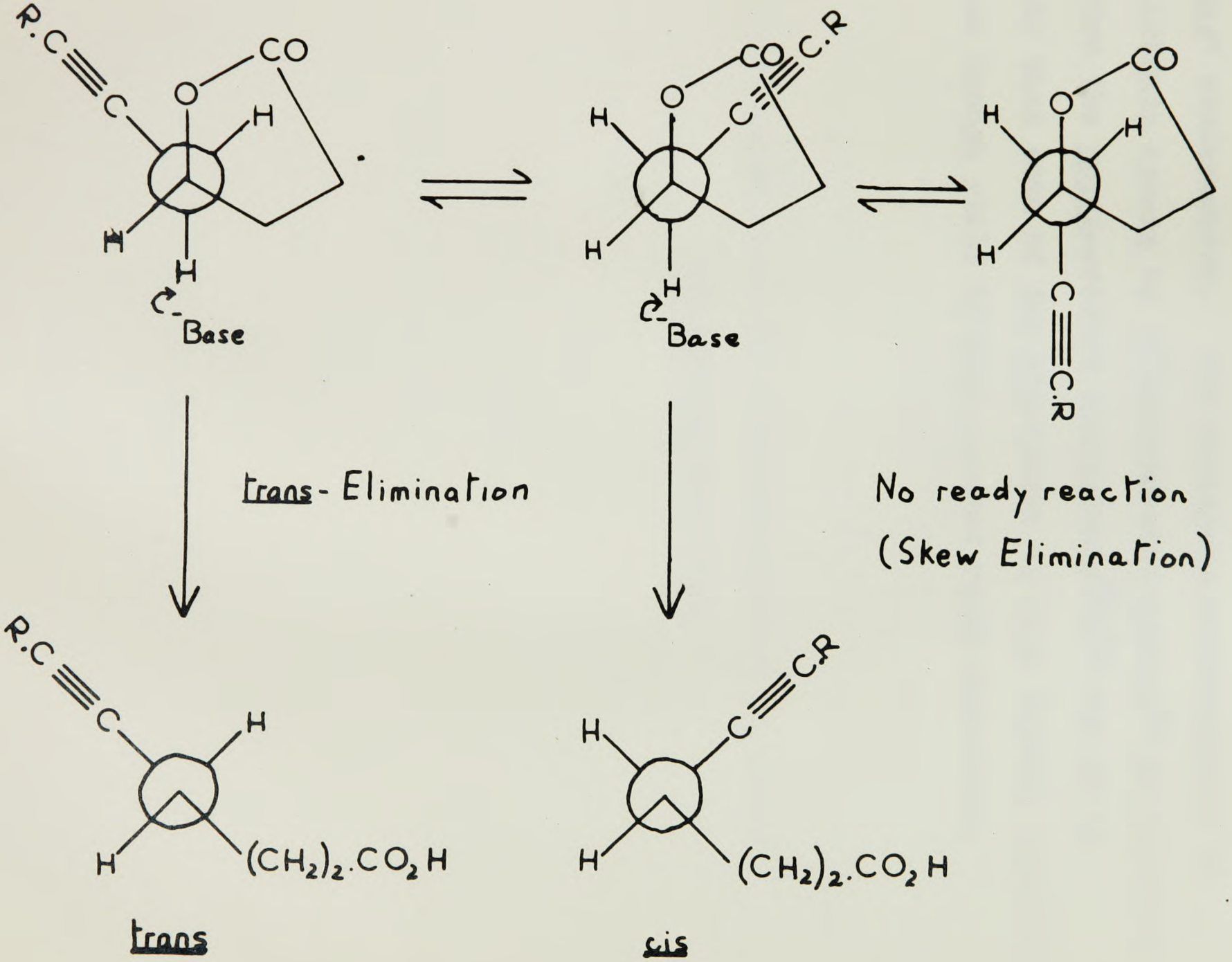
solution[5] proceeded only in 20% yield, the main product being iso-odyssic acid. It was considered that anhydrous conditions[52] would favour the isomerisation reaction over the carbonyl addition pathway, and that the latter reaction would be still further depressed by using a bulky anion. Potassium t-amyloxide was selected as a suitable base, and when mixed with iso-odyssic lactone in t-amyl alcohol, effected a 70% conversion to odyssin A (V). Purification by countercurrent distribution between ether and M/15 disodium hydrogen phosphate solution afforded odyssin A as a mixture of cis- and trans- isomers, the cis-isomer being subsequently removed by crystallisation. The pure trans- form had m.p. 110-155° (decomp.) in air or in vacuo, unchanged on repeated recrystallisation. A comparison with the naturally derived[5] and earlier synthetic[9] acids m.p.'s 190° (decomp.) was unfortunately not possible since no specimen had survived the long storage period, and it must be assumed that trans-odyssin A is dimorphous. The ultraviolet and infrared absorption spectra were identical with those of the authentic material.

Absolute proof of the identity of the synthetic

compound was provided by treatment with diazomethane to give the methyl ester, the physical and spectral characteristics of which were again identical with those of methyl trans-odyssin A obtained from natural sources.

The mother liquors from the crystallisation of the cis-trans mixture were re-examined in an attempt to isolate the cis-component, but only a concentrate of the latter could be obtained. Methylation of this gave an oily product, the infrared absorption of which contained bands at 740 (cis-CH=CH) and 950 cm.$^{-1}$ (trans-CH=CH). On the basis of infrared absorption it could be estimated that the amyloxide isomerisation of iso-odyssic lactone yielded ca. 90% of trans-odyssin A, compared with an estimated 75% of the trans-isomer produced by carbonate isomerisation of both naturally derived odyssin and iso-odyssic lactone[5]. From theoretical considerations, the reaction would not be expected to give wholly one or other of the isomers. The possible conformations of the lactone (which would undoubtedly be in a state of equilibrium) and the corresponding elimination products of each form are given below.

Possible Conformations of γ-Lactones with γ-Propargyl Substituents and the Corresponding Base-Elimination Products



The fact that the trans-isomer predominates shows that the above equilibrium lies to the left, probably as a result of the more favourable stereochemistry of the "trans" conformation. The analogous rearrangement of β-lactonic esters to αβ-unsaturated esters[53] is reported to give the trans-product exclusively[52,54] but it is likely that some of the cis-isomer is also formed, possibly in low enough yield to have escaped ready detection.

PART I, SECTION III

Model Experiments for Synthetic Routes to Odyssin and Related Compounds.

SECTION IIIa

Prior to the synthetic work described in Part I, Section II, a modification of the route to odyssin A investigated by Jones et al.[9] was considered in which Chodkiewicz coupling[30] in the final stage (see p.30) was to be used to overcome the difficulties of mixed coupling experienced by the earlier workers. Accordingly, methods for increasing the availability of trans-hept-4-en-6-ynoic acid (XXX) were investigated, as the earlier route[9] had proved a little unsatisfactory.

$HC{\equiv}C.CH_2.CH(OH).CH_2.CH_2.CO_2R$

(XXVI)

$\downarrow$ $POCl_3/Py.$

$HC{\equiv}C.CH{=}CH.CH_2.CH_2.CO_2H$

(XXX)

$\uparrow$ $-CEt$

$HC{\equiv}C.CH_2.CH.CH_2.CH_2.CO$ (O bridging CH and CO)

(XXVII)

Dehydration of the hydroxy-ester (XXVI; R=Et) with phosphorus oxychloride and pyridine[55], followed by hydrolysis, gave only a 16% yield of the trans-acid (XXX), while the action of phosphorus oxychloride and pyridine on the hydroxy-acid (XXVI; R=H) afforded only the lactone (XXVII). The conversion of this lactone to hept-4-en-6-ynoic acid (XXX) by base-induced β-elimination with sodium ethoxide[52-54] proved to be a far superior method (70% yield) giving a mixture estimated from its infrared absorption to contain 70% of the trans-isomer. The mixture of cis- and trans-forms was resolved by fractional crystallisation. This method could undoubtedly be improved still further, e.g. by amyloxide isomerisation, but no additional work was carried out as the route was abandoned in favour of the synthesis described in Part I, Section II, which had the advantage of giving iso-odyssic acid and lactone in addition to odyssin A.

SECTION IIIb

During the search for a synthetic route to odyssin the possibility of adapting the odyssin A synthesis was considered, and the following tentative route, starting from iso-odyssic acid (III), was drawn up.

$CH_3.(C{\equiv}C)_3.CH_2.CH(OH).CH_2.CH_2.CO_2H$

(III)

$\downarrow CrO_3$

$CH_3.(C{\equiv}C)_3.CH_2.CO.CH_2.CH_2.CO_2H$

$\downarrow \bar{O}H$

$CH_3.(C{\equiv}C)_2.CH{=}C{=}CH.CO.CH_2.CH_2.CO_2H$

$\downarrow [H]$

$CH_3.(C{\equiv}C)_2.CH{=}C{=}CH.CH(OH).CH_2.CH_2.CO_2H$

(I)

The final stage, selective reduction of the carbonyl group of the $-CH{=}C{=}CH.CO.CH_2-$ system, was known to be very difficult, Crombie and Jacklin[56] having shown the allenic

group in such a system to be very susceptible towards nucleophilic attack under the reducing conditions used, viz. sodium borohydride. However, further work was envisaged in order to ascertain whether or not selective carbonyl reduction of conjugated allenic ketones was possible, especially since a number of reducing reagents of varying selectivity, of the aluminium - and boro-hydride type, have recently become available.[57].

Attempts were made to prepare a model compound, 4-oxohept-6-ynoic acid (XXXI) by condensation of ethereal propargylmagnesium bromide[47] with succinic anhydride[58]. (N.B. Propargylmagnesium bromide could not be prepared in tetrahydrofuran, the reaction of propargyl bromide and magnesium giving an insoluble white precipitate, presumably of the di-magnesium bromide[47]). Under varying reaction conditions[59,60], small yields of the products of further reaction of (XXXI) with a second equivalent of propargyl-magnesium bromide, i.e. (XXXIII) and (XXXIV), were isolated, together with small quantities of an acid, m.p. 128°, with the empirical formula $C_7H_8O_3$. Its infrared absorption, with bands at 3280 (≡C-H), and 1740 and 1697 cm.$^{-1}$ (CO) was not unreasonable for structure (XXXI). However, the acid $(C_7H_8O_3)_n$ proved to be stable to alkali whereas a

compound of structure (XXXI) would be expected to be very sensitive to basic conditions, the β-keto-acetylene system

$$HC{\equiv}C.CH_2.CO.CH_2.CH_2.CO_2H$$

(XXXI)

$$H_2C{=}C{=}CH.CO.CH_2.CH_2.CO_2H$$

(XXXII)

$$(HC{\equiv}C.CH_2)_2.C(OH).CH_2.CH_2.CO_2H$$

(XXXIII)

$$(HC{\equiv}C.CH_2)_2.C(O).CH_2.CH_2.CO$$

(XXXIV)

in ketones[56,61,62] and aldehydes[63] having been shown to be extremely readily isomerised to the corresponding allene, e.g. $R.CH_2.CO.CH_2.C{\equiv}C.CH_2.R'$ gave $R.CH_2.CO.CH{=}C{=}CH.CH_2.R'$ on treatment with 0.001N-potassium hydroxide solution, where $R = C_5H_{11}$ and $R' = C_6H_{12}.CO_2H$, the reaction being complete in three minutes at 20°.[56] The acid $(C_7H_8O_3)_n$ was unaffected by basic conditions varying from sodium hydrogen carbonate

solution to 2N-potassium hydroxide solution, all at 20°. The lability of the system in structure (XXXI) was demonstrated during an attempted preparation from the hydroxy-acid (XXVI; R=H) by oxidation with chromic acid[61,64]. The β-keto-acetylene (XXXI)formed initially underwent prototropic rearrangement, even though acidic conditions were maintained throughout the experiment, and the only product isolated (in low yield) was 4-oxohepta-5,6-dienoic acid (XXXII), identified by the infrared absorption which contained bands at 1950, 1925, and 850 ($CH=C=CH_2$), 1720 (CO_2H), and 1675 $cm.^{-1}$ (αβ-unsaturated CO).

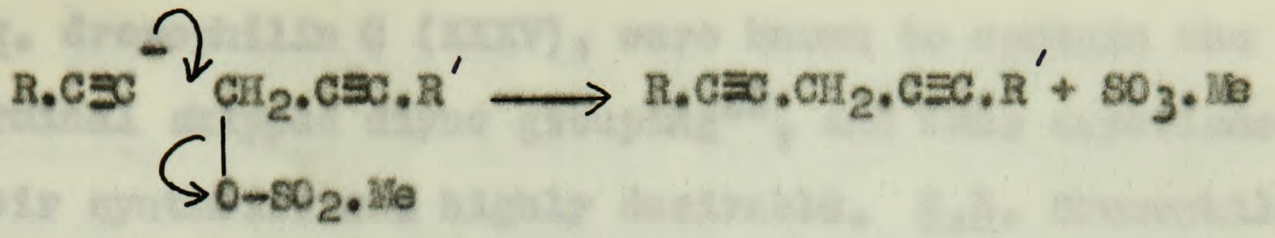
Further work on this approach was postponed at this stage in order that more promising routes might be investigated.

SECTION IIIc

Model investigations on compounds containing the $\equiv C.CH_2.C\equiv$ group, for which the phrase "skipped diyne" has been coined[40], were carried out before the commencement of the main odyssin work described in Part I, Section I which involved a skipped diyne intermediate, in order to gain experience of the synthetic procedures involved and to develop controlled isomerisation conditions for the rearrangement of skipped diynes to the corresponding allene-acetylenes.

The early routes to skipped diynes, in which βγ-acetylenic halides or methylene halides and metal acetylides were reacted under vigorous conditions, viz. at 140°[65] gave very poor yields[65,66] since the main reaction was followed by further substitution of the activated methylene group.

Mild conditions for the formation of skipped diynes were first described in 1950 by Raphael and Sondheimer[16], who condensed an acetylenic Grignard reagent with a βγ-acetylenic methanesulphonate as shown below, the reaction being an extension of the well known alkylation of acetylenic Grignard reagents with alkyl sulphonates[39,67].



Still milder conditions were evolved by several workers[17] shortly afterwards by application of the discovery by Nieuwland and co-workers[18] that the coupling of allyl bromide with acetylenic Grignard reagents was catalysed by cuprous halides. Using cuprous halide catalysis, many substituted βγ-acetylenic halides have been condensed with acetylenic Grignard reagents to give skipped diynes[19].

Terminal skipped diynes, 1,4-diynes, may also be prepared by the latter method[20], and the further successive condensation of both terminal and internal skipped diynes with βγ-acetylenic derivatives has been developed[19,21] as far as the syntheses of up to five triple bonds in skipped conjugation[21].

The 1,4-diyne series of compounds was selected for study for several reasons. Their ease of prototropic rearrangement was expected to be comparable with that of the skipped diyne group to be isomerised in the odyssin synthesis, and the presence of an ethynyl group greatly simplified the problem of purification. Also the polyacetylenes isolated from cultures of Drosophila subatrata,

e.g. drosophilin C (XXXV), were known to contain the terminal skipped diyne grouping[68], and thus experience in their synthesis was highly desirable. N.B. Drosophilin C

$$HC{\equiv}C.CH_2.(C{\equiv}C)_2.\underset{c}{CH{=}CH}.CH_2.CO_2H$$

(XXXV)

was known to be readily isomerised to the terminal allene by sodium hydrogen carbonate solution at 20°.[68]

Nona-1,4-diyne (XXXVI; R=C_4H_9) was prepared as described by Gensler et al.[20] by reaction of hex-1-ynyl-magnesium bromide and propargyl bromide in ether in the presence of cuprous chloride. The hydrocarbon (74%), when isolated was shown to be contaminated with 10% of allenic impurity (XXXVII; R=C_4H_9) from the intensity of the absorption maximum at 2190 Å in the ultraviolet spectrum. Purification via the copper derivative was found to be the most satisfactory method, silica-gel chromatographic separation proving of little value[20].

$$R.C{\equiv}C.CH_2.C{\equiv}CH \qquad \text{(XXXVI)}$$

$$\downarrow \ \bar{O}H$$

$$R.C{\equiv}C.CH{=}C{=}CH_2 \qquad \text{(XXXVII)}$$

The preparation of the more labile hydrocarbon oct-6-ene-1,4-diyne (XXXVIII) from pent-3-en-1-ynylmagnesium bromide and propargyl bromide with cuprous chloride catalysis gave only a 10% yield of allene-contaminated product after four days refluxing in ether. However, the use of tetrahydrofuran as the solvent raised the yield to 60% of almost pure 1,4-diyne (XXXVIII) and reduced the reaction period to two hours. Rigorous purification was once again effected *via* the copper-derivative. The alkali-catalysed isomerisation of (XXXVIII) to octa-1,2,6-triene-4-yne (XXXIX) and oct-6-ene-2,4-diyne (XL) was studied, the results being summarised below.

$CH_3.CH{=}CH.C{\equiv}C.CH_2.C{\equiv}CH$

(XXXVIII)

30 min. ↓ 0.01N KOH at 20°

$CH_3.CH{=}CH.C{\equiv}C.CH{=}C{=}CH_2$

(XXXIX)

10 hr. ↓

$CH_3.CH{=}CH.C{\equiv}C.C{\equiv}C.CH_3$

(XL)

Hexa-1,4-diyne (XXXVI; R=CH_3) was obtained in poor yield from propynylmagnesium bromide[50] and propargyl bromide in tetrahydrofuran. A pure sample was not obtained owing to the difficulties experienced in the isolation of the volatile hydrocarbon from the relatively high boiling reaction solvent.

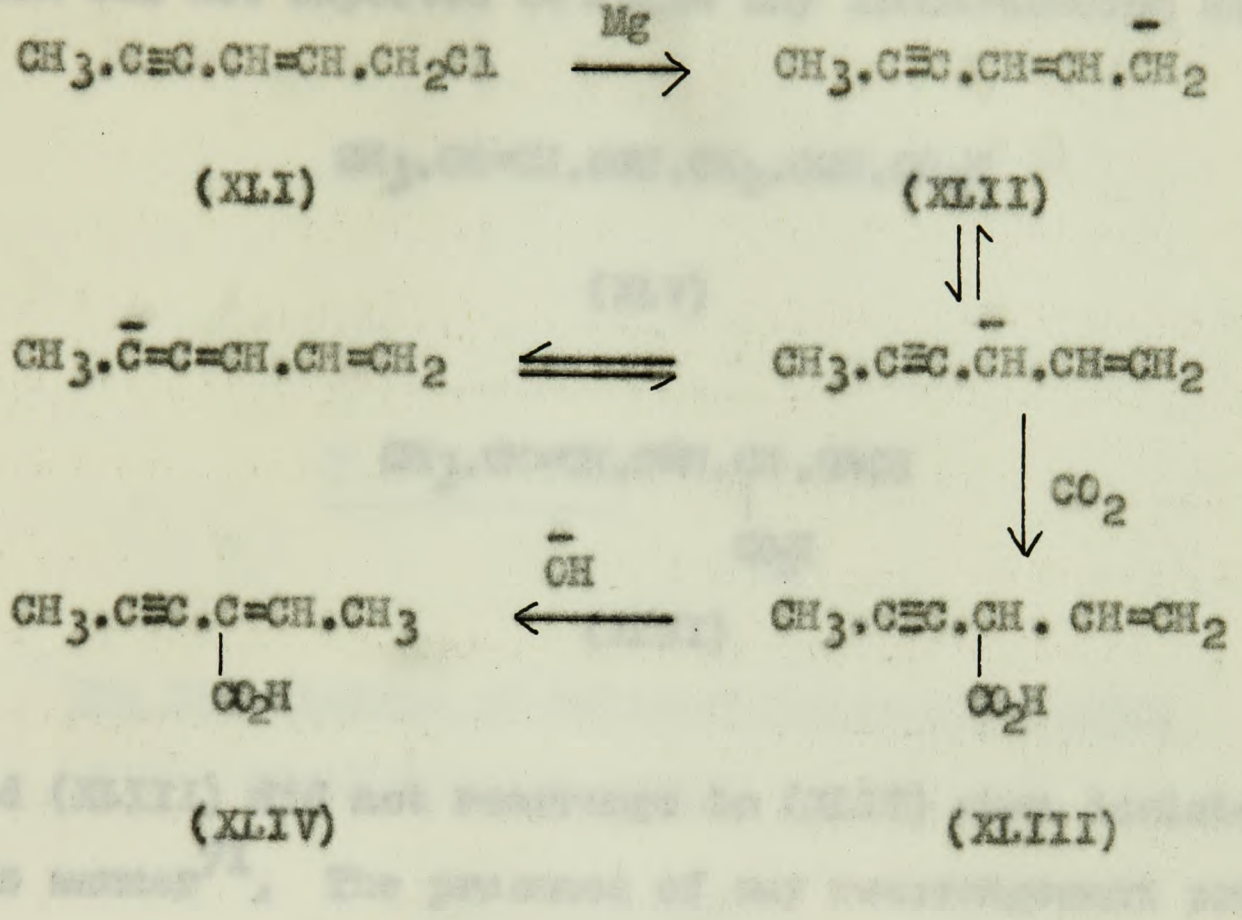
All the 1,4-diynes prepared contained a band at 1310 cm.$^{-1}$ in the infrared absorption. This absorption, which was the strongest band in the spectrum, was also observed in drosophilin C (XXXV), and the frequency was constant in all the compounds examined. The band was also present in the published spectra of non-terminal skipped diynes[19,40], and occurred in the range 1320-1310 cm.$^{-1}$. The absorption appeared to be characteristic of the $\equiv C.CH_2.C\equiv$ system as it disappeared from the spectrum on isomerisation, e.g. (XXXVIII) to (XXXIX).

A band in the same region was found in the spectra of 1-cyanobut-2-yne[69] (1320 cm.$^{-1}$, strong) and malononitrile[70] (1320 cm.$^{-1}$, medium) which both have methylene groups sandwiched between "triple" bonds. The 1320 cm.$^{-1}$ band in the latter compound was ascribed by Halverson and Francel[70] to the wagging deformation of the methylene hydrogen atoms, and it is probable that the 1320-1310 cm.$^{-1}$ bands in the

spectra of the skipped diyne compounds are due to the same deformation, with however, an enhanced intensity. Further work on the diagnostic possibilities of this band is being carried out.

Qualitative experiments were carried out to determine the relative activity of the hydrogen atoms of 1,4-diynes. The most active proton in nona-1,4-diyne (XXXVI; R=C_4H_9) had been shown to be that of C_1 by deuteration *via* the Grignard reagent and deuterium oxide, no replacement of the methylene protons being observed.[20] However, the intermediate methylene group in oct-6-one-1,4-diyne (XXXVIII) should be more active owing to the increased conjugation, and the possibility of the replacement of one of the methylene protons under Grignard conditions could not be ignored. Rearrangement of the anion so produced would not be unexpected in view of the ease with which βγ-acetylenic-magnesium halides isomerise to a mixture of all the possible structures[7,47]. Also, Jones, Allan, and Whiting[71] found that carboxylation of the Grignard reagent from 1-chlorohex-2-en-4-yne (XLI) gave a mixture of acids derived from reaction at all possible active centres, *i.e.* the initially formed anion (XLII) reacts partly at several carbon atoms, the possible reactive species being shown

in the scheme below.



Oct-6-ene-1,4-diyne (XXXVIII), on treatment with ethylmagnesium bromide followed by carbon dioxide under pressure[72], gave a very low yield of acidic product which proved to be mainly non-7-ene-2,5-diynoic acid (XLV), the structure being assigned on the basis of bands at 2240 ($C\equiv C.CO_2H$[73]), and 1692 cm.$^{-1}$ ($\equiv C.CO_2H$[73]) in the infrared spectrum. The presence of a small amount of the acid (XLVI), formed by initial replacement by the Grignard reagent of one of the methylene protons, was indicated by a band at 3300 cm.$^{-1}$ ($\equiv C-H$). The acids

were isolated *via* sodium hydrogen carbonate solution, which was not expected to cause any isomerisation as the

$$CH_3.CH{=}CH.C{\equiv}C.CH_2.C{\equiv}C.CO_2H$$

(XLV)

$$CH_3.CH{=}CH.C{\equiv}C.\underset{\displaystyle CO_2H}{\underset{|}{CH}}.C{\equiv}CH$$

(XLVI)

acid (XLIII) did not rearrange to (XLIV) when isolated in this manner[71]. The presence of any rearrangement products was excluded by the absence of allenic absorption bands in the infrared spectrum, and this was confirmed by the ultraviolet absorption which showed a maximal absorption at 2230 Å (inflexion at 2310 Å) characteristic of the ene-yne chromophore. It may therefore be concluded that the ethynyl proton in (XXXVIII) is the most active, but that as the activation of the skipped methylene group is increased, a greater amount of replacement at this position may be expected.

P A R T II

The Preparation of Polyacetylenes containing cis-Ethylenic Bonds.

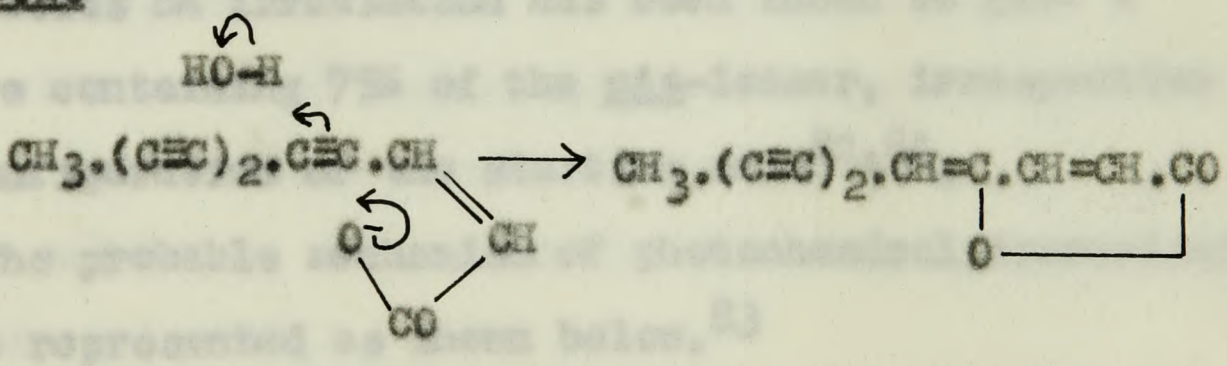
PART II, SECTION I

Synthetic Applications of Photochemical Isomerisation

INTRODUCTION

In a large proportion of the naturally occurring polyacetylenes containing an ethylenic linkage the double bond has the cis-configuration (designated hereafter as "cis-polyacetylenes"), which considerably increases the problems of synthesis. Starting materials containing a cis-double bond are of limited availability, and their purification is generally extremely tedious. Also the compounds of greatest utility, viz. alcohols and acids containing a cis-ethylenic bond, undergo ready acid or base catalysed cyclisation reactions.[50, 74]

e.g.[75]



Owing to the isolation in recent years of an increasing number of cis-polyacetylenes, it was decided to study the preparation of cis-ethylenes with a view to improving the available synthetic routes, and in order to

develop new methods of formation.

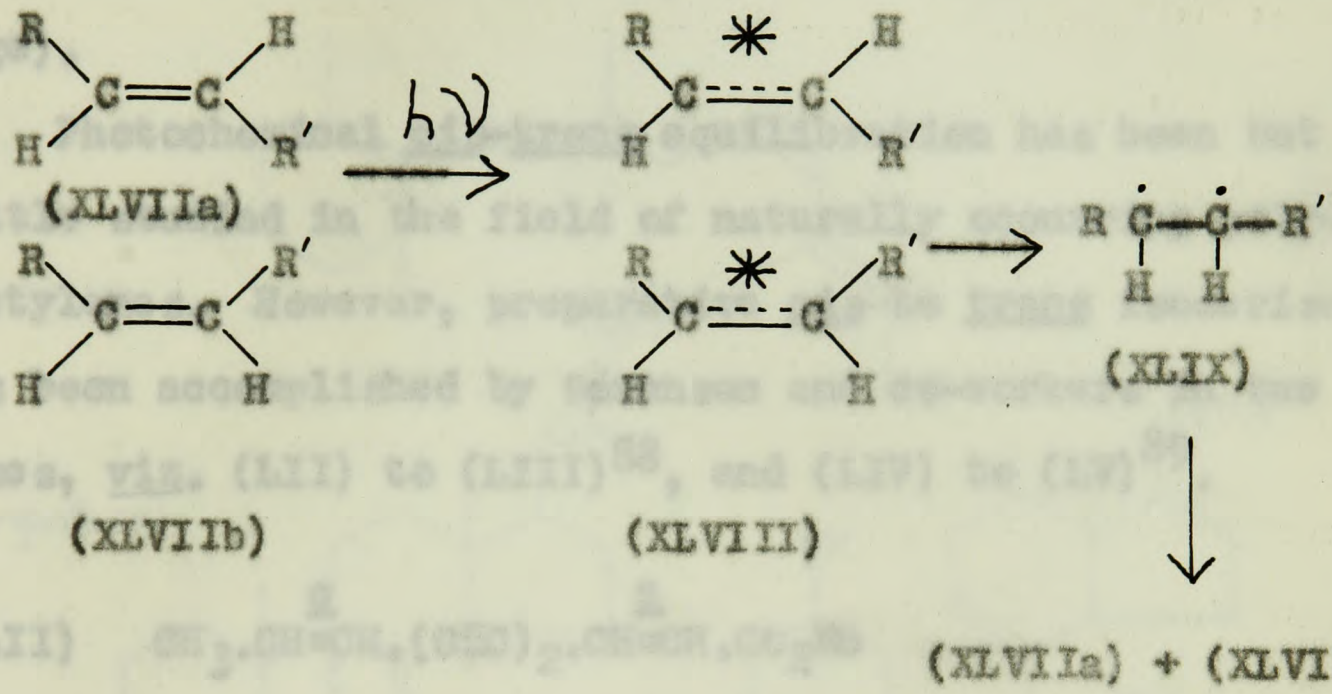
Chemical methods, involving dehydration[76], anionotropic rearrangement of 1-on-4-yn-3-ol systems,[50,77,78] and stereospecific reduction of a triple bond,[50,79] did not appear very promising owing to the difficulties mentioned above, and attention was turned towards the photochemical isomerisation of double bonds by visible or ultraviolet light.[80]

The isomerisation of certain ethylenic derivatives by visible or ultraviolet light was first observed many years ago[81], and was shown to give an "equilibrium" mixture of the cis- and trans- forms[80,82-84]. For example, the well known isomerisation of fumaric (trans) and maleic (cis) acids on irradiation has been shown to give a mixture containing 75% of the cis-isomer, irrespective of the configuration of the starting acid[82,84].

The probable mechanism of photochemical isomerisation may be represented as shown below.[83]

Absorption of light raises the molecule from the ground state (XLVII) to the excited singlet state (XLVIII), which then undergoes transition to the triplet (di-radical) state (XLIX) at the point of equal energy, i.e. where the potential energy curves of both states intersect.[83] In

the triplet state the molecule is relatively free to rotate



about the central bond, thereby giving rise to a mixture of cis- and trans-isomers, (XLVIIb) and (XLVIIa) respectively, on its return to the ground state.

A wide range of photochemical isomerisations has been observed and numerous examples are to be found in natural product chemistry, from which the following illustrations have been selected.

The carotenoids[85] have provided many instances of cis-trans isomerism, and the visual process is now known to be dependent on the isomerisation of all-trans-vitamin A aldehyde (L) to neo-retinene b (LI) by blue or violet light[77,86].

In the steroid field also a cis-trans light-catalysed

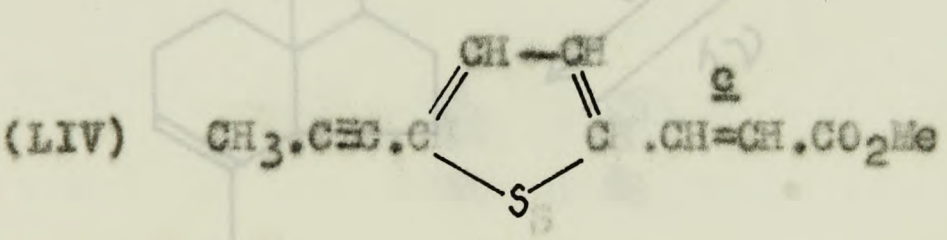
rearrangement is of biological importance in the interconversions of compounds related to Vitamin D[87] (see next page).

Photochemical cis-trans equilibration has been but little studied in the field of naturally occurring polyacetylenes. However, preparative cis to trans isomerisation has been accomplished by Sørensen and co-workers in two cases, viz. (LII) to (LIII)[88], and (LIV) to (LV)[89].

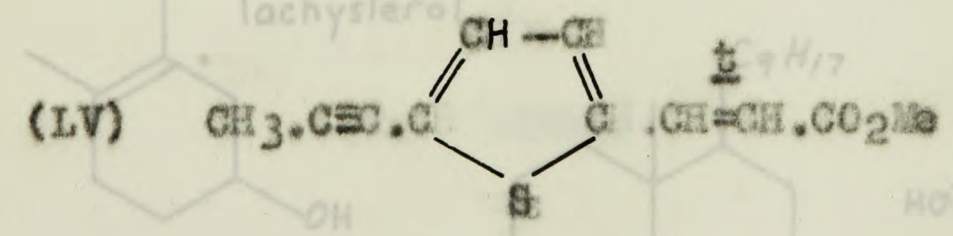
(LII) $CH_3.CH{=}\underset{c}{CH}.(C{\equiv}C)_2.CH{=}\underset{c}{CH}.CO_2Me$

(LIII) $CH_3.CH{=}\underset{c}{CH}.(C{\equiv}C)_2.CH{=}\underset{t}{CH}.CO_2Me$

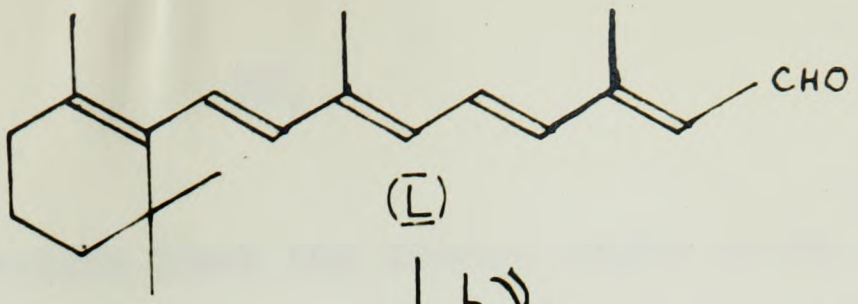
(LIV)



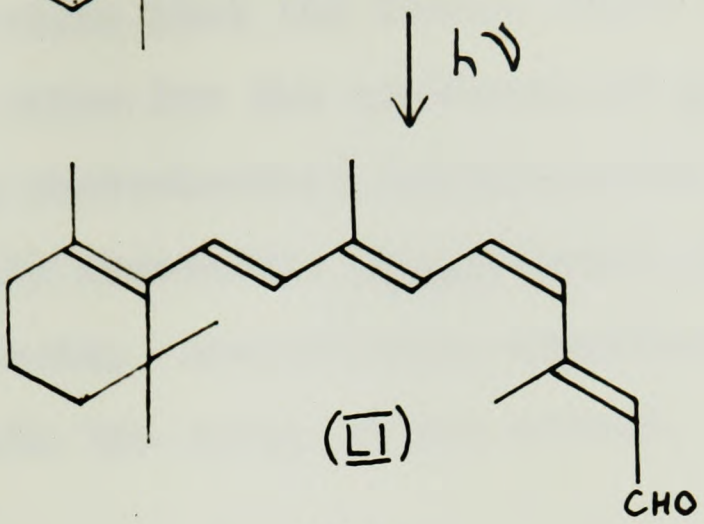
(LV)



All the examples quoted above served to give a

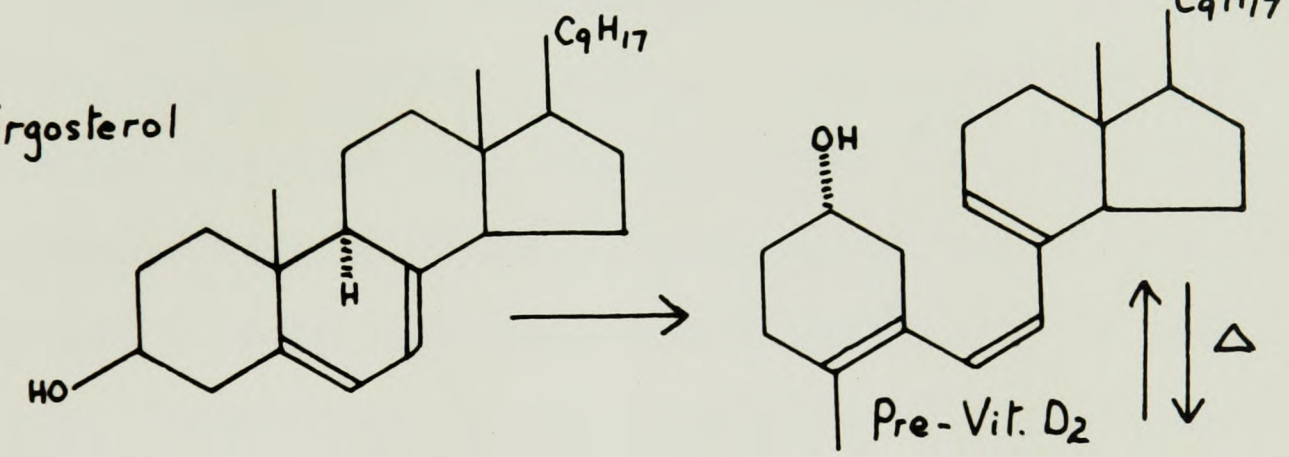


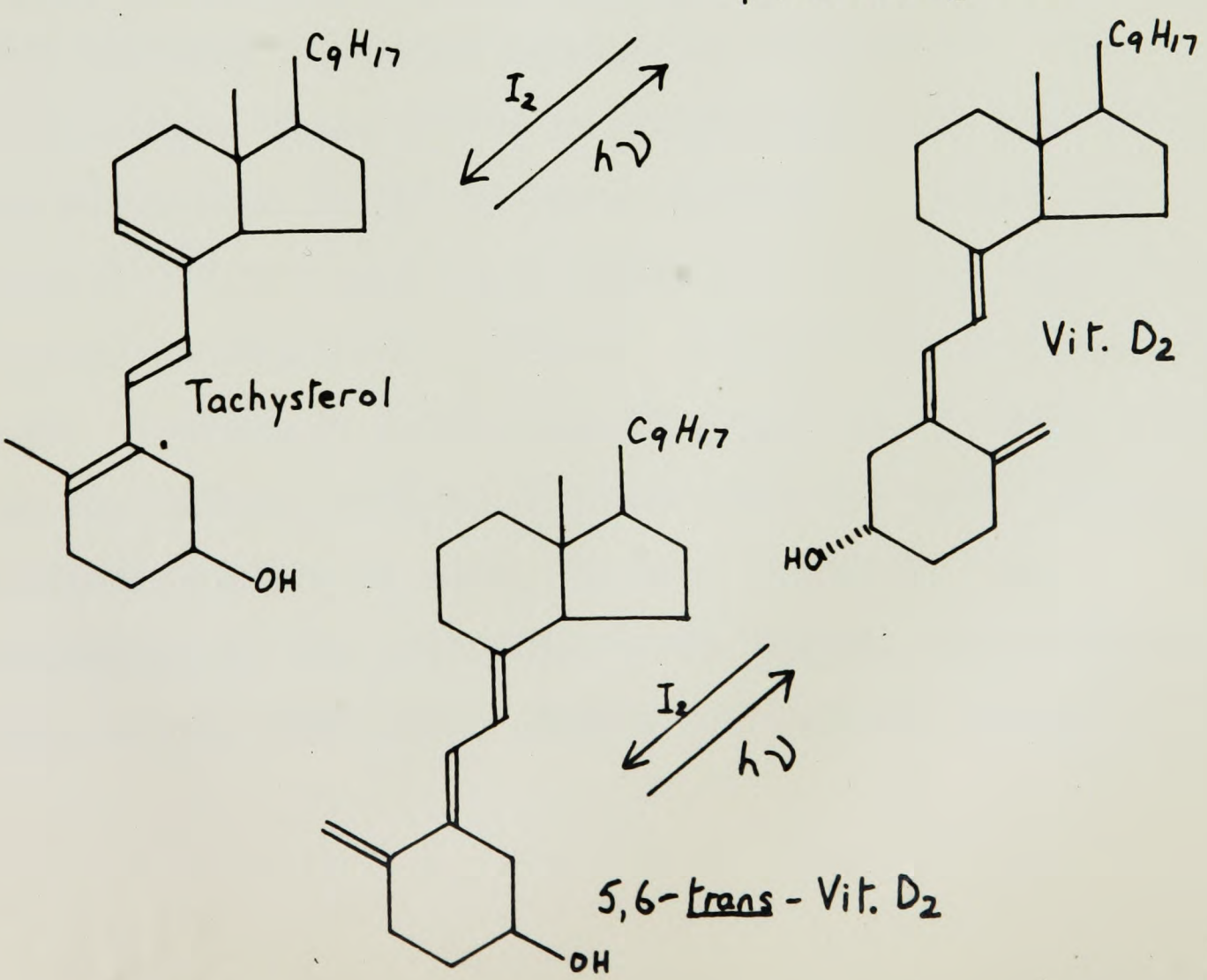
(L)



(LI)

Ergosterol





strong indication that the method might prove to be of preparative value for the synthesis of cis-polyacetylenes by employing photochemical equilibration of the usually fairly readily accessible trans-isomer at a late stage in the synthesis. Accordingly, experiments were planned to investigate the scope of the method.

PRESENT WORK

The light source selected for the irradiation experiments was a quartz, low-pressure mercury vapour-argon lamp. The wavelengths of the lines in the emission spectrum, and the transmission ranges of some apparatus materials are given overleaf.

The underlined wavelengths denote the most intense of the higher frequency lines in the spectrum[90] and this spacing, together with the judicious use of the relative transparencies of quartz, pyrex glass, and soft glass, enabled a broad selection of wavelengths to be made. Later, measurement of the efficiency of isomerisation in much narrower frequency ranges was envisaged[90]. The temperature, which had to be standardized for reproducibility[83,91] was maintained at 20° by water cooling. Initially, iodine[88,89] was used as a sensitiser, but was later found to have no beneficial effect. Polyacetylenic compounds which absorbed at relatively long wavelengths were selected for the initial studies in order that the lower energy radiations might be used, thereby minimising the disruption of the molecules by the higher energy frequencies. Also, as many functional groups, and certain active solvents,

Wavelengths of Lines in the Mercury Emission Spectrum[90] (in Å)											
Ultraviolet Region								Visible Region			
1849	1942	2537	2652-4	2804	3021	3126-31	3650-63	4046	4358	5461	5770-91
← Fused Quartz →											
← Quartz →											
← Pyrex Glass →											
← Soft Glass →											

e.g. alcohols, were known to participate in photochemical reactions[91], irradiations were carried out as far as possible in inert solvents and at high dilution. The use of ethers as solvents was precluded by the ease of peroxide formation, giving rise to the corresponding radicals which then attacked the polyacetylenic chain. Two sets of apparatus were used, and are referred to as either the "pyrex glass" or the "quartz" apparatus.

The observation by Sørensen et al.[88] that only the double bond adjacent to the ester group in cis-matricaria ester (LII) was isomerised during irradiation suggested considerable activation by the carbomethoxy group. Therefore systems in which the double bond was conjugated directly with an ester were studied first.

Lachnophyllum ester, which occurs in nature as both the cis-[92] and the trans-isomers[93], was used for the initial investigations. The trans-ester (LVI; R=Me), m.p. 18°, was obtained by esterification of trans-dec-2-ene-4,6-diynoic acid (LVI; R=H) with methanol-sulphuric acid.

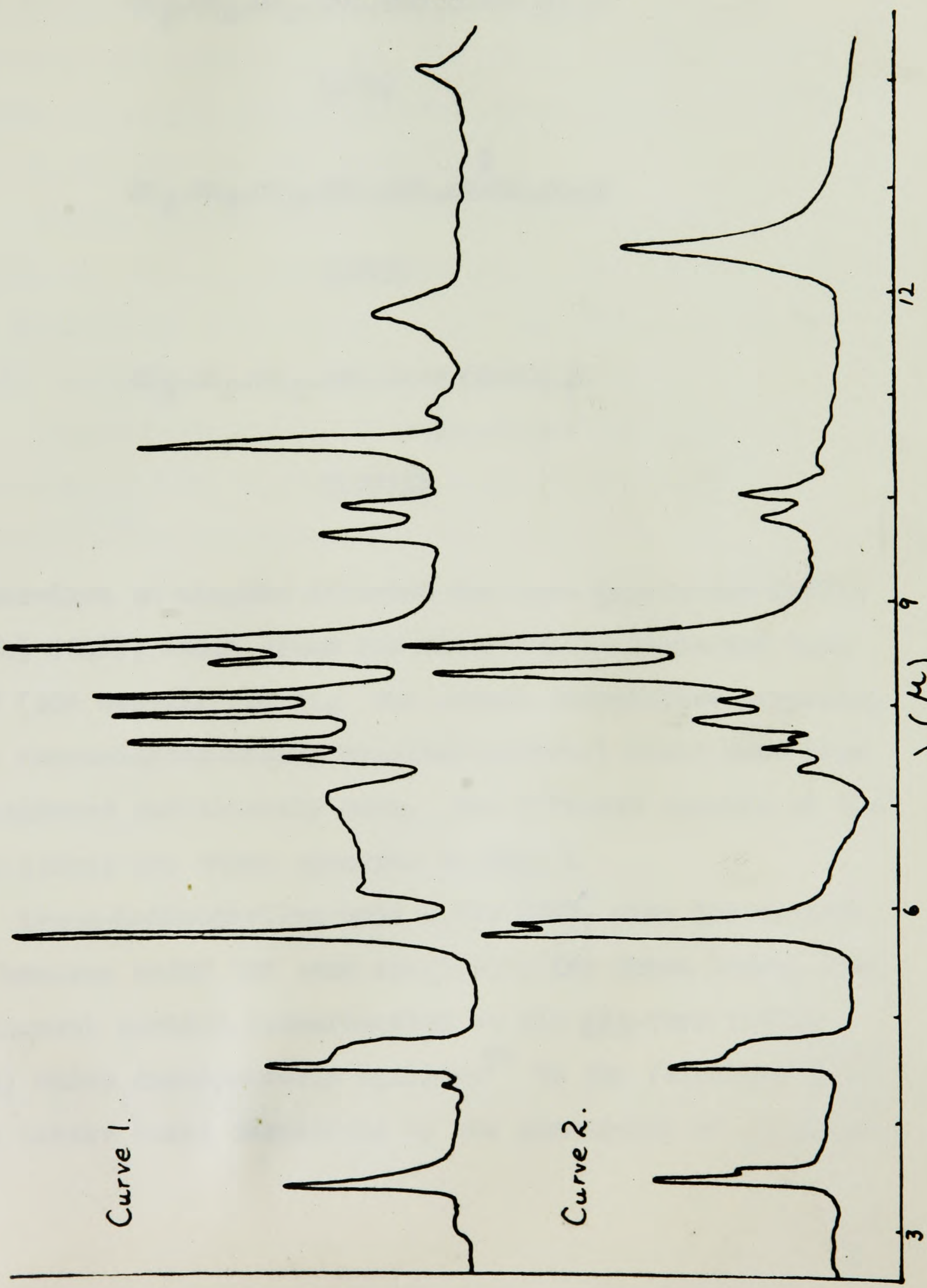
On irradiation in light petroleum in the pyrex glass apparatus for one hour at 20°, the trans-isomer was converted to the cis-ester (LVII; R=Me) to the extent of 80%, estimated from the intensity of the new band at 809 cm.$^{-1}$ (cis-CH=CH) in the infrared spectrum. Chromatographic

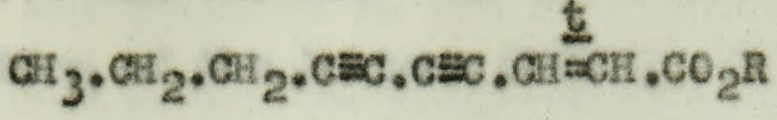
FIG. 1

Infrared Spectra of Lachnophyllum Esters

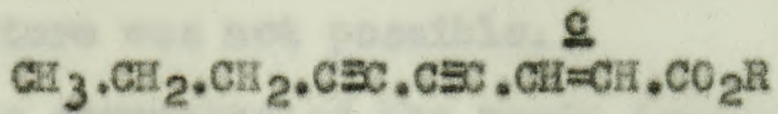
Curve 1. trans (LVI; R=Me). Curve 2. cis (LVII; R=Me)

(in CS_2)

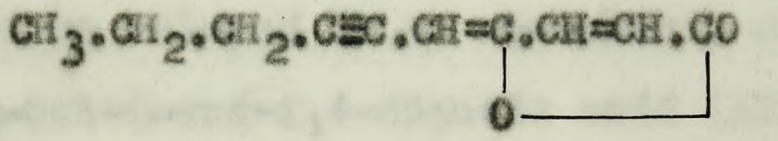




(LVI)



(LVII)



(LVIII)

separation on alumina afforded the pure cis-isomer (LVII; R=Me) (60%), which after two recrystallisations had m.p. 31° (30% overall yield). For normal preparative purposes, the chromatographically resolved material would have been considered sufficiently pure. The infrared spectra of the two esters are shown opposite in Fig. 1

trans-Lachnophyllum acid (LVI; R=H), when irradiated in benzene under the same conditions for three hours, also underwent partial isomerisation to the cis-form (LVII; R=H) which spontaneously cyclised[74] to the γ-lactone (LVIII), the latter being identified by the appearance of absorption

bands at 1778 and 819 cm.$^{-1}$ in the infrared spectrum. The proportion of the lactone (LVIII) was estimated spectroscopically to be 30%, but owing to decomposition during attempted chromatographic spearation, resolution of the mixture was not possible.

Having demonstrated the ready isomerisation of the ethylenic linkage when adjacent to an ester group, it was of interest to see whether or not the activation by the ester could be relayed by an acetylenic chain.

trans-Oct-6-ene-2,4-diynoic acid (LIX; R=H) was synthesised (95% yield) by Chodkiewicz coupling[30] of trans-1-bromopent-3-en-1-yne with propiolic acid. Esterification with methanol-sulphuric acid gave the trans-methyl ester (LIX; R=Me) (60%).

$$\underset{t}{CH_3.CH{=}CH.(C{\equiv}C)_2.CO_2R}$$

(LIX)

$$\underset{c}{CH_3.CH{=}CH.(C{\equiv}C)_2.CO_2R}$$

(LX)

For the purposes of comparison, the cis-ester

(LX; R=Me) was prepared in the same way from cis-1-bromopent-3-en-1-yne and propiolic acid, followed by esterification. The cis-compound proved to be a thermally unstable syrup which underwent appreciable decomposition during chromatographic purification. It was characterised by quantitative ultraviolet spectroscopy and by its infrared absorption. The yield (7%) was very low compared with that of the trans-ester, but the reluctance of some cis-compounds to couple under Chodkiewicz conditions has been encountered previously.[94]

The cis- and the trans- methyl esters, (LX; R=Me) and (LIX; R=Me) respectively, were found to have significantly different retention times when subjected to vapour phase chromatography,* thus providing a convenient method for the quantitative analysis of mixtures of the two isomers.

The trans-ester, when irradiated in light petroleum in the pyrex glass apparatus at 20°, was isomerised to a mixture of the cis- and trans-forms and the percentage of each isomer present was ascertained at intervals using vapour phase chromatographic analysis. The photochemical equilibrium mixture consisted of 55% of the trans- and

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* I am indebted to Dr.G.Read for advice on the application of this technique to polyacetylenes.

45% of the cis-ester after irradiation for 15 minutes, the composition being unchanged by any increase in the irradiation period. The relative intensities of the bands at 942 (trans-CH=CH) and 714 cm.$^{-1}$ (cis-CH=CH) in the infrared absorption were as would be expected from a mixture of the above composition. The reaction was not investigated on a preparative scale owing to the extensive decomposition which had occurred previously during chromatography of the cis-ester. Preparative vapour phase chromatography is not feasible as yet, as the long retention times which would be necessary would undoubtedly result in much decomposition owing to the high column temperatures (ca. 200°) needed. The short retention times (ca. 2 minutes) obtained in the qualitative work prevented decomposition from becoming a serious disadvantage.

The success achieved with the above vapour phase chromatography prompted a reinvestigation of the irradiation of trans-lachnophyllum ester (LVI; R=Me) in order that the "equilibrium" composition might be accurately determined. Unfortunately the isomers were not resolved on the "Apiezon L" column, but in view of the successful separation on alumina, it should be possible to select suitable column materials for satisfactory resolution.

After obtaining several confusing chromatographic experiments, the importance of analysing the mixtures immediately after dissolution in the alcohols used as carriers was realised, since nucleophilic addition to the triple bonds occurred relatively quickly, giving compounds with retention times similar to those of the pure esters.

The next stage in the investigation of the scope of the method was a study of ethylenic systems having acetylenic activation only. trans-Dehydromatricarianol (LXI), was selected as a suitable model and was readily prepared (80%) by the coupling of 1-bromopenta-1,3-diyne and trans-pent-2-en-4-yn-1-ol under Chodkiewicz conditions.[30] The chromatographically purified material was irradiated in ethanol (for solubility reasons) at 20° in the pyrex glass apparatus for up to 3 hours but no detectable isomerisation was achieved. However, on irradiation for 30 minutes under the same conditions in the quartz apparatus, trans-dehydromatricarianol (LXI) underwent considerable change, as indicated by the appearance of new bands at 1627, 1165, 1156, and between 900 and 700 $cm.^{-1}$ in the infrared absorption. Considerable decomposition had occurred, subsequently calculated to account for 41% of the starting material.

Chromatography of the irradiated mixture achieved a separation into a relatively non-polar component (10%) and dehydromatricarianol (49% recovery, see below for composition), the latter consisting of a mixture of cis- and trans-isomers as shown by the absorptions at 942 (trans-CH=CH) and 730 cm.$^{-1}$ (cis-CH=CH) in the infrared spectrum. The most probable structure for the non-polar compound was considered to be (LXIII), 1,4-epoxydeca-2,4-diene-6,8-diyne, formed by cyclisation under the reaction conditions of the cis-isomer (LXII), the configuration of which facilitates internal attack at C_4.[74]

Meticulous chromatography of (LXIII), during which further decomposition took place, effected a further resolution into two isomers which had very similar ultraviolet absorption properties. The isomer eluted first (α, 1.5% overall yield) could not be crystallised but was characterised by quantitative ultraviolet absorption spectroscopy and by its infrared spectrum. The other isomer (β, 4% overall yield) was obtained crystalline and had essentially the same ultraviolet chromophore. The differences in the infrared spectra could be ascribed to stereoisomerism about the 4,5 double bond in (LXIII). The spectra are given overleaf (Fig. 2).

The mixture of cis- and trans-dehydromatricarianol

FIG. 2a

Infrared Spectra of 1,4-Epoxydeca-2,4-diene-6,8-diyne

Curve 1. α-isomer (LXV). Curve 2. β-isomer (LXIV)

(in CS_2)

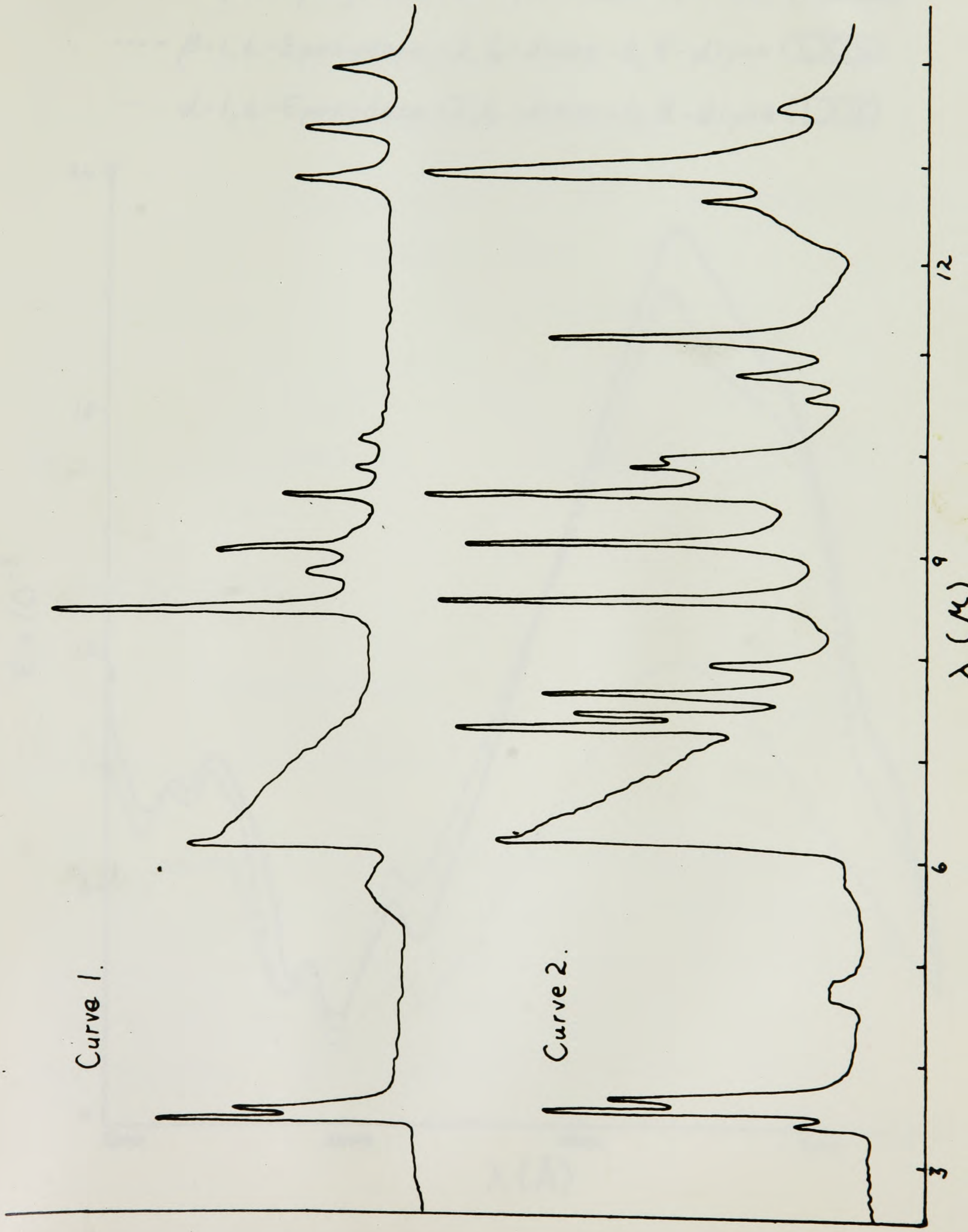


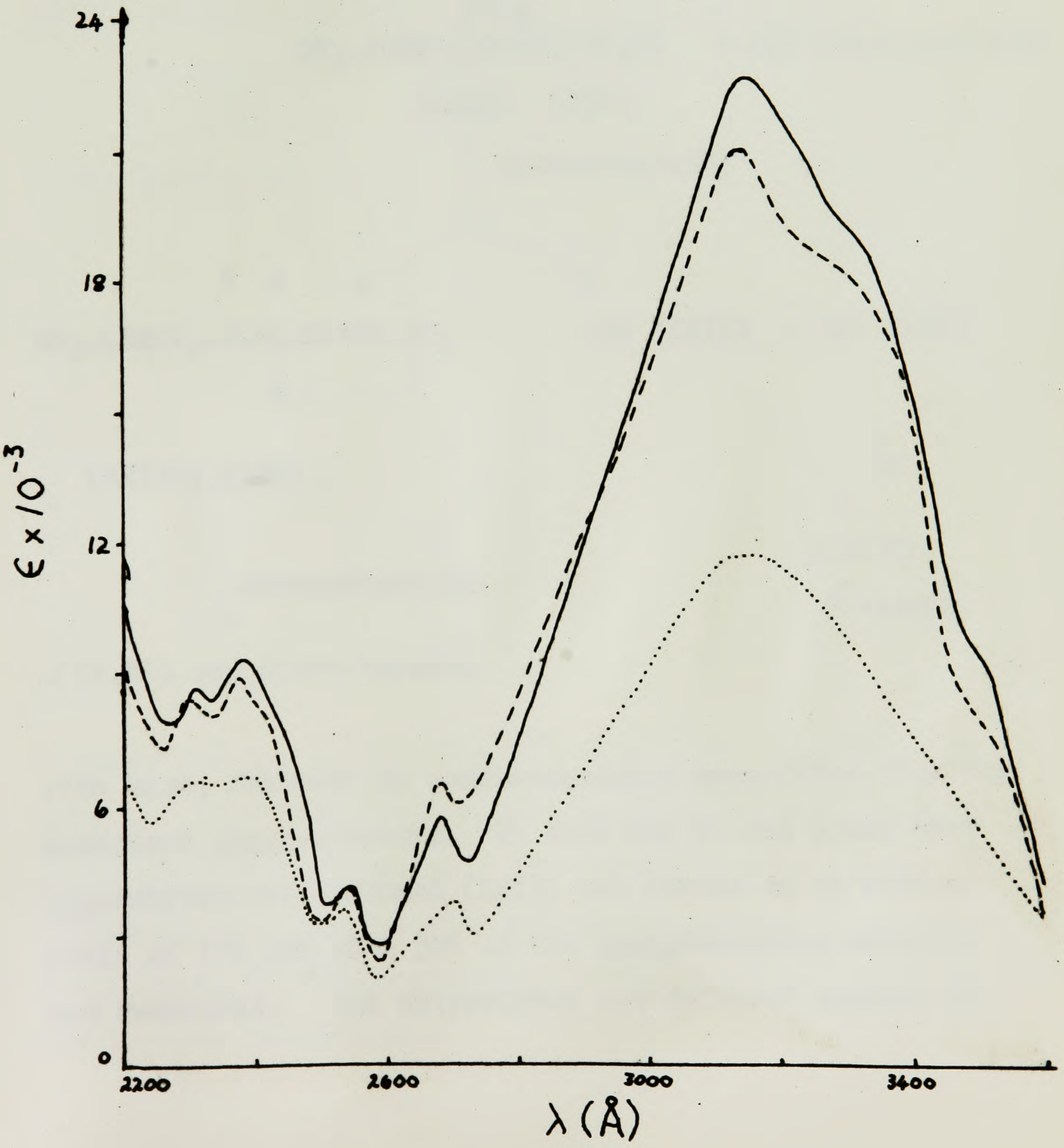
FIG. 2b.

Ultraviolet Spectra of

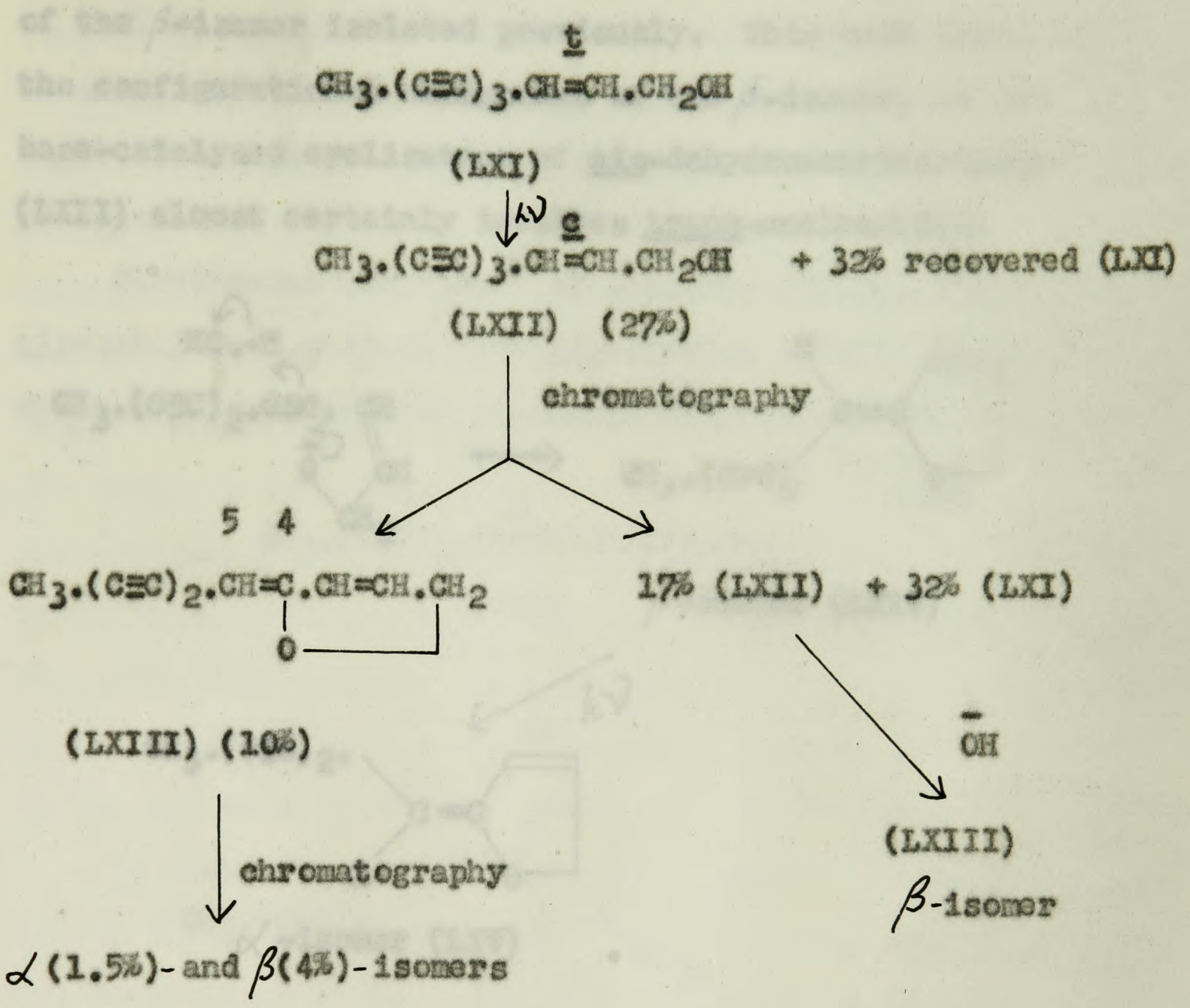
—— 2,5-Epoxyundeca-3,5-diene-7,9-diyne (LXVII)

---- β-1,4-Epoxydeca-2,4-diene-6,8-diyne (LXIV)

····· α-1,4-Epoxydeca-2,4-diene-6,8-diyne (LXV)

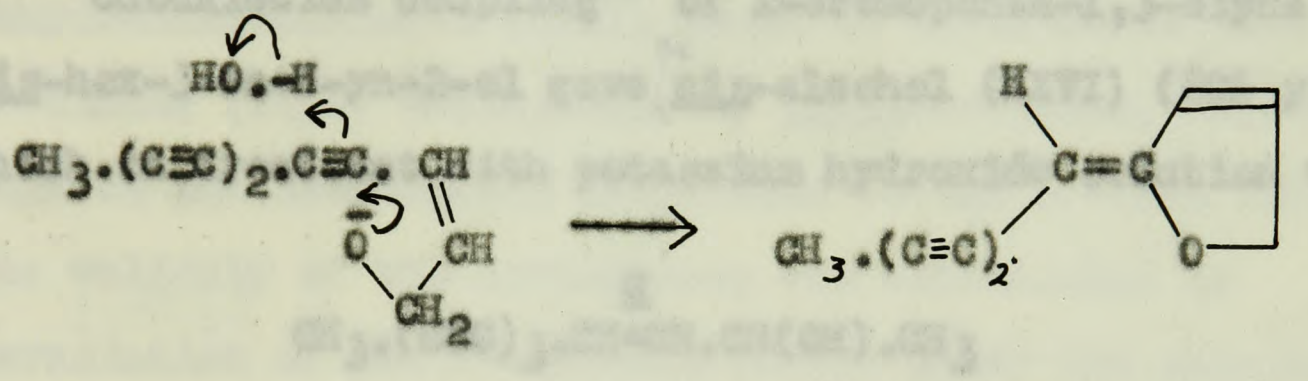


was analysed by cyclisation of the cis-isomer into (LXIII)

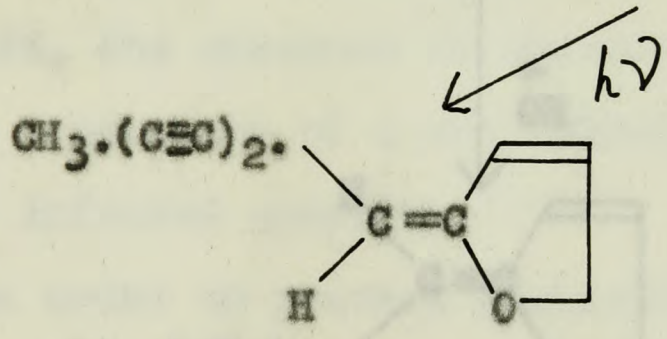


with base, followed by chromatographic separation from the unchanged trans-compound. In this way it was shown that cis-dehydromatricarianol (LXII) was formed in an overall yield of 17% and that 32% of the trans-starting material was recovered. The ultraviolet and infrared spectra of

the cyclised material were found to be identical with those of the β-isomer isolated previously. This made possible the configurational assignment of the β-isomer, as the base-catalysed cyclisation of cis-dehydromatricarianol (LXII) almost certainly involves trans-nucleophilic



β-isomer (LXIV)



α-isomer (LXV)

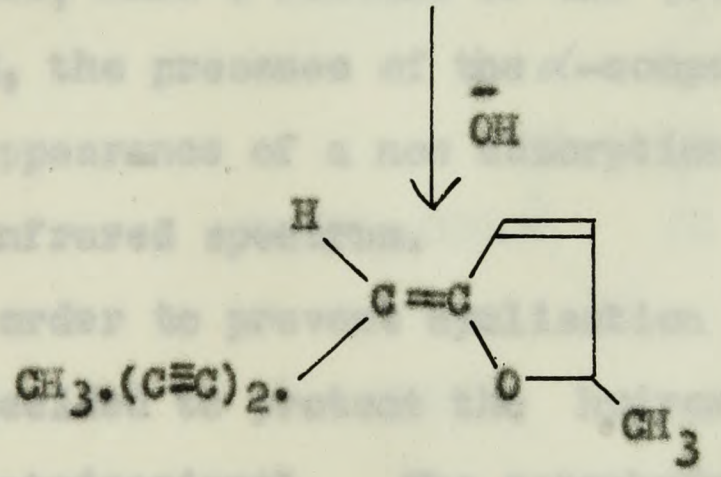
addition to the triple bond.[95] Thus the β-isomer must have the configuration depicted in (LXIV), and (LXV) must represent the α-form. The more extended chromophore of (LXIV) is in agreement with the observation that of the two isomers, the β-compound (LXIV) has the more intense ultraviolet absorption.

The ultraviolet absorption of the chromophore of (LXIII) had not been previously recorded, and in order to substantiate the structural assignments made, it was imperative that an authentic spectrum of the new chromophore be obtained.

Chodkiewicz coupling[30] of 1-bromopenta-1,3-diyne with cis-hex-3-en-5-yn-2-ol gave the cis-alcohol (LXVI) (80% yield) which on treatment with potassium hydroxide solution was

$$CH_3.(C{\equiv}C)_3.\underset{c}{CH}{=}CH.CH(OH).CH_3$$

(LXVI)



(LXVII)

quantitatively converted into the crystalline isomer (LXVII) by trans-nucleophilic addition.[95] The infrared spectrum was very similar to that of the β-isomer (LXIV) prepared analogously, and the ultraviolet absorption was essentially

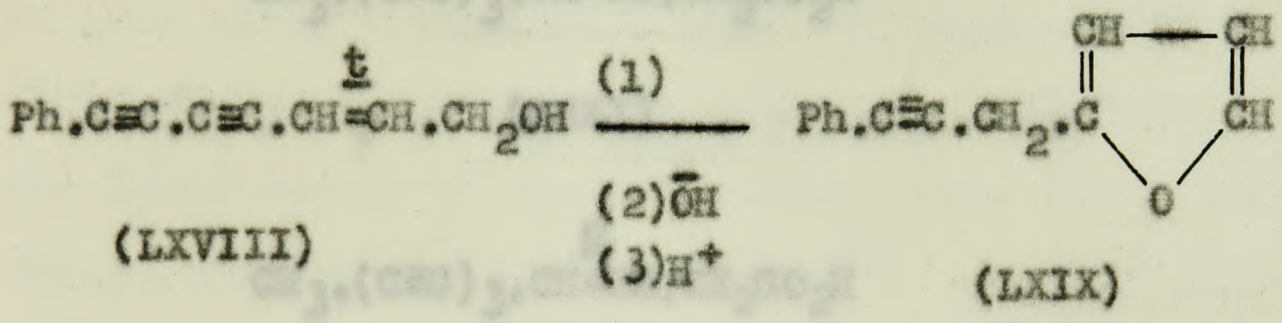
the same as those of the α- and β-isomers of (LXIII). (See Fig. 2, p. 66).

The question of the mechanism of formation of the α-isomer (LXV) during irradiation remained to be resolved. As discussed above, cyclisation of cis-dehydromatricarianol (LXII) would be expected to give the β-isomer (LXIV) exclusively by trans-addition, which might then be photochemically isomerised to the α-form (LXV). The validity of the latter step was established by irradiation of the β-compound (LXIV) under the original conditions, when a mixture of the α- and β-isomers was obtained, the presence of the α-compound being demonstrated by the appearance of a new absorption band at 1165 cm.$^{-1}$ in the infrared spectrum.

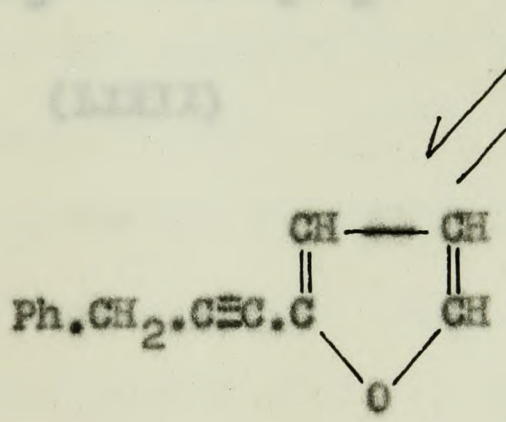
In order to prevent cyclisation during irradiation, it was decided to protect the hydroxyl group of trans-dehydromatricarianol. The tetrahydropyranyl ether was obtained in quantitative yield by treatment of (LXI) with 2,3-dihydropyran and phosphorus oxychloride. The one experiment carried out so far showed that on irradiation in the pyrex glass apparatus new bands due to cis-double bonds appeared at 752 and 723 cm.$^{-1}$ in the infrared absorption, but that the isomerisation was accompanied by a great deal

of decomposition of a complex character, as shown by the infrared bands in the carbonyl absorption region at 1772, 1720, and 1688 cm.$^{-1}$ A more detailed study of this reaction is being undertaken.

The experiments described above served to show that the method held considerable promise as a preparative route



(LXVIII) (LXIX)



(LXX)

to cis-polyacetylenes. Plans were therefore made to apply the technique to the general synthesis of cis-compounds in acetylene chemistry. In the immediate future, the trans-alcohol (LXVIII) is to be photoisomerised, and it is hoped eventually to effect the preparation if iso-carlina oxide (LXIX) as indicated above.[96] This may possibly be

further partly rearranged to carlina oxide (LXX).

Also, the synthesis of drosophilin C alk (LXXII)[68] by light-catalysed equilibration of the known trans-isomer (LXXI)[97] is to be attempted.

$$CH_3.(C{\equiv}C)_3.\underset{t}{CH{=}CH}.CH_2CO_2H$$

(LXXI)

$$CH_3.(C{\equiv}C)_3.\underset{c}{CH{=}CH}.CH_2CO_2H$$

(LXXII)

P A R T II, S E C T I O N II.

The Formation of cis-Double Bonds by Chemical Methods

A brief investigation into two chemical methods of cis-ethylene formation was carried out.

(a) The Wittig reaction[98] has been reported to give in some cases a mixture of cis- and trans-isomers[99,100], although usually the trans-compounds predominate owing to the lower energy of the transition state when the large groups are trans- to one another.[99] As the Wittig reaction with propargyl aldehyde had been shown to give 80% of the cis-isomer in one case[100], it was decided to investigate the preparation of ethyl hex-3-en-5-ynoate (LXXV) by the route below in the hope that the cis-isomer, a possible starting material for the synthesis of the Drosophila polyacetylenes, e.g. (XXXV), would predominate.

It was hoped that the activation by the phosphonium cation of the α-methylene group in (LXXIII; R=Et) would be sufficiently great to outweigh the opposing activation of the β-methylene by the ester group, so that dehydrobromination would proceed in the required direction to give (LXXIV). The possibility of self condensation of the phosphinmethylene (LXXIV) was not considered to constitute

a serious disadvantage, as several examples of selective reaction of phosphinmethylene esters with aldehydes had been reported.[99]

$$Ph_3P + BrCH_2.CH_2.CO_2Et$$

$$\downarrow$$

$$Ph_3\overset{+}{P}.\overset{\alpha}{CH_2}.\overset{\beta}{CH_2}.CO_2R \quad B\bar{r}$$

(LXXIII)

$$\downarrow \text{ base}$$

$$Ph_3P{=}CH.CH_2.CO_2Et$$

(LXXIV)

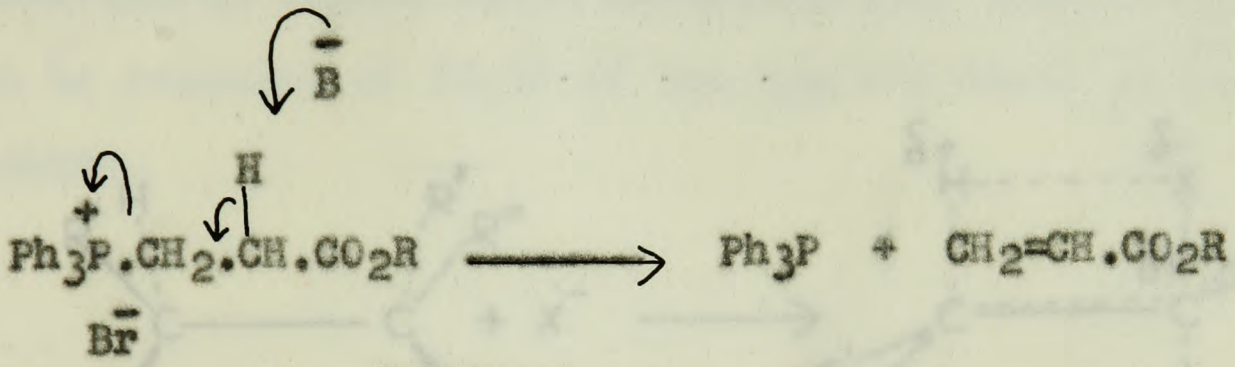
$$\downarrow HC{\equiv}C.CHO$$

$$HC{\equiv}C.CH{=}CH.CH_2.CO_2Et$$

(LXXV)

Ethyl β-bromopropionate reacted smoothly with triphenylphosphine to give a 70% yield of the phosphonium bromide (LXXIII; R=Et), which crystallised from water as

the monohydrate. On treatment with methyl-lithium[99] it did not undergo dehydrobromination in the required direction, but instead the products of the alternative elimination, triphenylphosphine and ethyl acrylate were formed, probably by the mechanism given below (R=Et).

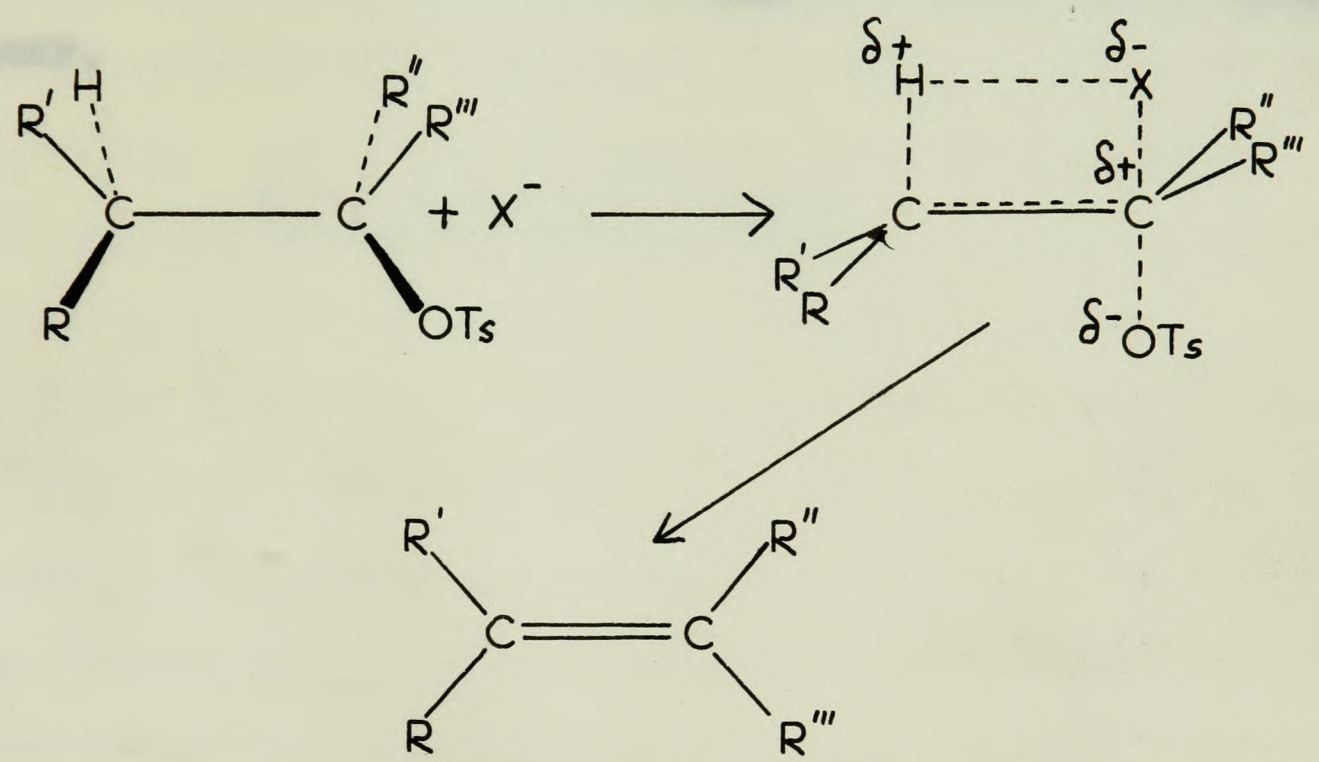


The use of aqueous sodium hydroxide solution[99] as the base merely effected hydrolysis of (LXXIII; R=Et) to triphenyl-(carboxyethyl) phosphonium bromide (LXXIII; R=H), which on dry distillation gave triphenylphosphine oxide (presumably by aerial oxidation of the triphenylphosphine probably formed initially) and acrylic acid, again possibly by the above mechanism (R=H).

(b) The detosylation of pent-1-yn-4-yl toluene-p-sulphonate with aqueous alkali is known to give a mixture of cis- and trans-pent-3-en-1-yne containing a predominance of the former isomer[76]. The discovery of new elimination conditions by Winstein and co-workers[101] prompted a re-investigation of the preparation in the hope that an

increased proportion of the cis-isomer would be formed.

Winstein et al.[101] in an attempt to replace a tosyl group by halide, observed the formation of an ethylene by a stereospecific trans-elimination process, for which the following mechanism was suggested.



However, treatment of pent-1-yn-4-yl tosylate with calcium chloride in boiling cellosolve accomplished the smooth replacement of the tosyl group by chloride[41] to give 4-chloropent-1-yne in 40% yield. Attempted elimination in ethanol under reflux gave a minute yield only of pent-3-en-1-yne, shown to consist of 70% of the

trans-isomer by vapour phase chromatography.

The original preparation of cis- and trans-pent-3-en-1-yne[41,76] was repeated as both isomers were required for the work described in Part II, Section I. An accurate analysis by vapour phase chromatography showed the mixture to be composed of 53.5% of the cis and 46.5% of the trans-isomer.

EXPERIMENTAL

Ultraviolet absorption spectra were measured in ethanol (unless otherwise stated) on a Cary Recording Spectrophotometer Model 14M, and infrared absorption spectra on a Perkin-Elmer Spectrophotometer Model 21. Melting points were determined on a Kofler block and are corrected. All evaporations of acetylenic solutions were carried out at 40° under reduced pressure. Light petroleum refers to the grade b.p. 40-60° unless otherwise specified. Solvents referred to as "dry" or "purified" were prepared as described by Fieser and Fieser in "Experiments in Organic Chemistry", Heath and Co., Boston, 1955. Chromatographic separations were effected on Woelm neutral alumina, deactivated by the addition of 3% of water.

PART I, SECTION I

β-Carbethoxypropionaldehyde.[24,25] (a) Freshly distilled diethyl succinate (200 g.), dry ethyl formate (120 g.), dry ether (1200 c.c.), and fine sodium wire (30 g.) were warmed gently on a water-bath until a vigorous reaction commenced. Sufficient external cooling was applied to maintain the reaction under gentle reflux. When the reaction had moderated (1 hr.), the cooling bath was removed, and the mixture kept overnight at 20°. Water (1600 c.c.) was added to dissolve the syrupy, brown sodium salt, the aqueous phase separated, and extracted with ether (200 c.c.). The aqueous solution was acidified with 4N-sulphuric acid (ca. 330 c.c.), and the precipitated oil extracted immediately with ether (2 x 300 c.c.). The ethereal extracts were washed with water (300 c.c.), dried ($MgSO_4$), and the ether evaporated *via* a 10" Dufton column at 100 mm. in a stream of nitrogen. Fractionation of the residual oil gave ethyl α-formylsuccinate (140-145 g.), b.p. 128-135°/10 mm., n_D^{20} 1.4450.

(b) Ethyl α-formylsuccinate (50 g.) and phosphate buffer solution[102] (150 c.c., pH7) were heated in an

autoclave at 140-145° for 1 hr. with magnetic stirring. The reaction mixture was saturated with salt, extracted with ether (2 x 75 c.c.), and the etheral solution washed with water (2 x 50 c.c.). Evaporation of the ether was carried out under reduced pressure *via* a 10" Dufton column. Fractionation of the residue afforded β-carbethoxypropionaldehyde (18 g.), b.p. 72°/10 mm., n_D^{19} 1.4230 (lit.,[22] b.p. 70-72°/10mm., n_D^{23} 1.4218).

Ethyl 4-Hydroxyhex-5-ynoate (XVI; R=Et).- Ethynylmagnesium bromide was prepared from ethylmagnesium bromide (from magnesium (4.26 g.)) and acetylene in dry tetrahydrofuran (200 c.c.) as described by Jones, Skattebøl, and Whiting[27]. The Grignard solution was added dropwise at -70° during 30 min. with stirring to freshly distilled β-carbethoxypropionaldehyde (13 g.) in dry tetrahydrofuran (150 c.c.). The solution was stirred for a further 1 hr. while warming to 20°, decomposed with saturated ammonium chloride solution, and the tetrahydrofuran layer separated.

The aqueous phase was extracted with ether (2 x 50 c.c.) and the combined organic phases dried ($MgSO_4$) and evaporated. The residue was distilled, the fraction (7.5 g.), b.p. 80-90°/0.05 mm., n_D^{20} 1.4520, being collected.

$\nu_{max.}$ (liquid film), 3500 (OH), 3320 (≡C-H), 2120 (C≡C) and 1735 cm.$^{-1}$ (ester CO). The presence of 5-10% of the lactone (XVII) was indicated by a band at 1802 cm.$^{-1}$

4-Hydroxyhex-5-ynoic Acid (XVI; R=H). - The above ester-lactone mixture (1.6 g.) with potassium hydroxide (1.7 g.) in 50% aqueous ethanol (80 c.c.) was kept overnight at 20°. The solution was then concentrated (to 10 c.c.) at 30° under reduced pressure, made just acid to litmus with N-hydrochloric acid, and extracted continuously with ether for 48 hr. The dried ($MgSO_4$) ethereal solution was evaporated at 25° under reduced pressure to a viscous oil (1.3 g.). $\nu_{max.}$ (liquid film), 3400 (OH), 3240 (≡C-H), 2100 (C≡C), 1705 (CO), and 930 cm.$^{-1}$ (CO_2H). No band due to γ-lactone was present.

Methyl 4-Hydroxyhex-5-ynoate (XVI; R=Me). - The above hydroxy-acid (0.64 g.) was treated with ethereal diazomethane for 15 min., and the excess diazomethane then destroyed with dilute acetic acid. The ethereal solution was washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated. Distillation afforded the methyl ester (300 mg.), b.p. 62°/0.01 mm., n_D^{21} 1.4540 (Found: C, 59.9; H, 7.2. $C_7H_{10}O_3$ requires C, 59.2; H, 7.1%).

$\nu_{max.}$ (in CCl_4), 3555(OH), 3280 (≡C-H), and 1738 $cm.^{-1}$ (ester CO).

Lactone of 4-Hydroxyhex-5-ynoic Acid (XVII).- The hydroxy-acid (XVI; R=H) (1.3 g.) was distilled in the presence of toluene-p-sulphonic acid to give the lactone (0.35 g.), b.p. 50°/0.05 mm., n_D^{18} 1.4668 (Found: C, 65.1; H, 5.4. $C_6H_6O_2$ requires C, 65.4; H, 5.5%). $\nu_{max.}$ (in CCl_4), 3300 (≡C-H), 2130 (C≡C), and 1802 $cm.^{-1}$ (γ-lactone CO).

Ethyl 4-(2'-Tetrahydropyranyloxy)hex-5-ynoate (XX; R=Et).- Ethyl 4-hydroxyhex-5-ynoate (3.12 g. containing 10% of the lactone (XVII)) and 2,3-dihydropyran (1.68 g., 1 mol.) were cooled to 0° and phosphorus oxychloride (2 drops) added, and the mixture kept at 20° for 1.5 hr.[32] Ether (50 c.c.) was added, the ethereal solution washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated. The residual oil (4.85 g.) was chromatographed in benzene-light petroleum (1:4) on alumina (200 g.) and the required product eluted with benzene-light petroleum (1:1). Distillation gave the tetrahydropyranyloxyester (3.3g.), b.p. 86°/0.01 mm., n_D^{20} 1.4596 (Found: C, 65.35; H, 8.3. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4%). $\nu_{max.}$ (in CCl_4), 3270 (≡C-H), and 1733 $cm.^{-1}$ (ester CO). No

band due to OH was present.

4-(2'-Tetrahydropyranyloxy)hex-5-ynoic Acid (XX; R=H).- The above ester (2.9 g.) and potassium hydroxide (2.9 g.) in 50% aqueous ethanol (100 c.c.) were kept overnight at 20°. The solution was cooled to 0° and brought to pH5 with phosphoric acid, extracted with ether (2 x 100 c.c.), and dried ($MgSO_4$). Evaporation yielded the acid as a viscous oil (2.6 g.). ν max. (in CCl_4), 3300 (≡C-H), 2110 (C≡C), and 1705 cm.$^{-1}$ (CO).

1-Bromoprop-1-yne[30].- A solution of sodium hypobromite was prepared from ice (100 g.), 10 N-sodium hydroxide solution (50 c.c.), and bromine (11 c.c.) in a flask fitted with a "Drikold"-acetone condenser, and propyne passed into the stirred solution at 20° at a rate equal to the formation of the bromopropyne. After the consumption of all the hypobromite (yellow to colourless change), the lower bromopropyne layer was washed with water by decantation, the dissolved propyne displaced by nitrogen, and the crude product (20 g.) stored at -40°. (N.B. It is inadvisable to dry with $MgSO_4$ as the heat of hydration ignites the bromopropyne. Distillation is also liable to cause deflagration).

Hexa-2,4-diyn-1-ol (XVIII; R=H)[30].- Propargyl alcohol (3.4 g.), water (9 c.c.), 33% aqueous ethylamine (16.8 c.c.), cuprous chloride (0.06 g.), and sufficient hydroxylamine hydrochloride to maintain the cuprous state, were stirred under nitrogen at 40° and 1-bromoprop-1-yne (7.2 g.) added dropwise during 10 min. After stirring for a further 10 min. the mixture was poured into N-hydrochloric acid, extracted with ether (2 x 150 c.c.), and the ethereal solution washed with ammoniacal silver nitrate solution to remove unreacted propargyl alcohol. Evaporation of the dried ($MgSO_4$) ethereal solution afforded a crystallising oil, which on distillation gave hexa-2,4-diyn-1-ol (4.8 g.), b.p. 106°/17 mm., m.p. 40° (lit.[48], m.p. 42°).

1-Bromohex-2,4-diyne (XIX). - Hexa-2,4-diyn-1-ol (6.5g.) and purified pyridine (1 c.c.) in dry ether (50 c.c.) were cooled to -20° and phosphorus tribromide (6.2 g., 0.33 mol.) in dry ether (20 c.c.) added dropwise with stirring under nitrogen during 15 min.[31] The mixture was stirred for a further 10 min. at -20°, and then allowed to warm to 20° during 30 min. Ether (50 c.c.) was added and the ethereal solution washed with sodium hydrogen carbonate solution, then with water, and dried ($MgSO_4$). Evaporation of the ether, followdd by distillation, gave 1-bromohexa-2,4-diyne

(4.8 g.), b.p. 94-96°/19 mm., 34°/0.2 mm., n_D^{25} 1.5830 (Found: C, 46.0; H, 3.3.. C_6H_5Br requires C, 45.85; H, 3.2%). λ max., 2270 (ϵ =2,040), 2400 (ϵ = 2,980), 2530 (ϵ = 3,750), and 2660 Å (ϵ=2,730). ν max. (liquid film), 2250 cm.$^{-1}$ (C≡C).

Hexa-2,4-diyn-1-yl Toluene-p-Sulphonate (XVIII; R=p-$SO_2.C_6H_4.CH_3$). - Hexa-2,4-diyn-1-ol (9.4 g.) and toluene-p- sulphonyl chloride (19.1 g., 1 mol.) were dissolved in acetonitrile (100 c.c.) and water (30 c.c.), and potassium hydroxide (4.6 g.., 1 mol.) in water (10 c.c.) added during 10 min. with vigorous stirring, the temperature being maintained at 10-20°[41]. The neutral solution was stirred for a further 10 min. at 20°, and was then poured into water (400 c.c.) and extracted with ether (2 x 100 c.c.). The ethereal solution was washed with water, dried ($MgSO_4$) and evaporated to a crystallising oil. Recrystallisation from ether-light petroleum afforded the toluene-p-sulphonate as prismatic needles (14.8 g.), m.p. 62° (Found: C, 62.8; H, 4.8. $C_{13}H_{12}O_3S$ requires C, 62.85; H, 4.9%). λ max. 2260 (ϵ = 16,000), 2445 (ϵ =1,680), 2580 (ϵ = 1,185), 2670 (infl.) (ϵ = 690), and 2730 Å (ϵ = 550). ν max. (in CCl_4 and CS_2), 2250 (C≡C), 1590 (aromatic CH=CH), 1373,

1185, and 1173 cm.$^{-1}$ (-O-SO_2-).

Diethylmagnesium. - A 0.7 N-solution (estimated by titration[103]) was prepared from magnesium (4.9 g.), ethyl bromide (21.8 g.), dry ether (200 c.c.), and purified dioxan (17.6 g., 1 mol.) as described by Wotiz, Hollingsworth, and Dessy[43], and the ethereal solution filtered, and stored, under nitrogen.

The Reaction of Dihex-1-ynylmagnesium and Hexa-2,4-diyn-1-yl Toluene-p-Sulphonate.- Hex-1-yne (410 mg.) was added to ethereal diethylmagnesium (7.2 c.c., 0.7 N-solution, 1 equiv.), and the solution refluxed under nitrogen for 30 min.[43] Hexa-2,4-diyn-1-yl toluene-p-sulphonate (495 mg., 0.4 mol.) in dry tetrahydrofuran (15 c.c.) was then added and the solution stirred under nitrogen at 45° for 12 hr. Di(toluene-p-sulphonyl)magnesium slowly separated. The mixture was worked up by pouring it into 2N-sulphuric acid, followed by extraction with ether. Quantitative ultraviolet spectroscopic analysis of the ethereal solution showed the presence of dodeca-2,4,7-triyne (19 mg., detected by isomerisation to dodeca-6,7-diene-2,4-diyne with 50% ethanolic 0.1N-potassium hydroxide solution), dodeca-6,7-diene-2,4-diyne (134 mg., λ max.,

2370, 2510, 2640, and 2800 Å), and dodeca-2,4,6-triyne (54 mg., λ max., 2100 Å). The total yield of $C_{12}H_{14}$ was 207 mg. (65%).

Attempted Coupling of 4-(2′-Tetrahydropyranyloxy)hex-5-ynoic Acid (XX; R=H) with Hexa-2,4-diyn-1-yl Toluene-p-Sulphonate.- (a) 4-(2′-Tetrahydropyranyloxy)hex-5-ynoic acid (212 mg.) in dry ether (10 c.c.) and ethereal diethylmagnesium (8.6 c.c., 0.7N-solution, 6 equiv.) were refluxed under nitrogen for 2 hr. (A white precipitate separated immediately). After the addition of the toluene-p-sulphonate (1.24 g., 5 mol.) in dry ether (15 c.c.), the mixture was refluxed for 5 hr. Samples were withdrawn at intervals and spectroscopic analysis showed that the toluene-p-sulphonate concentration decreased during 1 hr. (reaction with excess diethylmagnesium) and then remained constant. Working up with N-sulphuric acid gave an ethereal solution, the acidic components of which were isolated *via* 5% sodium carbonate solution. Quantitative ultraviolet spectroscopy showed the presence of 4-(2′-tetrahydropyranyloxy)-dodeca-5,6-diene-8,10-diynoic acid (odyssic acid tetrahydropyranylether) (0.16 mg., λ max. 2510, 2630, and 2800 Å), and dodec-4-ene-6,8,10-triynoic acid (odyssin A) (0.35 mg., λ max., 2420, 2570, 2730, 2890,

3080, and 3290 Å).

(b) The tetrahydropyranyloxy acid (212 mg.) in dry tetrahydrofuran (20 c.c.) and ethereal diethylmagnesium (2.9 c.c., 0.7N-solution, 2 equiv.) were heated at 35° for 1 hr. under nitrogen. Hexa-2,4-diyn-1-yl toluene-p-sulphonate (248 mg., 1 mol.) in dry tetrahydofuran (5 c.c.) was added, and the solution stirred for 4 hr. at 35°. Spectroscopic analysis showed the absence of any polyacetylenic chromophore, and a quantitative estimation revealed that none of the tosylate had reacted. No change was observed on stirring for a further 12 hr. at 35°.

Reaction of β-Phenylpropionic Acid with Diethylmagnesium. - β-Phenylpropionic acid (1.0 g.) in dry tetrahydrofuran (100 c.c.) and ethereal diethylmagnesium (22 c.c., 0.7 N-solution, 2.2. equiv.) were heated under reflux under nitrogen for 2 hr. The colourless solution was decomposed with saturated ammonium chloride solution, the layers separated, and the aqueous phase extracted with ether (150 c.c.). The combined organic extracts were washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated. Distillation of the residue afforded 1-phenylpent-3-one (0.8 g.), b.p. 118°/7 mm., n_D^{20} 1.5085 (lit.[104],

b.p. 128°/17 mm., n_D^{20} 1.5088). $\nu_{max.}$ (liquid film), 1712 (CO), 1605 (aromatic CH=CH), 747 and 690 cm.$^{-1}$ (mono-subs.phenyl).

PART I, SECTION II

Ethyl 4-Hydroxyhept-6-ynoate (XXVI; R=Et).- Propargylmagnesium bromide[47] was prepared under nitrogen from propargyl bromide (5.95 g.), magnesium (1.15 g.), and dry ether (50 c.c.). The Grignard solution was added dropwise at 0° during 45 min., with stirring under nitrogen, to freshly distilled β-carbethoxypropionaldehyde (7.15 g.) in dry ether (100 c.c.). When the addition was complete, the suspension was stirred for a further 15 min. at 0°, and the complex decomposed with saturated ammonium chloride solution (50 c.c.). The ethereal layer was separated and the aqueous phase extracted further with ether (2 x 50 c.c.). The combined extracts were dried ($MgSO_4$) and evaporated. Distillation gave a fraction (4.8 g.), b.p. 70-100°/0.1mm., which was shown to contain 5-10% of the lactone (XXVII) by the intensity of the band at 1785 cm.$^{-1}$ in the infrared absorption spectrum. Careful redistillation afforded the ethyl ester (4.2 g.), b.p. 75-76°/0.1 mm., n_D^{17} 1.4600 (Found: C, 63.55; H, 8.25. $C_9H_{14}O_3$ requires C, 63.55; H, 8.3%). $\nu_{max.}$ (in CCl_4), 3510 and 3400 (OH), 3270 (≡C-H), 2105 (C≡C), and 1727 cm.$^{-1}$ (ester CO).

4-Hydroxyhept-6-ynoic Acid (XXVI; R=H).- Ethyl 4-hydroxyhept-6-ynoate (before separation of the lactone) (8.5 g.) with potassium hydroxide (8.5 g.) in 50% aqueous ethanol (400 c.c.) was kept overnight at 20°. The solution was evaporated to a volume of 100 c.c., made just acid to litmus with N-hydrochloric acid, and extracted continuously with ether for 24 hr. The ethereal solution was dried ($MgSO_4$) and evaporated, yielding the hydroxy-acid as a viscous oil (7.7 g.). ν max. (liquid film), 3300 (≡C-H), and 1715 cm.$^{-1}$ (CO).

Lactone of 4-Hydroxyhept-6-ynoic Acid (XXVII).- Distillation of the above hydroxy-acid (4.05 g.) in the presence of toluene-p-sulphonic acid gave the lactone (2.9 g.), b.p. 72°/0.05 mm., n_D^{16} 1.4764 (Found: C, 67.65; H, 6.4. $C_7H_8O_2$ requires C, 67.75; H, 6.5%). ν max. (in CCl_4), 3280 (≡C-H), 2110 (C≡C), and 1785 cm.$^{-1}$ (γ-lactone CO).

Penta-1,3-diyne.- This method is a modification of the adaption by Allan, Jones, and Whiting[50] of the original preparation of Armitage, Jones, and Whiting[48]. Penta-1,3-diyne was prepared from 1,4-dichlorobut-2-yne[49] (77 g.), sodium (44.5 g.), and methyl iodide (88 g.) as described by Allan et al.[50] Water (ca. 2 l.) was added to the liquid

ammonia solution, and the vapours condensed with a "Drikold"-acetone condenser. A nitrogen bleed was then fitted to the flask and the mixture evaporated at 40° under reduced pressure into 3 cold-traps at -70° until all the hydrocarbon had distilled. The ammoniacal distillate was poured into water (500 c.c.), the upper layer separated, and washed with N-hydrochloric acid to remove the remaining dissolved ammonia. Drying over $MgSO_4$ gave penta-1,3-diyne (19.3 g., 49%), n_D^{21} 1.4740. (lit.[48] n_D^{15} 1.4790).

Extraction of the hydrocarbon from the aqueous ammoniacal solution with ether, and then isolation *via* the mercury derivative[51], followed by decomposition with 2N-hydrochloric acid-potassium iodide solution and distillation under reduced pressure into cold-traps, gave a 30% yield of penta-1,3-diyne, n_D^{20} 1.4750.

Iso-odyssic Ethylamide (XXVIII; R=Et). The lactone of 4-hydroxyhept-6-ynoic acid (620 mg.) was added with stirring under nitrogen to 33% aqueous ethylamine (1.4 c.c.), cuprous chloride (10 mg.), and a crystal of hydroxylamine hydrochloride[30]. 1-Bromopenta-1,3-diyne was prepared from penta-1,3-diyne (350 mg., 1.1 mol.) by shaking with sodium hypobromite solution (4 c.c., from ice (5 g.), 10N-sodium hydroxide solution (2.5 c.c.), and bromine (0.55 c.c.))[30]

at 0°. The bromo-compound was dissolved in methanol (1 c.c.) and added during 5 min. with stirring at 30° to the ethylamine solution. After stirring for a further 10 min. the mixture was poured into N-hydrochloric acid, and extracted with ether (2 x 50 c.c.). Evaporation of the dried ($MgSO_4$) ethereal solution gave a solid (400 mg.) which was well washed with light petroleum to remove hydrocarbon impurities. Recrystallisation from methylene-chloride-light petroleum gave iso-odyssic ethylamide, which separated as a microcrystalline solid (250 mg.), m.p. 89° (Found: C, 72.0; H, 7.2; N, 6.45. $C_{14}H_{17}NO_2$ requires C, 72.65; H, 7.4; N, 6.1%). λ max. see Table 1, p.117. ν max. (in CCl_4), 3430 (OH), 3280 (NH), 2223 (C≡C), 1656 (amide CO I), and 1532 cm.$^{-1}$ (amide CO II).

Iso-odyssic Acid (III).- The lactone (XXVII) (620 mg.) with potassium hydroxide (280 mg., 1 mol.) in 30% aqueous ethanol (1.5 c.c.) was kept overnight at 20°. The solution was then added to a mixture of 33% aqueous ethylamine (1.4c.c.), cuprous chloride (10 mg.), and a crystal of hydroxylamine hydrochloride[30]. The mixture was stirred under nitrogen at 30°, and 1-bromopenta-1,3-diyne (from penta-1,3-diyne (350 mg., 1.1 mol.)) in 80% aqueous methanol (1.5 c.c.) added

dropwise during 10 min. After stirring for a further 10 min., the solution was poured into N-hydrochloric acid (50 c.c.), and extracted with ether (3 x 25 c.c.). The ethereal solution was extracted with N-sodium hydroxide solution (2 x 50 c.c.), and the combined alkaline phases were well washed with ether. After acidification with 2N-hydrochloric acid, iso-odyssic acid was isolated *via* ether as a pale yellow solid (450 mg.). λ max. 2100, 2390, 2525, 2690, 2860, and 3080 Å. ν max. (in CH_2Cl_2), 2220 (C≡C), 1705 (CO), and 940 cm.$^{-1}$ (CO_2H).

Iso-odyssic Lactone (IV). - The above iso-odyssic acid (450 mg.) was immediately mixed with dry dioxan (97 c.c.) and concentrated sulphuric acid (3 c.c.) and kept in the dark at 20° for 4 days. Water (1 l.) was then added and the yellow solid obtained by isolation with ether was decolourised with charcoal in methylene chloride solution. Recrystallisation from methylene chloride-ether-pentane gave iso-odyssic lactone as needles (270 mg.), m.p. 98° (Found: C, 76.1; H, 5.35. Calc. for $C_{12}H_{10}O_2$: C, 77.4; H, 5.4%). (Bu'Lock, Jones, and Leeming[5] found the optically active, naturally derived, material to be polymorphic with m.p.'s 64°, 73-74°, and 93-98°). λ max.,

see Table 1, p.117. ν max. (in CS_2), 2215 (C≡C), and 1793cm.$^{-1}$ (γ-lactone CO).

4-Hydroxyundeca-5,7,9-triynoic Acid (XXIX). - The lactone of 4-hydroxyhex-5-ynoic acid (240 mg.) with potassium hydroxide (125 mg., 1 mol.) in 50% aqueous ethanol (2 c.c.) was kept overnight at 20° in the dark, and the solution then added to 33% aqueous ethylamine (0.8 c.c.), cuprous chloride (5 mg.), and a crystal of hydroxylamine hydrochloride[30]. The mixture was stirred under nitrogen at 30° and 1-bromo-penta-1,3-diyne[30] (from penta-1,3-diyne (160 mg., 1.1 mol.)) in methanol (1 c.c.) added dropwise during 5 min. After stirring for a further 30 min., the mixture was worked up in the usual way by pouring into N-hydrochlorid acid and extracting with ether. Purification via N-sodium hydroxide solution and re-isolation with ether gave a solid (350 mg.) which was recrystallised from methylene chloride-ether (with charcoal decolourisation), 4-hydroxyundeca-5,7,9-triynoic acid separating as extremely light sensitive, colourless, needles (146 mg.), m.p. 118-119° (decomp.) (Found: C, 69.75; H, 5.4. $C_{11}H_{10}O_3$ requires C, 69.45; H, 5.3%). λ max., see Table 1, p.117. ν max. (in CH_2Cl_2), 3540 and 3455 (OH), 2230 (C≡C), 1750 and 1712 (CO), 1130 (OH), and 930 cm.$^{-1}$ (CO_2H).

trans-Odyssin A (V).- Potassium (42 mg., 1.1 equiv.) was dissolved in dry t-amyl alcohol (5 c.c.) under reflux, and the cooled solution added to iso-odyssic lactone (180 mg.) in dry t-amyl alcohol (100 c.c.) After 5 min. at 20°, potassium hydroxide (6 g.) in water (100 c.c.) was added and the mixture made homogeneous with ethanol. After keeping overnight at 20° (hydrolysis of esters) water (500 c.c.) was added and the solution extracted with methylene chloride (3 x 150 c.c.). The aqueous phase was then acidified (Congo Red) with 5N-hydrochloric acid, and extracted with ether (3 x 100 c.c.). The combined ethereal extracts were evaporated to 40 c.c., and the mixture of odyssin A and iso-odyssic acid resolved by countercurrent distribution between ether and M/15 disodium hydrogen phosphate. Evaporation of the ethereal odyssin A fractions afforded a solid (125 mg.) which on crystallisation from methylene chloride-pentane at -40° gave trans-odyssin A as needles (80 mg.), m.p. 110-155° (with slow decomp.). λ max., see Table 1, p.117 . ν max. (in CCl_4) 2220 (C≡C), 1715 (CO), and 950 cm.$^{-1}$ (trans-CH=CH).

Methyl Ester of trans-Odyssin A. - Treatment of trans-odyssin A (35 mg.) with ethereal diazomethane gave the methyl ester, which separated from pentane at -40°

in needles (26 mg.), m.p. 62-63° (lit., m.p.'s 61.5 - 64.5°[5], 57.5-61.5°[9] (Found: C, 78.15; H, 5.9. Calc. for $C_{13}H_{12}O_2$: C, 77.95; H, 6.05%). λ max., see Table 1, p.117. ν max. (in CS_2), 1743 (ester CO), and 948 cm.$^{-1}$ (trans-CH=CH). No band due to cis-CH=CH was present.

PART I, SECTION III

trans-Hept-4-en-6-ynoic Acid (XXX).- (a) Ethyl 4-hydroxyhept-6-ynoate (850 mg.) in purified pyridine (3 c.c.) was cooled to 0°, and phosphorus oxychloride (1 c.c.) in purified pyridine (5 c.c.) added dropwise during 10 min.[55] The mixture was kept at 20° for 30 min. and then poured on to ice. Isolation with ether yielded an oil, which was immediately mixed with potassium hydroxide (1 g.) in 50% aqueous ethanol (50 c.c.) and kept overnight at 20°. The mixture was acidified with 2N-hydrochloric acid, extracted with ether (2 x 25 c.c.), and the ethereal solution well extracted with sodium hydrogen carbonate solution. Acidification with 2N-hydrochloric acid followed by isolation with ether afforded trans-hept-4-en-6-ynoic acid, which was crystallised from light petroleum as needles (100 mg.), m.p. 69-70° (lit.[9], m.p. 65-67°) (Found: C, 67.6; H, 6.25. Calc. for $C_7H_8O_2$: C, 67.75 H, 6.5%). λ max. 2220 Å (ϵ = 14,000). ν max. (in CS_2), 3240 (≡C-H), 1706 (CO), and 947 cm.$^{-1}$ (broad, trans-CH=CH and CO_2H).

(b) Sodium ethoxide (from sodium (230 mg., 2 mol.) and dry ethanol (10 c.c.)) was added dropwise with stirring at 0° during 15 min. to the lactone of 4-hydroxyhept-6-

ynoic acid (620 mg., 1 mol.) in dry ethanol (5 c.c.)[52,54]. After stirring for a further 1 hr. at 0°, the mixture was evaporated to dryness at 30° under reduced pressure, acidified with 2N-hydrochloric acid, and extracted with ether (2 x 30 c.c.). The acid was isolated from the ethereal solution *via* sodium hydrogen carbonate solution as a crystallising oil (450 mg.). Recrystallisation from light petroleum gave the pure *trans*-acid as needles (250 mg.), m.p. 69-70°.

The Reaction between Propargylmagnesium Bromide and Succinic Anhydride.- (a) Propargyl bromide (5.95 g.) in dry ether (25 c.c.) was added dropwise with stirring under nitrogen to magnesium (1.22 g., 1 equiv.) and dry ether (10 c.c.) to which a trace of mercuric chloride had been added, the temperature being kept below 20°.[47] The resulting solution of propargylmagnesium bromide was added dropwise with stirring during 1 hr. to a solution of succinic anhydride (10.5 g., 1.05 mol.) in dry tetrahydrofuran (100 c.c.) at -70°. Stirring was continued for a further 2 hr. and the temperature allowed to rise gradually to -10°. Decomposition of the complex with saturated ammonium chloride solution, followed by evaporation of the

dried ($MgSO_4$) tetrahydrofuran solution, afforded a white solid (10.1 g.). The products were separated from unchanged succinic anhydride by trituration with ether, the ethereal solution being then washed with water to remove succinic acid, and dried ($MgSO_4$). Evaporation gave a viscous oil (1.6 g.) which was resolved into an acid and a neutral component *via* sodium hydrogen carbonate solution. The acid, 4-hydroxy-4-(prop-2′-ynyl)hept-6-ynoic acid crystallised from ether-hexane as prisms (0.5 g.), m.p. 79° (Found: C, 66.6; H, 6.6. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.7%). ν max. (Nujol), 3300 (≡C-H), 2120 (C≡C), and 1710 cm.$^{-1}$ (CO). The methyl ester (prepared by the action of ethereal diazomethane) had ν max. (in CCl_4), 3580 (OH), 3310 (≡C-H), and 1740 cm.$^{-1}$ (ester CO).

The neutral component was the lactone of the above acid, and separated from ether-hexane at -40° as rhombic prisms (0.3 g.), m.p. 67° (Found: C, 74.3; H, 6.0. $C_{10}H_{10}O_2$ requires C, 74.05; H, 6.2%). ν max. (in CCl_4), 3300 (≡C-H), 2125 (C≡C), and 1795 cm.$^{-1}$ (γ-lactone CO).

(b) Addition of the propargylmagnesium bromide solution to succinic anhydride (10.5 g., 1.05 mol.) in refluxing ether [59], followed by decomposition with 2N-sulphuric acid, and working up by the procedure described above gave the lactone (1.0 g.) and the hydroxy-acid (0.5 g.).

(c) When the ethereal propargylmagnesium bromide was added to succinic anhydride (10.5 g., 1.05 mol.) suspended in ether-pyridine[60] at -70°, an acid was isolated, which crystallised from methylenechloride-hexane as prisms (0.3 g.), m.p. 128° (Found: C, 60.0; H, 5.75. $C_7H_8O_3$ requires C, 60.0; H, 5.75%. Mol.wt. (Rast) 266. $C_7H_8O_3$ requires 140, dimer 280). ν max. (Nujol), 3280 (≡C-H), 1740 and 1697 (CO), and 925 cm.$^{-1}$ (CO_2H).

Nona-1,4-diyne (XXXVI; R=C_4H_9).- Nona-1,4-diyne was prepared in ether in 74% yield by the method of Gensler, Mahadevan, and Casella[20] and purified *via* the copper derivative[20], which was well washed with ether to remove allenic impurities, centrifuged, and decomposed with 3N-hydrochloric acid at 20°. Isolation *via* ether, followed by distillation, gave nona-1,4-diyne as a colourless oil (40%), b.p. 57°/16 mm., n_D^{18} 1.4538 (*lit.*[20], b.p. 54°/14 mm., n_D^{25} 1.4497). ν max. (in CCl_4), 3310 (≡C-H), and 1310 cm.$^{-1}$ (≡C.CH_2.C≡). No absorption due to HC=C=CH was present.

Oct-6-ene-1,4-diyne (XXXVIII).- Ethylmagnesium bromide (from magnesium (8.7 g.)) was prepared under nitrogen in dry tetrahyrofuran (50 c.c.) and pent-3-en-1-yne[41]

(5.3 g.) in dry tetrahydrofuran (50 c.c.) added during 30 min. with stirring, the temperature being maintained at 15-20°. Cuprous chloride (0.2 g.) was added and the solution stirred for a further 15 min. The Grignard content was estimated[103], and propargyl bromide (5.95 g.) in dry tetrahydrofuran added dropwise during 30 min. at 20°. A heavy white precipitate gradually separated, and after stirring for a further 2 hr. at 20°, (estimation[103] showed 90% of the Grignard reagent to have reacted), the mixture was decomposed with saturated ammonium chloride solution. The tetrahydrofuran layer was separated and the aqueous phase extracted with ether (50 c.c.). The combined extracts were dried ($MgSO_4$) and evaporated *via* a 6" Fenske column at 50°/200 mm. in a stream of nitrogen. Distillation of the residue gave oct-6-ene-1,4-diyne as an unstable, colourless oil (2.6 g.), b.p. 44-47°/8 mm. (A trace of allenic impurity was detected by infrared spectroscopy). A sample, rigorously purified *via* the copper derivative as described above, had b.p. 46-47°/8 mm., n_D^{16} 1.4968 (Found: C, 92.1; H, 8.15. C_8H_8 requires C, 92.3; H, 7.75%). λ max., 2230 (ϵ =16,000), and 2300 Å (infl.) (ϵ =13,800). ν max. (in CCl_4), 3320 (≡C-H), 2140 (C≡C), and 1310 cm.$^{-1}$ (≡C.CH_2.C≡). No band due to HC=C=CH_2 was present.

Isomerisation of Oct-6-ene-1,4-diyne.- Purified oct-6-ene-1,4-diyne was treated with 0.01N-ethanolic potassium hydroxide solution. Isomerisation to octa-1,2,6-trien-4-yne (XXXIX), λ max. 2590 (ϵ = 14,600) and 2730 Å (ϵ = 11,200), was complete in 35 min. Further isomerisation to oct-6-ene-2,4-diyne (XL), λ max., 2100 (ϵ = 42,000), 2260 (ϵ = 2,100), 2380 (ϵ = 5,500), 2510 (ϵ = 11,400), 2640 (ϵ = 17,400), and 2800 Å (ϵ = 13,600), occurred during 24 hr.

PART II. SECTION I

The solvents used in the following irradiation experiments were of either "Analar" or "Spectroscopic" quality. Vapour phase chromatography of the polyacetylenic compounds, dissolved in ethanol or methanol, was carried out on the "Pye Argon Chromatograph" using a 4 ft., 10% "Apiezon L" grease on "Embacel", column maintained at a temperature of 200°. The inlet pressure was 10 lb./sq.in., the flow rate 6.5, and the detection voltage 1250 v. at sensitivity 3.

Apparatus.- (a) For irradiation experiments with light of wavelength greater than 3000Å.

A pyrex glass container of capacity 150 c.c. in which a water-cooled cold-finger could be inserted by means of a ground glass joint, was set up at a distance of 6 inches from the light source, a "Hanovia" 500 w. quartz, mercury vapour-argon, low pressure, lamp. During irradiation the temperature of the solution was maintained at 20° and the solvent vapours were led away from the vicinity of the lamp by means of a rubber tube.

(b) For irradiation experiments using light of wavelength greater than 2000 Å.

A commercially available apparatus, the "Hanovia

Photochemical Reactor" was used. The quartz, water-cooled, apparatus of capacity 250 c.c. was fitted with a 500 w. lamp similar to that described above. During irradiations, the temperature of the solution was maintained at 20°.

trans-Methyl Dec-2-ene-4,6-diynoate (trans-Lachnophyllum Ester) (LVI; R=Me).- trans-Dec-2-ene-4,6-diynoic acid (100 mg., sample prepared by Dr.I. Bell) in methanol (50 c.c.) and concentrated sulphuric acid (1 c.c.) was kept for 2 days in the dark at 20°. The solution was then poured into water (500 c.c.), extracted with ether (3 x 50 c.c.), and the combined extracts washed with sodium hydrogen carbonate solution. The ethereal solution was dried ($MgSO_4$), evaporated, and the residual oil crystallised from pentane at -40° to give trans-lachnophyllum ester as needles (60 mg.), m.p. 18° (lit., m.p.'s 16-17°[93], 19°[105]). λ max., see Table 2, p. 118 . ν max. (in CS_2), 2223 (C≡C), 1730 (ester CO), and 952 cm.$^{-1}$ (trans-CH=CH). No band due to cis-CH=CH was present. (See Fig 1, facing p. 61).

Irradiation of trans-Methyl Dec-?-ene-4,6-diynoate.- The above trans-ester (20 mg.) in light petroleum (b.p. 30-40°) (100 c.c.) containing a trace of iodine as sensitiser[88] was irradiated in the glass apparatus for 1 hr. at 20°. Evaporation of the solvent gave an oil which was estimated

to consist of 80% of the cis-ester from the intensity of the band at 809 cm.$^{-1}$ in the infrared spectrum. Chromatography in light petroleum in the dark on alumina (5 g.) and elution with the same solvent gave a mixture of the trans- and cis-esters, followed by pure cis-methyl dec-2-ene-4,6-diynoate (12 mg.) which was recrystallised from pentane at -40° as needles (6 mg.), m.p. 30-31° (lit., m.p.'s 31°[75], 32.5°[105]). λ max., see Table 2, p.118. ν max. (in CS_2), 2220 (C≡C), 1730 and 1715 (ester CO), and 809 cm.$^{-1}$ (cis-CH=CH). No band due to trans-CH=CH was observed. (See Fig. 1, facing p. 61).

Both the cis- and the trans-lachnophyllum esters could be chromatographed in the vapour phase on the "Pye" machine, but mixtures of the two were not resolved.

Irradiation of trans-Dec-2-ene-4,6-diynoic Acid. (LVI; R=H).- The acid (10 mg.) was dissolved in dry benzene (100 c.c.) and irradiated in the glass apparatus for 3 hr. at 20°. Evaporation of the solvent gave a solid, the infrared spectrum of which showed new absorptions at 1778 (γ-lactone CO) and 819 cm.$^{-1}$ (cis-CH=CH-CO[75]). The intensity of the 1778 cm.$^{-1}$ band suggested the presence of 30% of the lactone (LVIII), but chromatography in benzene-light petroleum (1:1) on alumina (2 g.) failed to effect a satisfactory resolution owing to decomposition on the

column.

trans-Methyl Oct-6-ene-2,4-diynoate (LIX; R=Me).- trans-1-Bromopent-3-en-1-yne[30] (from trans-pent-3-en-1-yne (260 mg.)) in methanol (2 c.c.) was added dropwise with stirring under nitrogen at 25° during 10 min. to 3% aqueous ethylamine (6 c.c.), cuprous chloride (80 mg.), a crystal of hydroxylamine hydrochloride, and propiolic acid[106] (280 mg., sample prepared by Dr.J.N.Gardner). After stirring for a further 10 min., the acid was isolated in the usual way via 2N-hydrochloric acid and ether, and purified via sodium hydrogen carbonate solution. Re-isolation with ether afforded trans-oct-6-ene-2,4-diynoic acid as a white solid (500 mg.). Esterification with methanol-sulphuric acid at 20° for 4 days gave the methyl ester which separated from pentane as needles (345 mg.), m.p. 34-35° (Found: C, 73.0; H, 5.55. $C_9H_8O_2$ requires C, 72.9; H, 5.5%. λ max., see Table 2, p.118 . ν max. (in CS_2), 2213 (C≡C), 1712 (ester CO), 942 (trans-CH=CH), and 740 cm.$^{-1}$ (≡C-CO_2Me). No cis-CH=CH absorption was present.

cis-Methyl Oct-6-ene-2,4-diynoate (LX; R=Me).- cis-Methyl oct-6-ene-2,4-diynoate was prepared by the method described above for the trans-ester, from cis-pent-3-en-1-yne (260 mg.) and propiolic acid (280 mg.). The pure ester was

obtained by chromatography of the crude methanolysis product in light petroleum in the dark on alumina (30 g.). Elution with the same solvent gave the cis-methyl ester as an unstable, viscous oil (40 mg.) which was shown to be pure by vapour phase chromatography on the "Pye" instrument, and by infrared absorption spectroscopy. The ester was characterised further by quantitative ultraviolet spectroscopy. λmax., see Table 2, p.118. ν max. (in CS_2), 2200(C≡C), 1712 (ester CO), 740 (≡C-CO_2Me), and 714 cm.$^{-1}$ (cis-CH=CH).

Irradiation of trans-Methyl Oct-6-ene-2,4-diynoate.- The trans-ester (20 mg.) in light petroleum (b.p. 30-40°) containing a trace of iodine as sensitiser[88] was irradiated at 20° in the glass apparatus, and the course of isomerisation followed by vapour phase chromatography on the "Pye Argon Chromatograph" of samples withdrawn periodically. The composition after 15 min. irradiation was shown to be:- trans-ester, 55% (retention time, 2.44 min.); cis-ester, 45% (retention time, 2.09 min.). The composition was unchanged by further irradiation for periods up to 2 hr., and the above percentage composition was confirmed by the intensities of the various bands in the infrared absorption of the mixture.

As purification of the cis-ester by chromatography on alumina had been previously shown to cause much decomposition, preparative separation of the irradiation mixture was not attempted.

trans-Dec-2-ene-4,6,8-triyn-1-ol (trans-Dehydromatricarianol (LXI).- 1-Bromopenta-1,3-diyne[30] (from penta-1,3-diyne (350 mg., 1.1 mol.)) in methanol (2 c.c.) was added dropwise under nitrogen during 10 min. at 30° to a stirred mixture of 33% aqueous ethylamine (1.4 c.c.), cuprous chloride (15 mg.), a crystal of hydroxylamine hydrochloride, and trans-pent-2-en-4-yn-1-ol[107] (410 mg., kindly provided by Dr. G. Read). The mixture was stirred for a further 15 min. and then poured into N-hydrochloric acid. Isolation with ether gave the alcohol (586 mg.) which was rigorously purified by chromatography in benzene (5 c.c.) on alumina (100 g.) prepared in light petroleum. Elution with benzene-light petroleum (1:50) gave trans-dehydromatricarianol, which crystallised from ether-pentane as rhombs (450 mg.), m.p. 129° (lit.[30,108], m.p. 129°). λ max., see Table 2, p.118 . ν max. (in CS_2), 3550 (OH), 2210 (C≡C), and 942 cm.$^{-1}$ (trans-CH=CH). No cis-CH=CH absorption was present.

Irradiation of trans-Dec-2-ene-4,6,8-triyn-1-ol.- The above trans-alcohol (210 mg.) in ethanol (250 c.c.) containing a trace of iodine[88] was irradiated for 45 min. at 20° in the quartz apparatus. The brown solution was evaporated in nitrogen, and the residue chromatgraphed in the dark in benzene-light petroleum (5 c.c., 1:1) on a column prepared in light petroleum from alumina (40 g.). Elution with light petroleum afforded 1,4-epoxydeca-2,4-diene-6,8-diyne (LXIII) (20 mg.), while elution with benzene-light petroleum (1:50) gave cis- and trans-dehydromatricarianol (105 mg.), shown to be a mixture of the isomers by the infrared absorption bands at 942 (trans-CH=CH) and 730 cm.$^{-1}$ (cis-CH=CH).

The 1,4-epoxydeca-2,4-diene-6,8-diyne was rechromatographed in light petroleum in the dark on alumina (5 g.). Elution with the same solvent gave first the α-isomer (LXV) (3.2 mg.), λ max., see Table 2, p.118, ν max. (in CCl_4 and CS_2), 1627 (C=C-O), 1165 (=C-O), 777 (cis-CH=CH, cyclic), and 745 and 711 cm.$^{-1}$ (α-CH=CR_2), followed by the β-isomer (LXIV) (8.2 mg.), λ max., see Table 2, p.118, ν max., see below. The spectra of the α- and β-compounds are given on Fig. 2, p.66.

The cis- and trans-dehydromatricarianol mixture (105 mg.) and 0.1 N-potassium hydroxide solution (30 c.c., 50% aqueous ethanolic) was kept at 20° for 1 hr. Water(200 c.c.) was then added, the aqueous solution extracted with ether (2 x 50 c.c.), and the ethereal solution dried ($MgSO_4$) and evaporated. Chromatography of the residue as described above gave β-1,4-epoxydeca-2,4-diene-6,8-diyne (36 mg., eluted with light petroleum), and trans-dehydromatricarianol (67 mg., eluted with benzene-light petroleum (1:50)). The β-compound was recrystallised from ether-pentane at -40° as prismatic needles (30 mg.), m.p. 78° (Found: C, 83.35; H, 5.6. $C_{10}H_8O$ requires C, 83.3; H, 5.6%). λ max., see Table 2, p. 118 . ν max. (in CCl_4 and CS_2), 1627 (C=C-O), 1156 (=C-O), 887 (β-$CH=CR_2$), and 768 cm.$^{-1}$ (cis-CH=CH, cyclic).

cis-Undec-3-ene-5,7,9-triyn-2-ol (LXVI).- cis-Hex-3-en-5-yn-2-ol (48 mg., kindly provided by E.E. Boehm) was mixed with 33% aqueous ethylamine (0.4 c.c.), cuprous chloride (10 mg.), and a crystal of hydroxylamine hydrochloride[30]. 1-Bromopenta-1,3-diyne[30] (from penta-1,3-diyne (35 mg.)) in methanol (0.2 c.c.) was added dropwise during 10 min. to the above mixture with stirring under nitrogen at 30°. After stirring for a further 10 min.,

the product was isolated via N-hydrochloric acid and ether. The solid obtained was chromatographed in the dark in benzene-light petroleum (1:2) on alumina (5 g.). Benzene elution gave cis-undec-3-one-5,7,9-triyn-2-ol (62 mg.), which separated from ether-pentane as very light sensitive, colourless rods (50 mg.), m.p. 87° (Found: C, 83.0; H, 6.65. $C_{11}H_{10}O$ requires C, 83.5; H, 6.4%). λ max., see Table 2, p.118 . ν max. (in CCl_4 and CS_2), 3550 (OH), 2215 (C≡C), and 750 cm.$^{-1}$ (cis-CH=CH).

2,5-Epoxyundeca-3,5-diene-7,9-diyne (LXVII).- The above cis-alcohol (20 mg.) in ethanol (5 c.c.) with 0.2N-potassium hydroxide solution (1 c.c.) was kept at 20° for 1 hr. Water (20 c.c.) was then added, the aqueous solution extracted with ether (2 x 30 c.c.), and the combined extracts washed with water (30 c.c.) and dried ($MgSO_4$). Evaporation of the ether afforded a solid which on recrystallisation from pentane at -40° gave 2,5-epoxyundeca-3,5-diene-7,9-diyne as needles (16 mg.), m.p. 47° (Found: C, 83.5; H, 6.5. $C_{11}H_{10}O$ requires C, 83.5; H, 6.4%). λ max. see Table 2, p.118 . ν max. (in CCl_4 and CS_2), 1630 (C=C-O), 1162 (=C-O), 956 (β-CH=CR_2), and 781 cm.$^{-1}$ (cis-CH=CH, cyclic).

trans-Dec-2-ene-4,6,8-triyn-1-ol Tetrahydropyranyl Ether.- trans-Dehydromatricarianol (10 5 mg.), 2,3-dihydropyran (60 mg., 1 mol.), and phosphorus oxychloride (1 drop) in dry ether (5 c.c.) were kept overnight in the dark at 20°. Water (20 c.c.) was then added, the mixture extracted with ether (30 c.c.), and the ethereal phase dried ($MgSO_4$). After evaporation of the ether, the residue was chromatographed in the dark in light petroleum on alumina (5 g.). Light petroleum elution afforded the tetrahydropyranyl ether (166 mg.), which crystallised from pentane at -70° in needles (150 mg.), m.p. 56° (Found: C, 78.65; H, 7.2. $C_{15}H_{16}O_2$ requires C, 78.95; H, 7.1%). λ max., see Table 2, p.118. ν max. (in CS_2), 2215 (C≡C), 1125, 1034, and 1022 (C-O-C), and 942 cm.$^{-1}$ (trans-CH=CH).

PART II, SECTION II

Triphenyl-(carbethoxyethyl)phosphonium Bromide (LXXIII; R=Et).- Ethyl β-bromopropionate (1.81 g.,) (prepared by the method of Kendall and McKenzie[109]) and triphenylphosphine (2.75 g., 1.05 mol.) were heated at 90° for 3 hr.[110] The resulting syrup was dissolved in water (75 c.c.), well washed with ether, and the aqueous phase concentrated. The phosphonium bromide mono-hydrate crystallised in needles (3.25 g.), m.p. 91-94° (Found: C, 59.4; H, 5.65. $C_{23}H_{24}BrO_2P$, $1H_2O$ requires C, 59.85; H, 5.7%). $\nu_{max.}$ (Nujol) 3560 (H-OH), 1735 (ester CO), and 1625 and 1590 $cm.^{-1}$ (aromatic-CH=CH).

Reaction of Triphenyl-(carbethoxyethyl)phosphonium Bromide with (a) Methyl-lithium, and (b) Sodium Hydroxide Solution.- (a) The phosphonium bromide monohydrate (576 mg.) suspended in dry ether (5 c.c.) and ethereal methyl-lithium[34] (10 c.c., 0.25-N-solution, 2 mol.) were kept under nitrogen at 20° for 3 days. The mixture was evaporated and the residue recrystallised from 95% aqueous ethanol, giving triphenylphosphine as rhombs (250 mg.), m.p. and mixed m.p. with an authentic sample, 80°.

(b) The phosphonium bromide monohydrate (576 mg.) in water (20 c.c.) and 0.1 N-sodium hydroxide solution[111] (12.5 c.c., 1 mol.) were kept overnight at 20°. The resulting neutral solution was washed with ether, 0.1 N-sulphuric acid (12.5 c.c.) added and the aqueous solution evaporated carefully to dryness. Extraction with boiling methylene chloride afforded triphenyl-(carboxyethyl) phosphonium bromide as a foamy syrup (400 mg.). (Sodium fusion and silver nitrate tests showed the presence of bromide). $\nu_{max.}$ (in CH_2Cl_2), 1730 (CO), 1590 and 1580 (aromatic -CH=CH), 1463 and 970 (P-phenyl), and 930 cm.$^{-1}$ (CO_2H).

Dry distillation of a portion gave acrylic acid (identified by comparison of its infrared spectrum with that of an authentic sample), and triphenylphosphine oxide, which formed plates from benzene, m.p. 158° (lit.[112], m.p. 157°). $\nu_{max.}$ (Nujol), 1590 (aromatic-CH=CH), 1440 (P-phenyl), 1185 (P—O), and 1000 cm.$^{-1}$ (P-phenyl).

4-Chloropent-1-yne.- Pent-1-yn-4-yl toluene-p-sulphonate[41] (10 g.) and calcium chloride (7 g.) in cellosolve (100 c.c.) were heated under reflux for 15 min.[41] A heavy white precipitate separated almost immediately. Water (100 c.c.) was added to the cooled solution, and the chloropentyne isolated by steam distillation. Traces

of cellosolve were removed by washing a pentane solution with water, and after drying ($MgSO_4$), the pentane was evaporated *via* a 10 in. Fenske column. Distillation gave the chloro-compound (1.8 g.), b.p. 91-92°/744 mm., n_D^{25} 1.4295 (Found: Cl, 34.6. C_5H_7Cl requires Cl, 34.7%). $\nu_{max.}$ (in CS_2), 3225 (≡C-H), and 693 cm.$^{-1}$ (C-Cl).

Analysis and Resolution of cis- and trans-Pent-3-en-1-yne.- A mixture of cis- and trans-pent-3-en-1-yne was prepared by the method of Eglinton and Whiting.[41] Vapour phase chromatography on a 10% silicone oil (MS 550) on "Embacel" column at 40°, with hydrogen as the carrier gas, showed it to consist of cis (54%) and trans (46%). Distillation of a sample (5 g.) through a spinning band column at atmospheric pressure gave cis-pent-3-en-1-yne (1.75 g.), b.p. 42.45-43.6°/747 mm., n_D^{19} 1.4332, and the trans-isomer (1.6 g.), b.p. 48.2-49.8°/747 mm., n_D^{17} 1.4390. Vapour phase chromatography showed both isomers to be pure.

Ultraviolet Absorption Spectra - Table 1.

Compound	Absorption Maxima (Å) and $x10^{-3}$ (in parentheses								
Iso-odyssic ethylamide (XXVIII; R=Et)	2100 (154)	2390 (0.19)	2530 (0.24)	2680 (0.33)	2860 (0.31)	3080 (0.16)			
Iso-odyssic lactone (IV)	2080 (174)	2390 (0.29)	2520 (0.31)	2670 (0.35)	2850 (0.33)	3070 (0.27)			
$CH_3.(C{\equiv}C)_3.CH(OH).CH_2.CH_2.CO_2H$ (XXIX)	2100 (172)	2400 (0.25)	2540 (0.28)	2700 (0.34)	2870 (0.31)	3080 (0.19)			
trans-Odyssin A (V)	2100 (31)	2230* (29.5)	2300 (69.5)	2420 (122)	2580 (3.4)	2725 (7.4)	2890 (13.9)	3080 (18.8)	3290 (12.9)
trans-Odyssin A methyl ester	2100 (33)	2230* (33)	2300 (76.5)	2420 (135)	2570 (8.6)	2720 (8)	2880 (16)	3070 (21.3)	3290 (14.6)

* inflexion

Ultraviolet Absorption Spectra - Table 2.

Compound	Absorption Maxima (Å) and $\epsilon \times 10^{-3}$ (in parentheses)								
trans-Lachnophyllum ester (LVI; R=Me)	2150 (30.5)	2230 (37.7)	2720* (12.4)	2870 (22)	3050 (22)				
cis-Lachnophyllum ester (LVII; R=Me)	2160 (20.2)	2240 (26.2)	2750* (9.6)	2900 (14.4)	3070 (13.4)				
trans-Methyl Oct-6-ene-2,4-diynoate (LIX; R=Me)	2150 (45)	2220 (38)	2530 (6.5)	2660* (9.1)	2730 (10.5)	2890 (13.5)	3070 (8.8)	3380 (0.93)	
cis-Methyl Oct-6-ene-2,4-diynoate (LX; R=Me)			2530 (4.5)	2600* (5.0)	2730 (7.3)	2880 (10.1)	3060 (6.4)	3370 (0.53)	
trans-Dehydromatricarianol (LXI)	2110 (14.4)	2225* (55.4)	2330 (90)	2420 (108)	2570 (3.5)	2710 (6.5)	2890 (12.4)	3075 (16.3)	3290 (11.2)
α-1,4-Epoxydeca-2,4-diene-6,8-diyne (LXV) (see Fig.2, p.66)	2290 (6.5)	2390 (6.6)	2520 (3.7)	2660 (3.8)	3175 (11.5)				
β-1,4-Epoxydeca-2,4-diene-6,8-diyne (LXIV) (see Fig.2, p.66)	2300 (8.2)	2375 (8.9)	2535 (4)	2670 (6.4)	3170 (21)				
cis-Undec-3-ene-5,7,9-triyn-2-ol (LXVI)	2100 (36)	2300 (65)	2420 (112)	2570 (3.3)	2720 (6.5)	2890 (11.8)	3080 (15.6)	3290 (10.8)	
2,5-Epoxyundeca-3,5-diene-7,9-diyne (LXVII) (see Fig.2, p.66)	2095 (14.0)	2175* (12.4)	2310 (8.5)	2380 (9.3)	2540 (4)	2680 (5.1)	3175 (22.6)		
Tetrahydropyranyl ether of trans-Dehydromatricarianol	2300 (73)	2420 (124)	2570 (3.6)	2720 (7.6)	2890 (14.6)	3075 (19.2)	3290 (13.2)		

* inflexion

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